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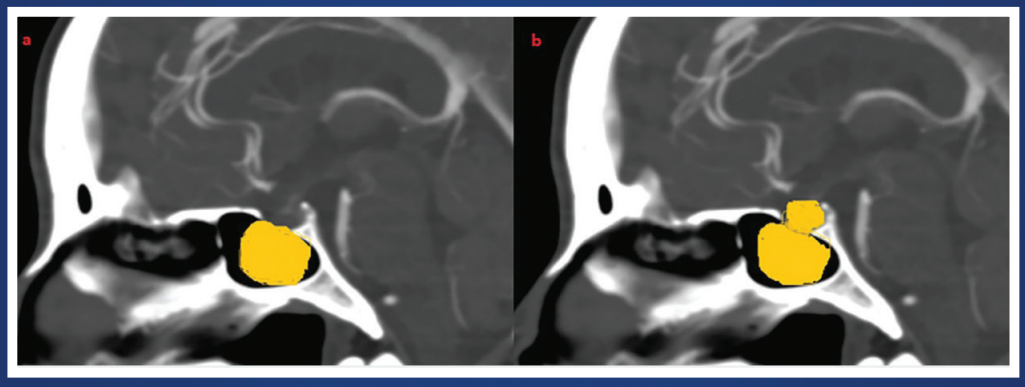

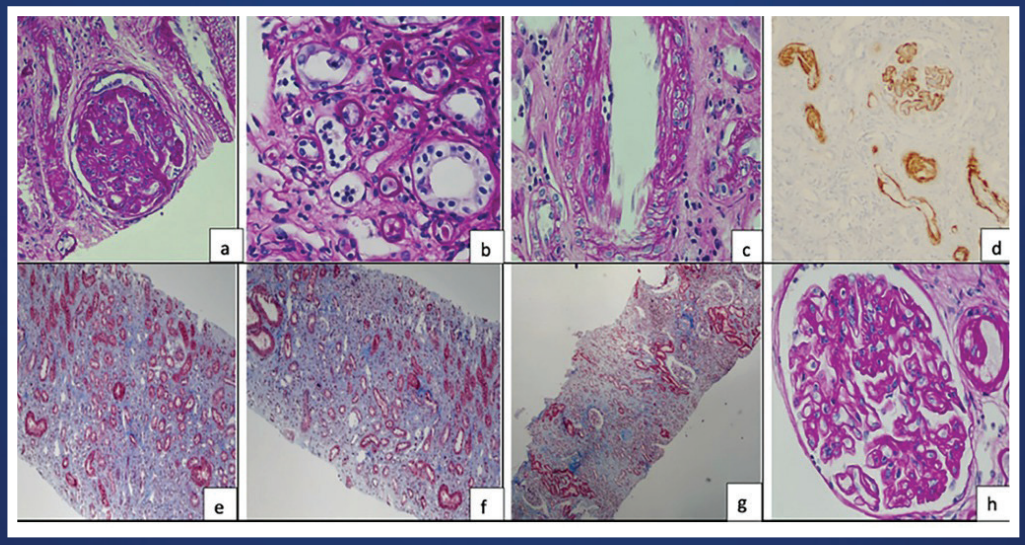

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LETTER TO THE EDITOR / EDİTÖRE MEKTUP

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Morgagni Hernia in a Patient with Seizures

Nöbetleri Olan Bir Hastada Morgagni Hernisi

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Keywords: Diaphragmatic hernia, epilepsy, morgagni hernia, seizure
Anahtar Kelimeler: Diyafram hernisi, epilepsi, morgagni hernisi, nöbet

To the Editor,

Morgagni diaphragmatic hernia (MDH) is characterized by an orifice in the diaphragm, usually on the right side, that allows herniation of abdominal contents into the thorax[1]. MDH accounts for approximately 3% of all diaphragmatic hernias[2,3]. It typically manifests later in life, either due to respiratory or gastrointestinal issues or as an incidental finding in asymptomatic adults. Diagnosis is confirmed through chest X-rays and computed tomography (CT) scans.

MDH is a rare clinical entity in adults, with no well-documented prevalence or natural history[4]. Predisposing factors such as trauma, obesity, and increased intraabdominal pressure due to chronic cough or constipation can contribute to herniation. However, only 50% of MDH cases present with predisposing factors.

We report a case of a 39-year-old female patient with MDH and epileptic seizures. She presented with worsening dyspnea over several years, exacerbated when lying supine. Her medical history included epilepsy for 17 years, type II diabetes, hypertension, and vitamin B12 deficiency. A heavy smoker for 20 years, she was on levetiracetam for epilepsy and metformin for diabetes. Physical examination revealed decreased breath sounds in the lower right hemithorax. A chest X-ray showed a homogeneous opacity in the right lower lung zone, and a CT scan confirmed the diagnosis of MDH (Figure 1). Pulmonary function tests indicated a mild restrictive ventilatory defect.

The patient underwent successful open surgery for hernia repair (Figure 2), and her postoperative course was uneventful. Follow-up chest X-rays confirmed a normal diaphragm and pulmonary structures (Figure 3). In a one-year follow-up after surgery, the patient reported significant improvement in dyspnea and had no epileptic seizures.

MDH was first described by Giovanni Battista Morgagni in 1761[1]. Among congenital diaphragmatic hernias, Bochdalek hernias are the most common, accounting for about 90% of cases[5]. MDH, which is less common, is predominantly found in females and obese individuals, and is usually located on the right side[2]. CT scans with contrast media are the preferred diagnostic tool for MDH, as they are more sensitive than standard X-rays[3].

There are few case reports linking MDH to neurological or respiratory symptoms. Pattnaik et al.[3] described a female patient with MDH and asthma, whose respiratory symptoms improved after hernia repair. Zisa et al.[4] reported a male patient with both MDH and seizures, suggesting that intra-abdominal pressure related to seizures may contribute to herniation. Acampora et al.[5] also reported a case where

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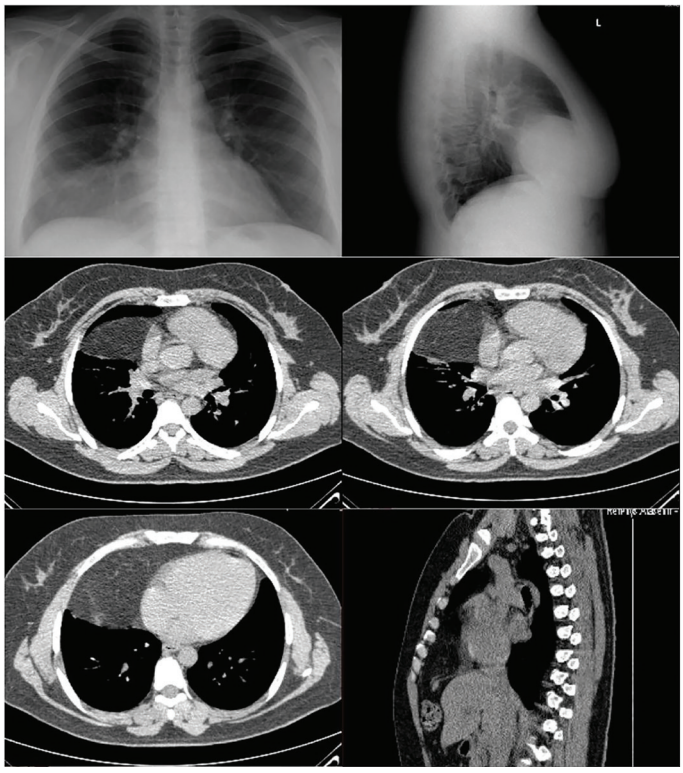

Figure 1. Preoperative posteroanterior, lateral chest X-ray and thorax CT images of the patient

CT: Computed tomography

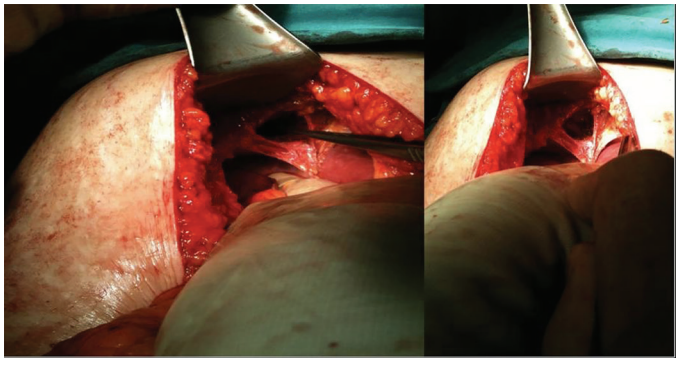

Figure 2. Intraoperative view of the diahragmatic defect due to Morgagni hernia

recurrent convulsive syncope resolved after MDH repair. In line with these findings, our patient's seizures subsided after surgical intervention, suggesting a potential relationship between MDH and seizure activity.

This case contributes to the limited literature on MDH and its possible association with seizures. Surgical repair of MDH in such cases may help alleviate neurological symptoms, and further studies are warranted to investigate this relationship.

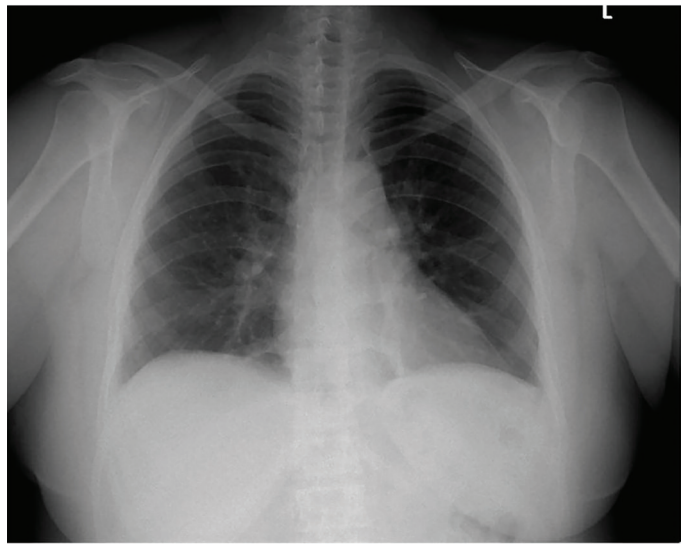

Figure 3. Postoperative posteroanterior chest X-ray of the patient

Footnotes

Authorship Contributions

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

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

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CASE REPORT / OLGU SUNUMU

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Efficacy of Plasmapheresis in Severe Leptospirosis Case

Ciddi Leptospiroz Olgusunda Plazmaferez Etkinliği

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Abstract

This study highlighted the efficacy of therapeutic plasma exchange and hemodialysis in a case of leptospirosis presenting with severe acute kidney injury. Leptospirosis is a zoonosis caused by spirochetes; it is more common in the tropics. It can be asymptomatic or present across a broad clinical spectrum, which may lead to mortality. A physically active 84-year-old male patient with a history of hypertension and prostate cancer, was admitted to our hospital with complaints of decreased oral intake for a week, weakness in the lower extremities, and subsequently developed a cough, fever, and jaundice. The patient was conscious, less cooperative than usual or expected, and appeared unwell on physical examination. His blood pressure was 155/94 mmHg, and he had tachycardia (111/min). The sclerae were icteric, and the conjunctivae were pale. Except for the presence of rales at lung bases, other systemic examinations were normal. Laboratory evaluation revealed anemia, thrombocytopenia, hyperbilirubinemia, and increased creatinine levels. Detection of risk factors for leptospirosis transmission in the patient's history, recreational activities such as long forest walks and consumption of contaminated raw vegetables, and compatible clinical findings suggested Weil's disease as the preliminary diagnosis. Leptospira polymerase chain reaction positivity in the urine confirmed the diagnosis. The patient developed oliguria during the course, and we started renal replacement therapy. The emergence of alveolar hemorrhage prompted us to apply plasmapheresis as rescue therapy. We achieved a dramatic renal recovery after ensuring diuresis with two sessions of plasmapheresis. Plasmapheresis as a rescue therapy successfully manages leptospirosis cases that present with multi-organ involvement, with high mortality.

Keywords: Leptospirosis, therapeutic plasma exchange, acute kidney injury, alveolar hemorrhage, hemodialysis

Öz

Bu çalışma ciddi akut böbrek hasarı ve alveoler hemoraji ile başvuran ciddi bir leptospiroz olgusunda plazmaferez etkinliğini vurgulamaktadır. Leptospiroz, spiroketlerin neden olduğu, tropik bölgelerde daha yaygın görülen bir zoonozdur. Asemptomatik olabileceği gibi mortaliteye neden olabilecek geniş bir klinik spektrumda gözlenebilir. Hipertansiyon ve prostat kanseri öyküsü olan, fiziksel olarak aktif 84 yaşında erkek hasta; bir haftadır oral alımda azalma, alt ekstremitede güçsüzlük ve sonrasında gelişen öksürük, ateş, sarılık yakınmaları ile hastanemize başvurdu. Başvuru muayenesinde hastanın şuuru açık, kooperasyon zayıf ve düşkün durumdaydı. Kan basıncı 155/94 mmHg, nabız dakika sayısı 111/dk, skleralar ikterik ve konjuktivaları soluktu. Akciğer bazallerinde raller dışında sistemik bakıları olağandı. Laboratuvar verilerinde anemi, trombositopeni, hiperbilirubinemi ve kreatinin yüksekliği saptandı. Hastanın öyküsünde leptospirosis bulaşına ilişkin risk faktörlerinin saptanması (uzun orman yürüyüşleri gibi rekreasyonel aktiviteler ve kontamine çiğ sebze tüketimi) ve uyumlu klinik bulgular ön tanıda Weil hastalığını düşündürdü. Tanı idrarda Leptospira polimeraz zincir reaksiyonu pozitifliği ile doğrulandı. Hastalığın seyrinde oligüri gelişmesi üzerine renal replasman tedavisi başlandı. Alveolar hemoraji başlaması üzerine hastaya son çare tedavi olarak plazmaferez uygulandı. Hastada iki seans plazmaferez tedavisi sonrası idrar çıkışı başlaması ve diyaliz ihtiyacının ortadan kalkması ile dramatik bir renal düzelme sağlandı. Yüksek mortalite riski olan çoklu organ tutulumlu leptospiroz olgularında plazmaferez tedavisi başarılı bir yönetim sağlamaktadır.

Anahtar Kelimeler: Leptospiroz, terapötik plazma değişimi, akut böbrek hasarı, alveolar kanama, hemodiyaliz

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Introduction

Leptospira is a spirochete that causes disease in humans. Although Leptospira is more common in tropical and temperate climates, it is in fact a common zoonotic agent throughout the world[1]. Rodents are the most important reservoir. However, many mammals can serve as primary reservoirs for Leptospira. It remains viable in the renal tubules of infected mammals, from where it is shed into the environment through urine[2]. Transmission to humans occurs through skin abrasions, mucous membrane, or conjunctival contact with soil or water contaminated with rodent urine, or oral ingestion of contaminated food and water. The bacteria can survive for months in soil and fresh water contaminated with urine, and even longer in temperate climates[3].

It is thought that the septicemic and immune responses may play a role in the development of clinical signs after the incubation period. Leptospirosis is usually an asymptomatic or self-limiting infection. In some cases, it can lead to multiple organ failure and even death[4]. Leptospirosis has two different clinical forms, anicteric and icteric forms. The rarer and more severe form is icteric leptospirosis, also known as Weil's disease[2]. Icteric leptospirosis is a disease characterized by acute kidney injury (AKI), jaundice, and fever. Thrombocytopenia, anemia, and neurological findings may also be observed. Rarely, it can lead to atypical presentations such as pulmonary hemorrhage, thrombotic thrombocytopenic purpura, and Guillain-Barré syndrome (GBS)[5]. We report a case of leptospirosis in which direct hyperbilirubinemia, anemia, thrombocytopenia, AKI, and pulmonary hemorrhage were at the forefront.

Case Report

A socially and physically active 84-year-old man with a history of hypertension and previous surgery for prostate cancer was admitted to our tertiary care hospital with complaints of decreased oral intake, lower extremity weakness, and subsequent cough, hemoptysis, fever, myalgia and yellowing of the skin for one week. The patient had no known allergy, history of antibiotic use, or hospitalization in the last three months. He had only used non-steroidal anti-inflammatory drugs (NSAIDs) for the same complaints. On the physical examination, the patient was conscious, fully oriented, and capable of cooperation, although collapsed. The vital signs were as follows: blood pressure 155/94 mmHg, respiratory rate 18/min, pulse rate 111/min, body temperature 36.4 °C. The sclerae were icteric and the conjunctivae were pale. Lung auscultation revealed bilateral basilar rales. Other systems were normal.

The laboratory results during hospitalization and outpatient follow-up are shown in Table 1. On admission, the leukocyte count was normal; however, there was an increased neutrophil percentage and the patient was anaemic and thrombocytopenic. The patient had hyperbilirubinemia with predominant direct bilirubin. The urea and creatinine levels of the patient were consistent with AKI. There were hyponatremia and transaminase levels that were slightly above the upper limit of normal. There was a 2+ result in the direct Coombs polyspecific, and IgG tests. The peripheral smear showed neutrophilia and sporadic echinocytes. No schistocytes were observed. The patient was evaluated for thrombotic microangiopathy. Thrombotic microangiopathy or haemolytic anaemia were not considered. In viral hepatitis serology, no significant feature was found.

Radiological examination revealed bilateral minimal pleural effusion on thoracic computed tomography (CT) and lesions compatible with dependent atelectasis or ground-glass opacities in the basal regions. The infiltrates in the lungs were not interpreted as alveolar hemorrhage. No biliary pathology was found on abdominal CT. Linear density increases in the bilateral perirenal regions were reported. With the diagnosis of pyelonephritis, a urine culture was performed and meropenem antibiotherapy was started.

On the third day of treatment with meropenem, the urine culture was negative. There was no response with regard to the AKI parameters and infectious parameters. The patient described intermittent bloody sputum, and ascending progression of lower extremity weakness. The patient was found to take long walks in the woods every day and consume raw roots of various vegetables and herbs such as ginger. Leptospirosis was considered in the differential diagnosis on the basis of medical history, clinical, and laboratory data. In the second week of symptoms, whole blood and urine samples were taken for a Leptospira polymerase chain reaction (PCR) test. Real-time PCR for Leptospira was performed with these samples using an in-house method at the Public Health Institute of Türkiye.

The treatment was changed to intravenous ceftriaxone 1x2 g for leptospirosis, while awaiting the results of the test. The ataxia that was present on neurological examination was considered secondary to the general condition. The patient was started on hemodialysis due to anuria, pulmonary hemorrhage, and severe AKI. Plasmapheresis was performed in two sessions on the 3rd and 4th day of hospitalization. After plasmapheresis, diuresis was achieved and renal function improved rapidly. The need for hemodialysis was

Table 1. Laboratory findings of the patient during hospitalisation and after discharge

	Day 0	Day 3	Day 4	Day 6	Day 12 (discharge)	Month 1 after discharge
Leukocyte (4.2-10.6 ×10³/mm³)	7.9	8.5	8.0	14.4	6.3	5.6
Neutrophil (37-80%)	94%	86%	85%	80%	70%	62%
Platelet (140-400×10³/mm³)	47	76	80	116	490	251
Haemoglobin (12.2-16.2 gr/dL)	10.9	10.8	12	12.2	10.9	10.9
CRP (0-5 mg/L)	233	193	63	28	25	
Procalcitonin (0.04-0.1 mcg/L)	2.17	54.9	19.37		0.07	
Total bilirubin (0.3-1.2 mg/dL)	7.14	9.82	8.69	5.12	1.51	
Direct bilirubin (0.0-0.2 mg/dL)	5.1	6.68	5.43	3	0.73	
Creatinine (0.8-1.3 mg/dL)	6	7.3	5.8	5.6	2.9	1.86
Urea (17-43 mg/dL)	144	191	174	190	145	55
Sodium (136-146 mmol/L)	126			124	138	143
ALT (0-50 U/L)	51	40	36	32	27	
AST (0-50 U/L)	58	32	44	35	25	
aPTT (21-36 sn)	32.3			24.2		
INR (0.8-1.2)	1.11			0.91		
Fibrinogen (170-420 mg/dL)	765			351		

Urinalysis: Leukocyte negative, Erythrocyte 3+, Protein 1+, Urobilinogen normal, Nitrite negative

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

eliminated after the second plasmapheresis treatment. The follow-up laboratory course of the patient whose laboratory parameters rapidly recovered is given in Table 1. On the 10th day of hospitalization, the diagnosis of leptospirosis was confirmed when Leptospira PCR was negative in the whole blood sample but positive in the urine. Ceftriaxone treatment was completed for ten days, and the patient had a creatinine level of 2.9 mg/dL, and was scheduled for outpatient follow-up. The creatinine level was 1.86 mg/dL at the end of month one. By the end of the first year of long-term follow-up, the creatinine level was 1.6 mg/dL. Written informed consent was obtained from the patient.

Discussion

This case report highlights the rapid urine output and clinical improvement achieved with plasmapheresis treatment in a case of leptospirosis with a high risk of mortality, that was followed by pulmonary hemorrhage, hematological involvement, and anuric renal damage. In the literature review, there were two successfully managed cases with meropenem antibiotherapy from Türkiye[6]. In some in vitro studies, carbapenems have been reported to have excellent activity against Leptospira[7]. However, renal and biliary parameters continued to deteriorate, and due to poor clinical/laboratory response, and no clear evidence of *in vivo* efficacy found in the literature, it was decided to replace antibiotherapy with ceftriaxone, as it is the recommended first-choice parenteral agent against Leptospira. In view of pulmonary hemorrhage, hematological, and possible neurological involvement, plasmapheresis treatment was started as a last resort.

Leptospirosis is a zoonotic disease that can lead to multi-organ involvement, and, in the presence of pulmonary hemorrhage, to a high mortality rate. Specific treatment options are very limited, especially in the presence of

alveolar hemorrhage, and the treatment options' efficacy has not been proven in large case series. In the literature, success with therapeutic plasma exchange (TPE) and/or extracorporeal membrane oxygenation has been reported in very few cases of severe leptospirosis[8-10].

In many infections such as coronavirus disease-2019 (COVID-19) and influenza, which "progresses with lung damage and multiple organ failure" similar to leptospirosis, TPE has proven to be beneficial in controlling hyperinflammation and cytokine storm, and the clinical course[11,12]. Based on the COVID-19 experience, TPE may be beneficial in preventing endothelial and end-organ damage through many mechanisms[13]. Leptospirosis is an infection with vasculitic consequences through immunological mechanisms. The first possible mechanism of action of TPE in leptospirosis is the removal of inflammatory cytokines, thereby stabilizing the endothelial membrane. Another mechanism is the removal of antigens that trigger the immune response against Leptospira and antibodies that are produced against them, which damage host cells due to molecular similarities.

Leptospira are 0.15 µm in diameter and 10 to 20 µm in length[14]. It may be technically feasible to remove the microorganism from micropores during processing due to the microorganism's diameter being larger than the micropores. Another possible mechanism of action is to reduce the infectious load: in this way. Turgutkaya et al.[15] claim that the viral load can be cleared by a similar mechanism and may have a beneficial effect on survival.

On the other hand, TPE is an invasive procedure involving the potential for complications and adverse effects. There are common but mild adverse effects such as temporary increases in body temperature, nausea, and vomiting. Serious complications, including hypotension, electrolyte imbalances and arrhythmias, have also been reported[13,16]. The removal of antibodies is not merely a therapeutic mechanism, but can also lead to a decline in immunity and predispose to infectious complications[16]. Another major limitation of TPE is that it requires specialised equipment and experienced medical staff[13].

Our patient's involvement in "recreational activities" (forest walks) and consumption of uncooked vegetables/plants are risk factors for transmission[17]. In addition to clinical and laboratory findings consistent with leptospirosis, the detection of the pathogen in the urine sample by Leptospira PCR confirmed the diagnosis. The fact that PCR was negative in the whole blood sample, but positive in urine was consistent with the natural course of leptospirosis, considering the timing of the patient's hospital presentation and investigations. In the patient who presented at least one week after the onset of symptoms, the bacteremia period (first week) ended and the urinary shedding period started in the second week[3].

Pulmonary hemorrhage is a complication that can occur in Weil's disease[10]. In the literature, the mortality rate in cases of alveolar hemorrhage is reported to be 50-70%[2]. Although the pulmonary infiltrates in the thorax imaging of our patient were not considered a sign of hemorrhage, pulmonary involvement was assessed clinically due to marked hemoptysis. This was decisive in the rapid decision to initiate plasmapheresis.

Similar to our patient who presented with AKI and regressed bilirubin levels after TPE, cases with diffuse pulmonary infiltrates on lung imaging that were not interpreted as hemorrhage have been reported[18]. There have been case series in which improvement has been achieved with plasma exchange using a continuous veno-venous haemofiltration pattern as well[19].

Although our patient had a history of GBS-like ascending progression of lower extremity weakness and trunk ataxia, this could not be confirmed by neurological conduction studies. A variant of GBS associated with leptospirosis has been described in the literature on the basis of case reports and confirmed by electroneurophysiological studies. Complete or partial response to plasmapheresis treatment has also been reported in cases of GBS secondary to leptospirosis[9]. Peripheral nerve involvement is rare in leptospirosis. However, there are cases of transient lower limb weakness and "GBS-like" findings during or after Leptospira interrogans infection[20]. Thus, ataxia can be considered a neurological involvement of leptospirosis, although the diagnosis of GBS was excluded in our case.

Few cases of success with plasmapheresis in leptospirosis complicated by multiple organ involvement have been reported in the literature[9,10]. The dramatic clinical response after the simultaneous initiation of ceftriaxone and plasmapheresis was thought to be a benefit of plasmapheresis.

Conclusion

Leptospirosis has a wide variety of clinical manifestations. Patients may present with signs and symptoms that

mimic a wide range of hematological, neurological, and rheumatological conditions. In addition to antibiotic therapy, it should be kept in mind that plasmapheresis may be a rescue treatment, especially in cases with high mortality risk.

Ethics

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

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Prognosis of Pregnancies Complicated by OHSS Following Ovulation Induction: A Retrospective Analysis

Ovulasyon İndüksiyonu Sonrası OHSS ile Komplike Olan Gebeliklerin Prognozu: Retrospektif Bir Analiz

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Abstract

Objective: This research investigates pregnancy outcomes in women who developed ovarian hyperstimulation syndrome (OHSS) after ovulation induction, with a focus on both maternal and newborn health. The study further explored how OHSS relates to unfavorable pregnancy outcomes, including the need for neonatal intensive care, the occurrence of multiple gestations, and complications affecting the mother.

Methods: Between January 2019 and August 2022, a retrospective evaluation was carried out in one tertiary-level hospital. The study population consisted of pregnant women who developed OHSS following ovulation induction. Data on demographic features, clinical findings, laboratory measurements, and pregnancy-related results were collected. Comparative statistical analyses were used to examine how OHSS influenced both maternal and newborn complications.

Results: The mean age of the study population was 31.1±5.1 years, and the mean body mass index was 30.5±1.4 kg/m^2. In vitro fertilization was the most commonly applied assisted reproductive technique, used in 60.0% of cases. Clinical symptoms were prevalent, with abdominal pain reported in 86.7% of patients, and nausea/vomiting in 73.3% of patients. The live birth rate was 66.7%, while pregnancy loss occurred in 33.3% of cases. Multiple pregnancy was present in 40.0% of cases, and neonatal intensive care unit (NICU) admission was required in 50.0% of newborns, with a statistically significant association between NICU admission and multiple pregnancy (p=0.010). Maternal adverse outcomes were observed in 63.6% of cases, and these were significantly correlated with higher albumin levels (p=0.002) and lower gestational age (p=0.030). However, OHSS was not identified as an independent risk factor for cesarean delivery, preterm birth, or pregnancy loss.

Conclusion: Our findings align with existing literature suggesting that OHSS is associated with neonatal morbidity and maternal complications but may not be an independent risk factor for adverse pregnancy outcomes. Differences in patient populations and inclusion criteria may explain variations across studies. To clarify the long-term influence of OHSS on pregnancy outcomes, additional research with broader sample sizes and prospective designs is required.

Keywords: Ovarian hyperstimulation syndrome, pregnancy complications, neonatal outcomes, maternal prognosis, in vitro fertilization

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Öz

Amaç: Bu çalışmanın amacı, ovulasyon indüksiyonu sonrası gelişen over hiperstimülasyon sendromu (OHSS) ile komplike olmuş gebeliklerde maternal ve neonatal prognozu değerlendirmektir. OHSS ile yenidoğan yoğun bakım ünitesi yatışı, çoğul gebelik ve maternal komplikasyonlar gibi olumsuz gebelik sonuçları arasındaki ilişki incelenmiştir.

Yöntem: Bu retrospektif çalışma, tek merkezli bir üçüncü basamak sağlık kuruluşunda gerçekleştirilmiş olup Ocak 2019 ile Ağustos 2022 tarihleri arasında ovulasyon indüksiyonu sonrası OHSS tanısı alan gebe hastalar dahil edilmiştir. Demografik özellikler, klinik semptomlar, biyokimyasal parametreler ve gebelik sonuçları analiz edilmiştir. OHSS'nin maternal ve neonatal komplikasyonlar üzerindeki etkisini değerlendirmek amacıyla istatistiksel karşılaştırmalar yapılmıştır.

Bulgular: Çalışma grubunun ortalama yaşı 31,1±5,1 yıl, ortalama vücut kitle indeksi ise 30,5±1,4 kg/m^2 idi. Yardımcı üreme teknikleri arasında en sık uygulanan yöntem %60,0 oranıyla in vitro fertilizasyon oldu. Klinik semptomlar yaygındı; hastaların %86,7'sinde abdominal ağrı, %73,3'ünde ise bulantı/kusma mevcuttu. Canlı doğum oranı %66,7 iken, gebelik kaybı %33,3 oranında gerçekleşti. Olguların %40,0'ında çoğul gebelik mevcuttu ve yenidoğanların %50,0'si yenidoğan yoğun bakım ünitesine yatırıldı. Çoğul gebelik ile yenidoğan yoğun bakım ünitesi yatışı arasında istatistiksel olarak anlamlı bir ilişki saptandı (p=0,010). Maternal advers sonuçlar %63,6 oranında gözlemlendi ve bu durum yüksek albümin düzeyleri (p=0,002) ile düşük gebelik yaşı (p=0,030) ile anlamlı şekilde ilişkiliydi. Bununla birlikte, OHSS sezaryen doğum, preterm doğum ya da gebelik kaybı için bağımsız bir risk faktörü olarak tanımlanmadı.

Sonuç: Bulgularımız, OHSS'nin neonatal morbidite ve maternal komplikasyonlarla ilişkili olduğunu ancak olumsuz gebelik sonuçları açısından bağımsız bir risk faktörü olmayabileceğini öne süren mevcut literatürle uyumludur. Farklı hasta grupları ve çalışma kriterleri, çalışmalar arasındaki bulgu farklılıklarını açıklayabilir. OHSS'nin gebelik sonuçları üzerindeki uzun vadeli etkilerini daha iyi anlayabilmek için ileriye dönük, geniş ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Over hiperstimülasyon sendromu, gebelik komplikasyonları, neonatal sonuçlar, maternal prognoz, in vitro fertilizasyon

Introduction

Ovulation induction and controlled ovarian hyperstimulation (COH) are commonly used methods in infertility treatment[1]. However, ovarian hyperstimulation syndrome (OHSS) may develop as a result of an excessive response to gonadotropins (Gn) during these processes[2]. OHSS is an iatrogenic complication characterized by excessive ovarian stimulation and increased vascular permeability, which potentially life-threatening[3]. While mild cases present with symptoms such as abdominal distension and nausea, severe forms may lead to ascites, pleural effusion, hemoconcentration, and thromboembolic complications[4].

Multiple factors have been associated with the onset of OHSS. These include conditions such as polycystic ovary syndrome (PCOS), younger maternal age, low body mass index (BMI), increased ovarian follicle count, higher anti-Müllerian hormone (AMH) concentrations, and a prior history of OHSS[5,6]. Among them, the use of human chorionic Gn (hCG) for ovulation induction is particularly important, as this hormone significantly contributes to OHSS pathogenesis. The condition is generally divided into two types: early and late. The early form typically arises within 10 days after administration of hCG, while the late type is more often linked to the natural production of hCG during pregnancy[7].

The effects of OHSS-complicated pregnancies on maternal and fetal prognosis have not been fully elucidated. The current literature contains a limited number of studies on the impact of OHSS on pregnancy outcomes. It has been suggested that pregnancies affected by OHSS have a higher incidence of complications such as miscarriage, preterm birth, low birth weight (LBV), and hypertensive disorders[8]. However, these findings may vary due to differences in patient populations and treatment protocols.

The aim of this study is to evaluate the prognosis of pregnancies complicated by OHSS following ovulation induction and COH. In our study, pregnancy outcomes of these patients (such as miscarriage, preterm birth, and birth weight) were retrospectively analyzed, and the impact of OHSS on pregnancy progression was discussed in light of the obtained data.

Materials and Methods

This retrospective study was conducted at the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Gynecology Training and Research Hospital, to evaluate the clinical and obstetric prognosis of patients who were hospitalized due to OHSS and had ongoing pregnancies between January 2019 and August 2022. Ethical approval for the study was obtained from the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Gynecology Training and Research Hospital (approval no: 11, date: 06.09.2022), and patient data were retrospectively reviewed from hospital records.

Study Group and Inclusion Criteria

The study included patients aged between 18 and 45 years who developed OHSS following ovulation induction and COH, had ongoing pregnancies. The selection of these patients was based on the regular follow-up of their pregnancies at our hospital and the availability of complete clinical and obstetric records. The study population was determined by selecting patients who were diagnosed with OHSS after infertility treatment and who had continuing pregnancies.

Exclusion Criteria

Patients excluded from the study included those younger than 18 or older than 45 years, those whose pregnancy follow-ups were not conducted regularly or whose records were inaccessible, and those who developed OHSS but did not achieve pregnancy. Furthermore, individuals with long-standing systemic illnesses-including conditions like diabetes, high blood pressure, or autoimmune diseases-that might influence pregnancy outcomes were excluded from the study. These criteria were established to eliminate other potential confounding variables and to assess pregnancy outcomes solely in the context of OHSS.

Data Collection and Evaluation Method

Patient data were retrospectively obtained from the hospital automation system and patient records. The parameters analyzed in the study included demographic data, OHSS severity, clinical findings, and pregnancy outcomes. Demographic data encompassed patient age, BMI, infertility duration, ovulation induction protocol, AMH level, estradiol (E2) levels, stimulation duration, and the total Gn dose used. The severity of OHSS was classified as mild, moderate, or severe according to the American Society for Reproductive Medicine classification[9].

Clinical Findings and Pregnancy Outcomes

In terms of clinical findings, patients were evaluated for abdominal pain, nausea and vomiting, oliguria, presence of ascites, hematocrit (Hct) levels, electrolyte imbalances, and hospital stay duration. Regarding pregnancy progression and outcomes, parameters such as abortion (early and late), preterm birth (<37 weeks), mode of delivery (vaginal or cesarean), birth weight, and neonatal intensive care unit (NICU) requirement were analyzed. These data were retrospectively examined to assess the impact of OHSS on pregnancy outcomes.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous data are summarized as mean ± standard deviation (SD), whereas categorical data are shown as numbers and percentages. The distribution of variables was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests. When the data followed a normal distribution, comparisons were made with the independent t-test; otherwise, the Mann-Whitney U test was applied. For categorical comparisons, either the chi-square test or Fisher's exact test was used. A p-value less than 0.05 was regarded as the threshold for statistical significance.

Results

The mean age of the patients included in the study was calculated as 31.1±5.1 years. The mean BMI was found to be 30.5±1.4 kg/m^2. Regarding obstetric history, the mean gravidity was determined to be 1.2±0.4, parity was 0.2±0.4, and the number of living children was 0.3±0.6.

Sixty percent (60.0%) of the patients underwent in vitro fertilization (IVF), making it the most common treatment modality compared to other methods. In terms of clinical symptoms, 86.7% of the patients reported abdominal pain, 73.3% experienced nausea and vomiting, and oliguria was observed in 13.3% of the patients.

The mean birth weight of the patients was calculated as 2840.0±380.4 g, and the mean gestational age was determined as 36.3±3.2 weeks. In cases of abortion, the mean gestational age at abortion was found to be 8.6±3.3 weeks. Regarding biochemical parameters, the mean Hct level was 38.5±4.5, the serum sodium (Na) level was 133.9±3.2 mmol/L, and the potassium (K) level was 4.1±0.5 mmol/L. The albumin level showed high variation (9.2±12.7 g/dL).

Among the patients included in the study, 6.7% underwent albumin replacement therapy, while none underwent paracentesis. The live birth rate was determined to be 66.7%, whereas pregnancy loss (abortion) occurred in 33.3% of cases. Regarding the mode of delivery, vaginal delivery was observed in 26.7% of the patients, while 40.0% underwent cesarean section. The multiple pregnancy rate was found to be 40.0%, and 50.0% of the patients required admission to the NICU.

In pregnancies requiring NICU admission, the rate of multiple pregnancies was found to be significantly higher (80.0% vs. 0.0%, p=0.010). However, when evaluating the

mode of delivery among neonates requiring NICU admission, the cesarean section rate was higher (80.0%), though this difference was not statistically significant (p=0.197). Other parameters associated with NICU admission were also examined. Abdominal pain was more frequently observed in the group requiring NICU admission (100.0% vs. 60.0%, p=0.114), although statistical significance was not reached. Additionally, no significant association was found between NICU admission and factors such as albumin replacement, oliguria, or COH (p>0.05) (Table 1).

Across the treatment groups, there were no meaningful statistical differences in age, BMI, electrolyte parameters (Na and K), Hct, or albumin levels (p>0.05). In terms of neonatal outcomes, the clomiphene citrate (CC)+intrauterine insemination (IUI) group showed the highest average birth weight (3240.0±84.9 g), whereas the recombinant follicle-stimulating hormone (rFSH)+IUI and IVF groups had lower values; nevertheless, this variation did not reach statistical significance (p=0.277). The average gestational period was slightly longer in the CC+IUI group (39.0±2.8 weeks) and shorter in the rFSH+IUI and IVF groups, though again the difference between groups was not significant (p=0.444). Likewise, gestational age at abortion showed no notable variation across groups (p=0.842) (Table 2).

In the group with maternal adverse outcome, the albumin level was measured as 7.4±10.9 g/dL, whereas in the group without maternal adverse outcome, it was 2.7±0.4 g/dL (p=0.002). The gestational age was 35.3±3.1 weeks in the group with maternal adverse outcome and 38.7±2.1 weeks in the group without the adverse outcome (p=0.030). There was no statistically significant difference between the groups with and without maternal adverse outcome in terms of age, BMI, Na, K, and Hct levels (p>0.05) (Table 3).

Discussion

In our study, IVF was identified as the most frequently preferred assisted reproductive technique, with a higher application rate compared to other treatment modalities. Regarding clinical symptoms, the majority of patients were found to experience abdominal pain, nausea, and vomiting as predominant complaints. The frequency of multiple gestations was notably increased among cases that required NICU admission. While cesarean deliveries occurred more often in the NICU group, the variation did not reach statistical significance. Additionally, a significant association was observed between maternal adverse pregnancy outcomes and both albumin levels and gestational age. These findings emphasize the need for careful evaluation of maternal and neonatal outcomes during the application of assisted reproductive techniques, and they highlight the impact of multiple pregnancies on neonatal morbidity, which should not be overlooked.

Table 1. Comparison of clinical and obstetric parameters based on NICU admission in patients with OHSS

		NICU admission (-) (n=5)	NICU admission (+) (n=5)	
		Count (%)	**Count (%)**	**p-value***
CC+IUI		2 (40%)	0 (0%)	0.114
COH		0 (0%)	1 (20%)	0.292
IVF		3 (60%)	4 (80%)	0.490
Nausea/vomiting		4 (80%)	4 (80%)	1.00
Abdominal pain		3 (60%)	5 (100%)	0.114
Oliguria		0 (0%)	1 (20%)	0.292
Albumin replacement		0 (0%)	1 (20%)	0.292
Paracentesis		0 (0%)	0 (0%)	-
Live birth		5 (100%)	5 (100%)	-
Mode of delivery	Vaginal	3 (60%)	1 (20%)	0.197
	C/S	2 (40%)	4 (80%)	
Multiple pregnancy		0 (0%)	4 (80%)	**0.010**

Data in the table are presented as number (percentage), statistically significant p-values are indicated in bold

*: Fisher's exact test, OHSS: Ovarian hyperstimulation syndrome, CC: Clomiphene citrate, IUI: Intrauterine insemination, COH: Controlled ovarian hyperstimulation, IVF: In vitro fertilization, C/S: Cesarean section, NICU: Neonatal intensive care unit

Table 2. Comparison of demographic, biochemical, and pregnancy outcomes among different treatment modalities in patients with OHSS

	CC+IUI (n=2)	rFSH+IUI (n=4)	IVF (n=9)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Age (years)	28.5±0.7	34.3±6.8	30.2±4.4	0.333[a]
BMI (kg/m²)	31.0±2.8	29.8±1.0	30.7±1.3	0.505[a]
Na (mmol/L)	137.5±0.7	132.0±2.9	133.9±3.1	0.143[a]
K (mmol/L)	3.8±0.4	4.4±0.3	4.0±0.5	0.225[a]
Hct (%)	36.0±4.2	39.0±3.9	38.9±5.1	0.726[a]
Albumin (g/dL)	3.7±0.9	11.2±15.9	9.6±13.3	0.807[b]
Birth weight (gr)	3240.0±84.9	2725.0±.	2742.1±386.2	0.277[a]
Gestational age (weeks)	39.0±2.8	35.0±.	35.7±3.3	0.444[a]
Gestational week of abortion	.	8.7±4.6	8.5±0.7	0.842

[a]: One-way ANOVA t-test, [b]: Kruskal-Wallis test, OHSS: Ovarian hyperstimulation syndrome, CC: Clomiphene citrate, IUI: Intrauterine insemination, rFSH+IUI: Recombinant follicle-stimulating hormone+intrauterine insemination, IVF: In vitro fertilization, SD: Standard deviation, BMI: Body mass index, Na: Sodium, K: Potassium, Hct: Hematocrit

Table 3. Comparison of demographic and clinical characteristics in OHSS patients with and without maternal adverse outcomes

	Maternal adverse outcome (-) (n=4)	Maternal adverse outcome (+) (n=7)	
	Mean ± SD	Mean ± SD	p-value
Age (years)	28.3±3.2	32.7±4.2	0.084[c]
BMI (kg/m²)	31.0±1.2	30.3±1.8	0.498[c]
Na (mmol/L)	133.8±4.2	134.7±2.9	0.662[c]
K (mmol/L)	3.9±0.4	4.1±0.6	0.535[c]
Hct (%)	39.5±7.7	38.3±2.9	0.780[c]
Albumin (g/dL)	2.7±0.4	7.4±10.9	**0.002[d]**
Gestational age (weeks)	38.7±2.1	35.3±3.1	**0.030[c]**

Data in the table are presented as mean ± SD, statistically significant p-values are indicated in bold

[c]: Independent Samples t-test, [d]: Mann-Whitney U test, OHSS: Ovarian hyperstimulation syndrome, SD: Standard deviation, BMI: Body mass index, Na: Sodium, K: Potassium, Hct: Hematocrit

Increasing maternal age plays a major role in fertility, as it gradually reduces reproductive capacity. This reduction is mainly linked to diminished ovarian reserve, poorer oocyte characteristics, and a higher likelihood of embryonic chromosomal abnormalities[10-12]. Conversely, younger women with elevated antral follicle counts (AFCs), higher serum E2 concentrations, and larger retrieval of oocytes face a greater probability of experiencing OHSS. Evidence from two prospective and five retrospective studies assessing the relationship between age and OHSS incidence has confirmed that younger age serves as a significant risk factor[12-16]. BMI is another patient-specific factor evaluated in relation to both the risk and severity of OHSS. The starting dose of Gn in COH is adjusted according to individual patient features, such as BMI. Results from a prospective cohort study showed that women with a BMI ≥25 kg/m² produced fewer mature oocytes, required greater amounts of rFSH, and were at elevated risk for severe OHSS[17]. In a separate study, Sun et al.[18] evaluated predictors of OHSS severity and reported that low BMI, high AFC, and increased baseline E2 concentrations were all strongly linked to OHSS occurrence. Our study observed that the majority of patients had undergone IVF and that NICU admission in OHSS cases was significantly associated with multiple pregnancies. Consistent with the findings of Sun et al.[18], our study also demonstrated that patients who developed OHSS had a high prevalence of symptoms such as

abdominal pain and nausea/vomiting. However, while Sun et al.[18] emphasized that BMI was an important determinant of OHSS development, our study did not find a significant association between BMI and NICU admission or pregnancy prognosis. This discrepancy may be attributed to differences in patient populations or the inclusion of groups beyond those with PCOS. Therefore, in the clinical management of OHSS, individual patient characteristics such as BMI should be considered, while also acknowledging that factors influencing neonatal outcomes are multifactorial.

A previous case-control study reported a positive correlation between prolonged hospitalization due to OHSS and an increased risk of miscarriage. Additionally, the study suggested that hospitalization for OHSS might be a negative factor in achieving and maintaining pregnancy in patients undergoing IVF treatment[19]. In our study, pregnancy loss (abortion) was observed in 33.3% of patients diagnosed with OHSS. This finding may support the potential association between OHSS and pregnancy loss as suggested in the literature.

Hospitalizations related to OHSS not only impose a significant economic burden but also negatively impact patients' mental well-being following IVF-embryo transfer[20]. However, factors such as racial and regional differences, variations among hospitals, and discrepancies in research methodologies may influence the observed effects of OHSS on pregnancy outcomes. Additionally, baseline patient characteristics and the severity of OHSS can affect the interpretation of clinical research findings. Up to now, the influence of OHSS on pregnancy outcomes has not been thoroughly explored, underlining the necessity for additional studies[21,22]. Hu et al.[23] investigated maternal and neonatal outcomes in pregnancies affected by moderate to severe OHSS and reported notably increased incidences of venous thrombosis, gestational diabetes mellitus (GDM), and admissions to NICU among these patients. Furthermore, the duration of pregnancy was shorter in the OHSS group compared with the control cohort, yet no statistically significant variation was observed in live birth rates. In addition, OHSS was not considered an independent predictor for adverse outcomes such as LBW, preterm delivery, or gestational hypertension. In the study by Vainer-Rotbart et al.[8], maternal and perinatal complications in pregnancies affected by OHSS were evaluated through a large-scale retrospective analysis. The findings indicated that OHSS is not considered an independent determinant of adverse pregnancy outcomes, including preeclampsia, GDM, intrauterine growth restriction, preterm delivery (<37 and <34 weeks), low and very LBW, and cesarean section. Nevertheless, in a subgroup analysis focusing on IVF patients, OHSS showed a significant association with preterm birth occurring before 34 weeks of gestation. In our study, maternal adverse pregnancy outcomes were found to be significantly associated with higher albumin levels and a lower gestational age. Moreover, multiple gestations were observed more frequently in cases that required NICU care. Consistent with the results reported by Vainer-Rotbart et al.,[8] our analysis showed that despite the elevated rate of cesarean sections, OHSS itself did not emerge as an independent determinant for cesarean delivery. However, while Vainer-Rotbart et al.,[8] reported that OHSS was not associated with preterm birth, our study found a significant correlation between gestational age and maternal adverse outcomes, suggesting that OHSS may have an indirect impact on pregnancy duration. Such inconsistencies might be explained by variations in study populations or the criteria used for participant selection. To gain clearer insights into how OHSS influences maternal and newborn outcomes, especially in IVF-associated pregnancies, extended longitudinal research will be required.

Study Limitations

This study has several limitations. First, due to its retrospective design, data collection was based on patient records. This approach carries the risk of missing data and observational bias. More comprehensive and controlled data could be obtained through prospective studies. Second, our study is single-center, and the patient population is limited to the hospital records of a specific institution. This limitation may affect the generalizability of the results. Larger, multicenter studies are necessary to better evaluate the impact of OHSS on maternal and neonatal outcomes. Lastly, our study did not analyze in detail the effects of hospital stay duration due to OHSS or specific treatment approaches (e.g., albumin replacement or anticoagulant use) on long-term pregnancy outcomes. Future prospective studies investigating the long-term effects of OHSS on maternal and neonatal prognosis could further expand our understanding in this field.

Conclusion

This study aimed to evaluate the impact of OHSS on maternal and neonatal prognosis in complicated pregnancies. Our findings indicate that OHSS is significantly associated with NICU admission and multiple pregnancies. Additionally,

maternal adverse pregnancy outcomes were found to be associated with higher albumin levels and lower gestational age. While the literature presents varying results regarding the effects of OHSS on pregnancy, our study supports the notion that OHSS may be particularly linked to neonatal morbidity and maternal complications. However, further large-scale and prospective studies are needed to determine whether OHSS is an independent risk factor for pregnancy loss, preterm birth, and obstetric complications. In conclusion, the management of pregnancies complicated by OHSS requires careful monitoring and a multidisciplinary approach. Early diagnosis, maintaining proper fluid-electrolyte balance, and close monitoring of high-risk patients may contribute to improved maternal and neonatal outcomes. Future large-scale and long-term follow-up studies are necessary to better elucidate the effects of OHSS on pregnancy progression and birth outcomes.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Gynecology Training and Research Hospital (approval no: 11, date: 06.09.2022).

Informed Consent: Patient data were retrospectively reviewed from hospital records.

Footnotes

Authorship Contributions

Concept: Ay.K., Ö.V.A., Design: Ay.K., Ah.K., Data Collection or Processing: Az.K., Ah.K., Analysis or Interpretation: Ay.K., Ö.V.A., Literature Search: Az.K., Writing: Ay.K., Ö.V.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Comparison of the Different Repair Models for Cerebrospinal Fluid Fistulas During Endoscopic Transsphenoidal Surgery

Endoskopik Transsfenoidal Cerrahi Sırasında Gelişen Beyin Omurilik Sıvısı Fistüllerinde Farklı Onarım Modellerinin Karşılaştırılması

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Abstract

Objective: Intraoperative cerebrospinal fluid fistula, one of the most concerning complications of endoscopic transsphenoidal surgery, may result in significant morbidity if not adequately managed. We performed an analysis for different methods, used for repair of cerebrospinal fluid fistula occurring during endoscopic transsphenoidal surgery.

Methods: Neurosurgical operations performed between November 2023-March 2025 were analyzed retrospectively using hospital records. In group 1, repair was performed by an irregularly shaped fat autograft, which was placed in the sphenoidal sinus with a Haddad nasoseptal flap. In group 2, a dumbbell-shaped fat autograft with a Haddad nasoseptal flap was used.

Results: Controlling the variables, such as age and sex, we found that there was no statistical difference in gender distribution in groups. Group 1 patients needed postoperative lumbar drainage more often and also had longer hospital stays. However, no significant difference was observed between the hospitalization costs.

Conclusion: Centers around the world make efforts to decrease the complication rates and invoices. Prolonged cerebral fistula can lead to serious consequences and cause distress to the patient, their relatives, and their doctor.

Keywords: Endoscopic, skull base, repair, transphenoidal

Öz

Amaç: Endoskopik transsfenoidal cerrahinin en endişe verici komplikasyonlarından biri olan intraoperatif serebrospinal sıvı fistülü, uygun şekilde yönetilmezse önemli morbiditeye neden olabilir. Endoskopik transsfenoidal cerrahi sırasında oluşan serebrospinal sıvı fistülünün onarımı için kullanılan farklı yöntemler için bir analiz gerçekleştirdik.

Yöntem: Kasım 2023-Mart 2025 arasında gerçekleştirilen nöroşirürjikal operasyonlar hastane kayıtları kullanılarak retrospektif olarak analiz edildi. Grup 1'de onarım, Haddad nazoseptal flep ile sfenoidal sinüse yerleştirilen düzensiz şekilli bir yağ otogreftiyle gerçekleştirildi. Grup 2'de, Haddad nazoseptal flep ile dumbell şekilli bir yağ otogrefti kullanıldı.

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Abstract

Bulgular: Yaş ve cinsiyet gibi değişkenleri kontrol ederek, gruplar arasında cinsiyet dağılımında istatistiksel olarak bir fark olmadığını bulduk. Grup 1 hastalarının postoperatif lomber drenaja daha sık ve ayrıca daha uzun hastanede kalmaları gerekti. Ancak hastane yatış maliyetleri arasında anlamlı bir fark gözlenmedi.

Sonuç: Dünya çapındaki merkezler komplikasyon oranlarını ve faturaları azaltmak için çaba göstermektedir. Uzun süreli serebral fistül ciddi sonuçlara yol açabilir ve hem hasta, hem yakınları hem de doktorları için ciddi sıkıntılara neden olabilir.

Anahtar Kelimeler: Endoskopik, kafa tabanı, onarım, transsfenoidal

Introduction

Endoscopic transsphenoidal surgery (ETS) is a minimally invasive approach widely used in the treatment of sellar, parasellar, and most skull base pathologies. This method is often preferred by patients because it is minimally invasive, does not require a craniotomy, does not leave a surgical incision scar on the patient, and is relatively more comfortable. However, cerebrospinal fluid (CSF) fistula developing during this surgery can be a significant complication. CSF fistula occurs when it leaks from the subarachnoid space into the nasal cavity as a result of a defect in the skull base during ETS. This can lead to serious complications such as meningitis. Therefore, early recognition and appropriate repair of CSF fistulas that develop during surgery are of great importance[1-4].

Also, it is clear that the patient group with rhinorrhea after ETS brings an additional cost burden. Patients who do not have any health insurance are quite distressed, especially. Besides all these, this undesirable condition significantly prolongs hospital stay. Additionally, the quality of life of the patients are also negatively affected[5].

Different techniques are used in the repair of CSF fistula. The method to be chosen depends on the size of the defect, its location, the pressure of the CSF that leaks from the fistula, and the general condition of the patient[6,7].

In small defects, conservative management should be performed as first-line treatment. This treatment plan includes bed rest and head elevation. Appropriate antibiotic prophylaxis should be initiated for the patient. If a high-flow fistula has developed, the use of multilayer repair methods may be considered. Fascia lata grafts, autologous fat grafts, free mucosa grafts, and pedicled mucosa flaps are among these methods. The Haddad-Bassagasteguy nasoseptal flap is especially the most commonly used method for repairing large defects and has a high success rate. In more difficult cases, collagen-based patches, fibrin adhesives and lumbar drainage are also among the preferred methods[2,4,6,7].

Materials and Methods

Ethics committee approval was obtained from University of Health Sciences Türkiye, İzmir City Hospital for this study (approval number: 2025/167, date: 16.04.2025). A total of 70 patients with hypophysis adenoma operated via endoscopic transsphenoidal approach between November 2023 and March 2025 in our hospital were analyzed retrospectively from patient medical records.

The patients whose CSF fistula was repaired with a traditional fat graft placed in the sphenoid sinus were named as group 1. Patients repaired with dumbbell-shaped fat grafts (Figure 1), where half of the dumbbell graft was pushed into the dura, and the remaining half remained in the sphenoid sinus, were named as group 2 (Figure 2).

The groups were analyzed for the perioperative hemostatic agents fibrin tissue glues synthetic dura lumbar drainage

Figure 1. Dumble shaped fat graft

catheter, primary or recurrent operation of the tumor, postoperative diabetes insipidus cavitron ultrasonic surgical aspirator, postoperative rhinorrhea, and the type of sphenoidal sinus. The differences between the groups were then investigated.

Statistical Analysis

In descriptive statistics, continuous data are given with mean, standard deviation, minimum and maximum values, and categorical data are given with number and percentage values. In the statistical comparison of the data, the suitability of the normal distribution for continuous data was evaluated with the Kolmogorov-Smirnov analysis, and the Mann-Whitney U test was used for non-parametric data. The chi-square test was used to compare categorical data.

P<0.05 was considered significant at a 95% confidence interval. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA), version 21.0.

Results

A total of 17 patients who had peroperative CSF fistula were included in the study. There were nine patients in group 1 and eight patients in group 2. The gender distribution of patients was as follows: 3 men (33.3%) and 6 women (66.7%) in group 1, and 6 men (75%) and 2 women (25%) in group 2. Age range was 30.0-74.0 with an average age of 42.0 years in group 1. In group 2, the age range was 33.0-76.0 with an average age of 46.5. Controlling for variables such as age and sex, we found that there was no statistically significant difference in gender distribution rates (p=0.481) for patients shown in Table 1 (group 1 and group 2). There was no significant difference between groups in terms of the use of hemostatic materials (p=0.944), use of fibrin glue (p=0.274),

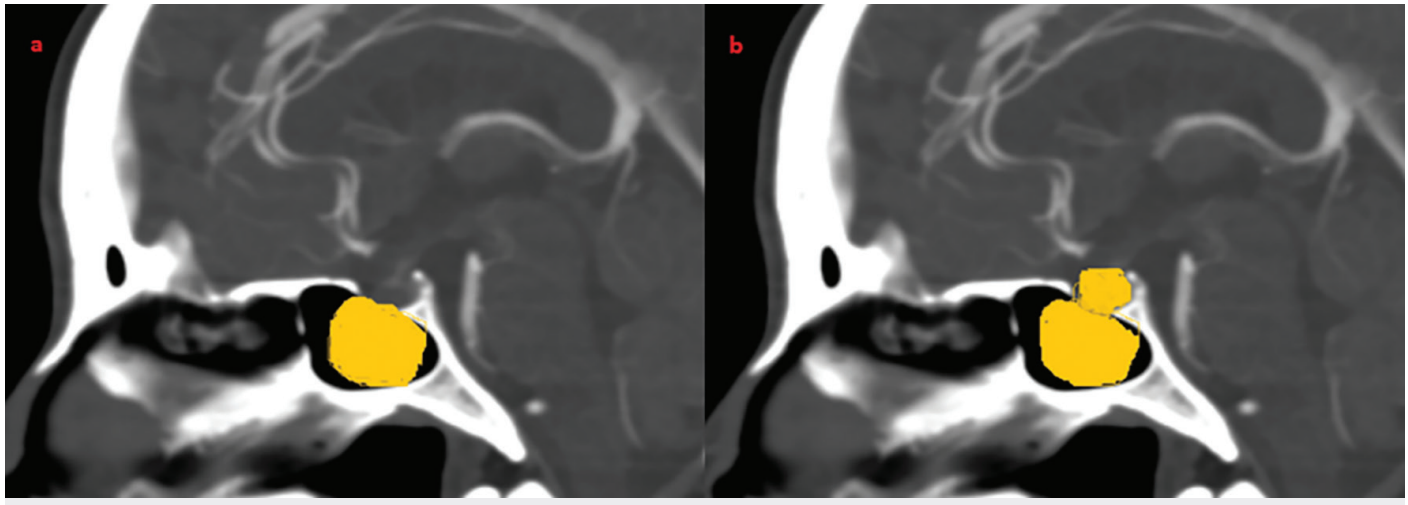

Figure 2. Representative illustration of fat graft placement in the sagittal plane, group 1 (a), group 2 (b)

Table 1. Postoperative complications and materials used after CSF fistula

		Group 1, number (%)	Group 2, number (%)	p-value
Gender	**Male**	2 (25.0%)	6 (66.7%)	0.086
	Female	6 (75.0%)	3 (33.3%)	
Use of hemostatic matrix		0	1 (11.1%)	0.944
Use of fibrin glue		7 (87.5%)	9 (100%)	0.274
Use of dural graft		1 (12.5%)	2 (22.2%)	0.6
Use of lombar dranaige		8 (100%)	3 (33.3%)	0.004
Postoperative diabetes insipitus		1 (12.5%)	1 (11.1%)	0.929
Use of CUSA		4 (50%)	2 (22.2%)	0.232
Postoperative rhinorrhea		4 (50%)	1 (11.1%)	0.079

CSF: Cerebrospinal fluid, CUSA: Cavitron ultrasonic surgical aspirator

use of dural graft (p=0.6), and use of cavitron ultrasonic surgical aspirator (p=0.232).

There was no significant difference in the incidence of postoperative diabetes insipidus between groups (p=0.929). Also, there was no significant difference in postoperative rhinorrhea rates (p=0.079). Group 1 patients needed postoperative lumbar drainage more often, and this was found to be statistically significant (p=0.004). Additionally, it was observed that group 1 patients had longer hospital stays (p=0.001). On the other hand, no statistically significant difference was observed between hospital costs (p=0.259).

Discussion

Today, endoscopic transsphenoidal approaches are widely accepted as the first-line technique in skull base surgery. Although these methods are considered less invasive, they are still susceptible to certain complications. Among the most common complications associated with this approach is the development of intraoperative CSF fistulas. Various repair techniques have been described in the literature to manage this issue[8-11]. In this study, we compared the postoperative outcomes of 17 patients who underwent ETS performed by the same primary surgeon at a single center, with each patient receiving a different type of fat graft.

The group in which standard abdominal fat grafts were used demonstrated a significantly higher need for postoperative lumbar drainage (p=0.004). The flow rate of CSF fistulas developing during endoscopic transsphenoidal procedures is directly proportional to the size of the arachnoid defect. In other words, larger defects tend to result in high-flow fistulas. When such defects are plugged using abdominal fat grafts, the graft often dislodges during patient awakening, extubation, or Valsalva maneuvers, leading to persistent CSF leakage due to graft migration or instability.

In contrast, in patients in whom dumbbell-shaped fat grafts were used-inserted gently so that one end remains within the arachnoid defect and the other fills the sphenoid sinus cavity-a significantly lower incidence of postoperative rhinorrhea and a reduced need for lumbar drainage were observed (p=0.004). Naturally, this also translated into a shorter hospital stay for this group.

To reinforce the repair following graft placement, nasoseptal flaps or synthetic dura substitutes may be applied, secured in place with tissue adhesives such as Tisseel or fibrin glue. Many centers utilize one or more of these techniques in various combinations. As institutions gain more surgical experience over time, they tend to refine their techniques and consequently observe a gradual decline in postoperative CSF fistula rates[9,11].

CSF fistula during ETC can be managed successfully with careful surgical techniques and appropriate repair methods. Primary repair and autologous grafts are sufficient for small defects, while pedicled flaps such as nasoseptal flaps are recommended for large defects. Lumbar drainage and fibrin adhesives also provide additional support and reduce the risk of complications. The prevention and management of CSF fistulas vary depending on the experience of the surgical team and the patient's characteristics. The management of CSF fistulas requires the selected method to be compatible with the size of the defect and the patient's condition. It is accepted today that multilayer repair techniques and pedicled flaps have the highest success rate[8,9,11].

Study Limitations

Although the group that received dumbbell-shaped fat grafts had significantly shorter hospital stays, no significant difference was found when comparing their overall hospital costs. Considering the fluctuating economic conditions and changes in insurance reimbursement policies in our country, a reliable cost comparison could not be made within the timeframe of this study due to differences in pricing between the beginning and end of the study period. Nevertheless, the observed reduction in hospitalization duration can be regarded as clinically meaningful, both in terms of patient comfort and potential cost-effectiveness. We believe that the limitations of this study can be addressed in future research involving larger patient cohorts.

Conclusion

As a result, although our study was conducted with a limited number of patients, we believe that the control of CSF fistula and the duration of hospital stay will be shorter with dumbbell-shaped fat autografts. We believe that this technique, which is simple to apply, offers a practical solution to one of the biggest problems in skull base surgery.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Türkiye, İzmir City Hospital for this study (approval number: 2025/167, date: 16.04.2025).

Informed Consent: Analyzed retrospectively from patient medical records.

Footnotes

Authorship Contributions

Surgical and Medical Practises: M.Ç., Concept: M.Ç., Design: M.Ç., Ç.T., Data Collection or Processing: M.Ç., Ç.T., Analysis or Interpretation: Ç.T., Literature Search: M.Ç., Ç.T., Writing: M.Ç., Ç.T.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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The Prognostic Significance of Banff Classification Lesions in Determining Renal Allograft Survival During Chronic Active Antibody-mediated Rejection

Kronik Aktif Antikor Aracılı Rejeksiyonda Banff Lezyonlarının Böbrek Allograft Sağkalımına Etkileri

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Abstract

Objective: Chronic active antibody-mediated rejection (ca-ABMR) has been identified as a primary cause of graft loss in kidney transplant recipients over an extended period. The outcomes of intravenous immunoglobulin and plasmapheresis treatments in ca-ABMR are controversial; therefore, no established effective treatment has yet been found. This study aims to identify the clinical and histopathological parameters that influence the decision to treat or not treat ca-ABMR cases.

Methods: Fourteen patients diagnosed with ca-ABMR, who underwent biopsy with a pre-diagnosis of kidney rejection between 2018 and 2024 at the pathology department, were included in the study. The histopathological features were evaluated using the Banff 2019 criteria.

Results: 28.6% of the patients (n=4) were female, and 71.4% (n=10) were male. The mean age of male patients was 46.40±12.63 years, while the mean age of female patients was 33.00±16.39 years. The average time from kidney transplantation to biopsy was 56.85±47.27 months. No statistically significant differences were found between the treated (n=10) and untreated (n=4) groups in terms of microvascular inflammation score (p=0.88), chronic tissue damage score (p=0.87), transplant glomerulopathy (p=0.99), intimal arteritis (p=0.99), and immunohistochemical C4d staining score (p=0.50). However, the high-risk group for microvascular inflammation (glomerulitis+peritubular capillaritis) had a significantly longer survival time than the low-risk group (p=0.03 <0.05). No statistically significant difference in survival time was found between the low- and high-risk groups for chronic tissue damage (tubular atrophy+interstitial fibrosis+total inflammation) score, (p=0.56 >0.05). No statistically significant differences were found in Banff lesion scores between the treated and untreated groups.

Conclusion: The early detection of graft histopathological changes, often achieved through protocol biopsies, facilitates the identification of ca-ABMR patients who will respond favorably to treatment.

Keywords: Banff lesions, chronic active antibody-mediated rejection, microvascular inflammation, renal transplantation

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Öz

Amaç: Kronik aktif antikor aracılı rejeksiyon (ca-ABMR), böbrek nakli alıcılarında uzun vadede greft kaybının önde gelen nedenlerinden biridir. ca-ABMR'de intravenöz immünglobulin ve plazmaferez tedavilerinin sonuçları tartışmalı olduğundan, belirlenmiş etkili bir tedavi bulunamamıştır. Bu çalışma, ca-ABMR vakalarını tedavi etme veya tedavi etmeme kararını etkileyen klinik ve histopatolojik parametreleri belirlemeyi amaçlamaktadır.

Yöntem: 2018-2024 yılları arasında patoloji bölümünde böbrek rejeksiyon ön tanısıyla biyopsi yapılan ve kronik aktif antikor aracılı rejeksiyon tanısı konulan on dört hasta çalışmaya dahil edildi. Histopatolojik özellikler Banff 2019 kriterlerine göre skorlandı.

Bulgular: Hastaların %28,6'sı (n=4) kadın, %71,4'ü (n=10) erkekti. Erkek hastaların yaş ortalaması 46,40±12,63 yıl iken, kadın hastaların yaş ortalaması 33,00±16,39 yıl olarak bulundu. Böbrek naklinden biyopsiye kadar geçen ortalama süre 56,85±47,27 ay olarak bulundu. Tedavi edilen (n=10) ve tedavi edilmeyen (n=4) gruplar arasında mikrovasküler inflamasyon skoru (p=0,88), kronik doku hasarı skoru (p=0,87), transplant glomerulopatisi (p=0,99), intimal arterit (p=0,99) ve immünohistokimyasal C4d boyanma skoru (p=0,50) açısından istatistiksel olarak anlamlı bir fark saptanmadı. Ancak mikrovasküler inflamasyon açısından yüksek riskli grup (glomerulit+peritübüler kapillerit), düşük riskli grupla karşılaştırıldığında anlamlı derecede daha uzun bir sağkalım süresine sahipti (p=0,03 <0,05). Kronik doku hasarı (tübüler atrofi+interstisyel fibrozis+toplam inflamasyon) skoru için düşük ve yüksek risk grupları arasında sağkalım süresinde istatistiksel olarak anlamlı bir fark bulunmadı (p=0,56 >0,05). Tedavi edilen ve tedavi edilmeyen gruplar arasında Banff lezyon skorlarında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: ca-ABMR hastalarında, protokol biyopsileri yoluyla greftlerdeki histopatolojik değişikliklerin erken tespiti, tedaviden fayda görecek hastaların belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: Banff lezyonları, kronik aktif antikor aracılı rejeksiyon, mikrovasküler inflamasyon, böbrek nakli

Introduction

Chronic active antibody-mediated rejection (ca-ABMR) is one of the leading long-term causes of graft loss in kidney transplant recipients. There is a lack of consensus regarding the relationship between renal transplant survival and clinical and histopathological findings in ca-ABMR patients[1].

When graft dysfunction develops, graft biopsy is considered the gold standard to identify the underlying pathology. Recently, graft biopsy has been utilized for histopathological and immunohistochemical examination as well as for genetic analysis[2].

The Banff classification, introduced in 1991, has become the most commonly used classification system for kidney transplant pathology. Banff scores are used to grade acute and chronic ABMR, as well as T-cell mediated rejection[3]. In addition to Banff lesions, the diagnosis of ca-ABMR is supported by the presence of circulating donor-specific antibodies (DSA) against donor human leucocyte antigen (HLA) and/or elevated levels of gene transcript/classifier expression within the biopsy specimens, strongly associated with ABMR[2,3].

Despite extensive studies, no Food and Drug Administration-approved treatments for ca-ABMR have shown definitive long-term benefits[4]. The standard treatment today includes plasmapheresis and intravenous immunoglobulin (IVIg) therapy, combined with single or combination therapies such as CD20 monoclonal antibody (rituximab)[5], proteasome inhibitors (bortezomib)[6], anti-IL-6R monoclonal antibody (tocilizumab)[7], and anti-complement monoclonal antibody (eculizumab)[8].

For patients diagnosed with ca-ABMR, the clinically important question is which cases are more likely to respond to treatment and which therapy yields better outcomes. In this study, we aim to analyze the clinical characteristics of ca-ABMR patients with cases confirmed by biopsy and the relationship between the Banff lesion scores in their biopsies and graft survival. By doing so, we aim to identify the clinical and histopathological parameters that influence the decision to treat ca-ABMR cases.

Materials and Methods

Patients and Study Design

This study included 14 patients diagnosed with ca-ABMR histopathologically, who applied to our pathology department with a suspected kidney rejection between 2018 and 2023. Data were collected regarding the patients' age, gender, primary kidney disease, and the source of the kidney graft (living/deceased donor). Follow-up data included serum creatinine (Cr) levels, estimated glomerular filtration rate (eGFR), transplant date, biopsy date, graft loss date, and treatments administered following diagnosis. Graft loss was defined as the initiation of dialysis or death related to transplantation.

Patients aged ≥18 years at the time of transplantation who had undergone kidney transplantation at our center or external centers were included in the study. Patients younger than 18 years old at the time of transplantation, patients undergoing combined organ transplantation (e.g. kidney, liver, pancreas), and patients lacking complete laboratory or clinical data were excluded from the final analysis.

This study was reviewed and approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (approval number: 16/16, date: 24.10.2024). Informed consent was waived by the institutional review board due to the retrospective nature of the study. This study was presented as an oral presentation at the 15th Congress of the Turkish Transplantation Centers Coordination Association (October 17-20, 2024, Gaziantep).

Histopathology

The histopathological features were evaluated using the Banff 2019 classification, which encompasses both acute and chronic rejection features. According to the 2019 Banff reporting standards, acute Banff lesions are characterized by interstitial inflammation, tubulitis, intimal arteritis (v), glomerulitis (g), peritubular capillaritis (ptc), and the presence of C4d staining. Chronic Banff lesions encompass a range of pathologies, including interstitial fibrosis (ci), tubular atrophy (ct), and the presence of C4d staining, transplant glomerulopathy (cg), and multilayering of the peritubular capillary basement membrane (ptcml)[3].

The 2019 Banff classification mandates that the identification of ca-ABMR is contingent upon histological evidence of both a vascular endothelial response to antibodies (specifically, linear C4d positivity in peritubular capillaries or g+ptc≥2) and concurrent indicators of chronic injury (such as cg, ptcml multilayering, or intimal fibrosis within arteries)[3].

All kidney graft biopsies were performed using a percutaneous technique under ultrasound guidance (2-3 samples per biopsy; 16-gauge needle). Transplant biopsies were examined by light microscopy using histochemical hematoxylin and eosin (HE), Jones HE, Masson's trichrome, periodic acid-schiff, Congo Red stains, and immunofluorescence microscopy for IgG, IgA, IgM, C3, C4d, C1q, fibrinogen, kappa and lambda light chains. C4d staining was applied both by immunofluorescence on frozen sections and by immunohistochemistry on paraffin sections.

HLA antibody testing and gene expression tests are not routinely performed at our hospital. Therefore, in patients who could not be tested for DSA, a positive C4d staining was accepted as the definitive diagnosis of ca-ABMR.

The microvascular inflammation (MVI) score (g+ptc) ≤3 was considered low-risk, ≥4 was considered high-risk[9]. Chronic tissue damage score [ci+ct+total inflammation (ti)] ≤5 was considered low-risk, and ≥6 was considered high-risk[10]. The cg score of 0 or 1 was considered low-risk, and a score of 2 or 3 was considered high-risk.

Statistical Analysis

A comprehensive array of descriptive statistics was employed to present the data, including sample size (n), relative percentages (%), arithmetic means, corresponding standard deviations, medians, absolute ranges, and interquartile range (Q1 and Q3). In instances where the percentage of cells exhibiting an expected value less than 5 was greater than 20%, Fisher's exact test was employed. Conversely, when the percentage was less than 20%, Pearson's chi-square test was utilized. The normality assumption was checked using the Shapiro-Wilk test. For the comparison of numerical data between the two groups, the independent samples t-test was used when the data were normally distributed, and the Mann-Whitney U test was used when the data did not follow a normal distribution. Statistical analyses were performed using SPSS 23.0 software. A p-value of <0.05 was considered statistically significant. To compare survival times between patients who received treatment and those who did not, Kaplan-Meier analysis and the Log-Rank test were applied.

Results

The genders of the patients were: 4 females (28.6%) and 10 males (71.4%). The mean age of the patients was 42.57±14.55 years (19-66 years). The average age of the male patients was 46.40±12.63 years (30-69 years), and the average age of the female patients was 33.00±16.39 years (19-54 years).

The underlying causes leading to end-stage kidney disease in the patients were as follows: 35.7% hypertension, 28.6% diabetes, 14.3% unknown chronic kidney disease, and 21.3% other causes. Among the "other" causes, hypoplastic kidney, familial Mediterranean fever, and systemic lupus erythematosus were identified.

Thirteen patients (92.9%) received a kidney transplant from a living donor, while only one patient (7.1%) received a kidney from a deceased donor. One patient had undergone a second kidney transplant. The average time from transplantation to biopsy was 56.85 ± 47.27 months (7-150 months).

The patients' serum Cr and eGFR values at different time points post-transplantation are presented in Table 1. The most recent Cr level in the patients was 1.80±0.77 mg/dL (range: 1.11-3.30), and the basal eGFR value was 44±10.86 mL/min/1.73m^2 . Note: verify consistency between the stated range and mean for eGFR values. At the time of biopsy, the average serum Cr level was 4.37±2.18 mg/dL, and the eGFR level was 18.21±10.15 mL/min/1.73m^2. One month after biopsy, the average serum Cr level was 5.13±2.18 mg/dL, and the eGFR level was 15.80±11.84 mL/min/1.73m^2. One year after biopsy, the average serum Cr level was 6.41±3.11 mg/dL, and the eGFR level was 12.83±9.68 mL/min/1.73m^2.

The distribution of Banff lesion scores in kidney biopsies diagnosed with ca-ABMR is shown in Figure 1. Of the 14 patients, 7 were classified as high-risk based on their MVI score (ptc+g), and they exhibited significantly different survival outcomes compared to those in the low-risk group (p=0.03). In the high-risk group, the graft survival time was longer. No statistically significant difference in survival times was found between the low-risk (n=7) and high-risk (n=7) groups for the chronic tissue damage score (ci+ct+ti) (p=0.56). There was no statistically significant difference in graft survival times between the low-risk (n=7) and high-risk (n=7) groups for cg (p=0.31).

Immunohistochemical C4d staining was positive in all biopsies, diagnosed with ca-ABMR. C4d was detected as exhibiting linear positivity exclusively in peritubular capillaries in 21.43% of patients, in both peritubular capillaries and glomerular basement membranes in 28.57% of patients, and in peritubular capillaries, glomerular basement membranes, and interlobular arterioles in 50% of patients. In 86% of the biopsies, C4d staining scores were 2 or 3 in intensity.

Microscopic images of acute and chronic Banff lesions in biopsies of patients diagnosed with ca-ABMR are presented in Figure 2.

Table 1. Time-dependent variations in serum Cr and eGFR levels in renal transplant recipients with ca-ABMR

	Most recent level	Level at the time of biopsy	Level at the 1st month after biopsy	Level at the 1st year after biopsy
Serum Cr level (mg/dL)	1.80±0.77	4.37±2.18	5.13±2.18	6.41±3.11
eGFR level (mL/min/1.73m^2)	44±10.86	18.21±10.15	15.80±11.84	12.83±9.68

Cr: Creatinine, eGFR: Estimated glomerular filtration rate, ca-ABMR: Chronic active antibody-mediated rejection

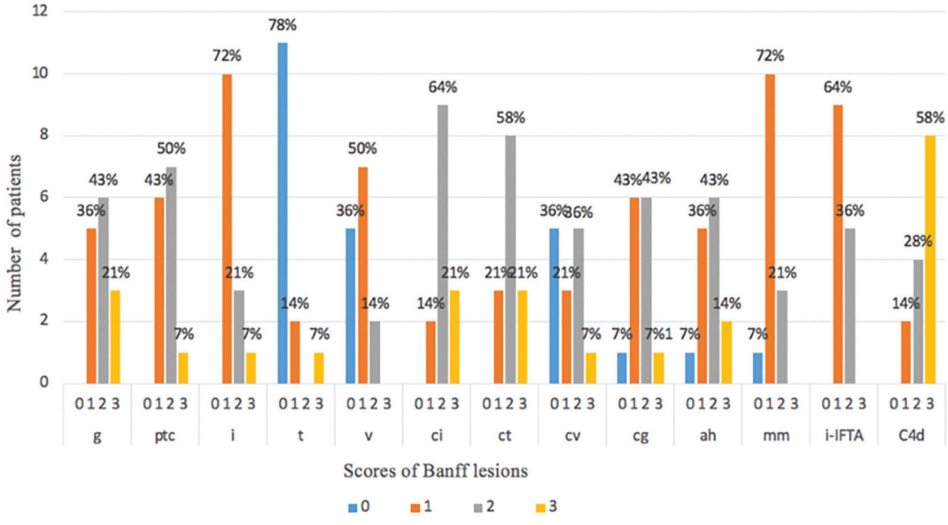

Figure 1. The distribution of Banff lesion scores in kidney biopsies diagnosed with ca-ABMR

ca-ABMR: Chronic active antibody-mediated rejection, g: Glomerulitis, ptc: Peritubular capillaritis, i: Interstitial inflammation, t: Tubulitis, v: Intimal arteritis, ci: Interstitial fibrosis, ct: Tubular atrophy, cv: Vascular intimal thickening, cg: Transplant glomerulopathy, ah: Arteriolar hyalinosis, mm: Mesangial matrix expansion, i-IFTA: Interstitial inflammation in areas of fibrosis and tubular atrophy, C4d: C4d staining score

The average follow-up time after transplantation was 93.64±52.14 months (range: 33-194 months). Following the pathological diagnosis, 10 patients (71.4%) received IVIg+plasmapheresis treatment, while 4 patients (28.6%) did not receive any treatment.

There was no statistically significant difference in MVI score (p=0.88), chronic tissue damage score (p=0.87), v (p=0.99), cg (p=0.99), or C4d score (p=0.50) between the treated and untreated groups.

There was no statistically significant difference in graft survival between the patients who received treatment (IVIg+plasmapheresis) and those who did not [p=0.94, log rank (Mantel-Cox) test]. The mean and median survival times in both treatment and non-treatment groups are presented in Table 2.

The average time from biopsy to graft loss was 58.50 months (range: 7-150 months). Graft loss was observed in 12 cases (85.7%). No statistically significant difference in age (p=0.95) or time from transplant to biopsy (p=0.99) was observed between the graft loss and non-graft loss groups. During the follow-up period, 3 patients (21.4%) died. The causes of death were coronavirus disease-2019 infection (n=2) and cardiovascular causes (n=1). The remaining 11 patients continue to live with hemodialysis.

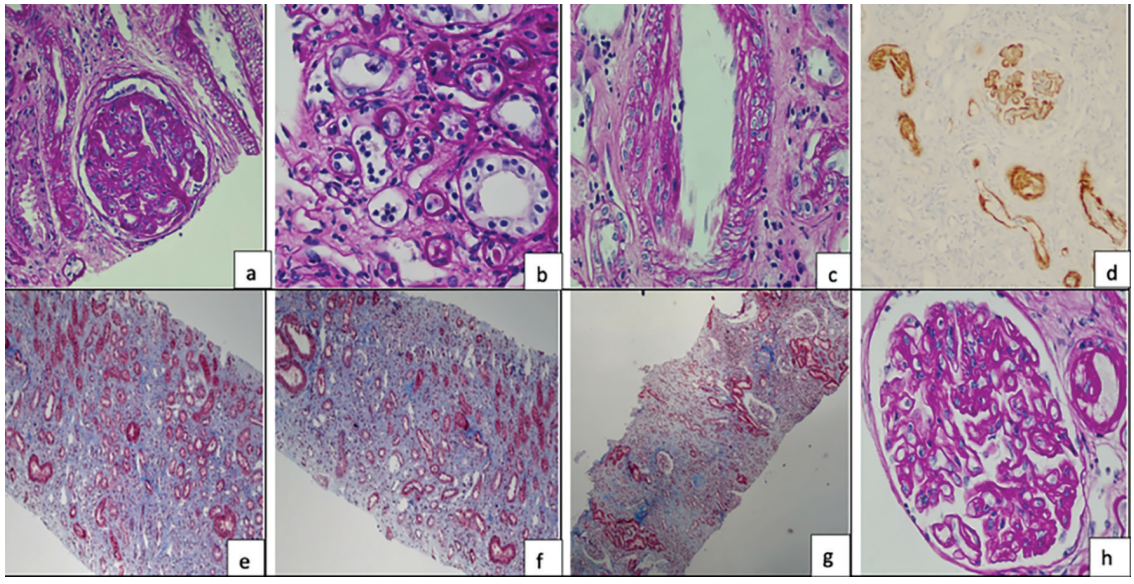

Figure 2. Acute (a,b,c,d) and chronic (e,f,g,h) Banff lesions in biopsies diagnosed with ca-ABMR

a: Glomerulitis (g) (PAS, x200), b: Peritubular capillaritis (pct) (PAS, x200) c: Intimal arteritis (v) (HE, x400) d: Positive C4d staining along the capillary basement membranes of glomeruli and in arterioles (C4d, x100), e: Interstitial fibrosis (ci) (Masson trichrome, x100) f: Tubular atrophy (ct) (Masson trichrome, x100), g: Total inflammation (ti) (Masson trichrome, x40), h: Transplant glomerulopathy (cg) (PAS, x400), ca-ABMR: Chronic active antibody-mediated rejection, PAS: Periodic acid-schiff, HE: Hematoxylin and eosin

Table 2. Mean and median survival times in treatment and non-treatment groups (month)

Treatment	Mean				Median			
	Estimate	Standard error	95% confidence interval		Estimate	Standard error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Patients not receiving treatment	118.75	38.03	44.21	193.28	72	45.66	0	161.50
Patients receiving treatment (IVIg +PEX)	104.94	19.27	67.15	142.72	97	22.13	53.61	140.38
Overall	107.78	16.61	75.21	140.34	97	20.67	56.47	137.52

The log rank (Mantel-Cox) test was used

IVIg: Intravenous immunoglobulin, PEX: Plasma exchange

Discussion

The present study investigates the effects on graft survival of histopathological lesions, evaluated according to the Banff classification, in renal allograft biopsies diagnosed with ca-ABMR on graft survival. ca-ABMR is a major cause of long-term kidney transplant failure and is characterised by MVI, which is triggered by the binding of DSA to endothelial structures, and by fibrosis that develops as a result[3]. This process results in tissue damage to the allograft, precipitated by chronic inflammation, which in turn leads to loss of graft function. Histopathological monitoring of this process is important in terms of treatment response and prognosis.

In the present study, graft survival was found to be significantly prolonged in patients exhibiting elevated MVI scores (g+ptc) compared to those with low-risk scores. The distinct outcome observed in this study may be attributable to the earlier diagnosis and initiation of more intensive immunosuppressive therapy in patients with high MVI scores. Furthermore, the mean recipient age was found to be 40 years in the high-risk group and 45 years in the low-risk group. A potential explanation for this finding may be found in the enhanced immune response observed in younger recipients, even in the presence of MVI.

However, a substantial body of research has demonstrated that high MVI is frequently associated with an unfavorable prognosis[11-14]. The prototypic lesion of ABMR, MVI, has been shown to result from a broad range of mechanistic pathways within the renal allograft. This finding has been confirmed by both clinical and experimental studies. It is well established that antibodies that bind to non-self HLA molecules are capable of precipitating damage to graft endothelial cells. However, accumulating data indicate that various non-HLA autoantibodies and alloantibodies are also implicated in the injury cascade[15].

A new and distinct phenotype, referred to as isolated MVI (iMVI), has been incorporated into the most recent Banff classifications. This unique form is specifically defined by the presence of MVI without accompanying deposits of HLA DSA in the peritubular capillaries. This phenotype is associated with reduced T cell and natural killer cell infiltration in both the allograft and peripheral circulation. Moreover, the presence of only sparse plasma cell infiltration suggests an underlying injury mechanism different from that of antibody-mediated rejection. Graft survival in patients with iMVI has been reported to be longer compared to that in patients with ABMR[16-18]. Due to the inability to assess HLA DSA in all patients, it is possible that those with longer graft survival belong to a different immunologic phenotype.

Conversely, Banff scores (ci, ct, ti), which indicate chronic tissue damage, and cg scores did not demonstrate a significant relationship with graft survival. Although ci and ct have been reported to be associated with graft loss in the literature[10], this relationship was not found in the present sample. This phenomenon may be due to patients being observed predominantly in the late stage at the time of biopsy, and advanced fibrotic changes were no longer considered prognostic indicators.

ca-ABMR has been observed to occur in patients who have previously developed DSA or who have *de novo* DSA due to inadequate immunosuppression[3]. *De novo* DSA is regarded as a significant risk factor for the development of ca-ABMR[19]. Approximately 10% of low-risk kidney transplant recipients develop *de novo* DSA within the first five years after transplantation, with an increase continuing in subsequent years[20]. It is imperative to emphasise the significance of protocol biopsies, given the inability of our hospital to perform DSA analysis. Protocol biopsies represent an indispensable tool in the long-term monitoring of renal transplant recipients and have been established as playing a pivotal role, especially in immunologically high-risk patients with previous DSA[21].

It has been suggested that the presence of DSA may trigger humoral rejection via complement activation, which could lead to tissue damage and coagulation. Furthermore, complement activation has been demonstrated to promote the migration of inflammatory cells via the innate immune response, which in turn causes endothelial damage. It may this inflammatory response may result in persistent g and ptc[22]. cg, severe EM-documented ptcml stratification, or unexplained new arterial intimal fibrosis is recognized associations of chronic tissue damage development[23].

Immunohistochemical C4d staining was positive in all cases, thus reinforcing its diagnostic utility for ca-ABMR. It is noteworthy that linear C4d accumulation was observed in peritubular capillaries, glomerular basement membranes, and interlobular arterioles. The significance of glomerular C4d (gC4d) accumulation remains a subject of debate. However, studies by Lee et al.[24] and Shimizu et al.[25] have demonstrated a strong correlation between gC4d and markers of antibody-mediated damage, including ptc, g, and cg. A further study indicated that gC4d could be a more reliable marker for ca-ABMR than peritubular C4d[26]. The findings of this study are consistent with the conclusions of

the aforementioned reports, which indicate that glomerular and arteriolar C4d positivity is frequently detected.

The initial treatment for active ABMR is usually plasma exchange (PEX) and IVIg or combinations of PEX, IVIg and steroids[27]. However, according to the extant literature, although histological improvement is achieved with combinations of IVig, PEX and rituximab in ca-ABMR patients, its impact on long-term allograft survival remains limited[28,29]. Current studies demonstrate that the administration of bortezomib, eculizumab, rituximab, PEX, and their combinations has not yielded a convincing benefit in kidney recipients diagnosed with ca-ABMR[6]. The heterogeneity of treatment methods and the variation in the histopathological features of patients complicate the evaluation of treatment efficacy[23]. Currently, there is no proven effective treatment for ca-ABMR. The present study lends further support to these findings. No significant difference was found in terms of graft survival between patients who received treatment and those who did not.

Study Limitations

In selecting patients who received treatment, the main criteria included the diagnosis of ca-ABMR, positive C4d staining, (particularly in ptc and glomerular basement membrane), a C4d score of ≥2 according to the Banff classification, the presence of proteinuria, and/or deterioration in graft function. However, treatment decisions were made by different clinicians within the same center, which introduced a degree of heterogeneity in therapeutic approaches. This constitutes a significant limitation of the study. Additionally, the patients who did not receive treatment exhibited similar histopathological findings but were managed conservatively due to stable clinical status or differences in clinical judgment.

The high-MVI group exhibited a significantly prolonged survival duration, an unexpected finding that may be attributable to several factors. This phenomenon could be attributed to lead-time bias, as high-MVI patients were frequently subjected to biopsies at earlier stages, while low-MVI cases exhibited more chronic injury. Furthermore, the intensity of treatment may have been a contributing factor, as high-MVI findings often result in more intensive therapy and enhanced monitoring. The findings might also be influenced by the heterogeneity in low MVI, since substantial chronic damage within this group has still been shown to predict poor outcomes. Finally, unmeasured immunologic factors, such as incomplete DSA data, could have affected the results. In summary, while this study suggests that MVI may have prognostic value in ca-ABMR, the findings must be interpreted with caution owing to the small cohort, lack of DSA, and treatment heterogeneity. The prognostic value of histopathological parameters should be re-evaluated in larger, prospective, DSA-followed cohorts.

Conclusion

The identification of predictors of treatment response in patients with ca-ABMR remains a significant clinical challenge. The results of the current study underscore the limited impact of currently available therapies on graft survival and emphasise the necessity for prospective studies with larger cohorts and novel biomarkers. The development of innovative therapeutic strategies and standardised monitoring protocols, including protocol biopsies and DSA surveillance, may facilitate earlier diagnosis and enable tailored interventions. According to this study, the majority of patients exhibited advanced graft dysfunction and late-stage histological changes, which limited the potential for therapeutic response. It is recommended that future research place a priority on the early detection and risk stratification of ca-ABMR, with a view to improving long-term outcomes.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (approval number: 16/16, date: 24.10.2024).

Informed Consent: Informed consent was waived by the institutional review board due to the retrospective nature of the study.

Footnotes

This study was presented as an oral presentation at the 15th Congress of the Turkish Transplantation Centers Coordination Association (October 17-20, 2024, Gaziantep).

Authorship Contributions

Surgical and Medical Practises: A.A., Concept: A.A., Design: A.İ., Ü.Y., Data Collection or Processing: S.G., Analysis or Interpretation: Ü.Y., Literature Search: S.G., Writing: Ş.Y., A.İ.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Transcatheter Closure of Patent Ductus Arteriosus with Detachable Flipper Cook Coil: Single-center Experience

Pediatrik Hasta Grubunda Flipper Cook Coil ile Patent Duktus Arteriyozusun Transkateter Yöntemle Kapatılması: Tek Merkezli Deneyimi

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Abstract

Objective: We evaluated the safety and effectiveness of the Flipper detachable Cook coil for transcatheter closure of small-to-medium-sized patent ductus arteriosus (PDA) in a large single-center cohort with long-term follow-up.

Methods: This retrospective study included consecutive patients who underwent PDA closure with a Flipper detachable Cook coil between 2004 and 2022. Indications for closure followed contemporary guidelines. Demographics, PDA morphology (Krichenko classification), procedural details, complications, and echocardiographic outcomes were recorded. Although cut-off values vary in the literature, for clarity in the present study, we considered PDAs <4 mm in diameter as small and ≥4 mm as large.

Results: A total of 201 patients were included (42.3% male). Mean age was 56.5±49.6 months and median weight was 15 kg (interquartile range: 11-23.5). Most PDAs were small (<4 mm; 69.7%), and type A morphology predominated (63.2%). Procedural success was achieved in 196/201 patients (97.5%). Complications were infrequent: coil embolization occurred in 4/201 (2.0%) and cardiac tamponade in 1/201 (0.5%). Residual shunt was detected in 2/201 (1.0%) on early echocardiography, with complete occlusion documented by ≤6 months in all cases. Mean echocardiographic follow-up was 121.8±49.4 months (~10.2 years).

Conclusion: Transcatheter closure of small-to-medium-sized PDA using the Flipper detachable Cook coil is safe and effective, with high procedural success and durable long-term outcomes in appropriately selected patients.

Keywords: Child, patent ductus arteriosus, Flipper detachable Cook coil, transcatheter occlusion

Öz

Amaç: Küçük ve orta boy patent duktus arteriyozus (PDA) kapatılmasında Flipper Cook coil kullanımının güvenliğini ve etkinliğini, uzun dönem takipli geniş bir tek merkez kohortunda değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif çalışmaya, 2004-2022 yılları arasında Flipper Cook coil ile PDA kapatılan ardışık hastalar dahil edildi. Kapatma endikasyonları güncel kılavuzlara göre belirlendi. Demografik özellikler, PDA morfolojisi (Krichenko sınıflaması), işlem ayrıntıları, komplikasyonlar ve ekokardiyografik sonuçlar kaydedildi. Bulgular hem tüm grup hem de PDA boyutuna göre (<4 mm ve ≥ 4 mm) raporlandı.

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Öz

Bulgular: Çalışmaya toplam 201 hasta dahil edildi (%42,3 erkek). Ortalama yaş 56,5±49,6 ay, medyan vücut ağırlığı 15 kg (çeyrekler arası aralık 11-23,5) idi. Hastaların çoğunda PDA küçüktü (<4 mm; %69,7) ve en sık görülen morfoloji tip A idi (%63,2). İşlemsel başarı 196/201 hastada (%97,5) sağlandı. Komplikasyon oranı düşüktü: 4 hastada (%2,0) coil embolizasyonu, 1 hastada (%0,5) kardiyak tamponad görüldü. İki hastada (%1,0) erken dönemde rezidüel şant saptandı ve tümü 6 ay içinde spontan olarak kapandı. Ortalama ekokardiyografik takip süresi 121,8±49,4 ay (yaklaşık 10,2 yıl) idi.

Sonuç: Küçük ve orta boy PDA'ların Flipper Cook coil ile transkateter kapatılması, uygun seçilmiş hastalarda yüksek başarı oranı ve düşük komplikasyon riskiyle güvenli ve etkili bir yöntemdir.

Anahtar Kelimeler: Çocuk, patent duktus arteriyozus, Flipper Cook coil, transkateter kapatma

Introduction

Patent ductus arteriosus (PDA) is one of the most common congenital heart lesions and has been the focus of continuous therapeutic innovation. The first transcatheter attempt at angiographic PDA closure was reported in 1967 by Porstmann et al.[1], who used an Ivalon plug. In subsequent decades, several devices were introduced, including the Rashkind umbrella in 1979 and coil systems in the early 1990s; these devices enabled safe and effective closure of small-to-medium-sized ducts[2]. In 1998, the introduction of the Amplatzer duct occluder further expanded the transcatheter approach to larger PDAs, making catheter-based closure the treatment of choice in most patients[3-6].

Among transcatheter techniques, detachable coils are still widely used, particularly in patients with favorable anatomy[4-7]; moreover, although cut-off values vary across the literature, in the present study we defined PDAs <4 mm in diameter as small and those ≥4 mm as large.

Flipper detachable Cook coils offer specific advantages over earlier coil systems because they can be repositioned prior to detachment, improving procedural safety and accuracy[8-11]. While many studies have confirmed the feasibility of coil closure, most reports are limited by small sample sizes or short follow-up periods.

Our institution has employed detachable coils for PDA closure since 2004, with systematic echocardiographic follow-up. This study presents our single-center experience with 201 patients over an almost 20-year period, providing one of the largest cohorts and the longest reported follow-up to date. We describe procedural success, complications, and long-term outcomes and discuss these findings in the context of the existing literature.

Materials and Methods

Study Design and Population

We conducted a retrospective analysis of consecutive patients who underwent the transcatheter closure of PDA using a Flipper detachable Cook coil at the Pediatric Cardiology Department of Ege University between January 2004 and December 2022. The study was approved by the Ege University Institutional Ethics Committee (approval no: 24-3T/74, date: 07.03.2024) and written informed consent was obtained from the parents or legal guardians of all patients.

Inclusion and Exclusion Criteria

Indications for PDA closure were based on the American Heart Association Guidelines (1998 and 2011)[12,13]. Eligible patients included those with evidence of left heart volume overload (left atrial or ventricular enlargement on echocardiography), a continuous murmur, and/or significant ductal flow demonstrated by color and continuous-wave Doppler, even in the absence of an audible murmur.

Patients with associated congenital heart defects requiring surgical or interventional treatment were excluded. Specifically, cases with atrial septal defect, ventricular septal defect, tetralogy of Fallot, or significant valvular disease were not included. Patients with chronic comorbidities (such as chronic lung disease, severe systemic illness, or genetic syndromes) were also excluded.

Age and Weight Distribution

To clarify the demographic profile, patients were analyzed both as a single cohort and in strata defined by 5-year enrollment periods (2004-2008, 2009-2013, 2014-2018, and 2019-2022). This allowed the assessment of possible

temporal changes in patients' age and weight at the time of the procedure.

Flipper Detachable Coils

The coil occlusion technique has been utilized across various anatomical sites since its introduction in 1972[14-20]. The pioneering closure of PDA using Gianturco coils in 1992 marked a significant advancement in the field. The principle of embolization with coils involves selecting a coil whose loop diameter is larger than the PDA diameter. Upon deployment, the loops on each side of the PDA (at the pulmonary and aortic ends) secure the coil in place through its inherent spring effect. Over time, the coil fibers promote clot formation, effectively obstructing flow through the PDA. Subsequently, the coil and clot become endothelialized, contributing to the permanent closure of the PDA[16-18].

Flipper coils are made of stainless-steel spring wires that are coated with tetrafluoroethylene and lined along their entire length with synthetic Dacron fibers[18-20]. They are first deployed and then detached (unscrewed) from the delivery wire. This allows the coil to be retrieved if the delivery position is unsatisfactory. This is different from the classical Gianturco coils, which are pushed out of a delivery catheter by a coil pusher wire and, once deployed, cannot be retrieved except by a snare. Therefore, they are considered non-detachable.

Coils are available in various sizes, with the most commonly used sizes being 3x3, 3x4, 3x5, 5x3, 5x4, 5x5, 6.5x3, 6.5x4, and 6.5x5. In these measurements, the first number represents the coil loop diameter in millimeters, and the second number represents the number of loops in the coil. Larger sizes (8x3, 8x4, 8x5) are also available but are not commonly used. The selected coil diameter should be twice the diameter of the PDA at its narrowest point. The number of loops chosen depends on the size of the ductal ampulla at the aortic end-the deeper the ampulla, the more loops that can be packed into it.

PDA Closure Protocol

The procedure for PDA closure was performed under sedation in all patients. Following local anesthesia, arterial sheaths were placed in some patients and venous sheaths in others, both using a percutaneous technique. Patients were administered 50 I.U./kg of heparin. The anatomy and diameter of the PDA were determined by injecting contrast material with the patient initially in the 90° left lateral position, using appropriate catheters. If optimal images could not be obtained, injections were made in the 30-40° right-oblique+10-30° cranial positions. The PDA was classified angiographically according to the criteria defined by Krichenko et al.[14]. The preferred coil diameter should be 1.5-2 times that of the narrowest portion of the PDA. Closure is performed using transvenous and transarterial approaches. Before releasing the device, the device location and the presence of residual shunt were assessed by injection of contrast material in all patients (Figure 1.1 and Figure 1.2). The device was repositioned when necessary.

Post-procedural Care and Follow-up

After the procedure, all patients were admitted for overnight observation. Clinical assessment, chest X-ray, and echocardiography were performed before discharge. Follow-up echocardiography was conducted at 24 hours, 1 month, 6 months, 1 year, and annually thereafter. Residual shunt, left pulmonary artery stenosis, and aortic obstruction were specifically assessed. The mean follow-up duration was 121.8±49.4 months.

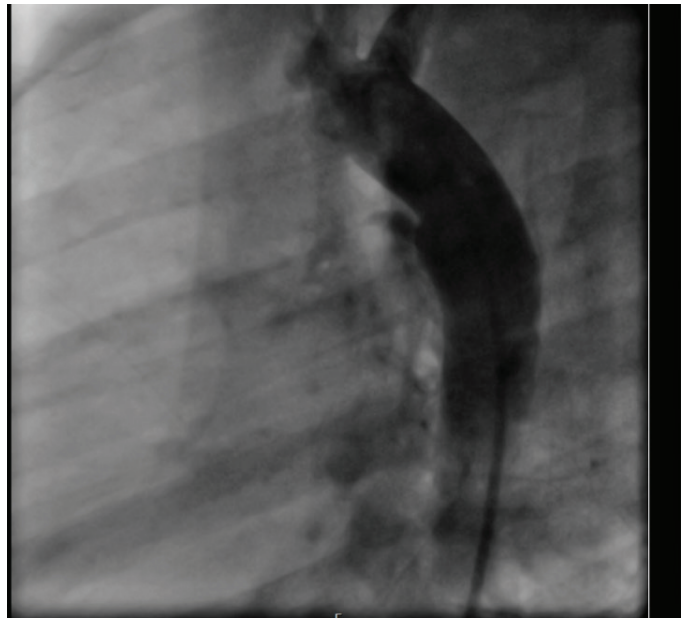

Figure 1.1. Angiographic visualization of PDA closed transcatheter with Cook coil device-detection of PDA with contrast medium before cook coil application

PDA: Patent ductus arteriosus

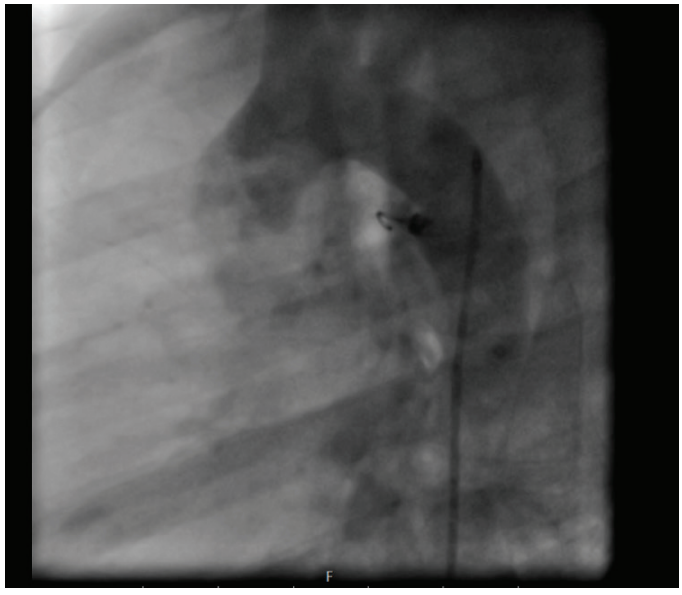

Figure 1.2. Control of the PDA occluded with Flipper detachable Cook coil with contrast medium

PDA: Patent ductus arteriosus

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Chicago, IL, USA). Categorical variables are presented as numbers and percentages. Continuous variables with normal distribution are reported as mean ± standard deviation (SD), and non-normally distributed variables as median with interquartile range (IQR). Comparative analyses were conducted between small (<4 mm) and large (≥ 4 mm) PDAs, as well as between type A and type E duct morphologies. Chi-square or Fisher's exact test was applied to categorical variables, student's t-test or Mann-Whitney U test was applied to continuous variables, and logistic regression was used to explore predictors of procedural success and complications. A p-value <0.05 was considered statistically significant.

Statistics

SPSS 22.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. In the analysis, categorical variables are presented as numbers and percentages. Normally distributed continuous variables were expressed as mean ± SD), and non-normally distributed variables were expressed as median and IQR.

Results

A total of 201 patients underwent attempted PDA closure with a Flipper detachable Cook coil. Of these, 85 (42.3%) were male and 116 (57.7%) were female. The mean age at the time of intervention was 56.5±49.6 months, and the median weight was 15 kg (IQR: 11-23.5). Patient age and weight at intervention were stable across the two decades, but subgroup analysis by 5-year enrollment periods showed a trend toward younger patients in the later years of the study.

PDA Size and Morphology

The median ductal diameter was 2 mm (IQR: 2-3). Based on size, 140 patients (69.7%) had a small PDA (<4 mm) and 61 (30.3%) had a large PDA (≥4 mm). Angiographic classification, according to the Krichenko criteria, revealed type A morphology in 127 (63.2%) patients, type E in 24 (11.9%), type C in 14 (7.0%), and types B, D, and F in 2 patients each (1.0% per type).

Procedural Success and Complications

Successful closure was achieved in 196 patients, yielding an overall success rate of 97.5%. In 192 (95.5%) patients, the coil was delivered via the arterial route, while 9 (4.5%) required a venous approach. The procedure failed in 5 patients (2.5%), all of whom were subsequently referred for alternative device closure.

Complications were rare. Coil embolization occurred in 4 patients (2.0%): one in the main pulmonary artery, two in the right pulmonary artery, and one in the descending aorta. Three were retrieved percutaneously, while one required surgical removal. One patient (0.5%) developed cardiac tamponade during the procedure, requiring urgent surgical intervention. Importantly, there were no deaths.

Residual Shunt and Follow-up Outcomes

Immediately after the procedure, trivial residual shunts were detected in 2 patients (1.0%). Both closed spontaneously within 6 months. At long-term echocardiographic follow-up (mean: 121.8±49.4 months, range: 29-230 months), complete closure was confirmed in all patients, and no cases of recanalization, hemolysis, endocarditis, pulmonary artery stenosis, or aortic obstruction were observed.

Subgroup Analyses

• **Small vs. Large PDA:** Procedural success was slightly higher in small PDAs (98.6% vs. 95.1%), though the difference was not statistically significant (p>0.05). Complications occurred more frequently in medium-sized ducts (4.9% vs. 1.4%), largely due to embolization.

• **Morphology (type A vs. type E):** Type A PDAs demonstrated higher closure rates and fewer complications than type E, although differences did not reach statistical significance.

Table 1. Patients demographic and angiographic datas

Patients demographic	And angiographic data
Gender	
Male	85 (%57.7)
Woman	116 (%42.3)
Age (month)	Mean 56.5 months (SD: 49.6)
Weight (kg)	Median 15 (IQR: 11-23.5)
Narrowest diameter of the duct (mm)	Median 2 mm (IQR: 2-3)
Moderate PDA (>2.5 mm PDA)	61 (%30.3)
Small PDA (≤2.5 mm PDA)	140 (%69.7)
Ductus shapes	
Type A	127 (%63.2)
Type B	2 (%1)
Type C	14 (%7)
Type D	2 (%1)
Type E	54 (%26.8)
Type F	2 (%1)
Ductus closure method	
Transarterial route	192 (% 95.5)
Transvenous route	9 (% 4.5)

SD: Standard deviation, IQR: Interquartile range, PDA: Patent ductus arteriosus

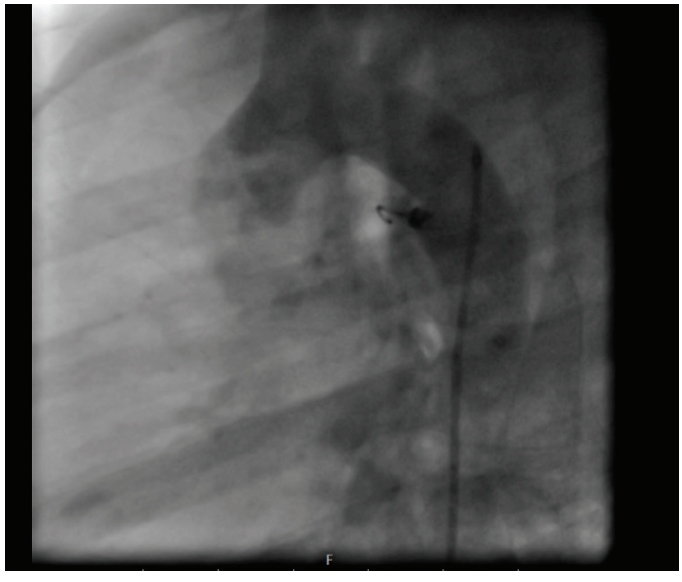

Figure 2. Schematization of success rates of patients undergoing coil closure and management of complications

Type A ductus was found in 127 patients (63.2%), type B in 2 (1%), type C in 14 (7%), type D in 2 (1%), type E in 24 (26.8%), and type F in 2 (1%) (Table 1). PDA was successfully closed with a coil in 196 patients. The duct was classified based on angiographic visualization. Type A ductus was found in 127 patients (63.2%), type B in 2 patients (1%), type C in 14 patients (7%), type D in 2 patients (1%), type E in 24 patients (26.8%), and type F in 2 patients (1%) (Table 1). PDA was successfully closed with a coil in 196 patients.

In 5 (2.48%) cases, the procedure was unsuccessful. Patients were followed up with echocardiography for an average of 121.8 months (SD±49.4). Only two patients had a residual shunt. Both of these patients experienced spontaneous closure during subsequent follow-ups.

The PDA was closed via the arterial route in 192 patients (95.5%) and via the venous route in 9 patients (4.5%). In our study, the procedure was unsuccessful in 5 cases (2.48%). Embolization occurred in four patients (1.9%). The coil embolized to the main pulmonary artery in one patient, to the right pulmonary artery in two patients, and to the aorta in another patient. The patient in whom the device embolized to the aorta was referred for cardiovascular surgery, and the coil was surgically removed. The embolized coils in the other three patients were removed using a transcatheter procedure. One patient (0.5%) developed tamponade during the procedure and required urgent intervention by the cardiovascular surgery team (Figure 2). Leakage was observed in two patients (1%) after closure of the PDA with a coil. In these patients, the ductus diameters were 3 mm and 4 mm, and the ductus lengths were 4 mm and 5 mm; all patients had type A ductus. The patients were monitored for any residual shunt, and none of them experienced complications such as hemolysis, infection, or thrombosis. Long-term follow-up also revealed no complications, such as ductus recanalization or stenosis of the pulmonary artery or aorta, in patients with complete occlusion.

Discussion

Transcatheter closure of PDA using detachable coils has been a well-established technique since the early 1990s[18-24].

Numerous studies have demonstrated its feasibility, safety, and cost-effectiveness, particularly in patients with small-to-medium ducts. However, most reports are limited by relatively small sample sizes and short follow-up durations. Our study, encompassing 201 patients with a mean follow-up of more than 10 years, represents one of the largest and longest single-center experiences with Flipper detachable Cook coils to date.

Clinical Outcomes and Procedural Success

Our overall procedural success rate of 97.5% aligns with previously published data, which reported coil closure success rates ranging from 89% to 100%. Similar to prior reports[20-26], we observed that complications were infrequent and that no mortality occurred. The durability of occlusion was excellent: residual shunt was documented in only 1% of patients during early echocardiography and resolved spontaneously in all cases within 6 months. Long-term follow-up confirmed sustained closure without recanalization, hemolysis, or device-related vascular obstruction.

Complications and Preventive Strategies

Device embolization remains the most frequent complication of coil closure, with reported rates varying between 0% and 6.5%[24-28]. In our series, embolization occurred in 2.0% of patients, typically in medium-sized ducts with a wider morphology. This finding reinforces the importance of careful coil sizing and angiographic assessment before release. The detachable feature of the Flipper coil likely contributed to our low embolization rate, as repositioning was possible in cases of suboptimal placement. One patient developed tamponade that required prompt surgical intervention and subsequently achieved a full recovery. These outcomes highlight that while complications are rare, procedural vigilance and immediate surgical backup remain essential.

Age, Weight, and Temporal Trends

The mean patient age in our cohort (56.5 months) is comparable to some reports in the literature[14-27], though higher than in other reports. This may reflect referral patterns over the nearly two-decade study period, as younger infants were increasingly treated in later years. Subgroup analysis across 5-year enrollment periods confirmed a trend toward earlier intervention in more recent years, consistent with global shifts in practice. The median weight (15 kg) also aligns with previous series, underscoring that coil closure can be safely performed in children across a broad weight range, provided the anatomy is suitable.

Morphology and Predictors of Outcome

As in prior reports, type A ducts were most common in our cohort (63.2%), followed by type E[21-29]. Success rates were slightly higher in type A than in type E, although the differences were not statistically significant. This suggests that ductal morphology remains an important consideration when selecting patients for coil closure, with elongated ducts (type E) presenting greater technical challenges.

Comparison with Other Devices

While detachable coils remain a reliable option for small-to-medium PDAs, newer occluder devices (e.g., Amplatzer duct occluder I and II) have gained favor for larger or more complex ducts[14,28-37]. Comparative studies suggest that occluders offer higher success rates and fewer reinterventions in such cases, though at greater cost[30-32]. Our study did not include direct comparisons with occluders, which is acknowledged as a limitation. Nevertheless, our long-term results confirm that coil closure remains an excellent therapeutic option in appropriately selected patients.

Contribution to the Literature

Recent publications (Ugan Atik and Saltık[17]; Adams et al.[21]; Narayan et al.[37] have emphasized the safety of PDA closure with both coils and occluders, but follow-up durations rarely exceed 3-5 years. Our cohort, with a mean follow-up of over 10 years, provides robust evidence that coil closure yields durable long-term outcomes without late complications. This finding strengthens the role of the Flipper Cook coil as a cost-effective and safe device for small-to-medium-sized PDAs, particularly in resource-limited settings.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective and single-center design inherently limits the generalizability of the findings. Although the sample size was large, the absence of randomization introduces potential selection bias. Second, while the long-term follow-up was a major strength, we did not directly compare the Flipper Cook coil with other closure devices, such as the Amplatzer occluder family. As newer devices were increasingly used for larger and more complex PDAs, the relative advantages and disadvantages of

coils versus occluders could not be assessed in this cohort. Third, our patient population was restricted to patients with anatomically suitable PDAs, which may have contributed to the high procedural success rate and low complication rate. Despite meticulous echocardiographic follow-up, subclinical complications such as minimal vascular obstruction may have been underdetected. Future multicenter prospective studies comparing devices are warranted to confirm and extend our results.

Conclusion

Our long-term follow-up data demonstrate that transcatheter closure of small-to-medium-sized PDA with the Flipper detachable Cook coil is safe and effective, characterized by high procedural success and a very low complication rate. Complete occlusion was achieved in nearly all patients, and outcomes remained durable over more than a decade of follow-up. These findings support the continued use of this method as a reliable and cost-effective therapeutic option in appropriately selected patients.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Institutional Ethics Committee (approval no: 24-3T/74, date: 07.03.2024).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practises: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Concept: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Design: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Data Collection or Processing: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Analysis or Interpretation: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Literature Search: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L., Writing: Ş.Ş.Ö., E.D., F.E., M.B.B., G.K.K., M.Y., B.B.A., B.K.B., H.K., Z.Ü.T., R.E.L.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

The Association Between C-reactive Protein/Albumin Ratio with the Stages of Malnutrition Defined by GLIM Criteria in Older Inpatient

Yaşlı Yatan Hastalarda C-reaktif Protein/Albümin Oranının GLIM Kriterlerine göre Tanımlanan Malnütrisyon Evreleri ile İlişkisi

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Abstract

Objective: This study aimed to determine the relationship between the C-reactive protein (CRP)/albumin ratio (CAR) and malnutrition, and its stages as defined by the global leadership initiative on malnutrition (GLIM) criteria. Additionally, it sought to establish CAR cut-off points to predict malnutrition and its stages.

Methods: The study included patients aged ≥60 years hospitalised at the clinic of internal medicine between June 2021 and May 2022. Serum CRP and albumin levels were measured within the first 24 hours of hospitalization. CAR was calculated as CRP (mg/L) divided by albumin (g/dL). Malnutrition and its stages were assessed using the GLIM criteria. ROC curve analysis was performed to identify CAR cut-off values for predicting stage 1 and stage 2 malnutrition.

Results: A total of 127 patients (46.5% male; median age 73) were included. Stage 1 malnutrition was present in 26% of cases and stage 2 in 23.6% of cases. Median CAR was 1.8 (0.07-50.4) in well-nourished patients, 6.8 (0.08-135.2) in patients with stage 1 malnutrition, and 9.8 (0.08-86.4) in patients with stage 2 malnutrition (p=0.014). CAR demonstrated an are under the curve (AUC) of 0.649 [95% confidence interval (CI): 0.552-0.747, p=0.004] for total malnutrition and an AUC of 0.669 (95% CI: 0.542-0.796, p=0.009) for stage 2. The CAR cut-off value for stage 2 malnutrition was determined as ≥8.4 (sensitivity: 53.3% and specificity: 79.7%).

Conclusion: CAR is associated with the diagnosis and staging of malnutrition according to GLIM criteria. It serves as a practical tool for assessing malnutrition risk, particularly for stage 2 malnutrition.

Keywords: Malnutrition, GLIM criteria, C-reactive protein/albumin ratio

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Öz

Amaç: Bu çalışma, C-reaktif protein (CRP)/albümin oranının (CAR) malnütrisyon ve malnütrisyon üzerine küresel liderlik girişimi (GLIM) kriterlerine göre belirlenen evreleri ile ilişkisini belirlemeyi amaçlamıştır. Ayrıca, CAR'ın malnütrisyon ve evrelerini öngörmedeki kesme noktalarını belirlemek hedeflenmiştir.

Yöntem: Çalışmaya, Haziran 2021-Mayıs 2022 tarihleri arasında iç hastalıkları kliniğine başvuran ve yaşları ≥60 olan hastalar dahil edildi. Hastaneye yatışın ilk 24 saati içinde serum CRP ve albümin düzeyleri ölçüldü. Malnütrisyon ve evreleri GLIM kriterlerine göre değerlendirildi. CAR'ın evre 1 ve evre 2 malnütrisyonu öngörmedeki kesme noktalarını belirlemek için ROC eğrisi analizi yapıldı.

Bulgular: Çalışmaya toplam 127 hasta (erkek %46,5; medyan yaş 73) dahil edildi. Hastaların %26'sında evre 1, %23,6'sında evre 2 malnütrisyon saptandı. Medyan CAR değerleri normal beslenenlerde 1,8 (0,07-50,4), evre 1 malnütrisyon grubunda 6,8 (0,08-135,2), evre 2 grubunda ise 9,8 (0,08-86,4) idi (p=0,014). CAR'ın total malnutrisyon için eğri altında kalan alan (EAA): 0,649 [%95 güven aralığı (GA): 0,552-0,747; p=0,004] ve evre 2 malnutrisyon için EAA: 0,669 (%95 GA 0,542-0,796; p=0,009) olarak bulundu. Evre 2 malnütrisyon için CAR kesme noktası ≥8,4 (duyarlılık: %53,3 ve özgüllük: %79,7) olarak bulundu.

Sonuç: CAR, GLIM kriterlerine göre malnütrisyonun tanı ve evrelemesiyle ilişkilidir. Özellikle evre 2 malnütrisyon açısından pratik bir belirteç olarak kullanılabilir.

Anahtar Kelimeler: Malnütrisyon, GLIM kriterleri, C-reaktif protein/albümin oranı

Introduction

Malnutrition is a common and substantial health problem. Its prevalence varies from 20% up to 50% according to patient characteristics, the care setting, and the diagnostic criteria used[1-4]. This variability makes it difficult to harmonize study results because there is no broadly accepted gold standard for assessing nutritional status. Delays in diagnosis and treatment may further increase health expenditures, morbidity, and mortality. Simplified, globally accepted, and easy-to-apply tests are needed.

Several malnutrition screening and assessment tools have been created and validated for specific populations, such as for older individuals, community-dwelling people or hospitalized patients[5-8]. In 2019, the global leadership initiative on malnutrition (GLIM) criteria were introduced to promote a consistent approach to diagnosing malnutrition worldwide. These criteria also aimed to reduce delays in initiating appropriate interventions[5]. In this two-step approach, patients at risk are first identified using one of the validated screening tools. Following the first step, the diagnosis and degree of malnutrition are determined. For the diagnosis, involuntary weight loss, low body mass index (BMI), and decreased muscle mass are phenotypic criteria, and poor dietary intake or absorption and inflammation are etiological criteria. Diagnosing malnutrition according to the GLIM criteria requires the identification of at least one phenotypic and one etiologic criterion. The severity of malnutrition is classified into two stages: moderate (stage 1) and severe undernutrition (stage 2), based on phenotypic criteria[5].

Since inflammation is one of the etiological criteria in the GLIM framework, laboratory markers such as C-reactive protein (CRP), albumin, and prealbumin are recommended as supportive indicators[5]. CRP is secreted in response to pro-inflammatory cytokines during inflammatory and infectious processes. Its levels can also be elevated in the presence of trauma, tissue injury, and cardiovascular diseases[9]. Albumin is a negative acute-phase protein. It decreases during inflammation and is frequently used in the diagnosis of malnutrition[10]. The CRP/albumin ratio (CAR) is obtained by dividing CRP by the albumin level. The literature indicates that CAR is a prognostic indicator of disease severity or activity in various rheumatologic diseases and in patients with coronavirus disease-2019 and Crohn's disease. It also predicts morbidity and mortality in critical conditions such as sepsis, septic shock, and malignant diseases[11-17]. Research has demonstrated its value as an independent predictor of overall mortality and amputation in patients undergoing endovascular surgery for peripheral arterial disease[18]. In a study conducted in cancer patients (solid or hematological neoplasms), CAR and length of hospital stay were significantly higher in patients diagnosed with malnutrition using GLIM criteria whereas; BMI and albumin values were significantly lower[19]. Another study in cancer patients assessed the predictive value of adding inflammatory markers such as the inflammatory burden index, CRP, neutrophil-to-lymphocyte ratio, and albumin to the GLIM criteria for diagnosing malnutrition. The modified criteria showed better predictive capacity for both short- and long-term prognosis, with CRP being identified as a valuable indicator of malnutrition severity in short-term outcomes[20].

The GLIM is widely used for the diagnosis of malnutrition. However, it includes many variables that create difficulties in its application. As inflammation is included in the GLIM criteria and CAR has been shown to be a prognostic indicator in many diseases, the use of CAR might be practical for indicating nutritional risk. Currently, no studies have investigated the correlation between CAR and GLIM-defined malnutrition stages in older patients. Consequently, we designed the study to determine the relationship between CAR and malnutrition, and between CAR and the stages of malnutrition using GLIM criteria, as well as to establish the cut-off points of CAR for predicting malnutrition and its stages.

Materials and Methods

In this retrospective study, sociodemographic, clinical, and laboratory data were collected from patient records, including age, sex, education level, living situation, income status, comorbidities, number of medications, length of hospital stay, BMI, grip strength (GS), CRP, and albumin levels.

Study Population

Patients aged 60 years and older who were hospitalized in the Internal Medicine Department of Ege University Hospital between June 2021 and May 2022 were retrospectively included in the study. Patients with missing anthropometric measurements, GS values, laboratory data, or GLIM evaluations were excluded.

The study was approved by the Ege University Medical Research Ethics Committee, İzmir, Türkiye (approval no: 22-12T/50, date: 06.12.2022). For this type of retrospective study formal consent is not required.

Anthropometric Measurements

BMI was calculated as weight (kg) divided by height squared (m^2).

GLIM Criteria

The GLIM criteria necessitate a two-step approach[5]. First, patients at risk of malnutrition are identified through validated screening tools; second, the diagnosis and degree of malnutrition are determined. Malnutrition according to GLIM required ≥1 phenotypic criterion (weight loss, low BMI, or reduced muscle mass) plus ≥1 etiologic criterion (reduced intake/absorption or inflammation). Inflammation may be associated with acute illness or injury, or with chronic disease. Severe inflammation related to acute illness or injury can be caused by major infection, burn or trauma. Chronic inflammation linked to various conditions, such as chronic obstructive pulmonary disease (COPD), malignant disease, chronic kidney disease, and other disorders involving persistent or recurring inflammation, can be assessed using CRP as a supplementary laboratory indicator[5].

Malnutrition was staged as follows: stage 1 (moderate) if weight loss was 5-10% within 6 months or 10-20% beyond 6 months, BMI <20 kg/m^2 if <70 years or <22 kg/m^2 if ≥70 years, or reduced muscle mass; stage 2 (severe) if weight loss was >10% within 6 months or >20% beyond 6 months, BMI <18.5 kg/m^2 if <70 years or <20 kg/m^2 if ≥70 years, or markedly reduced muscle mass. As muscle mass measurements were not available in our study, malnutrition staging was conducted based on the remaining GLIM criteria.

Muscle Strength Assessment

Handgrip strength was measured using a Takei dynamometer (Takei T.K.K. 5401 digital dynamometer, Takei Scientific Instruments Co. Ltd, Tokyo, Japan). Measurements were performed with a validated protocol[21].

Laboratory Measurements

Serum CRP and albumin values were retrieved from the measurements taken within the first 24 hours after hospitalization. CAR was calculated as CRP (mg/L) divided by albumin (g/dL).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). To evaluate the distribution of the data, the Kolmogorov-Smirnov test was applied. Normally distributed variables were shown as mean ± standard deviations and non-normally distributed variables were shown as medians (minimum-maximum values). Categorical variables were expressed as counts and percentages. Chi-square, Mann-Whitney U, or t-tests were used to assess differences between the two groups, when appropriate. Comparisons among three groups were performed using Kruskal-Wallis analysis, followed by adjacent post-hoc tests. P-values with Bonferroni corrections were used for post-hoc analysis. The area under the (AUC) receiver operating characteristic (ROC) curve was computed to evaluate and compare the predictive capabilities of CAR, CRP, and albumin in identifying malnutrition and its stages. An AUC value greater than 0.8

suggests strong diagnostic accuracy, while values between 0.6 and 0.8 indicate moderate accuracy, and values below 0.6 reflect limited diagnostic performance[22]. ROC curves were also constructed to determine CAR threshold values for predicting malnutrition stages according to the GLIM criteria. Optimal cut-off values were determined using the Youden index.

For correlation analysis, Pearson correlation was applied to normally distributed data, while Spearman correlation was applied to non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

Results

Of 127 patients, 46.5% were male, with a median age of 73. Table 1 provides the demographic and clinical characteristics of the study population, categorized by their nutritional status.

According to the GLIM criteria, 50.4% of patients were classified as well-nourished, 26% had stage 1 malnutrition, and 23.6% had stage 2 malnutrition. CRP, albumin, and CAR values differed significantly among the three groups (p=0.019, p=0.04, and p=0.014, respectively). Post-hoc analysis showed that CRP and CAR were significantly higher, and albumin was significantly lower, in stage 2 malnutrition compared with the well-nourished group (p=0.042, p=0.034, and p=0.005, respectively). No significant differences were found between stage 1 and the well-nourished group (p=0.104, p=0.157, and p=0.081).

CAR showed a strong positive correlation with CRP (r=0.929, p<0.001) and a strong negative correlation with albumin (r=-0.633, p<0.001). In addition, CAR demonstrated a moderate positive correlation with length of hospital stay (r=0.520, p<0.001) and a moderate negative correlation with handgrip strength (r=-0.307, p=0.020). Other correlations were weaker and are presented in Supplementary Table 1.

The AUC values of CRP, albumin, and CAR for predicting malnutrition (stage 1+2) according to GLIM criteria were 0.644 [95% confidence interval (CI): 0.546-0.742, p=0.005],

Table 1. The characteristics of the study population according to nutritional status

Variables	Total population (n=127)	Well nourished (n=64)	Stage 1 malnutrition (n=33)	Stage 2 malnutrition (n=30)	Total malnutrition (n=63)	p-value[a]	p-value[b]
Age (years)	73 (60-95)	69.5 (60-90)	72 (60-95)	76 (60-91)	73.7±9*	0.142	0.79
Gender, male (%)	46.5	42.2	45.5	56.7	50.8	0.331	0.419
The number of comorbidities	4 (0-11)	4 (0-11)	4 (1-9)	3 (0-9)	4 (0-9)	0.485	0.725
The number of medications	7 (0-19)	7 (0-19)	6 (1-11)	7 (0-11)	6 (0-11)	**0.048**	0.136
Duration of hospital stay (day)	8 (1-56)	7 (1-41)	12 (1-56)	9 (2-55)	10 (1-56)	**0.012**	0.059
Muscle strength (kg)	20.5±8.5*	21.4±8.5*	21 (7.1-37.2)	16 (1-39.6)	19.2±8.7*	0.151+	0.059
Body mass index (kg/m^2)	27±6.26*	30.4±5.4*	23.6 (15-37)	22.9 (14-36)	23.5±5*	**<0.001+**	**<0.001**
Calf circumference (cm)	34 (23-49)	36 (25-48)	33 (26-41)	31 (23-49)	32±4.6*	**<0.001**	**<0.001**
CRP	11 (0.3-305)	5.6 (0.3-126)	25 (0.3-305)	26.9 (0.3-190)	25 (0.3-305)	**0.005**	**0.019**
Albumin	3.5 (1.2-4.7)	3.7 (1.2-4.7)	3.4 (1.3-4.5)	3.1 (1.9-4.7)	3.2 (1.2-4-7)	**0.002**	**0.004**
CAR	3.2 (0.07-135.2)	1.8 (0.07-50.4)	6.8 (0.08-135.2)	9.8 (0.08-86.4)	8.8 (0.08-135.2)	**0.004**	**0.014**

Total malnutrition: stage 1 malnutrition+stage 2 malnutrition according to GLIM

[a]: p-values between well-nourished and total malnutrition, [b]: p-values between well-nourished, stage 1, and stage 2 malnutrition, *: Normally distributed variables were shown as mean ± SD, +: Independent sample t-test was used, CRP: C-reactive protein, CAR: C-reactive protein to albumin ratio, GLIM: Global leadership initiative on malnutrition, SD: Standard deviation

0.660 (95% CI: 0.564-0.755, p=0.002), and 0.649 (95% CI: 0.552-0.747, p=0.004) (Figure 1). For stage 2 malnutrition, the AUCs were 0.669 for CAR (95% CI: 0.542-0.796, p=0.009) and 0.662 for CRP (95% CI: 0.534-0.790, p=0.012) (Figure 2).

Optimal CAR thresholds determined by Youden index were ≥8.29 for overall malnutrition and ≥8.40 for stage 2 malnutrition. For overall malnutrition, the cut-off of ≥8.29 yielded a sensitivity of 50.0% and a specificity of 79.7%, with positive predictive value (PPV) 70.8% and negative predictive value (NPV) 61.8%. For stage 2 malnutrition, the cut-off of ≥8.40 provided a sensitivity of 53.3% and a specificity of 79.7%, with PPV 44.8% and NPV 84.7%.

Discussion

In this study, we investigated the association between CAR and malnutrition (including stages defined by the GLIM criteria) in hospitalized older adults. Our results showed that CAR values were significantly higher in patients with stage 2 malnutrition than in well-nourished individuals. However, no significant difference was observed between well-nourished patients and those with stage 1 malnutrition, or between patients with stage 1 and stage 2 malnutrition. The optimal CAR cut-off of ≥8.40 demonstrated moderate diagnostic accuracy for stage 2 malnutrition, with a sensitivity of 53.3% and specificity of 79.7%, yielding a relatively low PPV (44.8%) but a higher NPV (84.7%). These findings suggest that CAR may be more useful for ruling out severe malnutrition than for confirming its presence.

Our results align with previous studies highlighting the role of systemic inflammation in malnutrition pathogenesis and diagnosis[5,20]. CRP is a well-established biomarker of inflammation, while albumin reflects both nutritional status and inflammatory burden[14]. Eckart et al.[23] demonstrated that elevated CRP combined with hypoalbuminemia increased malnutrition risk during acute illness. In our study of hospitalized patients aged over 60 years, those

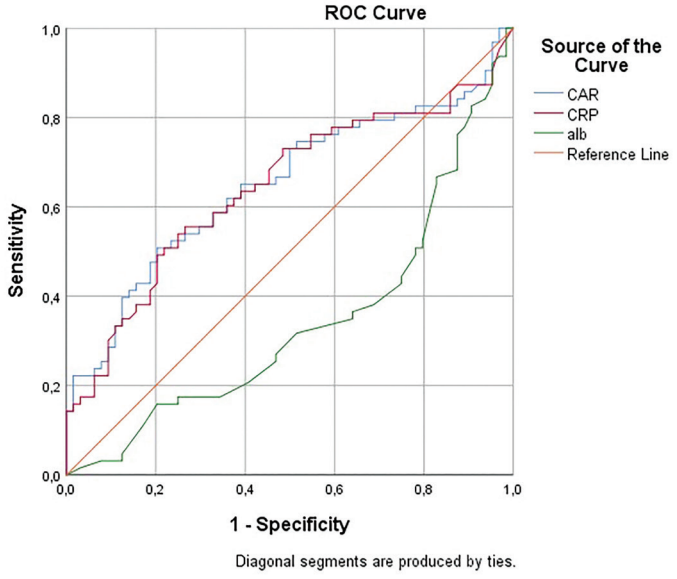

Figure 1. ROC curves of CRP, albumin, and CAR for predicting overall malnutrition (stage 1+stage 2) according to GLIM criteria

Optimal CAR threshold (Youden's J): ≥8.29; CAR=CRP (mg/L)/albumin (g/dL). AUC=0.649 (95% CI: 0.552-0.747); sensitivity 50.0%, specificity 79.7%, PPV=70.8%, NPV=61.8%

ROC: Receiver operating characteristic, CAR: C-reactive protein to albumin ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

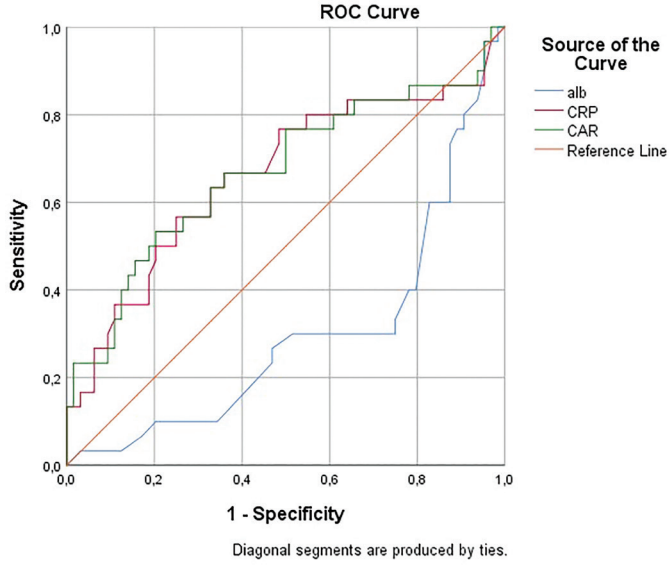

Figure 2. ROC curve of CAR and CRP for predicting stage 2 malnutrition according to GLIM criteria

Optimal CAR threshold (Youden's J): ≥8.40; CAR=CRP (mg/L)/albumin (g/dL). AUC=0.669 (95% CI: 0.542-0.796); sensitivity 53.3%, specificity 79.7%, PPV=44.8%, NPV=84.7%

ROC: Receiver operating characteristic, CAR: C-reactive protein to albumin ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

with malnutrition according to GLIM criteria had higher CRP, lower albumin, and higher CAR. A higher CAR ratio was observed as the stage of malnutrition increased. Since CAR is mathematically derived from CRP and albumin, the observed correlations largely reflect a mechanistic relationship. They should not be interpreted as independent biological associations. Our findings extend the evidence by demonstrating that CAR may not only be a prognostic marker but also serve as a supportive indicator for severe malnutrition as defined by GLIM.

The pathophysiological link between CAR and malnutrition is biologically plausible. Inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha suppress appetite, promote proteolysis, and reduce albumin synthesis, contributing to muscle wasting and weight loss[24]. In our study, despite a difference in BMI between well-nourished participants and those with stage 1 and stage 2 malnutrition, there was no difference in GS. Malnutrition can impair immune responses, perpetuating chronic inflammation and creating a vicious cycle[25]. In our study, there was no difference in the number of chronic diseases between the groups, but the inflammatory burden caused by the disease may differ between groups, and inflammatory responses may change depending on inflammaging.

CAR has been shown to predict adverse outcomes in sepsis, malignancies, and critical illness[13,17]. In older adults, high CAR has been associated with longer hospital stays and higher mortality[26,27]. Kaplan et al.[12] found a CAR exceeding 16.28 was identified as a significant predictor of mortality, demonstrating 92.1% sensitivity and 58.0% specificity. In line with these findings, our study showed that the duration of hospitalization was significantly longer in patients with malnutrition than in those without, and that CAR was positively correlated with length of hospital stay. Taken together, these findings reinforce the clinical importance of CAR as both a nutritional and a prognostic marker.

In 393 patients with COPD, CAR values were significantly higher in those with an nutritional risk screening (NRS)-2002 score ≥3, indicating a higher risk of malnutrition. A cut-off value of 3.26 predicted nutritional risk[28]. In that study, patients with NRS-2002 ≥3 also had significantly lower albumin and higher CRP levels. Moreover, among 234 emergency department patients, higher CAR was again associated with malnutrition risk according to NRS-2002[29]. Nutritional status was assessed using the mini nutritional assessment in 155 elderly outpatients after excluding those with CRP >10. A CAR threshold of ≥0.86 (CRP in mg/L, albumin in g/dL) predicted malnutrition (sensitivity 48.4%, specificity 71.7%)[30]. In our study, CAR cut-off values were considerably higher. This difference may be attributable to variations in study populations and exclusion criteria, particularly the exclusion of patients with CRP >10 mg/L.

From a clinical perspective, our results suggest that CAR could complement existing screening tools, particularly when rapid assessment is needed. A low CAR (<8.40) may reliably exclude severe malnutrition, potentially reducing unnecessary investigations. However, given the modest PPV, positive results should always be followed by a comprehensive nutritional assessment, including anthropometric and functional measures such as GS. Compared with the conventional application of GLIM, CAR measurement is simple, inexpensive, and widely available, thereby increasing its practical value in resource-limited settings.

Study Limitations

Our study has several strengths. To our knowledge, it is the first study to evaluate the association between CAR and GLIM-defined malnutrition stages in older hospitalized patients. Additionally, we determined specific cut-off values that may be clinically applicable. Nonetheless, limitations must be acknowledged. The retrospective design precludes causal inference, and the single-center sample limits generalizability. Furthermore, we relied on a single baseline measurement of CRP and albumin, which may not reflect dynamic changes during hospitalization. The sample size was modest, which may have limited the statistical power to detect differences between stage 1 patients and well-nourished patients.

Future research should aim to validate these findings in larger, prospective, multicenter cohorts. Longitudinal studies assessing dynamic changes in CAR may provide insights into CAR's role in monitoring nutritional interventions and predicting outcomes. Moreover, integrating CAR with other inflammatory markers (e.g., neutrophil-to-lymphocyte ratio, IL-6) could enhance diagnostic performance.

Conclusion

In conclusion, CAR is associated with malnutrition severity according to the GLIM criteria and may be particularly useful for identifying and especially rulling out patients at risk of severe malnutrition. While its diagnostic accuracy is moderate, its simplicity and availability make it a promising tool in the nutritional assessment of older hospitalized patients.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Medical Research Ethics Committee, İzmir, Türkiye (approval no: 22-12T/50, date: 06.12.2022).

Informed Consent: For this type of retrospective study formal consent is not required.

Footnotes

Authorship Contributions

Surgical and Medical Practises: N.S.G., Concept: N.S.G., S.Ç., S.S., Design: N.S.G., S.Ç., S.S., Data Collection or Processing: N.S.G., Analysis or Interpretation: N.S.G., S.Ç., S.S., Literature Search: N.S.G., F.E., Writing: N.S.G., S.S., F.E.

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Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/3a74cfc1-f221-49ee-9fe3-d44549560a6c.pdf

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Retrospective Evaluation of Coaxial Core Needle Biopsy Results Performed on Mammographic Suspicious Microcalcifications of the Breast

Memenin Kuşkulu Mikrokalsifikasyonlarına Mamografide Yapılan Koaksiyel Kalın İğne Biyopsi Sonuçlarının Retrospektif Değerlendirilmesi

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Abstract

Objective: Breast microcalcifications (MCs) are detected in approximately one-third of screening mammograms and are associated with about 40% of breast cancers. The gold-standard procedure for histopathological evaluation of MCs is stereotactic vacuum-assisted biopsy; however, it is costly and not easily accessible. The aim of this study was to evaluate the feasibility of stereotactic coaxial core needle biopsy (CNB), a less expensive and simpler technique, for MCs detected on mammography and to investigate its specificity, positive predictive value (PPV), negative predictive value (NPV), and sensitivity.

Methods: Between 2020 and 2024, 76 who underwent stereotactic coaxial CNB for breast imaging reporting and data system (BI-RADS) category 4-5 MCs detected on mammography were retrospectively reviewed.

Results: The specificity and PPV of the biopsy procedure were 100%, while the sensitivity and NPV were 71.4% and 85.7%, respectively. A calcification size of ≤10 mm (p=0.077) and obtaining ≥10 samples (p=0.034) were found to be significant factors for biopsy accuracy. Segmental distribution, fine pleomorphic and fine linear morphologies, and BI-RADS categories 4C and 5 were significantly associated with malignancy (p<0.001).

Conclusion: For MCs detected on mammography that are suspected to be malignant but not localized by ultrasonography, coaxial CNB performed under mammographic guidance provides high diagnostic accuracy and reliability.

Keywords: Mammography, microcalcification, core needle biopsy, breast cancer

Öz

Amaç: Meme mikrokalsifikasyonları (MK), tarama mamogramlarının yaklaşık üçte birinde tespit edilir ve meme kanserlerinin %40'ı ile ilişkilidir. MK histopatolojik yaklaşımda altın standart işlem sterotaktik vakum aspirasyon biyopsisidir fakat erişimi zor ve yüksek maliyetlidir. Bu çalışmanın amacı, mamografide saptanan MK'lara ucuz ve kolay bir teknik olan sterotaktik koaksiyel kalın iğne biyopsinin (KİB) kullanılabilirliğini değerlendirme özgüllüğü, pozitif öngörü değer (PPD), negatif öngörü değer (NPD), duyarlılığını araştırmaktır.

Yöntem: 2020-2024 yılları arasında, mamografide saptanan meme görüntüleme raporlama ve veri sistemi (BI-RADS) 4-5 MK'lara sterotaktik koaksiyel KİB yapılan 76 olgu retrospektif olarak taranmıştır.

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Öz

Bulgular: Biyopsi işleminin özgüllüğü ve PPD'i %100 bulunmuştur. Duyarlılığı %71,4, NPV'i %85,7 bulunmuştur. Kalsifikasyon boyutunun 10 mm ve altında olması biyopsi parça sayısının 10 ve üzerinde olması biyopsi doğruluğu için anlamlıydı (p=0,077, p=0,034). Dağılımının segmental, morfolojik bulgularının ince pleomorfik ve ince lineer olması, BI-RADS 4C ve 5 katagori malignite için anlamlıydı (p<0,001).

Sonuç: Mamografide saptanıp ultrasonografi ile lokalize edilemeyen malignite şüpheli MK'larda mamografide yapılan koaksiyel KİB'si, yüksek doğruluk ve güvenilirlik sunmaktadır.

Anahtar Kelimeler: Mamografi, mikrokalsifikasyon, kalın iğne biyopsi, meme kanseri

Introduction

Mammography is the primary imaging modality for the screening and early diagnosis of breast cancer[1,2]. On mammographic examination, microcalcifications (MCs), architectural distortions, and asymmetries-which may not be detected on ultrasonography-can be identified and are considered important indicators of early breast cancer[3].

According to the breast imaging reporting and data system (BI-RADS) classification system proposed by the American College of Radiology to standardize breast imaging reporting, high-risk breast lesions categorized as BI-RADS 4A, 4B, 4C, or 5 may represent ductal carcinoma *in situ* (DCIS) and/or invasive breast carcinoma; therefore, histopathological confirmation is required[4]. In the diagnosis of these lesions, core needle biopsy (CNB) methods are increasingly used. CNB is a rapid, easy-to-perform, cost-effective biopsy technique that is well tolerated by patients. However, for lesions detected only on mammography, the biopsy procedure must be performed under stereotactic guidance[5].

Obtaining an adequate tissue sample during biopsies of MCs is often challenging. Liberman et al.[6] showed that using 14-gauge needle biopsies, five biopsy samples were sufficient to achieve a definitive diagnosis in 99% of the 92 mass lesions, whereas only 53% of the 87 calcification clusters could be diagnosed with a similar tissue volume.

Unlike in ultrasound-guided procedures, needle localization is not possible in stereotactic biopsies. Therefore, to ensure procedural success, as much tissue as possible must be obtained. In stereotactic CNB, unlike vacuum-assisted biopsy (VAB), the biopsy gun is removed from the breast after each sampling; it is then reinserted and fired again for the next sample[7]. Therefore, the VAB technique is currently the preferred choice[5]. However, due to the high cost of the VAB unit and vacuum biopsy needles, access to this method is limited[8]. The cost of VAB is reported to be 2.2 to 12.5 times higher than that of CNB[9]. In one study, VAB demonstrated 100% specificity, 91.3% sensitivity, and 100% positive predictive value (PPV) in detecting malignant lesions, with an negative predictive value (NPV) of 80%[10]. Another study comparing stereotactic CNB and VAB found that for the VAB group, the overall PPV was 100%, the NPV was 95.8%, and the diagnostic accuracy was 97%, whereas for the CNB group, the PPV was 100%, the NPV was 80%, and the diagnostic accuracy was 84.8%[11]. CNB is a cost-effective procedure with a substantially lower complication rate. In our study, we performed the procedure under coaxial needle guidance, allowing multiple samples to be obtained from the same location without changing the entry site. Since only 22.4% of histopathological evaluations of MCs yield a malignant diagnosis, cost-effective procedures associated with fewer complications should be preferred[12].

The aim of this study was to investigate the specificity, PPV, sensitivity, and NPV of the minimally invasive coaxial CNB procedure performed for suspicious MCs detected on mammography. In this way, we aimed to provide a more cost-effective and more easily accessible approach for the evaluation of suspicious MCs detected on mammography.

Materials and Methods

Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval no: 0183, date: 25.04.2024).

Patient Selection

Between December 2020 and December 2024, the records of patients with BI-RADS category 4A-C and 5 lesions visible only on mammography who underwent stereotactic coaxial needle-guided CNB were retrospectively reviewed. To identify patients with mammographic MCs, our institutional database was queried. Exclusion criteria included the presence of a mass on imaging, a palpable mass on clinical examination, a mass detectable on ultrasound, an associated opacity on

mammography, and lack of available surgical pathology results at our institution. The gold-standard diagnostic method is surgical excision. For the 76 retrospectively reviewed patients, the following parameters were evaluated: the distribution and morphological characteristics of calcifications detected on mammography, size of the calcifications, BI-RADS category of the lesions, presence of calcifications on specimen mammography, number of biopsy samples obtained, presence of calcifications in pathology results, biopsy pathology findings, surgical excision pathology results, and follow-up findings.

Patients whose biopsy results were benign and radiologic–pathologic concordant were followed for at least 12 months.

Stereotactic Coaxial CNB Procedure on Mammography

The biopsy procedure was performed by a single radiologist with five years of breast radiology experience. Before the biopsy, all patients were informed about the procedure and provided written informed consent. Coagulation parameters were assessed. Mammography and biopsy procedures were performed using an IMS Giotto mammography device (Bologna, Italy). A 14-gauge semi-automatic coaxial biopsy needle (Geotek 14G, 15 cm) was used. After identifying the lesion on mediolateral projection, the biopsy area was cleaned with povidone-iodine (Betadine), locally anesthetized with 3-4 cc of prilocaine, and a small incision was made. Through this incision, under stereotactic guidance, the lesion was marked in the appropriate position using the coaxial needle. After determining the lesion depth with a craniocaudal projection, multiple samples were obtained sequentially from the center of the lesion using a 14-gauge core needle-guided by the coaxial system, with small angular adjustments to the right and to the left. The obtained samples were placed on a slide, and specimen mammography was performed to evaluate the presence of MCs. After assessment, the samples were placed in formalin and sent to the pathology laboratory (Figure 1). Post-surgical pathology results were used as the gold-standard, and specificity, PPV, and NPV were evaluated accordingly.

Data Analysis

The evaluation of findings was performed according to the 5th edition of the BI-RADS classification. On mammography, the distribution (diffuse, regional, linear, segmental, grouped) and morphologic types (amorphous, coarse heterogeneous, fine pleomorphic, and fine linear branching) of MCs were recorded according to BI-RADS criteria.

The histopathological diagnosis was obtained from coaxial CNB and from post-surgical specimens. Histopathological evaluations were performed by experienced breast pathologists. Among the 76 patients, those whose biopsy results revealed invasive carcinoma or DCIS were classified as the malignant group. Patients diagnosed with malignancy were referred for surgical excision. For lesions diagnosed as benign on CNB, radiologic-pathologic concordance was assessed. Cases showing radiologic-pathologic discordance or persistent suspicion of malignancy were also referred for surgical excision. Cases with radiologic-pathologic concordance were followed up for at least 12 months. No lesion showed an increase in size during follow-up. Cases

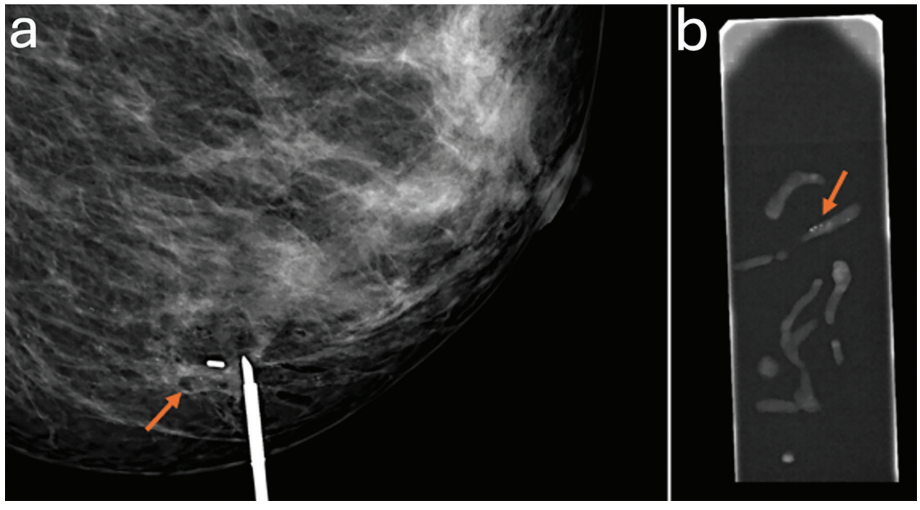

Figure 1. a) Tru-cut biopsy performed with a 14G needle in a case with segmental fine linear calcifications. b) Specimen radiograph (orange arrow indicates the calcification)

Diagnosis: Ductal carcinoma in situ with intermediate nuclear grade

that remained stable during follow-up were classified as benign.

Statistical Analysis

Descriptive statistics for qualitative variables in the study were presented as numbers and percentages. Relationships between qualitative variables were analyzed using the Pearson chi-square test and Fisher's exact test. The performance of the index test was evaluated against the reference standard (gold-standard) using 2×2 contingency tables. Sensitivity, specificity, PPV, and NPV were calculated based on standard definitions, and 95% confidence intervals were calculated.

The agreement between the index test and the gold-standard was assessed using Cohen's Kappa coefficient. A p-value <0.05 was considered statistically significant. All calculations were performed using the SPSS software package (version 28).

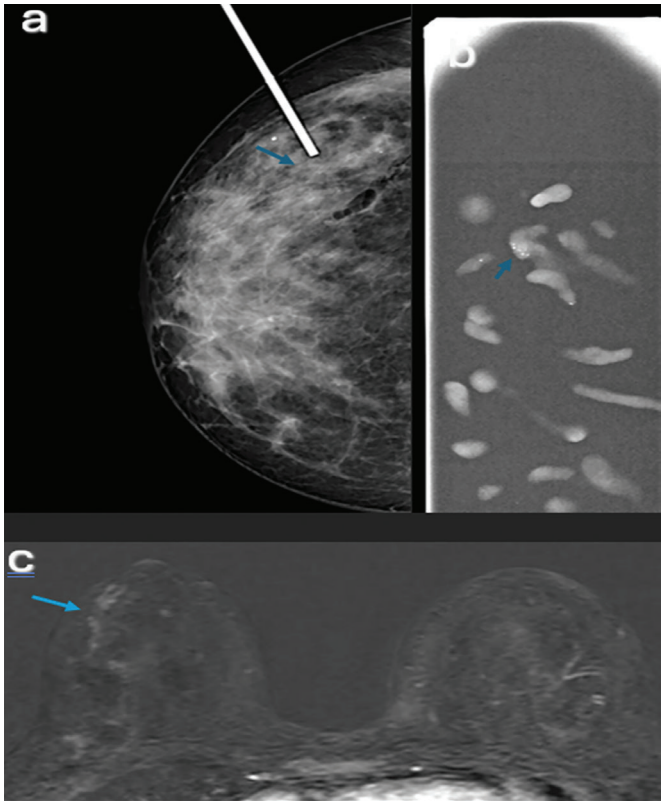

Figure 2. a) Stereotactic coaxial biopsy performed on a BI-RADS 4C calcification area showing fine pleomorphic regional distribution on mammography. b) Detection of calcification on the specimen radiograph. c) Contrast enhancement observed in the same area on MRI

BI-RADS: Breast imaging reporting and data system, MRI: Magnetic resonance imaging

Results

The mean age of the patients was 54.1±8.6 years (range: 40-76 years). Procedures were performed on the right breast in 39 patients (51.3%) and on the left breast in 37 patients (48.6%). Among the 76 cases, 56 (73.7%) were diagnosed as benign, and 20 (26.3%) as malignant. Biopsy results showed 15 cases of DCIS and 5 cases of invasive ductal carcinoma

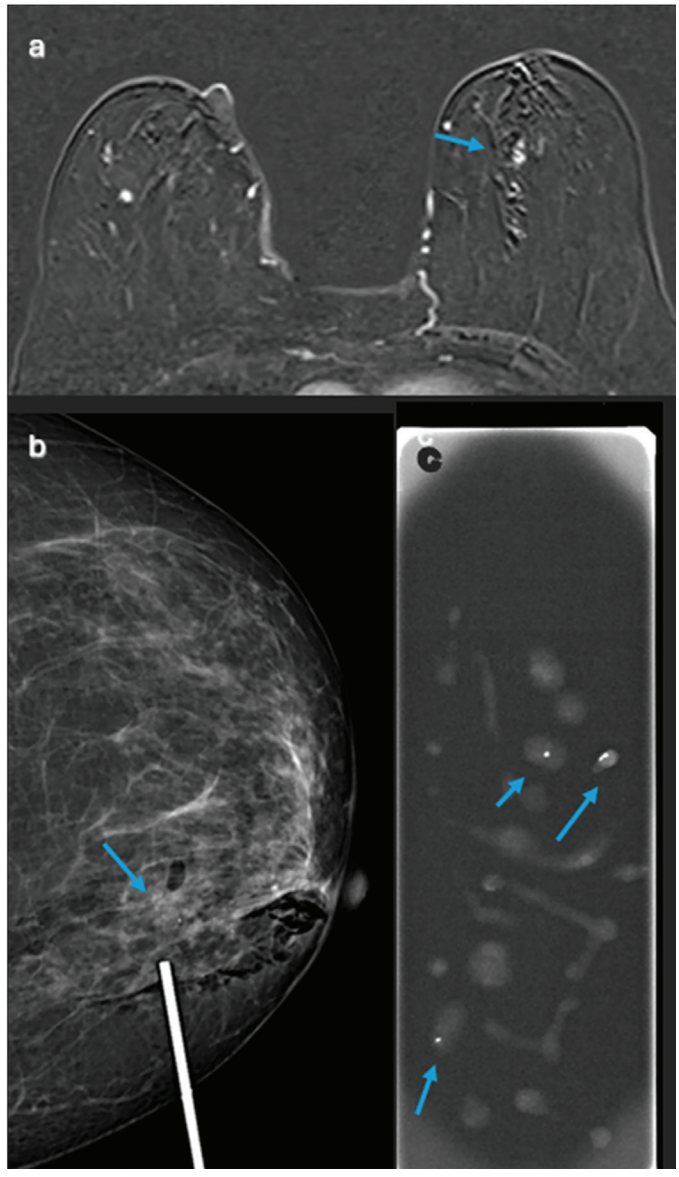

Figure 3. a) Non-mass enhancement observed on MRI. b) Stereotactic coaxial biopsy performed on a BI-RADS 4C calcification area showing fine pleomorphic segmental distribution on mammography. c) Detection of calcification on the specimen radiograph

BI-RADS: Breast imaging reporting and data system, MRI: Magnetic resonance imaging

among the malignant lesions. Among benign lesions, there were 3 cases of sclerosing adenosis (SA), 5 cases of atypical ductal hyperplasia (ADH), 2 cases of lobular carcinoma *in situ* (LCIS), 1 case of fat necrosis, 1 case of intraductal papilloma, and 44 other benign findings (such as fibrocystic changes or benign breast tissue). Surgical pathology results revealed 13 invasive ductal carcinomas, 15 DCIS, 1 calcified fibroadenoma, 3 LCIS, SA, 3 ADH, 1 atypical lobular hyperplasia, 1 intraductal papilloma, and 7 benign lesions. Twenty-eight patients were followed up without surgical intervention. All MCs diagnosed as malignant by CNB were referred for surgical excision (Figures 2 and 3). Among the 56 cases diagnosed as benign, 28 that showed no change in size or morphology during 1-2 years' follow-up were considered stable.

Mammographic and Biopsy Findings

Among the 76 patients included in the study, when biopsy results were compared with the gold-standard, the biopsy sensitivity for detecting malignant lesions was 71.4% and the specificity was 100%. The PPV was 100%, and the NPV was 85.7%. No false-positive cases were identified. The Kappa coefficient was 0.759, indicating strong agreement between the biopsy results and the gold-standard (Tables 1-2).

When calcifications observed in the specimens were compared with those in the pathology results, sensitivity was 100% and specificity was 71.4%. The PPV was 73.9% and the NPV was 100%. These results show that all cases in which calcifications were detected on specimen examination were also confirmed by pathological findings (Table 3).

When calcification size was evaluated in relation to biopsy accuracy, concordance between biopsy and the gold-standard was observed for MCs measuring ≤10 mm (52.9%), whereas discordance was found for MCs measuring 10-20 mm (17.6%) and >20 mm (29.4%) (p=0.004).

When the number of biopsy samples was evaluated, a statistically significant discordance between biopsy and gold-standard results was observed in cases with 10 or more samples: 7.4% (p=0.034). Although not statistically significant, the highest concordance (60.3%) was observed in cases with 5-10 samples. When the presence of calcifications in the specimen was compared with the biopsy (gold-standard) concordance, no significant difference was observed (p=1.000). Similarly, no significant difference was found between detection of calcifications on pathological examination and concordance with the biopsy gold-standard; (p=0.285; Table 4).

According to the gold-standard results, the regional distribution rate of malignant lesions (46.4%) and the grouped distribution rate of benign lesions (72.9%) were statistically significant (p=0.002). Regarding morphological features, malignant lesions showed significantly higher rates of pleomorphic (35.7%) and fine linear (64.3%) calcifications, whereas benign lesions more frequently exhibited coarse (35.4%) and amorphous (41.7%) calcifications (p<0.001). In terms of BI-RADS categories, malignant lesions were significantly more frequently classified as BI-RADS 4C (78.6%) and BI-RADS 5 (21.4%), whereas benign lesions were more frequently categorized as BI-RADS 4A (43.8%) and BI-RADS 4B (29.2%) (p<0.001) (Table 5).

Table 1. The relationship between the biopsy procedure and the gold-standard surgical pathology

Biopsy result	Malignant	Benign	Total
Malignant	20 71.4%	0 0.0%	20 26.3%
Benign	8 28.6%	48 100.0%	56 73.7%
Total	28 100.0%	48 100.0%	76 100.0%

Table 2. Diagnostic performance of the biopsy procedure

Metric	Value	95% CI
Sensitivity	0.714	(0.529-0.847)
Specificity	1.000	(0.926-1.000)
PPV	1.000	(0.839-1.000)
NPV	0.857	(0.743-0.926)
Kappa	0.759	-

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Table 3. The relationship between the detection of calcification in the specimen and the presence of calcification in pathology

Specimen	Pathology: calcification present	Pathology: calcification absent	Total
Calcification present	34 100.0%	12 28.6%	46 60.5%
Calcification absent	0 0.0%	30 71.4%	30 39.5%
Total	34 100.0%	42 100.0%	76 100.0%

Table 4. The relationship between variables and the concordance between biopsy and the gold-standard

Variable	Category	Incorrect (count, %)	Correct (count, %)	p-value
Calcification size	<10 mm 10-20 mm >20 mm	0 (0.0%) 4 (50.0%) 4 (50.0%)	36 (52.9%) 12 (17.6%) 20 (29.4%)	0.004
Number of samples	<5 5-10 >10	1 (12.5%) 4 (50.0%) 3 (37.5%)	22 (32.4%) 41 (60.3%) 5 (7.4%)	0.034
Specimen calcification	Present Absent	5 (62.5%) 3 (37.5%)	41 (60.3%) 27 (39.7%)	1.000
Pathology calcification	Present Absent	2 (25.0%) 6 (75.0%)	32 (47.1%) 36 (52.9%)	0.285

Table 5. The relationship between calcification morphology, distribution, and BI-RADS category with the gold-standard pathology result

Variable	Category	Malignant (count, %)	Benign (count, %)	p-value
Distribution	Diffuse Regional Segmental Linear Grouped	0 (0.0%) 13 (46.4%) 3 (10%) 5 (17.9%) 7 (25.0%)	0 (0.0%) 10 (20.8%) 1 (2.1%) 2 (4.2%) 35 (72.9%)	<0.001
Morphology	Coarse Amorphous Pleomorphic Fine linear	0 (0.0%) 0 (0.0%) 10 (35.7%) 18 (64.3%)	17 (35.4%) 20 (41.7%) 6 (12.5%) 5 (10.4%)	<0.001
BI-RADS	4A 4B 4C 5	0 (0.0%) 0 (0.0%) 22 (78.6%) 6 (21.4%)	21 (43.8%) 14 (29.2%) 13 (27.1%) 0 (0.0%)	<0.001

BI-RADS: Breast imaging reporting and data system

Discussion

Suspicious MCs detected on mammography are an important indicator in the diagnosis of early-stage breast cancer. In this study, the diagnostic performance of coaxial CNB results for BI-RADS 4-5 MCs detected on mammography was compared. The biopsy procedure, with its high specificity and PPV, is considered the gold-standard diagnostic method. In addition, the morphological and distributional characteristics of the MCs were statistically evaluated for correlation with pathological findings. This study demonstrated that coaxial needle CNB, performed under mammographic guidance, is a highly specific technique with strong clinical reliability.

VAB is recommended for the diagnosis of suspicious MCs, given its high diagnostic accuracy[8]. In the study by Göksu et al.[13] pathology results among 53 patients with BI-RADS 3-4 MCs detected on mammography revealed 47 benign and 6 premalignant or *in situ* lesions. A total of 89% of the MCs were reported as benign; two cases developed procedure-related complications[13]. In the study by Thakkar et al.[14] VAB results showed 100% specificity, 96% sensitivity, and a high NPV. Histopathologically, 42% of the lesions sampled by VAB were malignant and 58% were benign. A hematoma developed in 42 patients, but no other major complications were reported[14]. In the meta-analysis conducted by Yu et al.[15] which included 21 studies, the sensitivity and specificity of VAB were reported as 98% and 99%, respectively.

When CNB and VAB are compared in patients diagnosed with ADH and DCIS, the underdiagnosis rate is lower with VAB[8]. The rates of false negatives and radiologic-pathologic discordance are also lower for VAB than for CNB[8]. However,

stereotactic CNB requires a larger number of samples to achieve diagnostic accuracy[15]. Nevertheless, due to the high cost of the VAB unit and vacuum biopsy needles, access remains limited in many centers. In addition, because larger tissue samples are obtained, the risk of complications is higher and regional structural distortion may occur[13].

In our study, the sensitivity of the biopsy procedure was found to be 71.4%, while its specificity was 100%. The PPV was 100%, and the NPV was 85.7%. Therefore, biopsy provides diagnostic certainty when it yields a positive result, as it is considered the gold-standard. However, some malignant cases were not detected by biopsy, suggesting the possibility of false negatives due to sampling error, particularly in cases with MCs. The Kappa value of 0.759 obtained for biopsy results indicates strong agreement between biopsy results and the gold-standard diagnosis.

In cases with MC sizes between 10 and 20 mm or greater than 20 mm, and in cases where 10 or more tissue samples were obtained, the false-negative rate of the biopsy procedure was higher. These findings suggest that although more biopsy samples are taken in cases with more extensive calcifications, the accuracy of the procedure tends to decrease. The procedure achieved a higher success rate for more localized MCs (<10 mm). With respect to the number of samples, the best performance was observed in the group in which 5-10 cores were collected. However, the optimal number of samples required for a reliable histopathological diagnosis remains a matter of debate.

The detection of calcifications in the specimen and on pathology was not significantly associated with the diagnostic accuracy of the biopsy. No procedural complications were observed, and potential complications were similar to those seen with ultrasound-guided core needle biopsy. Compared with VAB, the cost of the procedure is considerably lower. It can be performed at any center equipped with a mammography unit. Since the procedure is performed using a coaxial needle, there is no risk of tissue seeding.

In our study, the distribution of MCs showed that malignant cases were significantly more likely to have a segmental distribution, whereas benign cases were more likely to exhibit a grouped distribution. With respect to MC morphology, coarse and amorphous calcifications were significantly associated with benignity, whereas pleomorphic and particularly fine linear calcifications were significantly associated with malignancy. Similarly, in the study conducted by Rizuana et al.[16] fine linear or branching, pleomorphic, and heterogeneous microcalcification morphologies, as well as segmental, regional, and linear distributions, were shown to be associated with a higher risk of DCIS. Moreover, heterogeneous calcifications with regional distribution were linked to an increased risk of invasive carcinoma[16]. In our study, no calcifications were found in the diffuse category. Diffuse calcifications are most commonly associated with mastopathy.

The rate of BI-RADS categories 4C and 5 was significantly higher in malignant cases. In our study, a higher BI-RADS score and the presence of segmental, fine linear, and fine pleomorphic MCs on mammography were associated with malignancy. According to the BI-RADS classification, fine linear branching calcifications on mammography have a 70% PPV for malignancy, and fine pleomorphic MCs are considered a high-risk feature. Çetin Tunçez et al.[17] reported that morphological and distributional features of MCs are associated with DCIS, consistent with our findings.

Study Limitations

The main limitation of our study is that it is retrospective and conducted at a single center. Studies involving larger patient groups with longer follow-up periods will enable more accurate and reliable analyses.

Conclusion

Our study showed that stereotactic CNB has high specificity and PPV but relatively low sensitivity in the evaluation of BI-RADS 4 and 5 MCs, and that it is an effective, low-cost diagnostic method that can be used in daily clinical practice.

Ethics

Ethics Committee Approval: Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval no: 0183, date: 25.04.2024).

Informed Consent: Before the biopsy, all patients were informed about the procedure and provided written informed consent.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Rising Incidence of Incidental Appendiceal Neoplasms and Complicated Appendicitis in the Geriatric Population: Predictive Performance of the HALP Score and the Systemic Immune-inflammation Index (SIII)

Geriatrik Popülasyonda İnsidental Apendiks Neoplazmlarının ve Komplike Apandisitin Artan İnsidansı: HALP Skorunun ve Sistemik İmmün-inflamasyon İndeksinin (SIII) Prediktif Performansı

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Abstract

Objective: To assess the frequency and predictive performance of clinicopathological factors associated with for incidental appendiceal neoplasms and complicated appendicitis in the geriatric population.

Methods: Adult appendectomy cases (≥18 years) performed from 2016 to 2024 were retrospectively reviewed. Age-based grouping classified patients as non-geriatric (18-64 years) or geriatric (≥65 years). Demographic data, laboratory findings, appendicitis type, and histopathology were recorded.

Results: Of the 859 patients, 16.3% were geriatric. Complicated appendicitis occured at a higher rate in geriatric group (31.1% vs. 12.5%; p<0.001). Incidental neoplasms were identified in 29 of 859 patients (3.4%). Detection was markedly more frequent in the ≥65 age group (15.0%) than in younger patients (1.1%; p<0.001). Malignant tumors accounted for 4.3% of cases in older patients, compared with 0.6% in the younger group (p=0.002). Age was independently associated with the presence of neoplasm (p<0.001). Receiver operating characteristic analysis supported an age threshold of 61 years, with an area under the curve of 0.87 (sensitivity, 79.3%; specificity, 83.1%).

Conclusion: Advanced age increases the risk of neoplasia and of a complicated clinical course in acute appendicitis. Clinical decisions should be individualized by taking into account age, clinical and radiological findings, and multiple inflammatory markers.

Keywords: Acute appendicitis, geriatric population, appendiceal neoplasms, complicated appendicitis

Öz

Amaç: Geriatrik popülasyonda tesadüfi apendiks neoplazileri ve komplike apandisit için klinikopatolojik parametrelerin sıklığını ve öngörü değerini değerlendirmek.

Yöntem: 2016-2024 yılları arasında bir üçüncü basamak sağlık merkezinde apendektomi uygulanan ≥18 yaş hastalar retrospektif olarak incelendi. Hastalar geriatrik olmayan (18-64 yaş) ve geriatrik (≥65 yaş) olmak üzere iki gruba ayrıldı. Demografik veriler, laboratuvar bulguları, apandisit tipi ve histopatoloji sonuçları kaydedildi.

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Öz

Bulgular: Toplam 859 hastanın %16,3'ü geriatrikti. Komplike apandisit, geriatrik grupta daha sık görüldü (%31,1'e karşı %12,5; p<0,001). Genel neoplazi oranı %3,4 (29/859) olup geriatrik hastalarda anlamlı derecede yüksekti (%15,0'a karşı %1,1; p<0,001). Malignite oranları ise sırasıyla %4,3 ve %0,6 idi (p=0,002). Yaş, neoplazi varlığı ile bağımsız olarak ilişkili bulundu (p<0,001). Alıcı işletim karakteristiği analizinde optimal eşik değer 61 yaş olarak hesaplandı (eğri altında kalan alan: 0,87, duyarlılık: %79,3, özgüllük: %83,1).

Sonuç: İleri yaş, akut apandisitte neoplazi ve komplike seyir riskini artırmaktadır. Klinik kararlar; yaş, klinik ve radyolojik bulgular ile birden fazla inflamatuvar belirteç birlikte değerlendirilerek bireyselleştirilmelidir.

Anahtar Kelimeler: Akut apandisit, geriatrik popülasyon, apendiks neoplazm, komplike apandisit

Introduction

Appendiceal neoplasms (AN) are rare entities, with a substantial proportion diagnosed incidentally during routine histopathological examination following appendectomy[1]. They account for less than 0.5% of all gastrointestinal malignancies and have historically been reported in approximately 1% of appendectomy specimens[2]. However, recent reports describe higher detection rates of AN, likely influenced by more comprehensive pathological examination of resected specimens[3-5].

ANs encompass a wide histopathological spectrum, including well-differentiated neuroendocrine tumors (NETs), low- and high-grade mucinous neoplasms, and adenocarcinomas[3]. While NETs predominantly occur in younger individuals and tend to be small and localized, mucinous neoplasms and adenocarcinomas are more common in older populations and may exhibit a more aggressive clinical course[4].

The clinical presentation of ANs is often non-specific; patients usually have either classic symptoms of acute appendicitis or non-specific abdominal pain. Therefore, even in routine cases of appendicitis, a meticulous histopathological assessment is essential to detect underlying malignancies[5]. The incidence of ANs increases with age, particularly in patients over 50 presenting with appendicitis[3,4]. Furthermore, the increasing adoption of non-operative management strategies for appendicitis raises additional concerns regarding the risk of missed occult neoplasms[5].

The limited availability of reliable clinical markers other than age and imaging findings has increased interest in hematological and biochemical composite indicators. In this context, parameters such as the hemoglobin, albumin, lymphocytes, platelets (HALP) score and the systemic immune-inflammation index (SIII) are valuable in predicting complications and prognosis in gastrointestinal tract tumors. Lower HALP scores are thought to indicate compromised nutritional reserve alongside systemic inflammation, and have been correlated with poorer prognosis[6,7]. Nonetheless, the clinical utility of these indices in ANs remains poorly defined. Particularly in the elderly, these biomarkers may facilitate earlier recognition of ANs and their aggressive subtypes.

In this study, we explored the occurrence and pathological spectrum of incidental appendiceal tumors among elderly individuals and examined whether HALP and SII provide meaningful predictive information in this setting.

Materials and Methods

This retrospective cohort comprised adult patients who were treated with appendectomy between 2016 and 2024 at the Department of General Surgery, Aydın Adnan Menderes University. Eligibility was restricted to individuals aged 18 years or above. Only cases with confirmed histopathological findings were analyzed, while negative appendectomy specimens were excluded. For comparative analysis, participants were stratified by age into non-geriatric (18-64 years) and geriatric (≥65 years) categories.

Demographic characteristics (age, sex), laboratory parameters [white blood cell count, neutrophils, lymphocytes, platelets, C-reactive protein (CRP), hemoglobin, albumin], histopathological findings, the type of appendicitis (complicated or uncomplicated), and the presence and subtypes of neoplasms were retrospectively retrieved from hospital records and patient charts.

The following formula was used for biomarker calculation: HALP score=hemoglobin (g/L)×albumin (g/L)×lymphocyte count ($\times 10^9$/L)÷platelet count ($\times 10^9$/L). SIII=neutrophil count ($\times 10^9$/L)×platelet count ($\times 10^9$/L)÷lymphocyte count ($\times 10^9$/L). Appendicitis was classified as complicated when perforation, abscess formation, or gangrene were identified.

The research ethics approval was obtained from the Ethical Review Board of the Aydın Adnan Menderes University

Ethical Committee (approval no: 2025/284, date: 02.10.2025). The study was performed in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants for the use of their clinical data and protected health information.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics (26.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous data are reported as mean ± standard deviation when normally distributed, and as median (range) otherwise. Categorical variables are presented as numbers and percentages. Between-group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables, and Student's t-test or the Mann-Whitney U test for continuous variables, depending on the distribution. Predictor candidates that showed significance in univariate testing and were deemed clinically meaningful were examined using receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) estimates reported. Where applicable, effect sizes are provided alongside 95% confidence intervals (CIs). The optimal cut-off value was selected based on the Youden index. A p-value of <0.05 was considered statistically significant in all analyses.

Results

Between 2016 and 2024, 870 appendectomies were performed at our tertiary referral center. Histopathological analysis revealed negative appendectomies in 11 cases (1.3%), with comparable rates between groups (p=0.1703). After excluding these cases, the final cohort consisted of 859 patients: 140 (16.3%) were geriatric and 719 (83.7%) were non-geriatric. The overall mean age was 43.6 years. The mean age in the geriatric group was 71.7 years (65-91), while it was 38.1 years (18-62) in the non-geriatric group. In the overall cohort, men accounted for 56.2% and women for 43.8%. The incidence of complicated appendicitis was more often in the geriatric group (31.1%) than the non-geriatric group (12.5%) (p<0.0001). The overall incidence of incidental AN was 3.4% (29/859). Among these, 65.5% (n=19) were benign and 34.5% (n=10) were malignant. Incidental neoplasms were more often detected in geriatric group (15.0%) than in non-geriatric group (1.1%) (p<0.0001). Malignant tumors were detected in 1.2% of the total cohort and was more common in geriatric group (4.3%) than in non-geriatric group (0.6%) (p=0.002). Among the 29 patients diagnosed with neoplasms, the most common neoplasm was low-grade appendiceal mucinous neoplasm (LAMN), accounting for 41.4%. In both age groups, LAMN was the most frequent benign subtype, whereas NET was the most common malignant subtype (Table 1).

Logistic regression,advancing age was independently associated with AN [odds ratio (OR)=1.09, 95% CI: 1.06-1.12; p<0.001]. Age showed substantial discriminative ability for neoplasm detection in ROC analysis (AUC: 0.87). An age threshold of 61 years provided optimal discrimination (sensitivity 79.3% and specificity 83.1%) (Figure 1). Figure 2 displays the age distribution of patients diagnosed with incidental neoplasms.

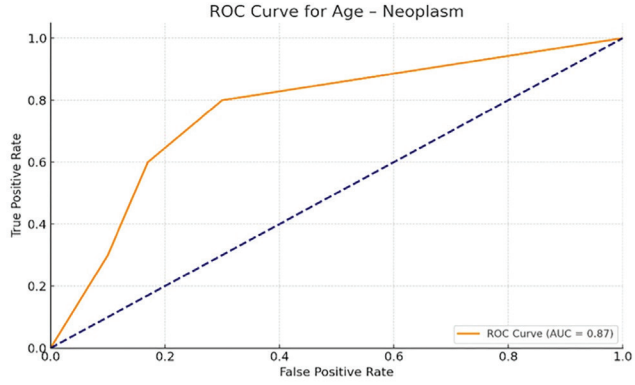

Figure 1. Receiver operating characteristic (ROC) curve illustrating the diagnostic performance of age for predicting neoplasm. The area under the curve (AUC) indicates age's discriminatory ability to distinguish between patients with and without neoplasm

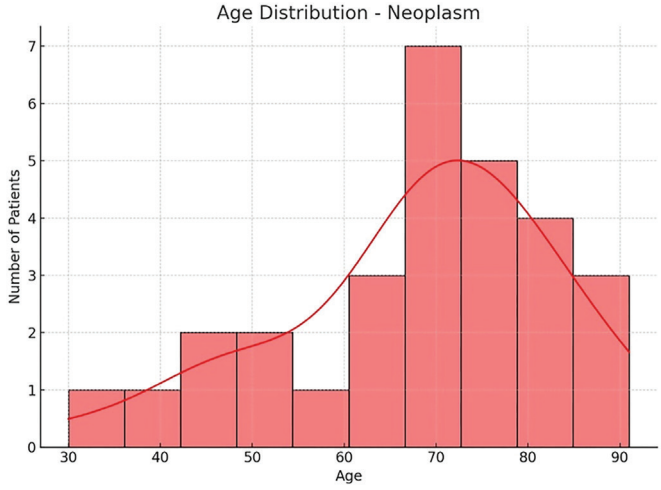

Figure 2. Age distribution among patients with appendiceal neoplasm. Histogram showing the frequency of patients according to age groups

Among geriatric patients, inflammatory markers differed significantly between complicated and uncomplicated appendicitis. CRP, neutrophil count, and SII values were higher in patients with complicated appendicitis (p<0.001, p=0.047, and p=0.008, respectively). Conversely, HALP scores were lower in complicated cases (p=0.007) (Table 2). ROC analysis was performed to evaluate how well laboratory parameters discriminated complicated appendicitis. CRP emerged as the most powerful biomarker (AUC: 0.748, p<0.001), demonstrating good discriminative ability. SII showed a moderate diagnostic performance (AUC: 0.652, p<0.001). In contrast, the HALP score (AUC: 0.345, p=0.814) exhibited poor diagnostic accuracy, limiting its utility as an independent clinical predictor (Table 3). The ROC curves for complicated vs. non-complicated cases in the geriatric group are displayed in Figure 3. In the ROC curve analysis to predict the presence of a neoplasm, none of the parameters showed significant discrimination (p>0.05).

Discussion

Although incidental ANs are rare in patients undergoing appendectomy for acute appendicitis, they hold substantial clinical significance. In most cases, the diagnosis is not anticipated preoperatively and is instead made through postoperative histopathological analysis. Earlier reports was reported AN incidence rates ranging from 0.5% to 2.5%[8-10]. However, the incidence has been reported to be higher in current studies than in previous literature. Dohner et al.[11] reported a 3.7% rate of neoplasms in a retrospective single-center study, while Gómez Báez et al.[12] reported a 3.2% rate. Our study was consistent with this pattern and detected neoplasms at a rate of 3.4%.

The presence of incidental ANs in elderly patients has been a matter of long-standing debate in the literature. Advanced age represents a significant predisposing factor for underlying neoplasia in patients presenting with acute appendicitis. Numerous recent chorts have demonstrated a marked rise in the likelihood of tumor detection with advancing age[8,13-18]. Fransvea et al.[19] reported neoplasia rates of 13% among individuals over 40 years, compared to only 3.8% in those under 30. Our findings align with this evidence, revealing a significantly higher rate of neoplasms in the geriatric group (15.0% vs. 1.1%, p<0.0001). Malignancy was more frequent in the elderly (4.3% vs. 0.6%, p=0.002). Higher age corresponded

Table 1. Baseline characteristics and histopathological diagnoses

	All, n (%)	Geriatric, n (%)	Non-geriatric, n (%)	p-value
Number	859	140	719	
Negative appendectomy	11 (1.3%)	4 (2.8%)	7 (1.0%)	0.17
Age				
Mean ± SD	43.6±16.4	71.7±6.9	38.1±11.3	
Median	40 (18-91)	70.0 (65-91)	36.0 (18-62)	
Sex				
Male	489 (56.2%)	72 (50.3%)	417 (57.4%)	0.146
Female	381 (43.8%)	71 (49.7%)	310 (47.6%)	
Non-complicated	704 (84.8%)	82 (68.9%)	622 (87.5%)	<0.001
Complicated	126 (15.2%)	37 (31.1%)	89 (12.5%)	
Incidental neoplasm	29 (3.4%)	21 (15%)	8 (1.1%)	<0.001
Benign	19 (2.2%)	15 (10.7%)	4 (0.5%)	<0.001
Malign	10 (1.2%)	6 (4.3%)	4 (0.6%)	0.002
Histology of neoplasms				
LAMN	12 (41.4%)	8 (38.1%)	4 (50.0%)	
Serrated adenoma	6 (20.7%)	6 (28.6%)	0 (0.0%)	
Hyperplastic polyp	1 (3.4%)	1 (4.8%)	0 (0.0%)	
NET	4 (13.8%)	2 (9.5%)	2 (25.0%)	
Adenocarcinoma	3 (10.3%)	2 (9.5%)	1 (12.5%)	
Mucinous adenocarcinoma	2 (6.9%)	1 (4.8%)	1 (12.5%)	
Signet-ring cell carcinoma	1 (3.4%)	1 (4.8%)	0 (0.0%)	

LAMN: Low-grade appendiceal mucinous neoplasm, NET: Neuroendocrine tumor, SD: Standard deviation

to greater odds of neoplasia (OR=1.09; 95% CI: 1.06-1.12; p<0.001), and ROC analysis confirmed a strong discriminative performance (AUC: 0.87), with 61 years identified as the optimal cut-off. These findings highlight the need to keep underlying neoplasia in elderly patients presenting with acute appendicitis. Even in available literature supporting non-operative approaches, the risk of missed malignancy ranges from 0.7% to 2.5%[11]. In patients aged ≥65 managed conservatively, this incidence was reported to reach 3.9%[17]. Therefore, the diagnostic and therapeutic advantages of appendectomy should be strongly considered, especially in geriatric patients and in those with high clinical and imaging suspicion. Notably, our data showed that the rate of negative appendectomy did not increase in elderly patients (p=0.1703), suggesting that concerns about "unnecessary surgery" in this population may be overstated. Conversely, diagnostic delays may pose greater risks, including disease complications and undetected malignancy.

AN exhibit a broad histopathological spectrum. LAMNs a are frequently encountered among benign or premalignant neoplasms, whereas NETs are most prevalent among malignant types[8,20-23]. Consistent with the literature, our series showed that the majority of benign and premalignant neoplasms were LAMNs, whereas NETs and adenocarcinomas were the most common malignant subtypes. Although our data and prior reports indicate that a significant portion of ANs are low-grade or have limited malignant potential, the risk of invasive cancer should not be underestimated.

Table 2. Comparison of biomarkers in complicated vs. non-complicated acute appendicitis in geriatric patients

Parameter	Complicated	Non-complicated	p-value
White blood cell count (×10³/µL)			
Mean ± SD	14.45 (6.66)	12.43 (4.58)	0.056
Median (min-max)	13.14 (2.82-31.47)	11.66 (4.57-24.27)	
Neutrophil count (×10³/µL)			
Mean ± SD	12.33 (6.29)	9.93 (4.47)	0.047
Median (min-max)	11.31 (2.21-29.99)	9.23 (2.73-21.55)	
Lymphocyte count (×10³/µL)			
Mean ± SD	1.31 (0.65)	1.55 (0.87)	0.319
Median (min-max)	1.21 (0.21-2.56)	1.38 (0.43-5.30)	
Platelet count (×10³/µL)			
Mean ± SD	280.05 (96.99)	247.70 (79.01)	0.067
Median (min-max)	254.00 (144.00-640.00)	231.50 (100.00-519.00)	
C-reactive protein (mg/L)			
Mean ± SD	178.90 (94.66)	91.76 (89.02)	<0.001
Median (min-max)	178.00 (2.00-332.70)	63.00 (2.00-363.19)	
Albumin (g/L)			
Mean ± SD	36.72 (4.79)	37.91 (5.13)	0.15
Median (min-max)	37.00 (26.90-45.00)	38.20 (22.00-49.00)	
Hemoglobin (g/dL)			
Mean ± SD	12.13 (1.93)	12.73 (1.73)	0.094
Median (min-max)	12.00 (7.80-16.10)	12.70 (7.00-15.80)	
SII			
Mean ± SD	3010.08 (2204.25)	2102.77 (1728.87)	0.008
Median (min-max)	2312.43 (430.81-9617.48)	1635.22 (164.63-9222.72)	
HALP score			
Mean ± SD	22.1 (12.9)	33.1 (21.7)	0.007
Median (min-max)	20.8 (3.7-51.1)	28.0 (4.7-104.2)	

HALP score: Hemoglobin (g/L)×albumin (g/L)×lymphocyte count (×10⁹/L)÷platelet count (×10⁹/L), SII: Systemic immune-inflammation index: neutrophil count (×10⁹/L)×platelet count (×10⁹/L)÷lymphocyte count (×10⁹/L), SD: Standard deviation

Table 3. ROC curve analysis of biomarkers for predicting the difference between complicated and non-complicated acute appendicitis in geriatric patients

Parameter	AUC (95% CI)	Cut-off	Sensitivity	Specificity	PPV	NPV	p-value
C-reactive protein (mg/L)	0.748 (0.639-0.838)	>147.2	70.3% (54.2-82.5)	75.6% (65.3-83.6)	56.5% (42.2-69.8)	84.9% (75.0-91.4)	<0.001
White blood cell	0.588 (0.471-0.695)	>12.4	67.6% (51.5-80.4)	56.1% (45.3-66.3)	41% (29.5-53.5)	79.3% (67.2-87.7)	0.067
Neutrophil count ($\times10^3/\mu L$)	0.614 (0.499-0.723)	>9.13	75.7% (59.9-86.6)	48.8% (38.3-59.4)	40.0% (29.3-51.7)	81.6% (68.6-90.0)	0.027
Platelet	0.605 (0.494-0.707)	>227.0	81.1% (65.8-90.5)	47.6% (37.1-58.2)	41.1% 30.5-52.6)	84.8% (71.8-92.4)	0.03
SII	0.652 (0.557-0.746)	>1394.0	86.5% (72.0-94.1)	45.1% (34.8-55.9)	41.6% (31.2-52.7)	88.1% (75.0-94.8)	<0.001
HALP score	0.345 (0.246-0.456)	<19.3	84.2% (62.4-94.5)	20.0% (10.5-34.8)	33.3% (21.7-47.5)	72.7% (43.4-90.3)	0.814

Cut-off values were determined according to the Youden index

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, HALP score: Hemoglobin (g/L)×albumin (g/L)×lymphocyte count ($\times10^9$/L)÷platelet count ($\times10^9$/L), SII: Systemic immune-inflammation index: neutrophil count ($\times10^9$/L)×platelet count ($\times10^9$/L)÷lymphocyte count ($\times10^9$/L)

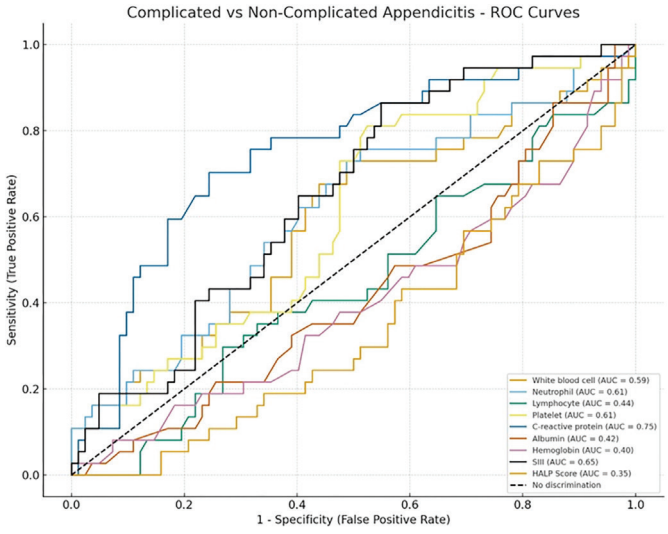

Figure 3. Receiver operating characteristic (ROC) curves of biomarkers for predicting complicated and non-complicated acute appendicitis in geriatric patients. The area under the curve (AUC) indicates the ability of these biomarkers to discriminate between the two patient groups

SII: Systemic immune-inflammation index, HALP: Hemoglobin, albumin, lymphocytes, platelets

In acute appendicitis, CRP has long been used as a marker associated with disease severity[19]. Recently, additional indices, including SIII and HALP scores, were evaluated in this context[24,25]. In our study, the incidence of complicated appendicitis was higher in geriatric patients than in non-geriatric patients (31.1% vs. 12.5%; p<0.0001). Among geriatric patients with complicated appendicitis, CRP, neutrophil count, and SIII values were higher than in uncomplicated cases (p<0.001, p=0.0479, and p=0.0083, respectively). The HALP score was notably lower (p=0.007). In ROC analysis, CRP demonstrated the strongest diagnostic performance (AUC: 0.744; p<0.001). SIII (AUC: 0.672; p=0.007) demonstrated moderate discriminatory ability. Although complicated cases were characterized by lower HALP scores (p=0.007), the ROC performance was limited (AUC: 0.339; p=0.0028). These results support the use of combined inflammatory markers rather than reliance on a single parameter to improve clinical accuracy. However, none of the biomarkers studied exhibited significant predictive value for AN (p>0.05).

Study Limitations

A number of limitations should be acknowledged. Most notably, the retrospective, single-center nature of the study may have increased the risk of selection bias. In addition, changes in pathology sampling protocols and reporting standards between 2010 and 2024 may have caused measurement inconsistencies. The absence of long-term oncologic outcomes limits the interpretation of prognostic implications.

Acute appendicitis in elderly patients may exhibit distinct biological behavior. Age should be recognized as a major

determinant of AN. Each case of appendicitis in an elderly patient must be approached as a potential neoplasm, with surgical and follow-up strategies tailored accordingly. Therefore, in elderly patients with diagnostic uncertainty, early surgical intervention should be strongly considered. This approach will facilitate the timely diagnosis of potentially occult neoplasms. Our findings, consistent with the current literature, support a more aggressive approach to the management of acute appendicitis in elderly individuals. Considering that the histopathological spectrum of ANs mostly consists of lesions with a better prognosis, appendectomy may provide adequate treatment in many cases. However, the need for additional oncologic treatment is more likely in the geriatric population.

Conclusion

Both our data and the current literature indicate that the likelihood of neoplasia and complicated disease is markedly higher among elderly patients with acute appendicitis. Management strategies should be planned, taking this reality into account. Even when considering non-operative approaches, the potential for underlying malignancy must be carefully assessed. Personalized treatment decisions should incorporate patient age, clinical and radiological findings, and laboratory profiles. Prospective multicenter cohorts are warranted to strengthen clinical decision-making algorithms.

Ethics

Ethics Committee Approval: The research ethics approval was obtained from the Ethical Review Board of the Aydın Adnan Menderes University Ethical Committee (approval no: 2025/284, date: 02.10.2025).

Informed Consent: Written informed consent was obtained from all participants for the use of their clinical data and protected health information.

Footnotes

Authorship Contributions

Surgical and Medical Practises: O.A., E.B.C., M.Ç.C., S.A., A.E., Concept: O.A., E.B.C., Design: O.A., Data Collection or Processing: O.A., E.B.C., M.Ç.C., S.A., A.E., Analysis or Interpretation: E.B.C., M.Ç.C., S.A., A.E., Literature Search: O.A., M.Ç.C., S.A., A.E., Writing: O.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Benign Breast Disorders in Levonorgestrel-releasing Intrauterine Device Users: Evidence from a Prospective Cohort Study

Levonorgestrel Salınımlı Rahim İçi Araç Kullanımında Benign Meme Bozuklukları: Prospektif Kohort Çalışması

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Abstract

Objective: This study aimed to evaluate the incidence of benign breast disorders in women using levonorgestrel-releasing intrauterine devices (LNG-IUD) and to assess the relationship between duration of use and these outcomes.

Methods: A prospective observational cohort study was conducted at a tertiary care center. The study included premenopausal women aged 18 years or older who had used an LNG-IUD for at least 12 months. Breast imaging was performed using standard ultrasonography. Lesions were classified according to the breast imaging reporting and data system. The primary outcome was the presence of benign breast diseases, including simple cysts, fibroadenomas, and fibrocystic changes.

Results: Eighty women with a mean age of 47.2±4.4 years and a mean body mass index (BMI) of 28.1±3.9 kg/m^2 were included in the study. Benign breast abnormalities were found in 57 women (71.2%); among these, the majority (61.3%) were simple cysts, followed by fibrocystic changes (15.0%) and fibroadenomas (1.3%). Women with benign outcomes had lower baseline hemoglobin levels than those without benign outcomes (12.4 vs. 13.1 g/dL, p=0.018). No significant differences were observed in age, BMI, or number of births. In multivariate logistic regression, LNG-IUD duration was not significantly associated with benign outcomes (adjusted odds ratio=0.44, 95% confidence interval: 0.12-1.57).

Conclusion: Benign breast complications are common among women using LNG-IUDs and are not affected by duration of device use. These findings support the safety profile of LNG-IUDs with respect to benign breast health and may help clinicians provide reassurance during contraceptive counseling.

Keywords: Levonorgestrel-releasing intrauterine device (LNG-IUD), Mirena®, benign breast disorders, breast cysts, fibrocystic breast disease

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Öz

Amaç: Bu çalışmanın amacı, levonorgestrel salan rahim içi araç (LNG-IUD) kullanan kadınlarda benign meme hastalıklarının insidansını değerlendirmek ve cihaz kullanım süresi ile klinik sonuçlar arasındaki ilişkiyi incelemektir.

Yöntem: Bu prospektif, gözlemsel kohort çalışması üçüncü basamak bir sağlık merkezinde yürütülmüştür. Çalışmaya, en az 12 aydır LNG-IUD kullanan, 18 yaş ve üzeri premenopozal kadınlar dahil edilmiştir. Meme görüntülemesi standart ultrasonografi yöntemiyle gerçekleştirilmiş ve saptanan lezyonlar meme görüntüleme raporlama ve veri sistemine göre sınıflandırılmıştır. Birincil sonlanım noktası, basit kistler, fibroadenomlar ve fibrokistik değişiklikleri içeren benign meme hastalıklarının varlığı olarak belirlenmiştir.

Bulgular: Çalışmaya ortalama yaşı 47,2±4,4 yıl ve ortalama vücut kitle indeksi (VKİ) 28,1±3,9 kg/m^2 olan toplam 80 kadın dahil edilmiştir. Katılımcıların 57'sinde (%71,2) benign meme bulguları saptanmıştır. Bu bulguların çoğunu basit kistler (%61,3) oluştururken, bunu fibrokistik değişiklikler (%15,0) ve fibroadenomlar (%1,3) izlemiştir. Benign meme bulguları saptanan kadınlarda başlangıç hemoglobin düzeylerinin, benign bulgusu olmayanlara kıyasla daha düşük olduğu görülmüştür (12,4'e karşı 13,1 g/dL; p=0,018). Yaş, VKİ ve doğum sayısı açısından gruplar arasında anlamlı fark saptanmamıştır. Çok değişkenli lojistik regresyon analizinde, LNG-IUD kullanım süresi ile benign meme bulguları arasında anlamlı bir ilişki bulunmamıştır (düzeltilmiş olasılık oranı=0,44; %95 güven aralığı: 0,12-1,57).

Sonuç: LNG-IUD kullanan kadınlarda benign meme bulguları sık görülmekte olup bu durum cihazın kullanım süresinden etkilenmemektedir. Bu bulgular, LNG-IUD'lerin benign meme sağlığı açısından güvenli profilini desteklemekte ve kontraseptif danışmanlık sırasında klinisyenlerin hastalara güven verici bilgi sunmasına katkı sağlayabilir.

Anahtar Kelimeler: Levonorgestrel salan rahim içi araç (LNG-IUD), Mirena®, benign meme hastalıkları, meme kistleri, fibrokistik meme hastalığı

Introduction

Levonorgestrel-releasing intrauterine devices [LNG-IUD, (Mirena®)] are one of the effective, long-acting, reversible contraceptive methods widely preferred not only for pregnancy prevention but also for the management of non-contraceptive indications such as excessive menstrual bleeding, endometrial hyperplasia, and dysmenorrhea[1]. Alongside increasing clinical use, the safety profile of LNG-IUDs has been extensively evaluated, particularly with respect to reproductive health outcomes. However, potential breast-related effects, common in women approaching perimenopause, remain an important area for discussion in clinical counseling.

Most current literature focuses on the possible association between LNG-IUD use and breast cancer risk. A large-scale Danish group study revealed a small rise in the rate of breast cancer in females utilising modern hormonal contraceptives, including LNG-IUDs[2]. Also, Yi et al.[3] similarly reported a slight increase in breast cancer risk in a nationally conducted Asian cohort study. However, there is no complete consensus on these findings in the literature, with systematic reviews and meta-analyses providing different results. While some studies suggest a low-level increase in risk, others have found no significant link between using an LNG-IUD and developing breast cancer[4,5]. In accordance with the current evidence, it should be noted that the absolute increase in malignancy risk is minimal, and this risk should be considered alongside the high contraceptive efficacy and substantial non-contraceptive clinical benefits of the LNG-IUD (American College of Obstetricians and Gynecologists)[6].

In contrast, the relationship between LNG-IUD use and benign breast diseases has received relatively limited attention in the literature. However, this concern, frequently encountered in clinical practice, leads to significant uncertainties in patient counseling and is not adequately represented in research focusing on contraceptive safety. Benign breast lesions such as simple cysts, fibrocystic changes, and fibroadenomas are commonly found in both premenopausal and perimenopausal women[7]. Although these lesions generally show a low risk of malignancy, their detection often increases patient anxiety, necessitates additional imaging, and complicates the contraceptive counseling process. Furthermore, benign breast diseases are not a homogeneous group; non-proliferative lesions are generally considered to have a minimal or negligible risk of subsequent breast cancer, while atypical proliferative lesions are known to indicate a significant increase in long-term breast cancer risk[8,9].

The biological significance of hormonal effects on benign breast pathologies also requires further investigation. Depending on dose, receptor expression, and systemic exposure levels, progesterone and synthetic progestins have been shown to modulate breast epithelial proliferation and stromal structure[10,11]. The local effect of LNG-IUDs with lower systemic hormone levels compared to oral or injectable hormonal contraceptives suggests that their potential effects

on benign breast outcomes may differ; however, evidence supporting this hypothesis is still limited[12].

This study aimed to prospectively evaluate benign breast findings in patients using LNG-IUDs, drawing on existing literature and employing standardized imaging protocols. Although the study did not include pre-treatment breast assessments and a control group not using LNG-IUDs, the research aimed to provide clinically significant prevalence data, to investigate possible associations between duration of LNG-IUD use and benign breast findings, and to lay the groundwork for more evidence-based contraceptive counseling.

Materials and Methods

Study Design, Setting, and Ethical Considerations

This prospective observational cohort study was conducted at the Obstetrics and Gynecology Department of University of Health Sciences Türkiye, Kayseri City Hospital. University of Health Sciences Türkiye, Kayseri City Hospital is a tertiary referral center serving a large urban and semi-urban population, providing routine contraceptive counseling, intrauterine device insertion, and long-term follow-up services.

The study protocol was approved by the University of Health Sciences Türkiye, Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 492, date: 08.07.2025). Prior to involvement in the study, written informed consent was obtained from all participants. All participants provided written consent for the use of anonymized data in scientific publications. The research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants

Inclusion criteria for the study were premenopausal women aged 18 years or older who had been using a LNG-IUD; (Bayer Healthcare, Germany) continuously for at least 12 months. The LNG-IUD was implanted either for contraception or for benign gynecological indications such as excessive menstrual bleeding, dysmenorrhea, or endometrial protection during hormone therapy. Individuals with a prior diagnosis of breast or gynecological malignancy, a history of breast surgery that could affect the interpretation of breast imaging, or a known hereditary predisposition to breast cancer, including BRCA1/2 mutations, were excluded. Additionally, women with incomplete medical records or who refused to undergo breast imaging were excluded. Eligible participants were identified through the hospital's electronic contraceptive registry system and verified during gynecology outpatient visits.

Sample size calculations were performed using G*Power software (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany) to ensure sufficient statistical power. The analysis assumed a moderate effect size (Cohen's d =0.5), a 5% significance level (α=0.05), and 80% statistical power. Based on this calculation, a minimum of 64 participants (32 per group) were needed. To account for potential missing data and loss to follow-up, the target sample size was set at 80 women.

Data Collection

Data were obtained from the hospital's electronic health record system and supplemented by structured clinical interviews during follow-up. Demographic variables included age at the time of LNG-IUD placement, parity, marital status, and education level. Clinical features included indication for LNG-IUD use, duration of device retention in the uterus, other medical conditions, and relevant gynecological history. Reproductive history, including age at menarche, menstrual cycle characteristics, and obstetric outcomes, was recorded in detail because these variables are known to be related to breast health and hormonal exposure.

Anthropometric measurements were obtained at the baseline visit as part of a routine gynecological evaluation. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters, in accordance with the World Health Organization definitions[13]. Height and weight measurements were performed by trained nurses using calibrated devices to minimize inter-observer variability.

Basic laboratory data included hemoglobin and hematocrit levels measured in routine clinical practice before or within one month after LNG-IUD placement. These parameters were included in the assessment because of their potential association with both gynecological conditions that lead to LNG-IUD placement (e.g., menorrhagia) and overall health status.

Lifestyle variables-such as family history of breast cancer and gynecological malignancies, and smoking-were systematically documented during patient interviews. To improve data accuracy and reduce recall bias, the collected information was cross-checked with electronic hospital

records. When missing or unclear data were identified, participants were contacted directly by telephone to verify the information. All data were anonymized after the collection process, and to protect confidentiality, analyses were performed only on the anonymized dataset.

Breast Imaging Assessment

All participants underwent bilateral breast ultrasonography as part of the clinical evaluation process. Imaging procedures in the radiology department were performed by board-certified radiologists with at least ten years of experience in breast imaging. High-frequency (10-14 MHz) linear-array transducers were used during the examinations, and standardized scanning protocols were followed to ensure systematic evaluation of all breast quadrants and the retroareolar region. To minimize observer bias, radiologists were not informed of the participants' contraceptive history or the clinical outcomes of the study.

In women aged 40 years and older, when breast tissue was assessed as dense or when ultrasonographic findings were unclear, additional mammographic evaluation was performed using full-field digital mammography systems. In cases where ultrasonography or mammography findings did not provide a definitive diagnosis, contrast-enhanced breast magnetic resonance imaging was performed in accordance with the diagnostic guidelines published by the American College of Radiology (ACR)[14]. This multimodal imaging approach aimed to provide a more comprehensive evaluation of lesions and to increase diagnostic accuracy.

All detected breast lesions were classified using the breast imaging reporting and data system (BI-RADS; 2013) criteria defined by the ACR. Simple cysts and typical fibrocystic changes were assigned to BI-RADS category 2 (benign), whereas fibroadenomas were assigned to BI-RADS category 2 or 3, depending on imaging characteristics. Lesions classified as BI-RADS category 3 were followed for six months to confirm stability, and cases that remained stability were considered benign. Cases requiring biopsy and those with atypical hyperplasia or malignancy detected on histopathological examination were excluded from the benign lesion group.

Imaging reports and raw images were reviewed by two senior radiologists during consensus meetings to ensure accurate and reproducible lesion classification. Inter-observer agreement was monitored by randomly selecting 15% of cases and evaluating them using the double-reading method, resolving any discrepancies through consensus. This quality control process was implemented to increase the reliability of imaging assessments and minimize classification errors.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation or median and interquartile range. Categorical variables were expressed as frequencies and percentages. Normality of the data was assessed using the Kolmogorov-Smirnov test and visual inspection. To assess demographic and clinical differences between women with and without benign breast disease, the independent samples t-test was used for normally distributed continuous variables and the Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. A two-sided p-value of <0.05 was considered statistically significant. A multivariate logistic regression model was used to evaluate the independent predictors of benign breast disease. Model fit was assessed using the Hosmer-Lemeshow test. Missing data were addressed using complete-case analysis, and LNG-IUD duration was divided into quartiles for sensitivity analyses.

Results

A total of 80 premenopausal women who had used an LNG-IUD for at least 12 months were included in the analysis. The mean age of participants was 47.2±4.4 years, and the mean BMI was 28.1±3.9 kg/m^2. The majority of women (71.2%) had at least one benign breast disorder detected on imaging. Baseline characteristics are presented in Table 1. A flow diagram of patient recruitment and analytic sample selection is provided in Supplementary Figure 1.

Among the 57 women with benign outcomes, 61.3% had simple cysts, 15.0% had fibrocystic changes, and 1.3% had fibroadenomas. Multiple lesions were detected in 22 women (27.5%), and bilateral lesions were present in 18 women (22.5%) (Table 2).

When women with and without benign breast disorders were compared, no significant differences were observed in mean age, BMI, or parity. However, baseline hemoglobin levels were significantly lower among women with benign outcomes (12.4 g/dL vs. 13.1 g/dL, p=0.018). No consistent trend was observed between the duration of LNG-IUD use and the prevalence of benign outcomes (Table 3).

To account for potential confounders, a logistic regression model was constructed, including LNG-IUD duration, age, BMI, and baseline hemoglobin. After adjustment, none of these variables were independently associated with benign breast disorders (Table 4).

Adjusted odds ratios with 95% confidence intervals from the multivariable logistic regression are illustrated in Supplementary Figure 2.

Discussion

This prospective cohort study provides important evidence regarding the prevalence and characteristics of benign breast abnormalities among LNG-IUD users. While most previous LNG-IUD safety studies have focused on malignancy, this study found that benign conditions-particularly simple cysts and fibrocystic changes-were frequently observed but were not associated with duration of device use. This distinction is clinically important because benign lesions, while not life-threatening, can affect women's perceptions of contraceptive safety and lead to discontinuation of, or hesitation to use, the device. This study documents the prevalence of non-proliferative benign lesions and reassures clinicians and patients that such findings are generally incidental rather than device-induced.

Table 1. Baseline characteristics of the study population

Characteristic	Total (n=80)	Benign breast disorder (n=57)	No benign disorder (n=23)	p-value
Age, years (mean ± SD)	47.2±4.4	47.5±4.2	46.5±4.8	0.42
BMI, kg/m² (mean ± SD)	28.1±3.9	28.3±4.1	27.7±3.6	0.61
Parity ≥2, n (%)	55 (68.7)	38 (66.7)	17 (73.9)	0.52
Baseline hemoglobin, g/dL	12.6±1.1	12.4±1.0	13.1±1.2	0.018*
Duration of LNG-IUD use, months	34.7±12.8	35.1±13.2	33.8±11.7	0.68

*: p<0.05, statistically significant, SD: Standard deviation, BMI: Body mass index, LNG-IUD: Levonorgestrel-releasing intrauterine device

Table 2. Distribution of benign breast disorders (n=57)

Lesion type	n (%)
Simple cysts	49 (61.3)
Fibrocystic changes	12 (15.0)
Fibroadenoma	1 (1.3)
Multiple lesions	22 (27.5)
Bilateral involvement	18 (22.5)

Table 3. Comparison of clinical variables between women with and without benign breast disorders

Variable	Benign disorder (n=57)	No disorder (n=23)	p-value
Age ≥45 years, n (%)	39 (68.4)	14 (60.9)	0.52
BMI ≥30 kg/m², n (%)	22 (38.6)	7 (30.4)	0.48
Hemoglobin <12 g/dL, n (%)	15 (26.3)	2 (8.7)	0.04*
LNG-IUD use ≥36 mo, n (%)	28 (49.1)	10 (43.5)	0.65

*: p<0.05, statistically significant, BMI: Body mass index, LNG-IUD: Levonorgestrel-releasing intrauterine device

Table 4. Multivariable logistic regression for predictors of benign breast disorders (n=18 complete cases)

Variable	Adjusted OR (95% CI)	p-value
LNG-IUD duration	0.44 (0.12-1.57)	0.21
Age (per year)	1.02 (0.87-1.18)	0.72
BMI (per kg/m²)	1.05 (0.90-1.23)	0.53
Hemoglobin (per g/dL)	0.81 (0.56-1.17)	0.26

OR: Odds ratio, CI: Confidence interval, LNG-IUD: Levonorgestrel-releasing intrauterine device, BMI: Body mass index

The current literature presents conflicting results regarding the association between LNG-IUD use and breast cancer. Dinger et al.[15] reported that they did not observe a significant increase in breast cancer risk in LNG-IUD users compared to copper IUD users in a large European cohort, supporting the safety of hormonal intrauterine systems. On the other hand, Goldštajn et al.[16] found a modest increase in breast cancer risk in those using combined hormonal therapy but acknowledged that the absolute risk remained low. These conflicting results reflect the ongoing debate regarding hormonal contraceptives and malignancy. The current findings contribute to this debate by focusing on benign pathologies that have been less systematically studied and by broadening the understanding of LNG-IUD safety.

The distribution of benign breast lesions detected in this cohort is consistent with prevalence patterns reported in general screening populations. El-Feky et al.[17] showed that cystic breast disease is among the most frequently reported incidental findings in ultrasonographic evaluations, particularly in women aged 40 and over. Similarly, Lohani et al.[18] reported no significant increase in long-term breast cancer risk in women with non-proliferative benign breast lesions such as simple cysts. The consistency between the findings of the present study and these reports suggests that benign breast findings detected in LNG-IUD users are more likely attributable to age and population-based background risk than to contraceptive exposure. This interpretation should be considered with particular caution due to the absence in the study of a control group that did not use LNG-IUDs; however, the observed prevalence rates, which overlap with age-matched reference cohorts, are reassuring in the context of an indirect comparison.

Possible biological mechanisms also support these observations. It has been previously reported that the effects of progestins on breast epithelium can vary depending on the hormonal context, receptor expression, and exposure level; they can exhibit proliferative effects in some conditions and inhibitory effects in others[19]. However, Zürcher et al.[20] showed that levonorgestrel released from intrauterine systems is associated with minimal systemic exposure compared to oral progestin formulations. This pharmacokinetic feature provides a biological explanation for the absence of either a dose-dependent or a duration-dependent relationship between LNG-IUD use and benign breast outcomes in the present study. Indeed, in additional analyses in which the duration of LNG-IUD use was divided into quartiles and a binary classification was performed using the median value, no trend was detected; these findings supported the main conclusion that the duration of device use did not affect benign breast outcomes.

From a patient counseling perspective, the reassurance provided by these findings offers a clinically significant contribution. Concerns about breast health are frequently raised during contraceptive counseling, particularly in women approaching perimenopause, when the possibility of breast pathology and the need for contraception arise simultaneously. Sanders et al.[21] demonstrated that anxiety about perceived breast health risks can influence women's contraceptive choices and lead to unnecessary abandonment of effective methods. In this context, the present study, which reveals that benign breast lesions are common but not associated with the duration of LNG-IUD use, facilitates the development of evidence-based counseling messages aimed at reducing unnecessary anxiety and supporting continuation of the method.

The present findings are also consistent with studies examining other hormonal contraceptive methods. Grandi et al.[22] evaluated the relationship between oral contraceptive use and fibrocystic breast disease and found no significant association. These results, considered together with the findings of the present study, point to a consistent pattern across hormonal contraceptive methods. Accordingly, it appears that neither systemically released nor locally released progestins significantly increase the frequency of benign breast pathologies. Obtaining similar results with different contraceptive methods reinforces the interpretation that detected benign breast lesions are largely age-related and incidental findings.

The psychological burden accompanying benign breast findings is another dimension that should not be overlooked in clinical practice. Gram et al.[23] reported that a significant proportion of women with benign breast findings during screening programs develop persistent anxiety, which often leads to unnecessary additional investigations. The current study emphasizes the importance of addressing such findings in an appropriate clinical context during contraceptive counseling. Clearly stating that most benign breast lesions are not related to LNG-IUD use can contribute to reducing patient anxiety and preventing subsequent unnecessary investigations, thus improving the quality of care while reducing the burden on healthcare services.

This study has several methodological strengths. The adoption of a prospective design, the systematic application

of standardized breast imaging according to the BI-RADS classification, and the blinded radiological evaluation enhance the internal validity of the findings. The consensus review of imaging results by two senior radiologists further reduced inter-observer variability. The participant inclusion and exclusion process is detailed in Supplementary Figure 1, and adjusted results from multivariate regression analyses are shown in Supplementary Figure 2 to ensure transparency in reporting. These methodological features increase the reliability of the results and strengthen the comparability of the findings with the international literature.

Study Limitations

However, some limitations must be considered. The lack of systematic breast imaging prior to LNG-IUD placement restricts definitive differentiation of newly developed from pre-existing lesions. Furthermore, the exclusion of a control group of individuals not using LNG-IUDs prevents direct comparison between users and non-users. Although stratified analyses were performed based on the duration of LNG-IUD use, the limited number of complete cases, particularly in multivariate models, may have reduced the power to detect weaker associations. Although image-based classification was rigorously applied, histopathological confirmation could not be obtained for all lesions.

This prospective cohort study reveals that benign breast disease is common among LNG-IUD users, but these findings are not associated with the duration of device use. Despite the current methodological limitations, the consistency of the results with age-matched, population-based prevalence data, together with additional analyses, increases confidence in the findings. To confirm these preliminary findings and to clarify the risk of rare but clinically significant malignancies, larger-scale, multicenter studies including pre-treatment breast evaluations, appropriate control groups, and long-term follow-up are needed.

Conclusion

This prospective cohort study shows that benign breast abnormalities-particularly simple cysts and fibrocystic changes-are common among LNG-IUD users, but these findings are not related to the duration of device use. The observed prevalence rates are consistent with the background risk associated with age, suggesting that these lesions may be incidental findings rather than related to LNG-IUD exposure. Although the lack of pre-treatment breast imaging, the absence of a non-user control group, and the relatively limited sample size limit the strength of the evidence, the current findings provide a reassuring framework for contraceptive counseling by demonstrating that benign breast outcomes are common but are not linked to LNG-IUD use. To confirm these results and more clearly address the question of the risk of rare but clinically significant malignancies, multicenter studies encompassing larger populations and including pre-treatment assessments and long-term follow-up are needed.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 492, date: 08.07.2025).

Informed Consent: Prior to involvement in the study, written informed consent was obtained from all participants. All participants provided written consent for the use of anonymized data in scientific publications.

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Footnotes

Authorship Contributions

Surgical and Medical Practises: M.Ç., T.Y.U., Concept: M.Ç., M.B.D., Design: M.Ç., T.Y.U., Data Collection or Processing: T.Y.U., M.B.D., K.K., Analysis or Interpretation: İ.U., Ö.B.Ç., Literature Search: Ö.B.Ç., Writing: M.Ç., M.B.D., Ö.B.Ç.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Artificial Intelligence Assisted Prediction in Acute Rheumatic Fever Patients with Carditis: The Utility of Complete Blood Count and Inflammatory Markers

Karditli Akut Romatizmal Ateşli Hastaların Yapay Zeka ile Tahmini: Tam Kan Sayımı ve Enflamatuvar Belirteçlerin Kullanılması

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Abstract

Objective: Acute rheumatic fever (ARF) is a serious inflammatory disease that results from an autoimmune reaction triggered by a group A beta-hemolytic streptococcal infection, primarily affecting cardiac tissues. It remains the primary etiology of acquired cardiac disorders in children worldwide, especially in developing countries. The present study seeks to examine the potential of inflammatory indices derived from the complete blood count and of machine-learning algorithms for the early diagnosis of the development of carditis associated with ARF.

Methods: In this retrospective study, 68 patients diagnosed with ARF and 71 healthy control subjects were examined between November 2020 and December 2025. Demographic data, blood tests, and transthoracic echocardiography reports were evaluated. Various inflammatory biomarkers, such as the neutrophil-monocyte index, neutrophil-platelet index, neutrophil-lymphocyte ratio, and systemic immune-inflammation index, were calculated. JASP 0.95.2 software and the random forest algorithm were used for data analysis and machine-learning modeling.

Results: As a result of the analyses, notable disparities achieved statistical were found between the control and patient groups in neutrophil (p=0.037), neutrophil-platelet index (p=0.025), neutrophil-lymphocyte ratio (p=0.012), and systemic immune-inflammation index (p=0.016) parameters. The machine-learning random forest model achieved a high test accuracy of 81.5% when using indices with significant p-values. In the feature-importance analysis, parameters such as systemic immune-inflammation index, monocyte, eosinophil and neutrophil were key determinants of the model's classification performance.

Conclusion: This study has demonstrated the potential of inflammatory indices derived from the complete blood count, combined with machine-learning algorithms, to predict, early and with high accuracy, the development of carditis associated with ARF. The significant correlations of markers such as neutrophil-lymphocyte ratio, neutrophil-platelet index, and SII with the presence of carditis, along with the predictive value of machine-learning models, suggest that complete blood count parameters may provide a critical advantage in the diagnosis and early detection of subclinical carditis.

Keywords: Acute rheumatic fever, carditis, inflammatory indexes, machine-learning, artificial intelligent

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Öz

Amaç: Akut romatizmal ateş (ARA), grup A beta-hemolitik streptokok enfeksiyonuna bağlı, kalbi etkileyen ciddi bir otoimmün enflamatuvar hastalıktır ve çocuklarda kazanılmış kalp hastalığının önde gelen nedenidir. Çalışma, tam kan sayımından türetilen inflamatuvar indeksler ve makine öğrenimi algoritmalarıyla ARA ilişkili kardit gelişiminin erken teşhis potansiyelini araştırmayı amaçlamaktadır.

Yöntem: Bu retrospektif çalışmada, Kasım 2020-Aralık 2025 arasında 68 akut romatizmal kalp hastalığı tanılı hasta ve 71 sağlıklı kontrol grubu incelenmiştir. Demografik veriler, kan testleri ve ekokardiyografi raporları değerlendirilmiştir. Nötrofil-monosit indeksi, nötrofil-trombosit indeksi, nötrofil-lenfosit oranı ve sistemik immün-inflamasyon indeksi gibi inflamatuvar biyobelirteçler hesaplanmıştır. Veri analizi ve makine öğrenimi modellemesinde JASP 0.95.2 yazılımı ve random forest algoritması kullanılmıştır.

Bulgular: Analizler, kontrol ve hasta grupları arasında nötrofil (p=0,037), nötrofil-trombosit indeksi (p=0,025), nötrofil-lenfosit oranı (p=0,012) ve sistemik immün-inflamasyon indeksi (p=0,016) parametrelerinde anlamlı farklılıklar ortaya koymuştur. Makine öğrenimi random forest modeli, anlamlı indeksleri kullanarak %81,5'lik yüksek bir test doğruluğu elde etmiştir. Özellik önem analizinde sistemik inflamatuvar indeks, monosit, eosinofil ve nötrofil gibi parametreler modelin sınıflandırma performansında belirleyici rol oynamıştır.

Sonuç: Bu çalışma, tam kan sayımı enflamatuvar indekslerinin ve makine öğrenimi algoritmalarının ARA ilişkili kardit gelişimini erken ve yüksek doğrulukla tahmin etme potansiyelini göstermiştir. Nötrofil-lenfosit oranı, nötrofil-trombosit indeksi ve SII gibi belirteçlerin kardit varlığı ile güçlü korelasyonu ve makine öğrenimi modellerinin öngörücü değeri, tam kan sayımı parametrelerinin subklinik kardit tanısı ve erken tespitinde kritik avantaj sağlayabileceğini düşündürmektedir. Bu hızlı ve düşük maliyetli indeksler, sınırlı kaynaklara sahip klinik ortamlarda bile önemli faydalar sunmaktadır.

Anahtar Kelimeler: Akut romatizmal ateş, kardit, enflamatuvar indeksler, makine öğrenimi, yapay zeka

Introduction

Acute rheumatic fever (ARF) is a multisystemic inflammatory disease that emerges as an autoimmune response to group A beta-hemolytic streptococcal infection in genetically susceptible individuals[1,2]. This condition is an inflammatory process that particularly affects major organ systems such as the heart, joints, brain, and skin[2]. The disease, frequently observed in the 5-15 age group, is recognized as the foremost cause of acquired cardiac disorders among the youth in developing nations and poses a heavy public health burden globally, with a yearly incidence of between 250.000 and 500.000 new cases[3]. The most serious complication of this autoimmune response is rheumatic heart disease, which leads to permanent valve damage and significantly increases morbidity and mortality[4,5]. In particular, Türkiye remains in the medium-high risk countries group[4]. Therefore, the early diagnosis of ARF and especially the prediction of carditis development are of critical importance for halting disease progression and preventing rheumatic heart disease[2,5]. Early diagnosis and treatment of ARF play a vital role in preventing valve involvement during disease progression and reducing the morbidity of rheumatic heart disease[2].

Developing an approach beyond the modified Jones criteria by evaluating inflammatory indices found in the hemogram can provide important preliminary information for the early diagnosis of carditis associated with ARF and for predicting its course[3,4]. In this context, inflammatory markers such as neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), platelet (PLT)-to-LYM ratio (PLR), and monocyte (MON)-to-LYM (ML) ratio derived from complete blood count parameters have been found to be significantly higher in patients with carditis compared to those without carditis[6,7]. These findings suggest that these indices should be investigated as potential biomarkers for predicting the development of carditis associated with ARF and examined through new studies in the literature[7].

Machine-learning methods have increasingly been used in the field of medicine. This offers significant potential, particularly in the diagnosis and risk stratification of cardiovascular diseases[8]. In this context, the potential of inflammatory indices derived from complete blood count to predict the development of ARF accompanied by carditis, and the early detectability of this condition using machine-learning algorithms, are of great importance for disease management and improving patient outcomes[9]. This study aims to investigate the capacity of complete blood count parameters and inflammatory indices to predict the development of ARF accompanied by carditis, to facilitate their early diagnosis using machine-learning models, and to determine which inflammatory and hemogram values can be most efficiently utilized in these models.

Materials and Methods

Data Collection and Groups

This retrospective study included 68 newly diagnosed cases of ARF at the Pediatric Cardiology Department of İzmir

Democracy University Buca Seyfi Demirsoy Training and Research Hospital between November 2020 and December 2025 as the patient group (PG) and 71 healthy children as the control group (CG). Patients diagnosed with ARF were evaluated by pediatric cardiologists and diagnosed according to the modified Jones criteria[10]. Demographic data, blood tests, and transthoracic echocardiography reports (Philips Ultrasound Inc./USA) were retrospectively included in the study. Echocardiographic findings and blood test values recorded at initial detection of ARF were included in the study.

The CG consisted of patients who presented to the outpatient clinic with complaints of chest pain or palpitations, in whom no pathology was detected. Echocardiography evaluations for the CG were normal. Retrospectively, only those CG patients whose acute phase reactants [sedimentation, C-reactive protein (CRP), anti-streptolysin O (ASO)] and hemogram were negative were included. Echocardiography report results and acute phase reactants were utilized during data collection to differentiate between the control and PGs. This study received formal ethical clearance from the Non-Interventional Research Ethics Committee of İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital (approval no: 2025/531, date: 26.11.2025). The authors further attest that all investigative procedures were carried out in strict adherence to the ethical standards of the Declaration of Helsinki.

Inflamatory Biomarkers

All inflammatory biomarkers used in this study were derived from routine complete blood count parameters measured in peripheral blood. Specifically, the NEU-MON (NM) index was calculated as the product of NEU count and MON count; the NEU-PLT (NP) index was calculated as the product of NEU count and PLT count; and the MON-PLT (MP) index was calculated as the product of MON count and PLT count. Additionally, the NLR, ML ratio, and PLR were determined by dividing the respective absolute cell counts by the LYM count. The systemic immune-inflammation index (SII) was defined as (PLT count×NEU count)/LYM count, and the systemic inflammation response index (SIRI) was computed as (NEU count×MON count)/LYM count. The aggregate index of systemic inflammation (AIRI) was calculated as (PLT count×NEU count×MON count)/LYM count.

Artificial Intelligence and Machine-learning Method

Using JASP 0.95.2 software[11], hemogram data were preprocessed for machine-learning algorithms and appropriate machine-learning model techniques were applied. Among these algorithms, various supervised learning models such as decision trees, support vector machines, and artificial neural networks were utilized to predict the carditis associated with ARF[8]. The performance metrics of each model were evaluated to determine the most suitable model, and the clinical predictive value of this model was investigated.

Optimizing Data Inputs for Machine-learning

Data from the patient and healthy groups were initially evaluated using classical statistical measures. Initially, data with significant p-values were obtained and added to the random forest model. Another aim of this study was to create the machine-learning model that achieved the highest predictive accuracy. For this purpose, starting with data that had significant p-values, all data were manually and sequentially added to and removed from the random forest model. Machine-learning modeling was concluded when the highest "model performance metrics" [hematocrit (HCT), MON, NEU, LYM, eosinophil (EOS), hemoglobin (Hb), NLR, AIRI, SIRI, white blood cell (WBC), PLT, SII] values were obtained (Figure 1). The most efficient random forest model was included in the study.

Statistical Analysis

Data evaluation was conducted using JASP version 0.95.2, an open-source platform integrating both statistical frameworks and machine-learning techniques[11]. For the descriptive analysis, continuous variables were summarized by mean and standard deviation when data were parametric, whereas variables with non-parametric distributions were represented by medians. Categorical factors were summarized as frequencies and corresponding percentages. To verify whether the data followed a normal distribution, the Kolmogorov-Smirnov test was applied. Bivariate associations were determined through simple correlation analyses, and chi-square tests were used to assess differences between categorical variables. To compare quantitative parameters, Student's t-test and one way analysis of variance were applied to normally distributed data, whereas the Mann-Whitney U and Kruskal-Wallis tests were used for variables with non-normal distributions. Statistical significance across all analyses was defined by a p-value threshold of <0.05.

Machine-learning Analyses

The machine-learning component used the random forest algorithm available in the JASP classification module. JASP

itself is an open-source initiative developed with structural contributions from the University of Amsterdam and a consortium of institutions, including Utrecht, Nyenrode Business, KU Leuven, and Tilburg University. The dataset was partitioned into a 65% training set, a 20% validation set, and a 15% testing set. Evaluation of the model's performance involved documenting metrics such as accuracy, precision, recall, support, and F1 score, alongside the Matthews correlation coefficient, false positive and false discovery rates, area under the curve, and negative predictive, true negative, and false negative rates. Additionally, feature importance and model dynamics were assessed using mean decrease in accuracy, total increase in node purity, and mean dropout loss.

Power Analyses

Based on the power analysis, a study design utilizing 68 subjects per group provides a minimum probability of 0.89 for identifying effect sizes of $|\delta| \geq 0.5$. This calculation assumes a one-sided detection threshold and a maximum type I error rate of $\alpha=0.05$.

Results

A total of 139 cases were included. There were 68 patients and 71 cases in the CG. Of these cases, 41 in the PG and 43 in the CG were girls. The median age was 12 years in the PG and 11 years in the CG. The median ASO value measured in the PG was 330 IU/mL. The median CRP value in the PG was 2.69 mg/dL (minimum 0.5 mg/dL, maximum 168 mg/dL). The ASO and CRP values in the CG were selected from negative values. Chorea was present in 2 patients and hemichorea was present in 1 patient. Steroid treatment was administered to 5 patients during hospitalization. Complete atrioventricular (AV) block was present in one patient, and first-degree AV block was present in 6 patients.

According to the hemogram values for the patient and CGs, WBC had a median of 7.06 in CG and 7.37 in PG, with no significant difference. PLT had medians of 287 and 292 for CG and PG, respectively, with no significant difference. The median Hb was 13.3 in both CG and PG, with no significant difference. HCT had a median of 39.5 in CG and 40.0 in PG, with no significant difference. NEU had median values of 3.55 for CG and 4.24 for PG; the difference was statistically significant. LYM had medians of 2.78 for CG and 2.68 for PG, with no significant difference between CG and PG. MONs had medians of 0.55 in CG and 0.47 in PG, with no significant difference between groups. EOS had a median of 0.15 in both CG and PG, with no significant difference. The NM index had a median of 2.07 in CG and 1.93 in PG, with no significant difference between CG and PG. The NP index had medians of 1.016 for CG and 1.175 for PG, and this difference was statistically significant. The MP index had a median of 165 in CG and 138 in PG, with no significant difference between CG and PG. The NL ratio had a median of 1.31 in CG and 1.50 in PG, and the difference between the groups was statistically significant. The ML ratio had medians of 0.208 and 0.179 in CG and PG, respectively, with no significant difference between groups. The PL ratio had a median of 107.2 in CG and 107.3 in PG, with no significant difference. SII had medians of 388.3 in CG and 427.2 in PG; this difference was statistically significant. SIRI had a median of 0.74 for both CG and PG, with no significant difference. AIRI median values were 209.1 for CG and 204.5 for PG; this difference was not statistically significant (Table 1).

Machine-learning Results

According to Table 2, the random forest classification model developed using significant indices was built with 7 trees and 3 features per split and achieved validation, test, and out-of-bag (OBB) accuracies of 65.2%, 81.5%, and 36.6%, respectively. These values indicate that the model has high test performance and has been optimized using the OOB criterion. The confusion matrix in Table 3 shows 9 correct and 0 incorrect predictions for CG, and 13 correct and 5 incorrect predictions for PG. According to Table 4, the model's performance metrics have been calculated for each of the two classes and for the average and total values. Support values are 9 for CG, 18 for PG, and 27 in total. Overall accuracy is 81.5%. Precision is 64.3% for CG, 100.0% for PG, and 88.1% on average. Recall is 100.0% for CG, 72.2% for PG, and 81.5% on average. The false positive rate is 27.8% for CG, 0.0% for PG, and 13.9% on average. The F1 scores are 0.783 for CG, 0.839 for PG, and 0.820 on average. The Matthews correlation coefficient is 0.681 across all classes, indicating a strong positive correlation for the model. The area under the curve is 0.728 for CG, 0.605 for PG, and 0.667 on average. The average negative predictive value, true negative rate, and threat score are 82.1%, 86.1%, and 1.750, respectively. All metrics are calculated for each class against all others, and the model exhibits high performance.

The feature importance of the random forest model developed using significant indices were calculated as the mean decrease in accuracy, the total increase in node purity, and the mean dropout loss. The highest mean decrease

in accuracy values are observed for SII, MON, and EOS; for total increase in node purity, MON, NEU, and LYM are prominent. Based on mean dropout loss, MON, EOS, and NEU were determined to be the most effective features; note that dropout loss was calculated based on 50 permutations. These metrics indicate that features such as MON, EOS, NEU, and SII play a decisive role in the model's classification performance (Table 5).

Discussion

Between ARF patients and the CG, the inflammatory hemogram indices presented in Table 1 differed significantly at the $p<0.05$ level. These indices reflect the differences in inflammatory response between groups; for example, ratios such as MON, EOS, and NEU for MONs, EOSs, and NEUs indicate inflammatory processes that play a role in ARF pathogenesis. SII, with its complex structure based on PLTs and NEUs, emphasizes the systemic dimension of the disease. Similarly, it has been reported that NEU, leukocyte, and NLR levels are significantly higher in children with ARF compared to healthy children, and these parameters can be used in the diagnosis of the disease[12]. However, some studies show that full blood parameters such as leukocytes, NEUs, PLTs, and MONs are insufficient in predicting the severity of carditis[12]. Nevertheless, other studies indicate that parameters such as NLR, ML ratio, and PLR are significantly higher in patients with cardiac involvement in ARF, and these indices can be evaluated as potential biomarkers in predicting carditis[7]. These findings suggest that evaluating inflammatory indices in the hemogram of children with ARF may provide important preliminary information for the early diagnosis and determination of carditis. Accordingly, comparing the healthy CG without echocardiographic pathology with patients exhibiting carditis findings due to ARF offers a valuable approach for the early detection of carditis using machine-learning algorithms[2,7,13].

The random forest model, automatically configured by JASP with 7 trees and 3 features per split, emerged as the superior machine-learning algorithm for this classification task, outperforming traditional methods and achieving high test accuracy (0.815). The random forest model was employed due to its superior performance-F1 score and Matthews correlation coefficient exceeding 0.60-among evaluated algorithms for predicting carditis from hemogram parameters, consistent with robust results in pediatric inflammatory conditions (Figure 1)[8,14,15]. The small sample size poses substantial challenges for reliable machine-

Table 1. Descriptive statistics

Descriptive statistics	Groups (CG: 71, PG: 68)	Median (IQR: Q3-Q1)	p-value
WBC	CG	7.06 (8.46-6.15)	0.075
	PG	7.37 (9.52-6.23)	
PLT	CG	287 (342-259)	0.916
	PG	292 (350-256)	
Hb	CG	13.3 (14-12.3)	0.305
	PG	13.3 (13.8-12.3)	
HCT	CG	39.5 (41.7-37.8)	0.410
	PG	40.0 (41.9-37.6)	
NEU	CG	3.55 (4.41-2.93)	**0.037**
	PG	4.24 (5.72-3.07)	
LYM	CG	2.78 (3.23-2.18)	0.107
	PG	2.68 (3.31-2.18)	
MON	CG	0.55 (0.65-0.45)	0.451
	PG	0.47 (0.58-0.39)	
EOS	CG	0.15 (0.24-0.09)	0.316
	PG	0.15 (0.22-0.09)	
NM index	CG	2.07 (2.59-1.32)	0.267
	PG	1.93 (3.58-1.30)	
NP index	CG	1.016 (1.416-781)	**0.025**
	PG	1.175 (1.903-712)	
MP index	CG	165 (216-121)	0.442
	PG	138 (184-110)	
NL ratio	CG	1.31 (1.81-0.98)	**0.012**
	PG	1.50 (2.41-1.06)	
ML ratio	CG	0.208 (0.263-0.159)	0.785
	PG	0.179 (0.248-0.144)	
PL ratio	CG	107.2 (130.1-90.1)	0.786
	PG	107.3 (138.1-78.3)	
SII	CG	388.3 (527.4-269.9)	**0.016**
	PG	427.2 (683-289.8)	
SIRI	CG	0.74 (1.10-0.49)	0.109
	PG	0.74 (1.16-0.46)	
AIRI	CG	209.1 (348.8-143.2)	0.078
	PG	204.5 (368.5-131.6)	

WBC: White blood cell, PLT: Platelet, Hb: Hemoglobin, HCT: Hematocrit, NEU: Neutrophil, LYM: Lymphocyte, MON: Monocyte, EOS: Eosinophil, NM: Neutrophil-monocyte, NP: Neutrophil-platelet, MP: Monocyte-platelet, NL: Neutrophil-to-lymphocyte, ML: Monocyte-to-lymphocyte, PL: Platelet-to-lymphocyte, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AIRI: Aggregate index of systemic inflammation, CG: Control group, PG: Patient group, IQR: Interquartile range

Table 2. Machine-learning model summary

Model summary: random forest classification

Trees	Features per split	n (train)	n (validation)	n (test)	Validation accuracy	Test accuracy	OOB accuracy
7	3	89	23	27	0.652	0.815	0.366

The model is optimized with respect to the out-of-bag accuracy
OOB: Out-of-bag

Table 3. Machine-learning model prediction

Confusion matrix

		Predicted	
		0	1
Observed	0	9	0
	1	5	13

Table 4. Machine-learning model performance metrics

Model performance metrics

	0	1	Average/ total
Support	9	18	27
Accuracy	0.815	0.815	0.815
Precision (positive predictive value)	0.643	1.000	0.881
Recall (true positive rate)	1.000	0.722	0.815
False positive rate	0.278	0.000	0.139
False discovery rate	0.357	0.000	0.179
F1 score	0.783	0.839	0.820
Matthews correlation coefficient	0.681	0.681	0.681
Area under curve	0.728	0.605	0.667
Negative predictive value	1.000	0.643	0.821
True negative rate	0.722	1.000	0.861
False negative rate	0.000	0.278	0.139
False omission rate	0.000	0.357	0.179
Threat score	0.900	2.600	1.750
Statistical parity	0.519	0.481	1.000

All metrics are calculated for every class against all other classes

learning results, particularly regarding overfitting, generalizability, and capturing subtle inflammatory patterns like MON, EOS, NEU, and SII in pediatric ARF with carditis[8,16]. Indeed, pediatric cardiology studies affirm random forest's precision and robustness in handling heterogeneous data and imbalanced classes despite such limitations[8,16].

By developing a machine-learning model based on hemogram parameters, high-risk patients can be predicted with high accuracy before the clinical onset of carditis.

Table 5. Machine-learning feature impotance metrics

Feature importance metrics

	Mean decrease in accuracy	Total increase in node purity	Mean dropout loss
HCT	-0.026	0.039	0.167
MON	0.040	0.025	0.235
NEU	0.018	0.021	0.180
LYM	0.021	0.011	0.131
EOS	0.040	0.001	0.191
Hb	-0.027	0.001	0.150
NL ratio	0.018	-0.004	0.144
AIRI	0.018	-0.006	0.146
SIRI	0.016	-0.011	0.154
WBC	-2.035×10^{-4}	-0.025	0.177
PLT	0.004	-0.039	0.146
SII	0.072	-0.041	0.170

Mean dropout loss (defined as 1-area under curve) is based on 50 permutations
WBC: White blood cell, PLT: Platelet, Hb: Hemoglobin, HCT: Hematocrit, NEU: Neutrophil, LYM: Lymphocyte, MON: Monocyte, EOS: Eosinophil, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AIRI: Aggregate index of systemic inflammation

The development of such models is supported by previous findings suggesting that inflammatory markers, particularly NLR, ML ratio, and PLR, can assist in the diagnosis and prognosis of carditis associated with ARF through serial measurements[1]. This is further corroborated by the feature importance metrics of the random forest model. SII, MON, and EOS rank highest for the mean decrease in accuracy; MON, NEU, and LYM are prominent for the total increase in node purity; and MON, EOS, and NEU play a decisive role in the mean dropout loss. These indices emerge as key biological markers, reinforcing the inflammatory distinction between ARF patients and the CG, and signaling their potential utility in clinical diagnostic processes, given the model's high test accuracy. This advancement holds particular promise for the early diagnosis of cardiac involvement and the management of ARF in children[12]. Accordingly, as supported by the literature, inflammatory indices such as NLR, PLR, and

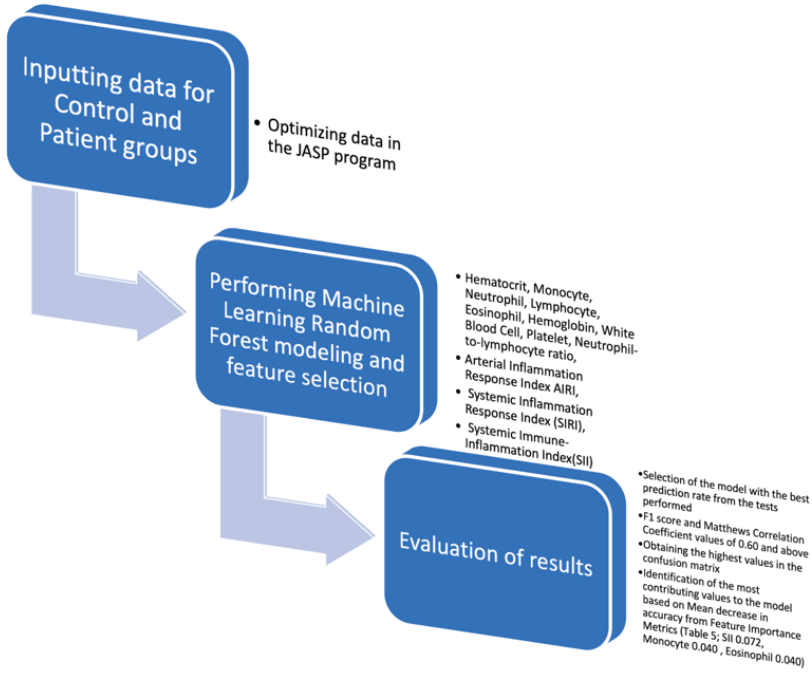

Figure 1. Schematic workflow of the data optimization process for the machine learning model integrating complete blood count parameters and inflammatory biomarkers

ML ratio have been found significantly elevated in patients with cardiac involvement due to ARF[7,9,13-17]. This integration enables the development of clinical decision support systems, particularly for preventing carditis progression and reducing morbidity rates[7,12]. However, some studies indicate that these inflammatory markers, whether used alone or in multiparametric evaluations, are insufficient for predicting carditis severity[7]; conversely, their combined use is thought to enhance diagnostic and prognostic accuracy[7]. In this context, machine-learning models can offer more robust predictive capabilities by integrating novel biomarkers and echocardiographic findings from large datasets of patients diagnosed using standardized Jones criteria[1,2,8].

As an important and innovative approach of our study, we evaluated the potential of p-value significant inflammatory indices and hemogram data using the machine-learning random forest method to predict ARF with findings, and determined that these parameters can predict the risk of ARF with high accuracy[7,14]. Particularly, parameters associated with WBC offer important predictive values in predicting the severity of rheumatic heart disease[8]. This innovative approach emphasizes the predictive potential of inflammatory indices and complete blood count parameters in pediatric patients diagnosed with ARF using Jones criteria, especially in the presence of carditis[18]. These findings suggest that complete blood count parameters may play an important role in the diagnosis of subclinical carditis, given their operator-independent nature and lack of requirement for technical expertise[7]. In this context, markers such as the NLR and ML ratio are reported to be helpful in the diagnosis and prognosis of ARF[7]. This can lead to significant progress, particularly in the early diagnosis of cardiac involvement and in the management of ARF in children. Indeed, while studies indicate that carditis presence in ARF is not associated with CRP, sedimentation, NLR, and PLR indices[9], the literature contains findings that cytokines such as interleukin (IL)-1 and IL-6 can be used as minor criteria in the diagnosis of carditis and arthritis, and anti-cytokine treatments may prevent valvular damage. In this context, machine-learning models offer significant potential for early diagnosis of carditis and for predicting its progression through the combined analysis of these cytokines and other inflammatory markers. We believe that prospective studies incorporating machine-learning models are necessary to obtain more detailed insights into inflammatory biomarkers and indices.

Future research can more thoroughly investigate the extent to which these integrated approaches can successfully predict carditis development and personalize treatment strategies[14]. Additionally, multicenter, prospective studies are required to evaluate the effectiveness of these models in clinical practice[15]. In the future, as machine-learning methods evolve and data availability increases, combining hemogram and simple biochemical values with clinical data will enable more precise and reliable diagnosis of ARF and earlier prediction of complications such as carditis. It is believed that such studies will further enhance their potential in predicting carditis by expanding the use of inflammatory indices found in hemograms[9] alongside next-generation systemic inflammatory indices[19].

Study Limitations

A primary constraint of this investigation is its retrospective methodological framework. Retrospective studies may be more vulnerable to unknown confounding factors and missing data because data are collected retrospectively. Additionally, the single-center design and limited patient population may limit generalizability. Despite the high test accuracy of our machine-learning model, larger-scale, international, multicenter, prospective studies are needed to confirm the validity and applicability of these findings in clinical practice. Furthermore, some conflicting findings in the literature regarding the inadequacy of the examined inflammatory indices-whether used alone or in multiparametric evaluations-for predicting carditis severity underscore the need for additional research to better understand their potential for comprehensive clinical use.

Conclusion

In this study, the potential of inflammatory indices found in the hemogram, together with that of machine-learning algorithms to predict the early development of carditis associated with ARF fever with high accuracy was evaluated. Analyses showed that markers such as the NLR, PLR, and ML ratios were significantly correlated with the presence of carditis and had high predictive value in machine-learning models. These findings suggest that complete blood count parameters may play an important role in diagnosing subclinical carditis, given their operator-independent nature and lack of requirement for technical expertise. Therefore, the rapid and low-cost availability of these indices offers a critical advantage in the management of ARF and in the early diagnosis of cardiac complications, even in clinical settings with limited resources.

Ethics

Ethics Committee Approval: This study received formal ethical clearance from the Non-Interventional Research Ethics Committee of İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital (approval no: 2025/531, date: 26.11.2025).

Informed Consent: Retrospective study.

Footnotes

Support for manuscript preparation, specifically for grammatical revisions and minor summarization or translation, was provided by Jenni.ai. The authors declare that the intellectual content of the current work has been thoroughly verified and remains their full responsibility.

Authorship Contributions

Surgical and Medical Practises: O.A., A.Ş., Concept: O.A., A.Ş., Design: O.A., A.Ş., Data Collection or Processing: O.A., A.Ş., Analysis or Interpretation: O.A., Literature Search: O.A., Writing: O.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Clinical-Endoscopic Finding, Risk Factors and Management of Peptic Ulcer Disease in Children

Çocuklarda Peptik Ülser Hastalığının Klinik-endoskopik Bulguları, Risk Faktörleri ve Yönetimi

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Abstract

Objective: Peptic ulcer disease (PUD) is less common in children than in adults and may present with non-specific symptoms. In this study, we aimed to evaluate the long-term clinical follow-up data from a large cohort of pediatric patients diagnosed with PUD.

Methods: All patients who underwent upper gastrointestinal system (GIS) endoscopy between August 2015 and October 2021 were evaluated; those with PUD were included in the study. Clinical, endoscopic, and histopathologic data were evaluated.

Results: PUD was detected in 107 of 3116 patients (3.43%) who underwent upper GIS endoscopy. Among these patients, 57.9% were male, with a mean age of 12.93±4.40 years. The prevalence of PUD by age group was 8.4% in children under 5 years, 19.6% in those aged 6-11 years, and 72% in adolescents aged 12-18 years. In children older than 5 years, The most common presenting symptom was generalized abdominal pain, followed by epigastric pain; in children younger than 5 years, hematemesis was the most frequent presenting symptom. Ulcers were most commonly located in the duodenal bulb (69.2%). In children under 5 years of age, ulcers were predominantly located in the antrum. *Helicobacter pylori* (*H. pylori*) positivity was found in 63.5% of PUD cases. Non-steroidal anti-inflammatory drug (NSAID) use was observed in 6.5% of the cases as a contributing factor. In 76.5% of *H. pylori*-positive patients, the ulcer was located in the bulb. Two patients required endoscopic hemoclip placement due to ulcer-related bleeding. Endoscopic balloon dilation and surgical intervention were performed in two separate cases of pyloric stenosis secondary to an ulcer. Surgical treatment was also required in one patient due to ulcer-related perforation.

Conclusion: PUD should be considered in patients presenting with generalized abdominal pain, even in the absence of isolated epigastric pain. *H. pylori* infection should be assessed in all PUD cases, and eradication therapy should be an integral part of the treatment for positive cases. Families should be informed in detail about the risks associated with NSAID use, and these medications should be used cautiously.

Keywords: Peptic ulcer disease, gastroduodenoscopy, etiology, management

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Öz

Amaç: Peptik ülser hastalığı (PÜH), çocuklarda yetişkinlere kıyasla daha az yaygındır ve spesifik olmayan semptomlarla ortaya çıkabilir. Bu çalışmada, PÜH tanısı almış geniş bir pediatrik hasta grubunun uzun dönem klinik takip verilerini değerlendirmeyi amaçladık.

Yöntem: Ağustos 2015 ile Ekim 2021 tarihleri arasında üst gastrointestinal sistem (GİS) endoskopisi yapılan tüm hastalar değerlendirildi ve PÜH'lü hastalar çalışmaya dahil edildi. Klinik, endoskopik ve histopatolojik veriler değerlendirildi.

Bulgular: Üst GİS endoskopisi yapılan 3116 hastanın 107'sinde (%3,43) PÜH saptandı. Beş yaş üstü çocuklarda en sık başvuru semptomu yaygın karın ağrısı, bunu epigastrik ağrı takip ederken, 5 yaş altı çocuklarda en sık başvuru şikayeti hematemezdi. Ülser yerleşimi en sık duodenum bulbustaydı (%69,2). PUD olgularının %63,5'inde *Helicobacter pylori* (*H. pylori*) pozitifliği bulundu. Olguların %6,5'inde non-steroid anti-enflamatuvar ilaç (NSAID) kullanımı katkıda bulunan bir faktör olarak gözlendi. *H. pylori* pozitif hastaların %76,5'inde ülser bulbusta yerleşmişti. İki hastada ülser ilişkili kanama nedeniyle endoskopik hemoklip yerleştirilmesi gerekti. Ülsere sekonder pilor stenozu olan iki ayrı olguda endoskopik balon dilatasyonu ve cerrahi girişim uygulandı. Bir hastada ülsere bağlı perforasyon nedeniyle cerrahi tedavi gerekti.

Sonuç: Yaygın karın ağrısı ile başvuran hastalarda PÜH düşünülmelidir. Tüm PÜH olgularında *H. pylori* enfeksiyonu değerlendirilmelidir. Aileler NSAID kullanımına bağlı riskler konusunda detaylı olarak bilgilendirilmeli ve bu ilaçlar dikkatli kullanılmalıdır.

Anahtar Kelimeler: Peptik ülser hastalığı, gastroduodenoskopi, etiyoloji, tedavi

Introduction

Peptic ulcer disease (PUD) refers to an acid-peptic injury within the gastrointestinal system (GIS). Peptic ulcers are deep mucosal lesions that extend through the muscularis mucosae of the stomach or duodenal wall[1]. Gastritis, duodenitis, and PUD develop as a result of an imbalance between mucosal defense mechanisms and aggressive factors[2]. PUD is classified as either primary or secondary based on etiology[3]. Most primary causes are associated with *Helicobacter pylori* (*H. pylori*) infection[4]. Secondary PUD is commonly caused by stress (such as sepsis, burns, shock, increased intracranial pressure, or postoperative states), medications [including non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, and aspirin], and certain systemic diseases[5,6]. Upper GIS endoscopy plays a crucial role in diagnosing PUD, determining the location of the ulcer and the severity of bleeding, and providing endoscopic treatment when necessary.

Patients typically present with abdominal or epigastric pain, or with hematemesis[7-10]. However, PUD may present with non-specific symptoms in children[11]. Unlike in adult cases, clinical symptoms in pediatric patients may not reliably predict PUD before GIS bleeding occurs[12]. Recognizing the clinical features, etiological factors, and management strategies of PUD in children is crucial for raising awareness and ensuring appropriate care. Therefore, we aimed to evaluate long-term clinical follow-up data from a large cohort of pediatric patients diagnosed with PUD.

Materials and Methods

Children who underwent upper GIS endoscopy in the pediatric gastroenterology clinic between August 2015 and October 2021 and who were diagnosed with PUD were included in the study. Clinical, endoscopic, and histopathological data obtained from medical records and hospital information systems were evaluated. Demographic characteristics, presenting complaints, endoscopic ulcer locations, Forrest classification, histopathological findings, risk factors, *H. pylori* infection status, medical and endoscopic treatments administered, complications related to PUD, and management of recurrent PUD were recorded. Additionally, findings in *H. pylori*-positive and *H. pylori*-negative patients were compared. Anthropometric measurements were classified based on body mass index (BMI) percentiles: underweight (<5th percentile), normal weight (5th-85th percentile), overweight (85th-95th percentile), and obese (>95th percentile). Ethical approval was obtained from University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval no: 2022/06-13, date: 15.06.2022). Patient data were reviewed retrospectively, and informed consent was obtained from the patients' families.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as counts (n), percentages (%), mean ± standard deviation, minimum, maximum, and median values. The Pearson chi-square test was used to compare categorical

variables between groups. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 3116 pediatric patients who underwent upper GIS endoscopy were evaluated; PUD was identified in 107 cases (3.43%). Of these patients, 57.9% were male and 42.1% were female. The mean age at diagnosis was 12.93±4.40 years (ranging from 3 months to 17 years). The age distribution showed that 8.4% of cases were aged 0-5 years, 19.6% were aged 6-11 years, and 72% were aged 12-18 years. Regarding BMI percentiles, 26.2% of patients were underweight, 59.8% were of normal weight, 5.6% were overweight, and 8.4% were obese.

The most common presenting complaints were generalized abdominal pain (44.9%), epigastric pain (29%), melena (15.9%), and hematemesis (15%). In children under 5 years, hematemesis was the most frequent symptom, followed by generalized abdominal pain. For patients older than 5 years, generalized abdominal pain and epigastric pain were the most common presenting complaints (Table 1). The ulcer was most frequently located in the duodenal bulb (69.2%). Among children under 5 years of age, ulcers were most commonly located in the antrum (55.5%), whereas in those over 5 years of age, the bulb was the most common site (73.5%). According to the endoscopic Forrest classification, 1.87% were classified as Forrest 1B (active oozing bleeding), 0.93% as Forrest 2A (visible non-bleeding vessel), 23.4% as Forrest 2B (adherent clot), 26.2% as Forrest 2C (flat pigmented spot), and 47.6% as Forrest 3 (clean base ulcer).Histopathological examination of endoscopic biopsy specimens from patients with PUD detected *H. pylori* in 68 patients (63.5%). When evaluating the distribution of *H. pylori* infection by gender, no significant difference was observed between males and females (p=0.328). The prevalence of *H. pylori*-positive cases was higher in patients older than 12 years (p=0.003; Table 2). Isolated epigastric pain was observed in 35.2% of *H. pylori*-positive cases and 17.9% of *H. pylori*-negative cases (p=0.057). Generalized abdominal pain was reported in 44.1% of *H. pylori*-positive patients and in 46.1% of *H. pylori*-negative patients (p=0.838). Histopathological evaluation of PUD cases revealed antral gastritis in 19 patients (17.8%), pangastritis in 82 patients (76.6%), bulbitis in 41 patients (38.3%), duodenitis in 21 patients (19.6%), and esophagitis in 32 patients (29.9%). The frequency of pangastritis was significantly higher in *H. pylori*-positive patients than in *H. pylori*-negative patients (p=0.02) (Table 3). When the etiological causes of PUD were evaluated, 62 cases (57.9%) were associated with *H. pylori* infection, 27 cases (25.2%) were idiopathic, 10 cases (9.3%) were related to drug use, 3 cases (2.8%) were stress-related, and 5 cases (4.6%) were

Table 1. Clinical presenting findings of peptic ulcer disease cases by age group

Presenting complaints	0-5 years, n (%)	6-11 years, n (%)	12-18 years, n (%)
Hematemesis	5 (55.5)	3 (14.3)	8 (10.4)
Generalized abdominal pain	4 (44.4)	10 (47.6)	34 (70.8)
Epigastric pain	-	3 (14.3)	28 (36.4)
Vomiting	-	4 (19)	13 (16.9)
Melena	2 (22.2)	4 (19)	11 (14.3)
Hematochezia	1 (11.1)	1 (4.76)	-
Weight loss	-	2 (9.5)	5 (6.5)
Anemia	2 (22.2)	2 (9.5)	3 (3.9)
Regurgitation	-	3 (14.3)	10 (13)

Table 2. Distribution of age groups in *Helicobacter pylori*-positive and negative cases

***Helicobacter pylori* infection status**			
	Positive, n (%)	**Negative, n (%)**	**p-value***
Age group			
0-5 years	2 (2.9)	7 (17.9)	
6-11 years	10 (14.7)	11 (28.3)	**0.003**
12-18 years	56 (82.4)	21 (53.8)	

*: Pearson's chi-square test was used

Table 3. Histopathological findings in *Helicobacter pylori*-positive and *Helicobacter pylori*-negative patients

	***Helicobacter pylori* infection status**				**p-value***
	Positive, n (%)		**Negative, n (%)**		
Histopathological finding	Present	Absent	Present	Absent	
Antral gastritis	9 (13.2)	59 (86.8)	5 (12.8)	34 (87.2)	0.951
Pangastritis	59 (86.7)	9 (13.3)	18 (46.1)	21 (53.9)	**0.02**
Duodenitis	9 (13.2)	59 (86.8)	7 (17.9)	32 (82.1)	0.511
Bulbitis	24 (35.2)	44 (64.8)	12 (30.7)	27 (69.3)	0.634
Esophagitis	18 (26.4)	50 (73.6)	9 (23.1)	30 (76.9)	0.697

*: Pearson's chi-square test was used

due to other causes. Among the 10 patients with drug-related PUD, 7 were linked to NSAID use, 1 to chemotherapy, and 2 to steroid use. Of the three patients with stress-related PUD, two were monitored in the intensive care unit due to respiratory distress, and one was monitored due to gastrointestinal bleeding after septic shock. Other causes included 4 patients who were subsequently diagnosed with Crohn's disease and 1 patient who was diagnosed with alpha-1 antitrypsin deficiency. Among those diagnosed with Crohn's disease, 2 cases tested positive for *H. pylori*, and among NSAID-related PUD cases, 4 also tested positive for *H. pylori*.

In terms of medical treatment, 100 patients (93.5%) received proton pump inhibitors, 8 patients (7.5%) received H2 receptor blockers, 67 patients (62.6%) received sucralfate, and 68 patients (63.5%) received *H. pylori* eradication therapy. Endoscopic intervention was performed in 3 patients (2.8%): 2 patients underwent hemoclip application, and 1 patient underwent endoscopic balloon dilation for pyloric stenosis secondary to an ulcer. According to the endoscopic Forrest classification, one of the patients who underwent hemoclip placement was classified as Forrest 1B, and the other was classified as Forrest 2A. Follow-up endoscopies in these three patients demonstrated mucosal healing. Among all 107 patients with PUD, complications were observed in only 3 cases (2.8%). Specifically, 2 patients developed pyloric stenosis, and 1 patient experienced perforation. Endoscopic balloon dilation was performed in one patient with pyloric stenosis, whereas surgical intervention was required in the other patient with pyloric stenosis and in the patient with perforation.

Discussion

The prevalence of PUD in children is lower than in adults. Studies conducted on pediatric patients in our country have reported a prevalence of PUD ranging from 3.4% to 7.6%[10,13]. Studies from different countries indicate that the prevalence of PUD in children ranges from 2% to 8%[8,14-16]. In our study, PUD was detected in 3.43% of cases. In the study by Chan et al.,[17] the prevalence of PUD was higher among male children. Similarly, in our study, PUD was more frequently observed in male patients (57.9%) than in female patients. In our study, 72% of the patients were in the adolescent age group (12-18 years), while 8.4% were under the age of 5. A study conducted in China reported that *H. pylori*-positive PUD cases were more commonly observed after the age of 12[18]. According to the literature, the rate of *H. pylori* positivity in pediatric PUD cases ranges from 45.8% to 77.8%[19,20]. Consistent with the literature, *H. pylori* was detected in 63.5% of our cases, which supports the strong association between *H. pylori* and PUD. Although *H. pylori* positivity was found to be higher in males than females in our study, the difference was not statistically significant. Similarly, Murray et al.[21] demonstrated no gender difference in *H. pylori* infection. Among Korean adults, obesity has been reported to be associated with PUD[22]. In our study, 5.6% of PUD patients were overweight, 8.4% were obese, and the majority had BMIs within the normal range.

Among our PUD cases, the most common presenting symptom was diffuse abdominal pain, observed in 44.9% of patients. Güven et al.[1] reported that 75% of *H. pylori*-positive PUD cases and 64.5% of *H. pylori*-negative PUD cases presented with diffuse abdominal pain. In our study, diffuse abdominal pain was observed in 44.1% of *H. pylori*-positive cases and 46.1% of *H. pylori*-negative cases. Although epigastric pain at presentation was more frequent among *H. pylori*-positive PUD cases, the difference was not statistically significant. As shown in many studies, neither epigastric pain alone nor diffuse abdominal pain alone is sufficient to predict PUD. In our study, the most common presenting symptom in PUD cases under the age of five was

hematemesis. According to the literature, 33% of PUD cases present with gastrointestinal bleeding, regardless of age[14]. Another study demonstrated that bleeding and perforation were the most prominent presenting symptoms during infancy[8]. Our study suggests that in younger age groups, early symptoms such as abdominal and epigastric pain may go unrecognized or that PUD may not be considered among the primary differential diagnoses.

In our study, PUD was most frequently detected in the gastric antrum among patients under 5 years of age, whereas in other age groups the duodenal bulb was the most common ulcer location. When all *H. pylori*-positive and *H. pylori*-negative PUD cases were evaluated, the duodenal bulb was the most frequent site of ulceration. Previous studies have also demonstrated that duodenal bulb ulcers are more common in both *H. pylori*-positive and negative *H. pylori*-negative pediatric groups[23]. However, Ecevit et al.[10] reported that antral ulcers were more common in both *H. pylori*-positive and *H. pylori*-negative groups. In our study, independent of *H. pylori* infection, the most frequently observed ulcer type was Forrest type III. It has been reported that approximately 95% of *H. pylori*-positive PUD cases present with pangastritis[10,14]. Similarly, in our study, the frequency of pangastritis was significantly higher in *H. pylori*-positive cases than in *H. pylori*-negative cases.

NSAIDs are the most common cause of drug-related PUD[24]. A pediatric study from Asia reported a prevalence of NSAID-related PUD of 16.5%[15]. Similarly, NSAIDs were the most frequent cause of drug-associated PUD in our study. The literature indicates that numerous chemotherapeutic agents can damage the gastrointestinal mucosa and subsequently lead to PUD[25-27]. In our study, in addition to NSAIDs, we identified steroid use and chemotherapeutic agents as potential etiological factors for PUD. Based on these findings, obtaining a detailed medication history is essential when evaluating the etiology of PUD in pediatric patients.

No endoscopic treatment, including hemoclip application, electrocoagulation, or sclerotherapy, has been proven superior for the management of peptic ulcers[28]. In our study, hemoclips were applied to two patients who were identified endoscopically as having Forrest 1B ulcers and at high risk of bleeding and complications, and balloon dilation was performed in one patient for pyloric stenosis secondary to PUD. All patients infected with *H. pylori* received eradication therapy. Considering that PUD can be a significant cause of morbidity and mortality in the pediatric population, proper management is essential. Pyloric stenosis secondary to ulcers may lead to persistent vomiting, feeding difficulties, and weight loss. Therefore, in cases of prepyloric, antral, or duodenal ulcers at risk for gastric outlet obstruction, clinical follow-up and endoscopic evaluation are important. Peptic ulcer perforation is one of the most serious causes of morbidity and mortality in the pediatric population[29,30]. In our study, one patient required surgical intervention due to perforation secondary to PUD.

Study Limitations

Patients whose full files were accessible were included in the study. Cases excluded from follow-up and whose data were not fully accessible are considered limiting factors. The retrospective nature of the study is the primary limitation. Numerous prospective studies are needed in this area.

Conclusion

PUD should be considered in pediatric patients presenting with diffuse abdominal pain, even in the absence of isolated epigastric pain. The presence of *H. pylori* should be evaluated in patients with PUD, and eradication therapy should be an integral part of treatment. Given the risk of PUD associated with NSAID use in children, these medications should be used cautiously and with appropriate parental counseling. Increasing awareness among healthcare professionals-especially family physicians and pediatricians-is crucial. Recognizing the nonspecific clinical signs of PUD can facilitate early diagnosis, appropriate management, and prevention of potential complications.

Ethics

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval no: 2022/06-13, date: 15.06.2022).

Informed Consent: Patient data were reviewed retrospectively, and informed consent was obtained from the patients' families.

Footnotes

Authorship Contributions

Surgical and Medical Practises: S.K., B.A., M.B., Y.Ç.A., Concept: Ö.B., B.A., Y.Ç.A., Design: Ö.B., S.K., Y.Ç.A., Data Collection or Processing: Ö.B., S.K., B.A., M.B., Y.Ç.A., Analysis or Interpretation: Ö.B., M.B., Y.Ç.A., Literature Search: Ö.B., Y.Ç.A., Writing: Ö.B., S.K., Y.Ç.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Patients Ask, AI Answers: An Evaluation of ChatGPT-4o Responses to the Most Frequently Googled Questions on Laparoscopic Hysterectomy

Hasta Eğitiminde Yapay Zeka: Laparoskopik Histerektomi Hakkında Google'da En Sık Aranan Sorulara ChatGPT-4o Yanıtlarının Değerlendirilmesi

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Abstract

Objective: Patients increasingly use search engines and artificial intelligence-based tools to obtain medical information prior to surgical consultations. This study aimed to evaluate the quality of ChatGPT-4o's responses to the patient questions most frequently searched on Google regarding laparoscopic hysterectomy.

Methods: This expert-based evaluation identified the most frequently searched patient questions on Google regarding laparoscopic hysterectomy using a newly created Google account with no prior search history. After eliminating duplicates, 24 unique questions were included. Each question was independently presented to ChatGPT-4o using a new account with no prior conversation history. Ten experienced gynecologic surgeons evaluated each response across four domains: accuracy, clarity, completeness, and relevance, using a five-point Likert scale. Descriptive statistics were calculated, and interrater reliability was assessed using intraclass correlation coefficients.

Results: Mean scores across all questions were 4.36 for accuracy, 4.55 for clarity, 4.21 for completeness, and 4.59 for relevance. No responses received a score below 3 in any domain. Interrater reliability varied across evaluation domains. Overall, ChatGPT-4o responses were perceived as highly relevant and easy to understand, with comparatively lower scores for completeness.

Conclusion: ChatGPT-4o provides responses to common online queries about laparoscopic hysterectomy that are generally accurate, relevant, and clearly presented. However, limitations in completeness highlight the need for clinician-led counseling. Artificial intelligence-generated information may serve as a supplementary resource for patient education but should not replace professional medical guidance.

Keywords: Laparoscopic hysterectomy, artificial intelligence, patient education, ChatGPT, minimally invasive surgical procedures

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Öz

Amaç: Hastalar, cerrahi girişimler öncesinde tıbbi bilgi edinmek amacıyla giderek artan şekilde arama motorları ve yapay zeka tabanlı araçlara başvurmaktadır. Bu çalışmanın amacı, laparoskopik histerektomi ile ilgili Google'da en sık aranan hasta sorularına ChatGPT-4o tarafından verilen yanıtların kalitesini değerlendirmektir.

Yöntem: Bu uzman temelli değerlendirme çalışmasında, laparoskopik histerektomiye ilişkin en sık aranan hasta soruları, daha önce arama geçmişi bulunmayan yeni bir Google hesabı kullanılarak belirlendi. Tekrar eden sorular çıkarıldıktan sonra toplam 24 soru çalışmaya dahil edildi. Her soru, daha önce konuşma geçmişi bulunmayan yeni bir hesap kullanılarak ChatGPT-4o'ya ayrı ayrı yöneltildi. Elde edilen yanıtlar, en az beş yıllık cerrahi deneyime sahip on jinekolog tarafından doğruluk, netlik, eksiksizlik ve alaka başlıkları altında beşli Likert ölçeği kullanılarak bağımsız olarak değerlendirildi. Tanımlayıcı istatistikler hesaplandı ve değerlendiriciler arası uyum sınıf içi korelasyon katsayısı ile analiz edildi.

Bulgular: Tüm sorular için ortalama puanlar doğruluk için 4,36, netlik için 4,55, eksiksizlik için 4,21 ve alaka için 4,59 olarak bulundu. Hiçbir yanıt herhangi bir değerlendirme alanında 3 puanın altında skor almadı. Değerlendiriciler arası güvenilirlik, değerlendirme alanlarına göre değişiklik göstermiştir. Yanıtlar genel olarak yüksek alaka ve anlaşılabilirlik düzeyi göstermesine karşın, eksiksizlik alanında görece daha düşük puanlar aldı.

Sonuç: ChatGPT-4o, laparoskopik histerektomi ile ilgili sık sorulan hasta sorularına genel olarak doğru, ilgili ve anlaşılır yanıtlar sunmaktadır. Bununla birlikte, eksiksizlik konusundaki sınırlılıklar, yapay zeka temelli bilgilerin hasta eğitimi açısından tamamlayıcı bir araç olarak değerlendirilmesi gerektiğini ve hekim danışmanlığının yerini alamayacağını göstermektedir.

Anahtar Kelimeler: Laparoskopik histerektomi, yapay zeka, hasta eğitimi, ChatGPT, minimal invaziv cerrahi

Introduction

Patients increasingly seek medical information online before consulting a physician, particularly for elective surgical procedures that raise concerns about safety, recovery, and long-term outcomes. Early studies demonstrated that a substantial proportion of patients use the internet as a primary source of health information, often prior to clinical encounters[1]. However, the quality, reliability, and interpretability of online medical content remain highly variable, and patients frequently struggle to distinguish accurate information from misleading or incomplete sources[2]. This phenomenon, commonly referred to as "Dr. Google", has reshaped the physician-patient relationship by influencing expectations, decision-making, and preoperative counseling[3,4].

With recent advances in artificial intelligence, large language models (LLMs) such as ChatGPT have emerged as a new generation of information tools that differ fundamentally from traditional web searches. Instead of directing users to static webpages, these models generate conversational, context-aware responses that may be perceived as personalized and authoritative. Consequently, LLMs have rapidly gained popularity among patients seeking answers to medical questions, including those related to surgical procedures. In obstetrics and gynecology, where patient education is often challenged by complex terminology and variable health literacy, AI-generated responses may offer both opportunities and risks[5-7]. While recent studies suggest that ChatGPT can provide generally accurate and readable information across various medical domains, concerns remain regarding consistency, completeness, and potential omissions of clinically relevant details[8,9].

Laparoscopic hysterectomy is one of the most commonly performed minimally invasive gynecologic surgeries worldwide and is associated with numerous patient concerns related to perioperative safety, postoperative recovery, sexual function, and long-term quality of life. These concerns frequently drive patients to search online for information prior to surgery. Despite the growing use of LLMs by patients, limited data exist on the quality of ChatGPT-generated responses to frequently searched questions about laparoscopic hysterectomy. This study aimed to evaluate the accuracy, clarity, completeness, and relevance of ChatGPT-4o responses to the most frequently Googled patient questions about laparoscopic hysterectomy, as assessed by experienced gynecologic surgeons.

Materials and Methods

This expert evaluation study assessed the quality of artificial intelligence-generated responses to patient-centered questions regarding laparoscopic hysterectomy. The study did not involve direct patient participation or the collection of personal health data. The ChatGPT-generated responses were independently evaluated by expert gynecologic surgeons using standardized assessment forms, and written informed consent was obtained from all expert gynecologic surgeons who served as evaluators in the study. Ethical approval was obtained from the University of Health Sciences

Türkiye, İzmir Tepecik Education and Research Hospital Non-Interventional Research Ethics Committee (approval no: 2025/08-25, date: 11.09.2025), prior to study initiation, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

A new Google account without prior search history was created to minimize personalization bias when identifying patient-centered questions. The "people also ask" and related question features were reviewed using predefined search terms related to laparoscopic hysterectomy to generate an initial pool of commonly searched questions. Approximately 100 questions were collected during this phase. Two investigators independently reviewed the questions to remove duplicates, merge conceptually overlapping items, and exclude questions unrelated to patient education. Any disagreements were resolved by consensus. This process resulted in a final list of 24 unique questions reflecting patients' most frequently searched concerns on Google regarding laparoscopic hysterectomy. The full list of the most frequently Googled patient questions about laparoscopic hysterectomy that were included in the analysis is presented in Table 1.

Table 1. Frequently Googled patient questions about laparoscopic hysterectomy included in the study

Question number	Question
1	What are the do's and don'ts after a laparoscopic hysterectomy?
2	What are the disadvantages of laparoscopic hysterectomy?
3	How long is bed rest after laparoscopic hysterectomy?
4	What food to avoid after laparoscopic hysterectomy surgery?
5	Which surgery is best for a hysterectomy?
6	What can prolapse after a laparoscopic hysterectomy?
7	What to know before having a laparoscopic hysterectomy?
8	What is the most common complication of a laparoscopic hysterectomy?
9	How much blood is lost during a laparoscopic hysterectomy?
10	What helps you heal faster after a laparoscopic hysterectomy?
11	How much walking is okay after a laparoscopic hysterectomy?
12	What is the best position to sit after a laparoscopic hysterectomy?
13	Why is the stomach swollen after a laparoscopic hysterectomy?
14	What are the risk factors for a laparoscopic hysterectomy?
15	What to expect 3 months after a laparoscopic hysterectomy?
16	What size uterus can be removed laparoscopically?
17	Is it okay to push to poop after a laparoscopic hysterectomy?
18	How soon can I fly after a laparoscopic hysterectomy?
19	How can I naturally lubricate after a laparoscopic hysterectomy?
20	Where do eggs go after a laparoscopic hysterectomy?
21	How many days bleeding after laparoscopic hysterectomy?
22	What is the best alternative to a laparoscopic hysterectomy?
23	What is the best age to get a laparoscopic hysterectomy?
24	What is the regret rate for a laparoscopic hysterectomy?

All questions were presented individually to ChatGPT (version 4o) via a newly created account with no prior conversation history to avoid contextual carryover. No additional prompts, clarifications, or follow-up questions were provided. Each question was entered separately, and responses were recorded verbatim. To reduce temporal and sequential biases, questions were administered at different time points rather than during a single session. The generated responses were not edited, summarized, or reformatted prior to evaluation.

Ten board-certified gynecologic surgeons with at least five years of independent clinical experience in minimally invasive gynecologic surgery participated as evaluators. All evaluators were blinded to the study design details and informed only that they were assessing written responses to patient questions related to laparoscopic hysterectomy. Evaluators were not informed that the responses had been generated by an artificial intelligence model.

Each response was independently evaluated by all ten surgeons using a five-point Likert scale across four predefined

domains: accuracy, clarity, completeness, and relevance. Accuracy reflected the factual correctness of the information provided; clarity assessed how easily the response could be understood by a lay audience; completeness evaluated whether key aspects of the question were adequately addressed; and relevance measured how well the response aligned with the patient's original question. Scores ranged from 1 (very poor) to 5 (excellent) for each domain.

The primary outcomes of the study were the mean scores for accuracy, clarity, completeness, and relevance across all questions. The secondary outcome was interrater reliability among evaluators within each evaluation domain.

Statistical Analysis

Descriptive statistics were used to summarize scores for each evaluation domain and were reported as mean ± standard deviation. Interrater reliability was assessed using intraclass correlation coefficients (ICCs) estimated from a two-way random-effects model with absolute agreement and average measures. This model was selected to reflect agreement among multiple independent raters evaluating the same set of responses. ICC values were interpreted according to established guidelines.

Results

A total of 24 ChatGPT-4o-generated responses corresponding to the most frequently Googled patient questions about laparoscopic hysterectomy were evaluated independently by 10 experienced gynecologic surgeons. Each response was scored across four predefined domains: accuracy, clarity, completeness, and relevance.

The mean accuracy score across all questions was 4.36±0.51. No response received a score below 3 from any evaluator. Several questions received a perfect mean score of 5.0, indicating unanimous agreement that the information provided was factually correct. Interrater reliability for accuracy yielded an ICC of 0.43 (95% confidence interval, 0.27-0.54).

Clarity received high overall ratings among the four evaluation domains. The mean clarity score was 4.55±0.32, with many responses showing minimal variability between evaluators. Multiple questions exhibited complete agreement, as reflected by a standard deviation of zero. Interrater reliability for clarity yielded an ICC of 0.48 (95% confidence interval, 0.29-0.64), which was the highest ICC observed among the evaluated domains.

The mean completeness score across all responses was 4.21±0.50. Although this domain yielded the lowest average score compared with those for accuracy, clarity, and relevance, each response was still rated above 3 by all evaluators. Interrater reliability for completeness yielded an ICC of 0.42 (95% confidence interval, 0.23-0.55).

Relevance achieved the highest mean score overall, with an average of 4.59±0.38. Responses were consistently judged to be well aligned with the corresponding patient questions, and no response was considered irrelevant. Interrater reliability analysis for relevance yielded an ICC of 0.33 (95% confidence interval, 0.17-0.45).

Across all four domains, ChatGPT-4o responses were rated favorably by expert evaluators, with mean scores exceeding 4.0 in each category. Mean scores for each evaluation domain, along with interrater reliability results, are summarized in Table 2.

Discussion

This study evaluated the quality of ChatGPT-4o responses to the most frequently Googled patient questions about laparoscopic hysterectomy using expert surgeon assessments across four domains: accuracy, clarity, completeness, and relevance. The findings demonstrate that ChatGPT-4o generally provides responses that are perceived as accurate, highly relevant, and easily understandable, with mean scores exceeding 4.0 in all evaluated domains. These results support the growing body of literature suggesting that LLMs can serve as a valuable adjunct source of medical information for patients seeking preliminary guidance before clinical consultation.

Among the evaluated domains, relevance and clarity achieved the highest mean scores. This finding indicates that ChatGPT-4o is particularly effective at aligning its responses with the intent of patients' questions and presenting information in a manner accessible to a lay audience. Similar observations have been reported in previous evaluations of

Table 2. Mean scores of ChatGPT-4o responses across evaluation domains

Evaluation domain	Mean ± SD	ICC
Accuracy	4.36±0.51	0.43
Clarity	4.55±0.32	0.48
Completeness	4.21±0.50	0.42
Relevance	4.59±0.38	0.33

SD: Standard deviation, ICC: Intraclass correlation coefficient

ChatGPT in surgical and gynecologic contexts, where clarity and relevance consistently outperformed other qualitative dimensions[8-10]. From a patient education perspective, these strengths are clinically meaningful, as misunderstandings related to surgical procedures often arise from unclear or overly technical explanations.

Accuracy scores were also high, with no response receiving a rating below 3 from any evaluator and several responses achieving unanimous agreement. This finding aligns with earlier studies demonstrating that ChatGPT frequently provides factually correct information across a range of medical and surgical topics[10,11]. However, accuracy alone does not equate to clinical adequacy. While responses were largely correct, they were not uniformly comprehensive, underscoring the importance of clinician involvement in patient counseling.

Completeness emerged as the lowest-scoring domain, although mean scores remained above 4.0. This pattern has been consistently reported in prior studies and reflects an inherent characteristic of LLMs, which tend to prioritize concise and broadly applicable responses rather than exhaustive clinical detail[8,12]. In the context of laparoscopic hysterectomy, this tendency may result in the omission of nuanced considerations such as individualized risk factors, rare complications, or institution-specific practices. While brevity may enhance readability for patients, it also highlights a key limitation of relying on AI-generated information for comprehensive preoperative counseling. This observation is consistent with broader evaluations of LLMs in clinical settings, which emphasize that although AI systems can support information delivery and patient engagement, they lack the capacity to replace clinician judgment and individualized decision-making[13].

According to established guidelines, the observed ICCs fall within the poor reliability range. However, ICC values should not be interpreted in isolation. As highlighted in recent methodological literature, studies characterized by restricted score variability and clustering of ratings at the upper end of the scale are expected to yield lower ICC estimates, despite consistent evaluator judgments. In the present study, the high mean scores and limited dispersion across evaluation domains suggest a ceiling effect, which likely contributed to reduced ICC values rather than true disagreement among evaluators[9,10,14-16].

The results of this study have practical implications for patient education in minimally invasive gynecologic surgery. As patients increasingly turn to search engines and conversational AI tools for health-related information, ChatGPT-4o may function as an accessible entry point for understanding common aspects of laparoscopic hysterectomy. However, the observed limitations in completeness reinforce the notion that AI-generated responses should complement, rather than replace, physician-led counseling. Clinicians should be aware of the types of information patients may encounter online and proactively address gaps or misconceptions during preoperative discussions.

Study Limitations

Several limitations warrant consideration. First, the study evaluated responses generated by a single version of ChatGPT at a specific time point, and model performance may evolve with future updates. Second, assessments were conducted exclusively by expert surgeons, which may not reflect patients' perceptions of quality or usefulness. Third, the study focused on commonly searched questions and may not capture less frequent but clinically important concerns. Another important limitation of this study is the absence of a direct comparator. ChatGPT-4o responses were not evaluated against established patient education resources, such as professional society guidelines, institutional websites, or standardized patient information leaflets. Therefore, the present findings should be interpreted as an assessment of AI-generated information in isolation rather than a comparative evaluation against existing educational standards. Future studies incorporating direct comparisons with validated patient education materials may provide additional insights into the relative strengths and limitations of AI-based tools. Despite these limitations, the standardized methodology, expert blinding, and use of multiple evaluative domains strengthen the robustness of the findings.

Conclusion

ChatGPT-4o provides responses to commonly searched questions about laparoscopic hysterectomy that are generally accurate, relevant, and clear, though occasionally incomplete. These findings suggest that while LLMs hold promise as supplementary tools for patient education, their outputs should be interpreted within the context of professional medical guidance.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, İzmir Tepecik

Education and Research Hospital Non-Interventional Research Ethics Committee (approval no: 2025/08-25, date: 11.09.2025).

Informed Consent: Written informed consent was obtained from all expert gynecologic surgeons who participated in the study by completing the evaluation forms.

Footnotes

Authorship Contributions

Concept: A.K., A.H.İ., Design: A.K., A.G., V.K., Data Collection or Processing: A.K., S.K., U.D., A.G., İ.U., V.K., A.H.İ., Analysis or Interpretation: U.D., İ.U., Literature Search: A.K., S.K., A.G., İ.U., V.K., Writing: A.K., S.K., U.D., A.H.İ.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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The Role of Nutritional Status in Patients with Type 1 Diabetes Mellitus

Tip 1 Diyabetes Mellitus Hastalarında Beslenme Durumunun Rolü

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Abstract

Objective: To comprehensively evaluate nutritional status in adults with type 1 diabetes mellitus (T1DM) by assessing both the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score and determining factors associated with malnutrition risk.

Methods: This retrospective cross-sectional study included 262 adults (132 T1DM and 130 healthy controls) who were followed at an internal medicine outpatient clinic. Demographic characteristics and routine laboratory measurements were retrieved from electronic medical records and patient files. PNI and CONUT were analyzed both as continuous and as categorical variables. Malnutrition risk, defined as CONUT ≥2, was explored using univariate and multivariate logistic regression adjusting for relevant metabolic and inflammatory parameters.

Results: Individuals with T1DM demonstrated significantly poorer nutritional profiles than controls, as reflected by lower PNI values and higher CONUT scores (both p<0.001). Severe nutritional impairment, based on PNI, was notably more frequent in T1DM, whereas optimal nutritional status was predominantly observed in controls (p<0.001). Similarly, malnutrition risk as assessed by CONUT was higher in patients with T1DM (p=0.003). In univariate analyses, both PNI and CONUT parameters were associated with compromised nutritional status. In the multivariate model, serum albumin, low-density lipoprotein cholesterol, and C-reactive protein remained independent correlates of malnutrition after adjustment.

Conclusion: Adults with T1DM exhibit substantial impairment in nutritional indices, as indicated by concordant abnormalities in both PNI and CONUT scores. Incorporating these complementary markers into routine clinical evaluations may facilitate early identification of biochemical malnutrition and support targeted nutritional and metabolic interventions.

Keywords: Type 1 diabetes mellitus, nutritional status, prognostic nutritional index

Öz

Amaç: Tip 1 diyabetes mellituslu (T1DM) erişkinlerde beslenme durumunu hem prognostik beslenme indeksi (PNI) hem de beslenme durumunu değerlendirme (CONUT) skoru üzerinden kapsamlı bir şekilde değerlendirmek ve malnütrisyon riski ile ilişkili faktörleri belirlemek.

Yöntem: Retrospektif ve kesitsel tasarıma sahip bu çalışmada, iç hastalıkları polikliniğinde izlenen 262 erişkin (132 T1DM, 130 sağlıklı kontrol) değerlendirildi. Demografik özellikler ile rutin laboratuvar ölçümleri elektronik tıbbi kayıtlar ve hasta dosyalarından elde edildi. PNI ve CONUT hem sürekli hem de kategorik değişkenler olarak analiz edildi. CONUT ≥2 ile tanımlanan malnütrisyon riski, ilgili metabolik ve inflamatuvar parametreler için yapılan uyarlamaları içeren tek değişkenli ve çok değişkenli lojistik regresyon modelleri ile incelendi.

Bulgular: T1DM'li bireylerde, kontrol grubuna kıyasla anlamlı derecede daha kötü beslenme profilleri saptandı; PNI değerleri daha düşük, CONUT skorları ise daha yüksekti (her ikisi için p<0,001). PNI'ya göre ciddi beslenme bozukluğu T1DM grubunda daha sık görülürken, optimal beslenme durumu çoğunlukla kontrol grubunda mevcuttu (p<0,001). Benzer şekilde, CONUT'a göre malnütrisyon riski T1DM'de daha yüksekti (p=0.003). Tek değişkenli analizlerde PNI ve

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Öz

CONUT parametrelerinin tümü bozulmuş beslenme durumuyla ilişkiliydi. Çok değişkenli modelde serum albümin, düşük yoğunluklu lipoprotein kolesterol ve C-reaktif protein, uyarlamalar sonrası malnütrisyonun bağımsız belirleyicileri olarak kaldı.

Sonuç: Erişkin T1DM hastalarında, hem PNI hem de CONUT skorlarındaki uyumlu bozukluklar beslenme indekslerinde belirgin bir kötüleşmeye işaret etmektedir. Bu tamamlayıcı beslenme belirteçlerinin rutin klinik değerlendirmelere entegre edilmesi, biyokimyasal malnütrisyonun erken tanımlanmasına yardımcı olabilir ve hedefe yönelik beslenme ile metabolik müdahaleleri destekleyebilir.

Anahtar Kelimeler: Tip 1 diyabetes mellitus, beslenme durumu, prognostik beslenme indeksi

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune condition in which pancreatic β-cells are progressively destroyed by immune mechanisms, leading to a complete loss of endogenous insulin production and the need for lifelong insulin replacement. Although T1DM may occur at any age, it is most frequently diagnosed in childhood, adolescence, and early adulthood[1]. Globally, the incidence of T1DM has continued to rise over the past decade, with the most recent epidemiological reports indicating an annual increase of 3-4%, particularly in Europe and North America[1]. This rising trend highlights the increasing health burden posed by T1DM and underscores the need to improve understanding of its metabolic, inflammatory, and nutritional consequences.

Nutritional status plays a pivotal role in the clinical course and metabolic control of individuals with T1DM. Chronic hyperglycemia, increased catabolic activity, autoimmune comorbidities (e.g., celiac disease, autoimmune gastritis), dyslipidemia, and persistent low-grade inflammation may negatively influence protein synthesis, lipid regulation, intestinal absorption, and immune competence. These mechanisms can impair serum albumin concentrations, reduce lymphocyte counts, and alter cholesterol homeostasis-parameters that collectively reflect immunonutritional health[2]. Evaluating nutritional status in T1DM is therefore clinically advantageous, as early identification of biochemical malnutrition may enable individualized dietary interventions, optimization of glycemic control, reduction in susceptibility to infection, and prevention of long-term complications. Furthermore, nutritional assessment may serve as a risk-stratification tool, providing complementary prognostic information beyond traditional glycemic markers.

Conventional approaches to nutritional evaluation, including body mass index (BMI) and subjective screening tools, may overlook early biochemical deterioration. Consequently, objective laboratory-based indices such as the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score have gained increasing prominence. PNI, which incorporates serum albumin and lymphocyte count, provides an integrated measure of protein reserves and immunologic competence. CONUT combines serum albumin, total cholesterol (TC), and total lymphocyte count, providing a broader assessment of metabolic and immune-nutritional status. Both indices are simple, reproducible, and cost-effective, relying on laboratory parameters routinely obtained in clinical practice, and are thus practical tools for screening malnutrition in metabolic diseases. Importantly, PNI and CONUT have been extensively validated across a wide range of chronic illnesses, including cardiovascular disease, chronic kidney disease, malignancies, cirrhosis, and heart failure, where they demonstrate strong associations with mortality, complications, hospitalization, and inflammation[3,4].

Despite their widespread application in chronic diseases, PNI and CONUT have been insufficiently studied in T1DM. Existing literature primarily focuses on type 2 diabetes mellitus (T2DM) or mixed diabetic cohorts, where poor PNI and elevated CONUT scores have been linked to suboptimal glycemic control, sarcopenia, microvascular complications, and increased mortality[5,6]. However, whether similar nutritional impairments occur in adults with T1DM-who often differ from T2DM patients in terms of age, body composition, autoimmune status, and metabolic profile-remains largely unexplored. To date, no study has comprehensively evaluated PNI and CONUT scores in a well-defined adult T1DM population compared with healthy controls. Thus, the lack of characterization of immunonutritional status in T1DM represents an important gap in current knowledge, with potential implications for early intervention, personalized dietary planning, and long-term risk mitigation.

Assessing PNI and CONUT in adults with T1DM may offer significant contributions to the literature for several reasons. First, identifying early biochemical malnutrition in this population-often young and without overt complications-may help anticipate future vulnerability to sarcopenia,

frailty, and poor metabolic resilience. Second, given emerging evidence linking PNI and CONUT to diabetic retinopathy, nephropathy, cardiovascular disease, and mortality in broader diabetic cohorts[7,8], understanding their behavior in T1DM could inform individualized risk-stratification strategies. Determining whether albumin, cholesterol, inflammatory markers, or glycemic indicators predominantly drive nutritional impairment in T1DM could elucidate underlying pathophysiological mechanisms distinct from those in T2DM.

Therefore, the present study aimed to evaluate immunonutritional status in adults with T1DM by analyzing PNI and CONUT scores and comparing them with age-matched healthy controls. Additionally, we sought to determine the prevalence of biochemical malnutrition in T1DM, to identify laboratory predictors of CONUT-defined malnutrition risk, and to assess whether T1DM itself remains an independent determinant of nutritional impairment after adjustment for metabolic and inflammatory variables. By addressing these objectives, this study provides novel insight into the immunonutritional profile of adults with T1DM and contributes meaningful evidence to an underexplored area of diabetes research.

Materials and Methods

Study Design and Population

This retrospective cross-sectional study was conducted at the Internal Medicine outpatient clinics of University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital between January 2023 and May 2025. A total of 262 individuals aged 18-75 years were included, comprising 132 patients diagnosed with T1DM and 130 age-matched healthy controls without any known chronic disease. The study was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital (approval no: 2025/11-11, date: 12.06.2025).

Inclusion criteria: Patients aged 18-75 years with a confirmed diagnosis of T1DM based on the American Diabetes Association 2024 criteria (clinical symptoms of hyperglycemia, age <35 years at onset, random plasma glucose ≥200 mg/dL, fasting glucose ≥126 mg/dL, 2-hour oral glucose tolerance test ≥200 mg/dL, positive autoantibodies, C-peptide <0.6 ng/mL, and/or hemoglobin A1c (HbA1c) ≥6.5%)[9]. Healthy individuals aged 18-75 years with no chronic medical conditions.

Exclusion criteria: T2DM patients, gestational diabetes, acute or chronic inflammatory diseases, active infection, hematologic disorders, malignancy, use of medications affecting lipid metabolism, chronic liver or kidney disease.

Data Collection

As this was a retrospective study, no additional laboratory tests were performed. Demographic characteristics (age, sex) and laboratory data were retrieved from electronic medical records. The following parameters were recorded: leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts; Hb, glucose, glycated HbA1c, urea, creatinine, aspartate aminotransferase, alanine aminotransferase (ALT), TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), C-reactive protein (CRP), and serum albumin.

Nutritional Indices

PNI was calculated as: PNI =albumin(g/L)+5×lymphocyte count (10^9/L)[7-8]. PNI was evaluated both as a continuous variable and in three categories: PNI <45=severe impairment, 45-49.9=moderate risk ≥50=good nutritional status[7,8].

The CONUT score was determined using serum albumin, TC, and total lymphocyte counts. Each parameter is assigned a specific score. A serum albumin level of ≥3.5 g/dL receives 0 points; levels between 3.0 and 3.4 g/dL receive 2 points; levels between 2.5 and 2.9 g/dL receive 4 points; and values below 2.5 g/dL are assigned 6 points. For TC, a level of ≥180 mg/dL is scored as 0 points; 140-179 mg/dL as 1 point; 100-139 mg/dL as 2 points; and <100 mg/dL as 3 points. For the total lymphocyte count, ≥1600 cells/μL corresponds to 0 points; 1200-1599 cells/μL to 1 point; 800-1199 cells/μL to 2 points; and <800 cells/μL to 3 points (Table 1)[7,8]. The sum of these three components provides an overall indication of nutritional status. Malnutrition risk was defined as CONUT ≥2[7,8].

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Normality of distribution was assessed using the Kolmogorov-Smirnov test. Group comparisons were conducted as follows: independent samples t-test: for normally distributed continuous variables, chi-square test: for categorical variables (e.g., PNI categories, CONUT ≥2).

Nutritional indices (PNI and CONUT) were compared between groups both as continuous and categorical variables.

Malnutrition risk (CONUT ≥2) was further evaluated using: univariate logistic regression to identify crude associations, multivariate logistic regression including variables significant in univariate analysis (T1DM status, albumin, LDL-C) odds ratios (ORs) and 95% confidence intervals were reported.

Results

A total of 262 participants were included in the study, comprising 132 individuals with T1DM and 130 healthy controls. Age and sex distributions were comparable between the groups (p>0.05) (Table 2).

Regarding hematologic parameters, including leukocyte, neutrophil, lymphocyte, platelet, and Hb values, no significant differences were observed between the groups (p>0.05). Glucose and HbA1c levels were markedly elevated in the T1DM group (both p<0.001). Urea levels were significantly higher among patients with T1DM (p=0.004), while creatinine

Table 1. CONUT score calculation

Variables	Undernutrition status			
	Normal	Light	Moderate	Severe
Albumin (g/dL)	≥3.5	3.0-3.49	2.5-2.9	<2.5
Points	0	2	4	6
Total lymphocyte count (/mm³)	>1,600	1.200-1.599	800-1.199	<800
Points	0	1	2	3
Total cholesterol (mg/dL)	>180	140-180	100-139	<100
Points	0	1	2	3
Total CONUT score	0-1	2-4	5-8	9-12

CONUT: Controlling nutritional status

Table 2. Demographic, hematologic, and biochemical characteristics of the study population

Parameter	T1DM (n=132)	Control (n=130)	p-value
Age (years)	26.93±7.26	27.58±5.69	0.424
Male sex, n (%)	64 (48.5)	61 (46.9)	0.897
Leukocyte (10^3/µL)	7389.02±1820.30	7413.08±1592.10	0.909
Neutrophil (10^3/µL)	4360.76±1547.48	4390.08±1290.03	0.868
Lymphocyte (10^3/µL)	2287.58±710.50	2228.77±563.62	0.458
Platelet (10^3/µL)	284219.70±72220.43	268369.23±69260.90	0.071
Hemoglobin (g/dL)	13.86±1.84	14.08±1.54	0.297
Glucose (mg/dL)	231.44±120.70	87.45±8.70	**<0.001**
HbA1c (%)	9.28±2.12	5.23±0.25	**<0.001**
Urea (mg/dL)	27.64±16.90	23.09±6.51	**0.004**
Creatinine (mg/dL)	0.83±1.17	0.80±1.44	0.819
AST (U/L)	20.30±8.83	21.32±6.91	0.298
ALT (U/L)	18.53±11.13	23.54±17.38	**0.006**
Triglyceride (mg/dL)	135.81±112.51	110.02±66.27	**0.025**
LDL-C (mg/dL)	107.98±35.26	92.64±24.67	**<0.001**
HDL-C (mg/dL)	52.32±12.61	49.62±10.21	0.058
Total cholesterol (mg/dL)	184.37±44.93	164.49±30.64	**<0.001**
CRP (mg/L)	3.70±2.81	2.45±2.13	**<0.001**
Albumin (g/L)	37.58±6.85	42.00±3.55	**<0.001**

Continuous variables are presented as mean±standard deviation and were compared using the independent samples t-test. Categorical variables were compared using the chi-square test. A p-value <0.05 was considered statistically significant

T1DM: Type 1 diabetes mellitus, HbA1c: Hemoglobin A1c, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein

levels did not differ between groups. ALT levels were significantly higher in the control group (p=0.006; Table 2).

In the lipid profile, TG levels, LDL-C levels, and TC levels were significantly higher in the T1DM group (p<0.05 for all), whereas HDL-C levels showed no significant difference (p=0.058). CRP levels were markedly elevated in the T1DM group (p<0.001). Albumin levels were lower in patients with T1DM than in controls (p<0.001) (Table 2).

Nutritional indices showed significant differences between the groups: PNI values were lower, and CONUT scores were higher in the T1DM group (both p<0.001) (Table 3). In categorical PNI analysis, severe nutritional impairment (PNI <45) was notably more common in T1DM patients (36.4%) compared with controls (5.4%), whereas optimal nutritional status (PNI ≥50) was more prevalent in controls (77.7%) (p<0.001) (Table 4, Figure 1).

Based on CONUT ≥2, malnutrition risk was significantly higher in the T1DM group (54.5%) than in controls (35.4%) (p=0.003) (Table 5, Figure 1).

Table 3. Comparison of nutritional indices between groups

Parameter	T1DM (n=132)	Control (n=130)	p-value
PNI	49.01±7.61	53.14±4.80	**<0.001**
CONUT	2.04±1.81	1.22±0.92	**<0.001**

Continuous variables are presented as mean±standard deviation. Groups were compared using the independent samples t-test
T1DM: Type 1 diabetes mellitus, PNI: Prognostic nutritional index, CONUT: Controlling nutritional status

Table 4. Distribution of PNI categories in T1DM and control groups

Group	PNI <45	PNI 45-49.9	PNI ≥50	p-value
Control	7 (5.4%)	22 (16.9%)	101 (77.7%)	
T1DM	48 (36.4%)	20 (15.2%)	64 (48.5%)	**<0.001**

Group comparisons were performed using the chi-square test. PNI<45=severe nutritional impairment; PNI 45-49.9=moderate nutritional risk, PNI≥50=good nutritional status, T1DM: Type 1 diabetes mellitus, PNI: Prognostic nutritional index

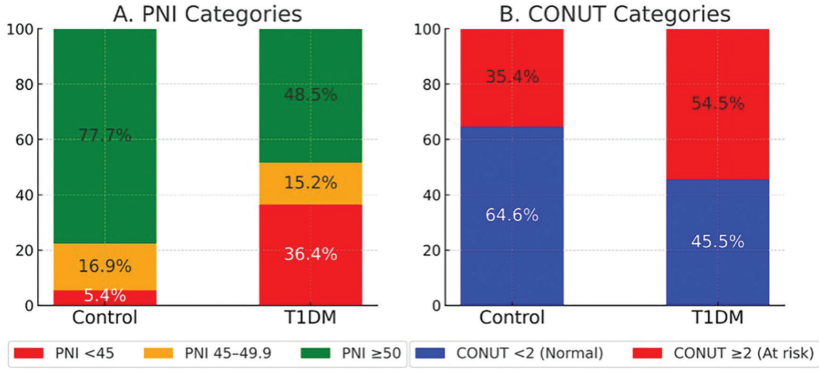

Figure 1. Distribution of nutritional status based on PNI and CONUT in adults with T1DM and controls

Panel A (PNI categories): stacked bar chart showing the distribution of PNI categories in the control and T1DM groups. Nutritional status is classified as PNI <45 (red; severe impairment), PNI 45-49.9 (orange; moderate impairment), and PNI ≥50 (green; optimal nutritional status). Controls predominantly exhibited optimal PNI values (77.7%), whereas individuals with T1DM showed markedly higher proportions of severe (36.4%) and moderate (15.2%) nutritional impairment. Panel B (CONUT categories): stacked bar chart illustrating CONUT categories. CONUT <2 (blue) indicates normal nutritional status, while CONUT ≥2 (red) reflects malnutrition risk. The T1DM group demonstrated a substantially higher prevalence of risk of malnutrition (54.5%) compared with controls (35.4%), whereas normal nutritional status was more common among controls (64.6%). Both panels highlight that adults with T1DM exhibit a significantly altered nutritional profile compared with healthy controls, consistent with group-level differences observed in PNI and CONUT scoring. Percentages displayed on each bar represent the proportion of participants within each category

PNI: Prognostic nutritional index, CONUT: Controlling nutritional status, T1DM: Type 1 diabetes mellitus

In univariate logistic regression analysis, T1DM status was significantly associated with malnutrition risk (OR=2.19; p=0.002). Albumin, LDL-C, and CRP were all significantly related to CONUT ≥2 in univariate analyses. In the multivariate model, albumin (adjusted OR=0.75; p<0.001), LDL-C (adjusted OR=0.96; p<0.001), and CRP (adjusted OR=1.05; p=0.026) remained independent predictors of malnutrition risk, whereas the association between T1DM and malnutrition risk became non-significant (p=0.139) (Table 6, Figure 2).

Table 5. Malnutrition risk based on CONUT ≥2

Group	CONUT <2 (normal)	CONUT ≥2 (at risk)	p-value
Control	84 (64.6%)	46 (35.4%)	
T1DM	60 (45.5%)	72 (54.5%)	**0.003**

OR=2.19, 95% CI: 1.33-3.60 interpretation: T1DM patients have approximately 2.2-fold higher odds of malnutrition compared with healthy controls. Group comparisons were made using the chi-square test.

CONUT <2=normal nutritional status; CONUT ≥2=at risk of malnutrition, T1DM: Type 1 diabetes mellitus, CONUT: Controlling nutritional status, OR: Odds ratio, CI: Confidence interval

Table 6. Logistic regression analysis for CONUT ≥2

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
T1DM (vs. control)	2.19 (1.33-3.60)	0.002	1.67 (0.85-3.28)	0.139
LDL-C (per 1 mg/dL)	0.98 (0.97-0.99)	<0.001	0.96 (0.95-0.98)	**<0.001**
Albumin (per 1 g/L)	0.80 (0.75-0.85)	<0.001	0.75 (0.69-0.81)	**<0.001**
CRP (mg/L)	1.08 (1.03-1.14)	0.006	1.05 (1.01-1.11)	0.026

Univariate and multivariate logistic regression analysis for predictors of malnutrition risk (defined as CONUT ≥2). Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Variables with p<0.05 in univariate analysis were included in the multivariate model. OR <1 indicates an inverse association with malnutrition risk; OR >1 indicates increased odds of malnutrition risk. OR: Odds ratio, CI: Confidence interval, CONUT: Controlling nutritional status score, T1DM: Type 1 diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol

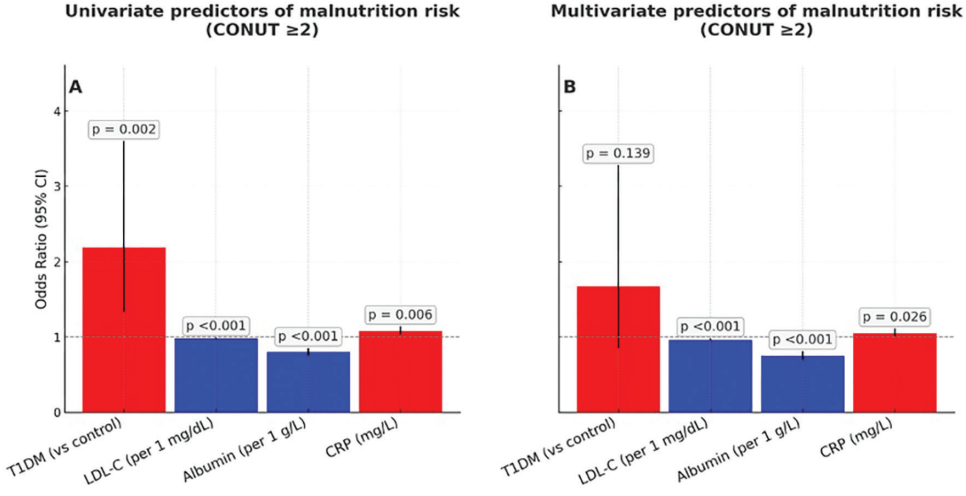

Figure 2. Univariate and multivariate logistic regression results for predictors of malnutrition risk (CONUT ≥2)

Panel A and Panel B display the univariate and multivariate logistic regression analyses evaluating predictors of malnutrition risk (defined as CONUT ≥2). Bars indicate odds ratios, and error bars represent 95% CIs; the dashed line denotes OR=1. Red and blue are used only to visually distinguish variables with ORs above or below 1. In the univariate model (Panel A), T1DM, lower LDL-C, lower albumin, and higher CRP were significantly associated with malnutrition risk. In the multivariate model (Panel B), albumin, LDL-C, and CRP remained independent predictors, whereas T1DM was no longer statistically significant

CONUT: Controlling nutritional status, OR: Odds ratio, CI: Confidence interval, T1DM: Type 1 diabetes mellitus, CRP: C-reactive protein

Discussion

In this retrospective case-control study, we evaluated objective immunonutritional indices (PNI and CONUT) in adults with T1DM and found that these adults exhibited significantly lower PNI and higher CONUT scores than age-matched healthy controls. These findings indicate that biochemical malnutrition is common, even among relatively young adults with T1DM. Our results complement growing evidence suggesting that nutritional disturbances-particularly those affecting albumin, lymphocyte count and lipid metabolism-are increasingly recognized as clinically relevant components of the metabolic and inflammatory milieu of T1DM.

Data on objective laboratory-based malnutrition indices in T1DM are sparse. Most recent work has focused either on dietary intake or on body-composition-derived measures, such as sarcopenia. A recent systematic review of older adults with T1DM reported that nutritional status and dietary intake are often suboptimal in this population, highlighting persistent nutrition-related challenges despite advances in diabetes care[10]. Similarly, a 2025 systematic review found that sarcopenia was associated with T1DM, with inflammation, poor glycemic control and reduced physical activity as major contributors[11]. Our observation that more than one-third of T1DM patients had PNI <45 and more than half had CONUT ≥2 is consistent with these reports and indicates that biochemical markers capture a substantial burden of malnutrition that may not be apparent from BMI alone.

Most studies using PNI and CONUT in diabetes have been conducted in T2DM or mixed diabetic cohorts. Piersa et al.[12] evaluated PNI and CONUT in adults with T2DM and showed that a substantial proportion of patients met malnutrition criteria, and that lower PNI and higher CONUT scores were significantly associated with poorer glycemic control and a higher burden of comorbidities. In a large cardiology cohort of patients with type 2 diabetes and angiographically confirmed coronary artery disease, malnutrition defined by the CONUT score was highly prevalent (over half of patients), and poorer nutritional status was independently associated with increased long-term all-cause mortality and adverse cardiovascular outcomes[13]. Our prevalence estimates in T1DM (54.5% with CONUT ≥2) are somewhat higher than those reported in T2DM and mixed diabetic populations[12,13]. This discrepancy may have several explanations: (I) our T1DM cohort being hospital-based and likely enriched for patients with suboptimal control; (II) autoimmune T1DM being frequently accompanied by concomitant autoimmune thyroid disease, celiac disease, or gastritis, which can negatively affect nutritional status; and (III) differences in age structure and duration of diabetes between studies. Nonetheless, the direction of effect-a shift towards poorer nutritional indices in diabetes compared with non-diabetic controls-is consistent across studies.

While our study identified albumin and LDL-C as key predictors of CONUT-defined malnutrition, other investigators have emphasized BMI, skeletal muscle mass and functional measures as predominant determinants of nutritional indices in diabetes[14]. We lacked body composition data or detailed dietary assessments, which may have limited our ability to identify sarcopenic or cachectic phenotypes. Consequently, our findings should be interpreted as primarily reflecting the biochemical rather than the functional dimension of malnutrition.

Recent narrative and systematic reviews have highlighted the tight interplay between diabetes, malnutrition and sarcopenia, emphasizing that chronic hyperglycemia, low-grade inflammation, and hormonal changes accelerate muscle catabolism and worsen functional outcomes[14,15]. Our finding of lower albumin and PNI in T1DM is in line with this concept of a "diabetes-malnutrition-sarcopenia" axis. Although we did not directly assess muscle mass or function, the presence of biochemical malnutrition in a relatively young cohort may herald subsequent sarcopenia and frailty if left unaddressed. Growing evidence indicates that PNI and CONUT are not only markers of nutritional status but also predictors of micro- and macrovascular complications in diabetes. In a large T2DM cohort, lower PNI independently predicted all-cause and cardiovascular mortality[16]. PNI has also been associated with diabetic nephropathy[17], diabetic peripheral neuropathy[18] and diabetic retinopathy[19]. Likewise, higher CONUT scores have been linked to diabetic retinopathy[20] and diabetic kidney disease, with some reports suggesting sex-specific differences, particularly stronger associations in women[20].

Our study did not specifically evaluate microvascular complications or long-term outcomes; however, the degree of PNI and CONUT impairment we observed in T1DM is similar to or worse than that reported in these complication-focused cohorts[21]. This suggests that even in the absence of overt complications, many adults with T1DM may already be on an unfavorable immunonutritional trajectory. From a

pathophysiological perspective, the same composite deficits-hypoalbuminemia, lymphopenia, and dyslipidemia-that lower PNI or raise CONUT may also promote endothelial dysfunction, oxidative stress, and impaired tissue repair, thereby predisposing to microvascular injury.

The biological plausibility of our findings is supported by recent work linking PNI and CONUT with systemic inflammation. PNI integrates serum albumin with lymphocyte count; both components are influenced by chronic inflammatory activity. Large observational studies have shown that lower PNI predicts adverse outcomes in infectious conditions[22,23]. Similarly, the CONUT score is now recognized as a practical immunonutritional screening tool in hospitalized patients, with higher scores consistently associated with complication and mortality risk[24,25].

In our cohort, CRP levels were higher in T1DM than in controls, paralleling lower albumin and PNI and higher CONUT. This mirrors data from broader diabetic and cardiovascular populations where composite indices that combine nutritional parameters-such as the HbA1c or hybrid scores incorporating PNI-have been shown to outperform single markers in risk prediction[26]. While we did not test such composite indices, our data support the notion that immunonutritional derangements reflect the convergence of poor metabolic control, chronic inflammation, and catabolic stress in T1DM.

Notably, after adjustment, serum albumin and LDL-C-but not T1DM status per se-remained independent predictors of CONUT-defined malnutrition risk. This suggests that within a mixed diabetic/non-diabetic population, the biochemical expression of malnutrition is more strongly driven by direct nutritional and metabolic parameters than by the diagnostic label of diabetes itself.

Previous studies in heterogeneous diabetic cohorts have identified older age, low BMI, reduced energy and protein intake, longer diabetes duration, and comorbid conditions as key determinants of malnutrition[14]. Very few studies have specifically examined LDL-C as an independent covariate. In T2DM, some authors reported that higher CONUT scores coincide with lower TC and LDL-C, reflecting a catabolic or inflammatory state rather than classical atherogenic dyslipidemia[24,25]. Our finding of an inverse association between LDL-C and CONUT is consistent with these observations and highlights the dual role of cholesterol as both a cardiovascular risk factor and a surrogate marker of nutritional reserves. Aggressive statin use is less common in young adults with T1DM than in older adults with T2DM; therefore, lower LDL-C in the malnourished subgroup is unlikely to be driven solely by lipid-lowering therapy and may instead reflect reduced dietary intake, malabsorption, or chronic disease-related catabolism.

The loss of statistical significance for the "T1DM vs. control" variable in our multivariable model aligns with the growing evidence that the prognostic impact of diabetes is often mediated through deterioration in immunonutritional status, rather than acting as an entirely independent risk factor. Recent analyses in diabetic and prediabetic cardiovascular cohorts have demonstrated that low PNI strongly predicts all-cause and cardiovascular mortality, underscoring the central role of immunonutrition in shaping long-term outcomes[27]. Similarly, studies comparing T1DM and T2DM patients undergoing dialysis show that poorer nutritional profiles substantially modify clinical risk, further supporting the concept that diabetes-related adverse outcomes may, at least in part, reflect downstream nutritional and inflammatory disturbances rather than the binary presence of diabetes alone[28]. Accordingly, once key biochemical components of nutritional status, such as albumin and LDL-C, are included in our model, the incremental contribution of the diabetes label diminishes, without implying that T1DM itself lacks prognostic relevance.

Certain aspects of our results differ from some reports in the literature and merit discussion. While many T2DM studies have noted strong associations between higher CONUT scores and the presence or severity of specific complications-such as retinopathy, nephropathy or diabetic kidney disease[29,30]-we did not include complication data in our analysis. As a result, we cannot test whether similar relationships hold in T1DM. The absence of outcome data might give the impression that CONUT is less informative in T1DM; however, this is likely a limitation of our design rather than a true biological difference.

Mechanistic reviews have shown that lipid abnormalities in T1DM are shaped by complex interactions involving insulin deficiency, hepatic lipid handling, and inflammatory pathways, indicating that dyslipidemia in T1DM differs qualitatively from that observed in T2DM[31]. These discrepancies may stem from differences in statin use, diet, physical activity, regional dietary patterns, and healthcare access. Regional dietary habits, genetic background, and socioeconomic factors may influence albumin and cholesterol levels in Turkish adults with T1DM, warranting

careful interpretation of PNI and CONUT thresholds. In our study, the T1DM group had higher TG, LDL-C, and TC levels than the controls. Our cohort represents routine clinical practice at a single center and may include patients with suboptimal adherence or limited access to lipid-lowering therapy, which could accentuate the association between dyslipidemia, malnutrition, and inflammation.

Clinical Implications and Future Directions

Despite these limitations, our study has several important clinical implications. First, it demonstrates that simple, routinely available laboratory parameters-albumin, lymphocyte count, and TC-can be combined into indices that detect a high burden of malnutrition in adults with T1DM, even when BMI may appear normal. Given emerging data linking PNI and CONUT with diabetic complications and mortality, early identification of at-risk individuals using these tools may allow timely nutritional interventions, optimization of glycemic control, and more intensive cardiovascular risk management.

Second, our results support the integration of immunonutritional screening into routine diabetes care and suggest that T1DM should not be viewed solely through the lens of glucose metrics. Comprehensive assessment of diet quality, protein intake, body composition, and functional status should accompany biochemical indices to provide a multidimensional picture of nutritional health. Interventional trials are now needed to test whether targeted nutritional support in patients with T1DM who have low PNI or high CONUT can reduce incident sarcopenia, improve quality of life, and mitigate microvascular or cardiovascular complications.

Finally, multicenter prospective cohorts with longer follow-up and detailed characterization of both T1DM and T2DM populations are required to clarify whether the prognostic thresholds for PNI and CONUT should differ by diabetes type, age, sex, or comorbidity profile. The development of composite indices that integrate nutritional markers may provide an additional avenue for refining risk-stratification in clinical practice.

Study Limitations

The strengths of our study include the focus on a relatively understudied population (adults with T1DM), the use of two complementary, widely validated nutritional indices (PNI and CONUT), and the inclusion of a contemporaneous healthy control group.

Nonetheless, several limitations must be acknowledged: a retrospective, single-center design; lack of detailed data on diabetes duration, insulin dose, BMI, body composition, and dietary intake (calorie and protein); and absence of information on microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications.

Additionally, urinary protein excretion (e.g., albuminuria or proteinuria) was not systematically recorded due to the retrospective design of the study. Although patients with clinically diagnosed chronic kidney disease were excluded, we cannot fully exclude the possibility that unrecognized proteinuria may have contributed to lower serum albumin levels in some individuals with T1DM. Therefore, albumin-based nutritional indices should be interpreted with this limitation in mind. Prospective studies incorporating quantitative measurements of proteinuria are warranted to further refine albumin-based nutritional assessment in T1DM.

Conclusion

In summary, our findings demonstrate that adults with T1DM exhibit significantly poorer immunonutritional profiles-reflected by lower PNI and higher CONUT scores-than healthy controls and have a high prevalence of biochemical malnutrition. These results align with and extend emerging evidence that malnutrition and inflammation are integral components of the diabetic phenotype and may contribute to adverse outcomes. Further prospective studies are warranted to determine whether routine screening and targeted correction of nutritional deficits in T1DM can improve long-term prognosis.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital (approval no: 2025/11-11, date: 12.06.2025).

Informed Consent: Retrospective cross-sectional study.

Footnotes

Authorship Contributions

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

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