

# ZK

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Table 1: Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
Review Article	5000	350	50	6	10
Case Report	1500	200	15	No tables	5
Letter to the Editor	1000	No abstract	10	No tables	No media
Image	200	No abstract	3	No table	3

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*Book section:* Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. *Infectious Diseases*. Philadelphia: Lippincott Williams; 2004.p.2290–308.

*Books with a single author:* Sweetman SC. *Martindale the Complete Drug Reference*. 34<sup>th</sup> ed. London: Pharmaceutical Press; 2005.

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# Healthcare-associated infection in neonates and risk factors: A four-year surveillance study (2020–2024)

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## ABSTRACT

**Objective:** Healthcare-associated infections (HAIs) represent a significant source of morbidity and mortality in neonatal intensive care units (NICUs). During the neonatal period, risk factors include prematurity, an immature immune system, invasive procedures, and prolonged hospitalization. This study aimed to identify the causative agents and risk factors associated with HAIs.

**Material and Methods:** This study encompassed 297 patients who were hospitalized in the NICU and diagnosed with HAIs between January 1, 2020, and December 30, 2023. Demographic, clinical, and laboratory data were retrospectively analyzed.

**Results:** According to the type of HAIs, bloodstream infection (BSI) accounted for 53% (n=158), central line-associated BSI (CLABSI) for 4.3% (n=13), urinary tract infection for 8.7% (n=26), ventilator-associated pneumonia (VAP) for 0.3% (n=1), bone and joint infection for 1% (n=3), and skin and soft tissue infection for 1.3% (n=4). The CLABSI and VAP rates were 5.45 and 1.67, respectively. The overall mortality rate was 3% (n=9). The most commonly isolated agents were Gram-positive bacteria (79.8%), Gram-negative bacteria (17.8%), and *Candida spp.* (2.4%). Statistically significant differences were observed in prematurity ( $p=0.010$ ), birth weight ( $p<0.001$ ), mode of delivery ( $p=0.010$ ), postnatal days ( $p=0.012$ ), duration of hospitalization ( $p=0.004$ ), mechanical ventilation ( $p=0.009$ ), operation ( $p=0.031$ ), presence of total parenteral nutrition ( $p<0.001$ ), and central venous catheter use ( $p<0.001$ ) between the groups.

**Conclusion:** Consistent with the existing literature, Gram-positive microorganisms were identified as the predominant causative agents of HAIs. However, the incidence of Gram-negative bacteria and *Candida spp.* increased in the presence of specific risk factors. Identifying causative agents and associated risk factors is crucial for mitigating HAIs in the NICU.

**Keywords:** Bloodstream infection, healthcare-associated infections, neonatal intensive care unit.

This study was presented as an oral presentation at a symposium  
(4<sup>th</sup> Eastern Pediatric Congress, 26–29 September 2024, University of Dicle, Congress Center, Diyarbakır, Türkiye).

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## INTRODUCTION

Healthcare-associated infections (HAIs) are a considerable source of morbidity and mortality, including long-term neurodevelopmental impairment, in neonatal intensive care units (NICUs), thereby contributing to increased hospital expenditure.<sup>[1,2]</sup> The Centers for Disease Control and Prevention (CDC) reports that one in 31 hospital patients has an HAI.<sup>[3]</sup> HAIs are considered infections characterized by their onset within 48 hours of birth or hospital admission during the neonatal period. During the neonatal period, various factors, such as prematurity, an immature immune system, invasive interventions performed in the NICU, and the coexistence of underlying diseases, increase the risk of HAIs.<sup>[4]</sup> HAIs include bloodstream infections (BSIs), ventilator-associated pneumonia (VAP), urinary tract infections (UTIs), meningitis, skin and soft tissue infections (SSIs), and central line-associated BSIs (CLABSIs).<sup>[5]</sup>

The incidence of HAIs varies across countries and hospitals. In low- and middle-income countries, the incidence of HAIs in NICUs ranges from 15.2 to 62.0 per 1000 patient-days, which is nine times higher than the rates observed in certain high-income settings.<sup>[6]</sup> In resource-constrained contexts, such as sub-Saharan Africa, where 42% of global neonatal deaths occur, research focused on infection prevention and the establishment of surveillance systems aims to reduce the rate of neonatal infections.<sup>[7]</sup> However, HAIs have also been reported in high-income countries, such as Italy (5%), Canada (24%), and Germany (12.3%).<sup>[8–10]</sup> Considering that HAIs in the neonatal period are among the preventable causes of death, healthcare centers should identify risk factors and causative microorganisms to reduce morbidity and mortality. The objective of this study was threefold: first, to ascertain the incidence of HAIs; second, to identify the implicated microorganisms; and third, to examine the risk factors associated with HAIs within the NICU of our center.

## MATERIAL AND METHODS

### Participants

This retrospective cohort study encompassed 297 patients who were hospitalized in the NICU between January 2020 and December 2023 and from whom microorganisms were isolated from clinical samples (blood, urine, and respiratory). During the four-year study period, 4,303 neonates were observed in the NICU; however, those who did not fulfill the criteria for HAIs were excluded from the study.

### Data Analysis

A retrospective evaluation of the clinical and microbiological characteristics of the patients was conducted using medical records. The patients' sex, birth weight, gestational age, mode of delivery, comorbidities, invasive devices (central line catheterization), mechanical ventilation, day of hospitalization, operation, exposure to antimicrobial therapy, site of infection, and day of postpartum onset of infection were recorded. The causative microorganisms were classified into three categories: Gram-positive, Gram-negative, and fungal. A comparative analysis of the clinical and microbiological characteristics of the patients was conducted.

## Definitions

HAIs were considered to occur within 48h after birth or admission. All infections, including BSI, CLABSI, and VAP, were defined using the CDC NHS surveillance guide and local surveillance guidelines adapted to neonatology.<sup>[11–13]</sup>

BSI was diagnosed based on clinical findings and hemoculture results. The microorganism was accepted as the causative agent if it was not associated with an infection elsewhere in the body and if skin flora agents, such as *Bacillus spp.*, *Corynebacterium*, or coagulase-negative staphylococci, were detected in two or more samples.

UTI was diagnosed according to CDC criteria for patients aged <1 year (with or without a urinary catheter). The presence of an indwelling urinary catheter for a duration exceeding two consecutive days led to the diagnosis of catheter-associated urinary tract infection (CAUTI).

Ventilator-associated pneumonia (VAP) was defined in patients who met the modified pneumonia criteria for children aged <1 year according to the CDC definition and who were on mechanical ventilation for at least two consecutive calendar days.

CLABSI was defined as the recovery of a pathogenic organism from a blood culture in a patient who had received a central line for a minimum of two consecutive days during the period of infection.

The HAI rate was defined as (number of healthcare-associated infections/number of hospitalized patients)×100. Incidence density was defined as (number of healthcare-associated infections/patient days)×1000. Invasive device-related infection rates were defined as CLABSI per catheterization day and VAP per 1000 ventilation days.

## Statistical Analysis

Statistical analyses were performed using SPSS version 21. Descriptive statistics were presented as means, standard deviations, numbers, and percentages. Group comparisons were conducted using analysis of variance (ANOVA) and post hoc analyses for parametric variables, and the Kruskal–Wallis and Mann–Whitney U tests for non-parametric variables. Statistical significance was set at  $p < 0.05$ . This study was approved by the Mardin Artuklu University Clinical Research Ethics Committee (2024/3-25). Informed consent was obtained from the parents. The study was conducted in accordance with the principles of the Declaration of Helsinki.

## RESULTS

### Demographic and Clinical Characteristics

The study included 297 patients who were followed up in the NICU of our hospital between 2020 and 2023, in whom microbiological agents were detected in clinical specimens and who met the definition of HAIs. The patients' mean age was  $8 \pm 7.7$  (2–52) postnatal days; 36.7% (n=109) were female, 63.3% (n=188) were male, 31% (n=92) were preterm, and 69% (n=164) were term. Based on birth weight for gestational age, 84.5% (n=251) were appropriate for gestational age (AGA), 14.5% (n=43) were small for gestational age (SGA), and 1% (n=3) were large for gestational age (LGA). Regarding mode of delivery, 55.2% (n=164) were vaginal deliveries and 44.8% (n=133) were cesarean sections. The mean birth weight was  $2807 \pm 803$  (900–4550) g, and the mean duration

of hospitalization was 15.6±22 (2–245) days. Comorbidities were present in 19.9% (n=59) of patients; exposure to antibiotics was 34% (n=101); operations were performed in 5.7% (n=17); total parenteral nutrition (TPN) was administered to 26.9% (n=80); central venous catheter (CVC) use was 24.9% (n=74); and mechanical ventilation (invasive/noninvasive) was required in 50.1% (n=149).

### Types of Infections and Distribution of Pathogens for HAIs

Bloodstream infections (84.3%) were the most common HAIs, followed by UTIs (8.8%), CLABSIs (4.3%), SSIs (1.34%), bone and joint infections (1.01%), and VAP (0.3%). The incidence of HAIs was 12.49 per 1000 patient-days, and the overall HAI rate was 6.9% per 100 admissions. The rates of CLABSI and VAP were 5.45 and 1.67 per 1000 device-days, respectively. A total of 62% of subjects with UTIs had a documented history of catheterization. Data were unavailable for the remaining subjects; however, all cases met the established criteria for symptomatic UTIs in children aged <1 year.

The most prevalent pathogens were Gram-positive microorganisms (*Staphylococcus spp.*, *Streptococcus spp.*, *Enterococcus spp.*) (79.8%), followed by Gram-negative microorganisms (*Klebsiella pneumoniae*, other *Enterobacteriaceae spp.*, *Pseudomonas aeruginosa*) (17.8%) and *Candida spp.* (2.4%) (Table 1). The causative agents of CLABSI were *Klebsiella pneumoniae* (n=8), *Staphylococcus aureus* (n=2), and *Pseudomonas aeruginosa* (n=1). The prevalence of ESBL positivity in *Klebsiella pneumoniae* infections was 1% (n=3). All *Pseudomonas aeruginosa* isolates were susceptible to carbapenems. All *Staphylococcus* and *Enterococcus spp.* were susceptible to vancomycin. All *Candida spp.* were susceptible to fluconazole, itraconazole, and amphotericin B.

### Comparison of Risk Factors According to Causative Pathogens

The three groups showed statistically significant differences in postnatal days (p=0.012), duration of hospitalization (p=0.004), birth weight (p<0.001), gestational age (p=0.01), mode of delivery (p=0.01), comorbidity (p=0.002), mechanical ventilation (p=0.009), CVC use (p<0.001), TPN (p<0.001), and operation (p=0.031).

In the fungal group, birth weight and duration of hospitalization were significantly lower in Gram-positive (p<0.001 and p=0.03) and Gram-negative (p<0.001 and p=0.013, respectively) cases, whereas postnatal days were significantly higher only in Gram-positive cases (p=0.024). Additionally, gestational age, mode of delivery, comorbidities, mechanical ventilation, CVC use, and TPN were significantly higher in the fungal group compared with the other groups. The overall mortality rate was 3% (n=9), with no statistically significant difference between groups (Table 2). A total of 66.6% of deceased patients had comorbid conditions, including congenital heart disease, trauma, necrotizing enterocolitis, and congenital metabolic disease.

## DISCUSSION

Although the global burden of HAIs in the neonatal period cannot be precisely determined because of differences in definitions and reporting, studies have indicated that HAIs are more frequent in the NICU than in other ICUs.<sup>[1,14]</sup> In Europe, approximately one in

**Table 1: The distribution of pathogens of Healthcare-Associated Infections**

	n	%
Gram-positive microorganisms	237	79.8
<i>Staphylococcus spp</i>		
<i>Coagulase Negative Staphylococci</i>	196	65.9
<i>S. aureus</i>	7	0.3
<i>Streptococcus spp</i>	20	6.7
<i>Enterococcus spp</i>	14	4.7
Gram-negative microorganisms	53	17.8
<i>K.pneumoniae</i>	20	6.7
<i>P.aeruginosa</i>	7	2.3
<i>Acinetobacter spp</i>	1	0.3
<i>Serratia spp</i>	4	1.3
<i>Enterobacteriaceae spp</i>	19	6.3
Other	2	0.6
Fungus	7	2.4
<i>Candida albicans</i>	5	1.7
<i>Candida guilliermondii</i>	1	0.3
<i>Candida parapsilosis</i>	1	0.3
Total	297	100

10 infants requires hospitalization in the NICU during the first days of life. Although survival rates for these infants have improved, bacterial colonization in hospital settings, combined with various risk factors, increases vulnerability to infections caused by resistant microorganisms. Therefore, in 2021, a surveillance toolkit was developed through the European Union (EU)-funded NeolPC project (establishing innovative approaches for optimal infection prevention of resistant bacteria in NICUs by integrating research, implementation science, and surveillance on a sustainable global platform) to monitor and prevent HAIs in at-risk infants, particularly those born preterm.<sup>[15]</sup>

The World Health Organization (WHO) has focused on healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) in G7 countries and has published a global report on infection prevention and control strategies.<sup>[16,17]</sup> According to this report, the global incidence of HAIs was 15.4 cases per 1000 adult patients and was >7 times higher among neonates, with 112.9 cases per 1000 neonates.<sup>[18,19]</sup> Newborns were found to be at higher risk of acquiring HAIs, with infection rates in low-income countries being 3–20 times higher than those in high-income countries.

In Türkiye, the incidence of HAIs in the NICU was reported as 23.5% and 7.6% in two national point-prevalence studies conducted at different times.<sup>[20,21]</sup> Atıcı et al.<sup>[22]</sup> reported an overall HAI rate of 29.1% and a density of 21.8 per 1000 patient-days. In two retrospective studies, HAI rates of 4.9% and 14.9% were reported in NICUs.<sup>[23,24]</sup> In the present study, the overall HAI rate was 6.9%, which was slightly lower than those reported in comparable national studies.

**Table 2: Comparison of Gram positive/Gram negatives microorganisms/Candida spp (n/% or mean±SD)**

	Gram positives			Gram negatives			Candida spp			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Sex										0.139
Female	91	30		14	4.7		4	1.3		
Male	146	49		39	13		3	1.1		
Birth weight for gestational age										0.99
AGA	203	68.3		45	15		6	2		
SGA	34	11.4		8	26		1	0.3		
Gestational age								2.3		<b>0.010</b>
Term	163	54		42	14		0			
Preterm	74	25		11	37		7			
Mode of delivery								2.3		<b>0.010</b>
VD	132	44		32	11		0			
CS	105	35		21	7		7			
Birth weight (g)			2811.6878± 759			2978.7736± 853			1350±341	<b>&lt;0.001</b>
Length of hospital stay (day)			14.51±22.1			16.96±19.76			42±23.29	<b>0.004</b>
Postnatal day			7.19±8.12			8.9±7.09			15.42±6.5	<b>0.012</b>
Comorbidity	42	14		12	4		5	1.7		<b>0.002</b>
Mechanical ventilation										<b>0.009</b>
No	117	39.4		30	10		1	0.3		
NIV	79	26.5		9	3		0			
Invasive	41	13.8		14	4.7		6	2		
CVC	52	17.5		16	5.4		6	2		<b>&lt;0.001</b>
TPN	54	18.2		20	6.7		6	2		<b>&lt;0.001</b>
Operation	12	4		3	1		2	0.6		<b>0.031</b>
Previous antibiotic exposure	80	26.9		16	5.4		5	1.7		0.095
Mortality	8	2.7		0			1	0.3		0.093

AGA: Appropriate for gestational age; SGA: Small for gestational age; CVC: Central venous catheter; TPN: Total parenteral nutrition; NIV: Non-Invasive; CS: Cesarean sections, VD: Vaginal delivery.

Although the incidence of bloodstream infections has decreased with improved preventive measures, BSIs remain an important problem in the neonatal period due to emerging resistant pathogens.<sup>[25]</sup> Previous studies have reported that BSIs accounted for 44%, 51.8%, and 83% of HAIs in the NICU.<sup>[26–28]</sup> According to the CDC, hospital-onset bacteremia (HOS) is classified as an HAI, with an incidence rate of 1.1 per 1000 patient-days (2%), and occurs in the absence of a central line in 54.2% of cases. Low birth weight is a significant risk factor, and among patients with HOS, the risk increases with postnatal age and is associated with mortality.<sup>[29]</sup> In the present cohort, BSI (84.3%) was the most prevalent HAI, followed by UTI (8.8%) and CLABSI (4.3%). Ventilator-associated pneumonia accounted for only 0.3% of cases. The rate of hospital-acquired pneumonia was lower in our cohort than in previous studies reporting higher rates of 33.3% and 24.4%, respectively.<sup>[22,30]</sup> Prematurity, prolonged hospitalization,

and low birth weight have been documented as risk factors for VAP. Avoidance of prolonged mechanical ventilation and strict adherence to hand hygiene are key preventive strategies against VAP.<sup>[31]</sup> Compliance with these preventive measures, along with potential underdiagnosis or underreporting of VAP, may have contributed to the low incidence observed in this study. In contrast, BSI was identified as the predominant cause of HAIs, which is consistent with the existing literature.

A study by Castrillo (Spanish National Network for the Surveillance of Neonatal Infections) found that the most common pathogens causing nosocomial sepsis were Gram-positive bacteria (66%), followed by Gram-negative bacteria (28%) and *Candida spp.* (6%) in very-low-birth-weight infants.<sup>[32]</sup> Findings from a point-prevalence study indicated that coagulase-negative staphylococci (CNS) constituted the most prevalent pathogens

among HAIs, with *Enterobacteriaceae* ranking second.<sup>[33]</sup> In a meta-analysis conducted in Brazil, CNS (32.1%), *Staphylococcus aureus* (13.8%), and *Klebsiella spp.* (12.4%) were identified as the most common pathogens.<sup>[27]</sup> However, Gram-negative pathogens also represent an important proportion of HAI pathogens in neonates. In a study by Bedir Demirdağ et al.,<sup>[21]</sup> Gram-negative pathogens were identified in 43% of cases, with *Klebsiella pneumoniae* being the most common (22%). The most frequently isolated pathogens in Italy were *Pseudomonas aeruginosa* (17%), *Candida parapsilosis* (16.3%), *Escherichia coli* (13.1%), and *Candida albicans* (10.5%).<sup>[26]</sup>

*Candida spp.* are considered part of the normal microbiota of the skin and vaginal mucosa. Newborns may be colonized with *Candida spp.* through vaginal transmission at birth or via nosocomial transmission in the hospital setting.<sup>[34]</sup> In the presence of various risk factors, colonization may progress to invasive infection and result in serious complications.<sup>[35]</sup> Although low birth weight and prematurity are well-known risk factors, one study reported that the mean birth weight of infants with invasive candidiasis was 1270g and that 19% were born at <28 weeks of gestation.<sup>[36]</sup> Additional risk factors have also been identified,<sup>[37]</sup> including prolonged use of broad-spectrum antibiotics, CVC use, TPN administration, corticosteroid therapy, and poor adherence to infection control practices.<sup>[38]</sup> Both CVCs and peripherally inserted central catheters increase the risk of skin barrier disruption, dissemination of *Candida spp.* to sterile sites, and biofilm formation on catheter surfaces.<sup>[39]</sup>

In addition to isolated candidemia, complications such as endophthalmitis, endocarditis, liver or splenic abscesses, and neurological involvement may occur during the neonatal period.<sup>[34]</sup> In the present study, risk factors including TPN and CVC use, low birth weight, and prolonged hospitalization were significantly more frequent among patients with *Candida spp.* infections; however, no difference in mortality was observed, and *Candida spp.*-related tissue involvement (endophthalmitis) was identified in one patient.

## Limitations

This retrospective study was conducted at a single center over a four-year period. The COVID-19 pandemic occurred during the study timeframe, and various factors, such as disruptions in infection control practices and surveillance systems, may have influenced the results. Although several studies have addressed this issue, the potential impact of the pandemic on HAI rates in the NICU remains unclear, as comparisons with pre-pandemic data were not performed.

## CONCLUSION

The neonatal period, particularly in preterm infants, is characterized by increased susceptibility to HAIs due to immune immaturity and the presence of multiple risk factors. Although Gram-positive organisms were predominant, Gram-negative bacteria and *Candida spp.* also constituted significant challenges in the NICU. The implementation of effective surveillance systems, minimization of modifiable risk factors (such as duration of CVC use and TPN administration), and strict adherence to basic infection prevention measures, including hand hygiene, are essential for reducing HAIs.

## Statement

**Ethics Committee Approval:** The Mardin Artuklu University Clinical Research Ethics Committee granted approval for this study (date: 05.03.2024, number: 2024/3-25).

**Informed Consent:** Informed consent was obtained from the parents.

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# Therapeutic curettage as a safe and effective first-line approach in cesarean scar pregnancy: A single-center comparative analysis with the literature

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## ABSTRACT

**Objective:** Cesarean scar pregnancy (CSP) is a rare ectopic pregnancy implanted in a previous cesarean scar and is associated with risks of hemorrhage, uterine rupture, and infertility. Rising cesarean rates have increased its incidence, accounting for up to 6% of ectopic pregnancies. Diagnosis is made by transvaginal ultrasound, which typically shows an empty uterine cavity and a gestational sac at the anterior isthmus with thin myometrium. Treatment options include methotrexate, uterine artery embolization, hysteroscopic or laparoscopic excision, and curettage. No consensus standard exists; management should be individualized.

**Material and Methods:** We retrospectively analyzed 129 CSP patients treated between 2015 and 2025 at Zeynep Kamil Hospital, Istanbul. Inclusion required an ultrasound-confirmed diagnosis and complete hematologic data. Patients managed conservatively or with incomplete records were excluded. Treatment included primary curettage, methotrexate plus curettage, or laparoscopic repair. Curettage was ultrasound-guided using a Karman cannula. Hemoglobin and hematocrit levels were compared pre- and postoperatively, and transfusion needs were documented.

**Results:** Of the 129 patients, 123 (95.4%) underwent curettage, 3 underwent methotrexate plus curettage, and 3 underwent laparoscopic repair. The mean hemoglobin drop was 0.8 g/dL ( $p < 0.001$ ), and the mean hematocrit decrease was 2.2% ( $p < 0.001$ ). Only 3 patients (2.3%) required transfusion. Subgroup analysis showed greater hemoglobin decline in patients with a gestational age  $\geq 8$  weeks and fetal cardiac activity. Compared with the literature reporting larger declines and higher transfusion rates, our outcomes were favorable.

**Conclusion:** Ultrasound-guided therapeutic curettage is a safe, effective, and fertility-preserving first-line treatment for CSP. It achieved low blood loss and minimal transfusion requirements compared with prior reports. Despite the retrospective design and lack of long-term follow-up, our results support curettage as a reliable option in appropriately selected patients.

**Keywords:** Blood transfusion, cesarean scar pregnancy, ectopic pregnancy, hemoglobin drop, therapeutic curettage, ultrasound-guided aspiration.

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## INTRODUCTION

Cesarean scar pregnancy (CSP) is a rare but increasingly recognized form of ectopic pregnancy, in which the gestational sac implants at the site of a previous cesarean section scar. This condition poses serious risks, including massive hemorrhage, uterine rupture, and loss of fertility. With the global rise in cesarean delivery rates, the incidence of CSP is also increasing. CSP may account for up to 6% of all ectopic pregnancies and is one of the most challenging conditions to manage in early pregnancy.<sup>[1]</sup>

The pathophysiology of CSP involves implantation of the embryo into a microscopic tract or defect in the myometrium at the site of a prior uterine incision. As the pregnancy progresses, the gestational sac may invade deeply into the myometrium or even beyond the uterine serosa, leading to catastrophic complications. Diagnosis is primarily established via high-resolution transvaginal ultrasonography, which reveals an empty uterine cavity, an empty cervical canal, and a gestational sac located at the anterior uterine isthmus with thin or absent myometrial tissue between the sac and the bladder.<sup>[2]</sup>

Several treatment options have been proposed, including systemic or local methotrexate (MTX) administration, hysteroscopic or laparoscopic resection, and surgical evacuation via suction or sharp curettage. The choice of therapy depends on factors such as gestational age, presence of fetal cardiac activity, extent of myometrial invasion, CSP type, hemodynamic status, and fertility preservation goals.<sup>[3]</sup>

Previous studies have shown varying degrees of success and complications with each treatment modality. MTX may require multiple doses and prolonged follow-up and can be less effective in cases with fetal cardiac activity or high  $\beta$ -hCG levels. Surgical approaches, especially curettage, are technically simple but may result in significant hemorrhage if not carefully planned.<sup>[4]</sup>

Despite advances in medical and surgical management, there is currently no universally accepted gold standard for CSP treatment.<sup>[5]</sup> Management must be individualized according to gestational age, presence of fetal cardiac activity, residual myometrial thickness, and fertility goals.<sup>[6]</sup>

The aim of our study is to present the outcomes of patients treated for CSP at a high-volume tertiary center where therapeutic curettage is the primary intervention and to evaluate hemoglobin and hematocrit changes and transfusion requirements. We also aim to compare these outcomes with those reported in recent literature.

## MATERIAL AND METHODS

This retrospective study reviewed the medical records of 129 patients diagnosed with CSP between January 2015 and December 2025 at Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Istanbul, Türkiye. Diagnosis was confirmed using transvaginal ultrasonography. Ethics approval was obtained from the institutional ethics committee of Zeynep Kamil Women and Children's Diseases Training and Research Hospital with decision number 82, dated December 11, 2024. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were a confirmed diagnosis of CSP on transvaginal ultrasound, a history of at least one cesarean delivery, and complete documentation of pre- and postoperative hemoglobin and hematocrit values. Patients were excluded if they had incomplete records, underwent only conservative treatment without surgical intervention, were younger than 18 or older than 45 years, or had chronic medical conditions that could affect hematologic parameters.

Therapeutic strategies included primary curettage, methotrexate followed by curettage, and laparoscopic repair.<sup>[5,6]</sup> Hemoglobin and hematocrit levels were assessed preoperatively and postoperatively. Transfusion requirements were recorded.

To enhance safety, all procedures were performed in the operating room under anesthesiologist supervision. Hemostasis was ensured through continuous ultrasound monitoring, gentle negative-pressure aspiration, and stepwise evacuation. In cases with moderate bleeding, intravenous tranexamic acid and uterotonics were administered, while surgical hemostatic measures (balloon tamponade, bipolar coagulation, or laparoscopic conversion) were considered as backup strategies but were not required in our cohort.

## Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM SPSS Statistics 22). Descriptive statistics were presented as frequency, mean $\pm$ standard deviation, median, and minimum–maximum values. The Wilcoxon signed-rank test was used to compare dependent variables. A p-value of  $<0.05$  was considered statistically significant. The findings were also compared with selected studies from the literature.

## RESULTS

Of the 129 patients, 123 (95.4%) underwent therapeutic curettage, while 3 patients received methotrexate followed by curettage, and another 3 underwent laparoscopic repair.

In the therapeutic curettage group, the mean preoperative hemoglobin was  $12.2\pm 1.2$  g/dL, and the mean postoperative hemoglobin was  $11.4\pm 1.1$  g/dL, indicating a mean hemoglobin drop of 0.8 g/dL ( $p<0.001$ ). The mean hematocrit decreased from 36.9% to 34.7%, corresponding to an average reduction of approximately 2% ( $p<0.001$ ). Only three patients (2.3%) in this group required blood transfusion (Table 1).

Compared with recent literature, which has reported hemoglobin reductions ranging from 1.7 to 2.2 g/dL and transfusion rates as high as 9.9% following surgical management of CSP, our findings suggest favorable hematologic outcomes with minimal transfusion requirements.<sup>[6]</sup>

## DISCUSSION

Our study demonstrates that therapeutic curettage, when performed under continuous ultrasound guidance using vacuum aspiration with a Karman cannula, is a safe and effective first-line option for the management of cesarean scar pregnancy (CSP). The mean hemoglobin drop of 0.8 g/dL and the transfusion requirement of only 2.3% in our cohort compare favorably with previously reported

**Table 1: Demographic, clinical, and hematologic characteristics of patients with cesarean scar pregnancy (n=129)**

Parameter	Value
Age, years	33.5±5.2 (20–45)
Gravida, median (min–max)	3 (2–9)
Parity, median (min–max)	2 (1–8)
Previous cesarean deliveries, mean±SD (range)	1.8±0.76 (1–4)
Treatment method, n (%)	Therapeutic curettage: 123 (95.4%) Methotrexate+curettage: 3 (2.3%) Laparoscopic repair+curettage: 3 (2.3%)
Gestational age, weeks	7.5±1.56 (4–11)
Fetal cardiac activity, n (%)	Present: 35 (27.1%) Absent: 94 (72.9%)
BMI (n=74)	29±5.2 (20–43)
Gestational sac size, mm (n=65)	14.8±8.9 (3–36)
Crown-rump length, mm (n=68)	9.2±7.2 (2–32)
Preoperative hemoglobin, g/dL	12.2±1.2
Postoperative hemoglobin, g/dL	11.4±1.1
Mean Hb drop, g/dL (p-value)	0.8 (p<0.001)
Preoperative hematocrit, %	36.9±3.5
Postoperative hematocrit, %	34.7±3.2
Mean Hct drop, % (p-value)	2.2 (p<0.001)
Blood transfusion, n (%)	Yes: 3 (2.3%) No: 125 (97.7%)
Subgroup analysis	Hb drop ≥8 weeks GA: 1.0 g/dL vs <8 weeks: 0.6 g/dL (p=0.04) Hb drop with FHR present: 1.1 g/dL vs absent: 0.7 g/dL (p=0.03)

SD: Standard deviation; BMI: Body Mass Index.

figures, in which hemoglobin reductions of 1.7–2.2 g/dL and transfusion rates approaching 10% have been documented.<sup>[7]</sup> These favorable outcomes likely reflect early diagnosis, meticulous patient selection, and consistent institutional expertise.

A previous study emphasized that outcomes of curettage vary by CSP type, with type I and II cases responding better to minimally invasive approaches, whereas type III CSP carries a higher risk of hemorrhage and often requires more complex interventions.

<sup>[7]</sup> Similarly, Alameddine et al.<sup>[1]</sup> reported that gestational age at diagnosis and residual myometrial thickness are strong predictors of intraoperative bleeding risk. In our study, CSP type stratification was not performed, which represents a limitation; nonetheless, the low rate of major complications suggests that careful selection of candidates for curettage was achieved.

Alternative management strategies have been widely explored in the literature. Methotrexate, either systemic or local, has been used to avoid surgical intervention; however, it is less effective in cases with positive fetal cardiac activity or high β-hCG levels and requires prolonged follow-up. Uterine artery embolization (UAE) can be effective in controlling hemorrhage, but concerns remain regarding its impact on subsequent fertility.<sup>[8]</sup> Minimally invasive surgical approaches, particularly hysteroscopic resection, have shown high success rates in selected series. Laparoscopic repair with defect closure has also been reported to be effective for deeply invasive type III CSP.<sup>[9]</sup> Recent studies have further demonstrated that combining hysteroscopy with suction curettage may enhance visualization and safety, offering an alternative in selected cases.<sup>[10]</sup> Similarly, contemporary series have confirmed the safety of ultrasound-guided suction curettage with low complication rates.<sup>[11]</sup>

Another important area of concern is reproductive outcomes following CSP treatment. Studies have shown variable subsequent pregnancy rates and have highlighted the risk of recurrent CSP.<sup>[8,12]</sup> In our cohort, long-term fertility outcomes were not systematically assessed, which is a notable limitation. Future studies should address these outcomes in a standardized manner, ideally within prospective multicenter frameworks.

The strengths of our study include the large single-center cohort, a standardized treatment protocol, and detailed perioperative hematologic assessment. Limitations include the retrospective design, absence of CSP type stratification, and lack of long-term follow-up on reproductive outcomes. Despite these limitations, our findings add robust evidence that therapeutic curettage, when carefully planned and executed, is a reliable and fertility-preserving treatment option for appropriately selected CSP patients.

In summary, early diagnosis, meticulous patient selection, and the use of standardized ultrasound-guided aspiration techniques allow therapeutic curettage to be considered a safe and effective first-line management strategy for CSP. Further prospective multicenter studies incorporating CSP typing and reproductive outcomes are warranted to establish optimal treatment algorithms.

## CONCLUSION

Therapeutic curettage, when performed under ultrasound guidance and within standardized protocols, represents a safe, effective, and fertility-preserving first-line treatment for cesarean scar pregnancy in carefully selected patients. Our findings demonstrate significantly lower hemoglobin decline and transfusion requirements compared with previously reported outcomes. These results highlight the importance of early diagnosis, meticulous patient selection, and consistent institutional expertise. Future multicenter prospective studies incorporating CSP type stratification and long-term reproductive outcomes are warranted to establish evidence-based management algorithms.

## Statement

**Ethics Committee Approval:** The Zeynep Kamil Women and Children's Diseases Training and Research Hospital Ethics Committee granted approval for this study (date: 11.12.2024, number: 82).

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

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# Women's experiences of fighting migraine during the menstrual cycle: A qualitative study

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## ABSTRACT

**Objective:** To determine pain characteristics, pain intensity, and symptom changes during migraine attacks in premenstrual and menstrual women.

**Material and Methods:** This qualitative phenomenological study was conducted from April 1 to April 30, 2024, involving 21 women aged between 18 and 52 years who had been diagnosed with migraine. The participants presented to the neurology outpatient clinic of a training and research hospital with complaints of pain during their menstrual periods. Data were collected through individual in-depth interviews, which were audio recorded.

**Results:** A total of 21 female patients with migraine participated in the study. The mean age of the participants was 30.90±7.1 years, the mean age at migraine onset was 19.19±3.49 years, and the mean duration of migraine pain was 11.95±7.16 hours. Migraine pain was described as unilateral or bilateral in 12 cases (57.14%). Pain frequency was 1–4 times per month in 12 participants (57.14%), pain duration was 1–4 hours in 9 participants (42.86%), 12 participants (57.14%) took medication within 30 minutes to 4 hours after pain onset, and 18 participants (85.71%) reported difficulty concentrating due to pain. Five main themes were identified: “characteristics of migraine pain,” “symptoms initiating a migraine attack,” “physical findings accompanying migraine,” “psychosocial findings accompanying migraine,” and “coping with migraine.”

**Conclusion:** The findings emphasize the need for better management of perimenstrual migraine attacks in all menstruating women. Patients' knowledge about the disease and its characteristics should be improved, and they should be informed that migraine is an incurable but controllable chronic disease and that its attacks can be prevented.

**Keywords:** Menstrual cycle, migraine, qualitative study.

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## INTRODUCTION

Migraine is a common and disabling neurological disorder that affects approximately 14% of the global population, with a significantly higher prevalence in women, particularly during their reproductive years. It typically occurs in younger individuals, with a higher prevalence in women.<sup>[1,2]</sup> Hormonal fluctuations associated with the menstrual cycle have been consistently implicated as key triggers for migraine attacks. The International Classification of Headache Disorders (ICHD-3) categorizes menstrual migraine (MM) into two types: menstruation-related migraine (MRM) and pure menstrual migraine (PMM). Women diagnosed with MM often report that these menstrual attacks are more painful, longer-lasting, more disabling, and less responsive to treatment.<sup>[3]</sup>

The “estrogen deprivation hypothesis” suggests that fluctuations in estrogen levels associated with female fertility contribute to increased susceptibility to migraine in women.<sup>[4]</sup> Specifically, estrogen levels experience a sudden decrease in the days leading up to menstruation. Consequently, the highest susceptibility to migraine occurs during the premenstrual period. The years surrounding menopause can heighten the risk of severe migraine in women, largely due to significant fluctuations in estrogen levels during this period.<sup>[5,6]</sup> The influence of hormonal changes on migraine is substantial enough that menstrual migraine is classified as a distinct headache disorder in the current international classification.<sup>[7]</sup>

Despite advancements in understanding the neurobiological mechanisms, the precise pathophysiology underlying menstrual migraine remains elusive, and effective management strategies are limited. While epidemiological studies have provided valuable insights into the prevalence and clinical features of menstrual migraine, qualitative data exploring women’s lived experiences during these attacks are scarce. Most existing studies focus on physiological mechanisms or treatment modalities, often overlooking the personal, emotional, and functional impact of migraine attacks coinciding with menstruation.

Understanding how women perceive and cope with menstrual migraine episodes is crucial for developing comprehensive management approaches that extend beyond pharmacological interventions. Exploring these experiences through qualitative inquiry can provide nuanced insights into symptom variability, psychosocial burden, and coping strategies employed by affected women.

The present study aims to explore women’s experiences of pain intensity, symptom changes, and the impact on daily life during migraine attacks in the premenstrual and menstrual periods using a qualitative phenomenological approach. This exploration is essential to address the gap in the literature regarding the subjective experience of menstrual migraine and to inform the development of patient-centered care strategies.

## MATERIAL AND METHODS

This qualitative phenomenological study was conducted from April 1 to April 30, 2024, involving 21 women aged 18–52 years who had been diagnosed with migraine. The participants presented to the neurology outpatient clinic of a training and research hospital with complaints of pain during their menstrual periods. Data were collected through individual in-depth interviews, which were audio recorded.

## Sampling

A purposive sampling method was used among individuals who met the research criteria, and maximum variation sampling was applied to recruit participants. In purposive sampling, the aim is to select individuals who can provide the most appropriate responses relevant to the aims of the research.<sup>[8]</sup> Before starting the study, women with migraine who met the inclusion criteria were identified. A total of 38 female patients with migraine who were eligible according to the research criteria were reached. A suitable outpatient clinic room was arranged to conduct one-to-one in-depth interviews. The study was completed with 21 female patients with migraine when data saturation was achieved (i.e., repetition of the same or similar data).

## Inclusion Criteria

Diagnosis of migraine; being menstruating; being aged 18–52 years; having experienced migraine attacks in the last three premenstrual cycles; being able to read and write; having no communication barrier; and volunteering to participate in the study.

The researcher collected data by conducting individual in-depth interviews with women with migraine. The interviews were conducted in a private room with the participant alone, seated at the same level as the interviewer, with active listening. A semi-structured question form was used, and the interviews were audio recorded.

Participants provided written consent for involvement in the study. Audio recordings were stored on the computer hard disk. Each participant was interviewed once for approximately 30–40 minutes.

Before initiating the study, the researchers conducted a literature review and developed an information form consisting of seven questions, open-ended questions related to the topic, and 14 questions about migraine and the menstrual period. Questions about migraine and the menstrual period were asked after the open-ended questions. The open-ended questions were structured in a semi-structured format to create a general profile of the participants and identify characteristics that may be useful for future research. The interview guide covered four topics relevant to the study. The questions were as follows: (1) Can you describe the migraine pain you experience during the menstrual period? (2) What do you experience during migraine pain during the menstrual period? (3) How do you feel during migraine pain during the menstrual period? (4) What do you do during migraine pain during the menstrual period?

“The data obtained in all interviews and the findings from the analyses were reported, enabling in-depth exploration of participants’ experiences and perspectives. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study methods were reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) established by Tong and colleagues in 2007.<sup>[9]</sup> The final number of participants interviewed was determined based on achieving data saturation. The research received ethical approval from the Research Ethics Committee of Maltepe University in Istanbul, Türkiye (decision number: 2024/03-01).

**Table 1: Demographic characteristics of the participants (n=21)**

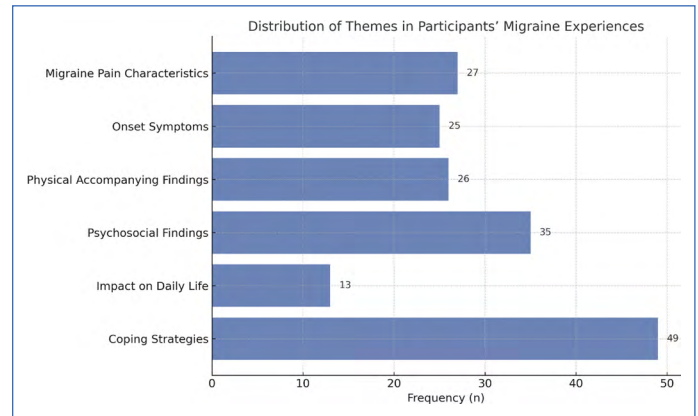
Characteristic	n	%	Mean±SD
Age (years)	–	–	30.90±7.1
Marital status			
Single	15	71.4	
Married	6	28.6	
Occupation			
Housewife	8	38.1	
Healthcare Personnel	6	28.6	
Other (banker, teacher, academic)	7	33.3	
Working hours			
Not working	1	4.8	
5–8 hours/day	14	66.7	
9+ hours/day	6	28.6	
Mode of work			
Day shift	16	76.2	
Shift work	5	23.8	
Age at first menstruation (years)	–	–	13.29±0.78

This table summarizes the demographic profiles of the participants, including age, marital status, occupation, working hours, work shifts, and age at first menstruation. Data are presented as frequencies (n), percentages (%), and mean±standard deviation (SD) where appropriate

### Statistical Analysis

The one-to-one interviews were read multiple times and coded by two research analysts using content analysis and grounded theory methods appropriate for concept elicitation for measurement development. The coded content was analyzed and exported to Excel to condense the data within each code by measuring and summarizing, identifying themes in the data and documenting instances of non-confirmation. All interviews were transcribed verbatim, and the transcripts were analyzed thematically using NVivo, a software designed for qualitative data analysis. The analysis followed the steps recommended by Braun and Clarke. Thematic analysis was selected due to its flexibility in identifying patterns of meaning (themes) within a dataset to address a research question and to “give voice” to lived experiences. Accordingly, our approach was primarily inductive, as we coded data based on participants’ experiences to explore how migraine pain during the menstrual period affected them. A small degree of deductive assumption was used to elicit meaning across all aspects of the individual. Therefore, an inductive and deductive phenomenological approach was used.

For quality control, the first author employed a two-stage review process in collaboration with co-authors with expertise in various fields. Initially, themes were organized into categories based on the data collection questions (initial codes). As familiarity with the data increased, the themes were reviewed against the coded data and reorganized into new themes (code sets) that articulated the narrative in alignment with the research question. Ultimately, the

**Figure 1:** Distribution of themes in participants’ migraine experiences.

Critical Appraisal Skills Programme (CASP) checklist for qualitative studies was used as a standardized tool to critically evaluate the process undertaken.

### RESULTS

In this study, 21 female patients with migraine participated. The demographic characteristics of the participants are presented in Table 1. The mean age of the participants was 30.90±7.1 years. The majority were single (71.4%) and housewives (38.1%). The mean age at menarche was 13.29±0.78 years.

Table 2 summarizes the migraine characteristics. Pain was predominantly unilateral or alternating between sides (57.1%), with attacks occurring 1–4 times per month in more than half of the participants (57.1%). The majority (66.7%) described their most recent migraine attack as mild. Notably, 85.7% reported difficulty concentrating at home or work during migraine attacks. A family history of migraine was present in 42.9% of participants.

The distribution of themes derived from the qualitative data is presented in Figure 1.

Figure 1 illustrates the frequency distribution of the six main themes derived from the qualitative analysis of participants’ experiences with migraine. Coping Strategies were the most frequently mentioned theme (n=49), followed by Psychosocial Findings (n=35), Migraine Pain Characteristics (n=27), Physical Accompanying Findings (n=26), Onset Symptoms (n=25), and Impact on Daily Life (n=13). The horizontal bar chart visually demonstrates the prominence of coping mechanisms and psychosocial impacts among the participants.

Detailed themes, sub-themes, frequencies, and sample expressions are summarized in Table 3.

In the qualitative analysis, six main themes and associated sub-themes were identified regarding participants’ experiences with migraine. The most frequently mentioned theme was Coping Strategies (n=49), in which participants described various methods, such as taking medication, resting in a dark and quiet room, applying cold compresses, and increasing water intake, to alleviate migraine symptoms.

The Psychosocial Findings theme (n=35) reflected the emotional and social impacts of migraine, including irritability, tension, despair, social withdrawal, and perceptual disturbances. Participants

**Table 2: Clinical characteristics of migraine in participants (n=21)**

Variable	n	%
<b>Pain side</b>		
Unilateral	5	23.8
Bilateral	4	19.0
Alternating (unilateral/bilateral)	12	57.1
<b>Frequency of pain</b>		
<1 per month	6	28.6
1–4 times per month	12	57.1
Several times a week/day	3	14.3
<b>Duration of pain</b>		
1–3 days	3	14.3
1–4 hours	9	42.9
5–8 hours	4	19.0
9–24 hours	5	23.8
<b>Time to take medication after pain onset</b>		
Within 30 min	8	38.1
30 min – 4 hours	12	57.1
4–24 hours	1	4.8
<b>Pain severity (last attack)</b>		
Mild	14	66.7
Moderate	7	33.3
<b>Impact on home/work life</b>		
Difficulty concentrating	18	85.7
No impact	2	9.5
Cancelling activities	1	4.8
<b>Family history of migraine</b>		
First-degree relative	3	14.3
First/second-degree relative	6	28.6
None	9	42.9
<b>Control visit frequency</b>		
More than 1 year	15	71.4
6 months – 1 year	4	19.0
1–6 months	2	9.5
<b>Previous pain treatment methods</b>		
Medication only	15	71.4
Medication + alternative (physio, massage)	6	28.6

This table outlines the migraine-related clinical features reported by participants, including the laterality of pain, frequency and duration of attacks, timing of medication intake, severity of pain, impact on daily life activities, family history of migraine, frequency of medical follow-ups, and previous pain management strategies. Results are expressed as frequencies (n) and percentages (%)

expressed feelings of helplessness, isolation, and emotional vulnerability during migraine attacks.

Migraine Pain Characteristics (n=27) included descriptions of unilateral or bilateral pain, continuous pain sensations, and increased pain severity during menstruation. Participants frequently reported throbbing, intense headaches localized to one side of the head, which sometimes persisted throughout the day.

The Onset Symptoms theme (n=25) highlighted hypersensitivity to light, sound, and odors as prominent warning signs of an impending migraine attack. These sensitivities often served as early indicators, prompting participants to take preventive actions.

Under the Physical Accompanying Findings theme (n=26), participants described symptoms such as nausea, vomiting, visual disturbances (e.g., blurred vision, black spots), sleep disorders, persistent fatigue, and loss of appetite, which exacerbated the burden of migraine attacks.

Finally, the Impact on Daily Life theme (n=13) captured how migraine affected work productivity, social life, emotional well-being, and the ability to perform daily activities. Many participants reported canceling plans, struggling with concentration, and experiencing a significant reduction in functional capacity during migraine episodes.

These findings reveal the multifaceted nature of migraine experiences, encompassing not only physical symptoms but also significant psychosocial and functional impacts on individuals' daily lives (Table 3).

**DISCUSSION**

Our interviews showed that migraine pain is prominent during the premenstrual and menstrual periods, that women try to cope with migraine pain in their own ways, and that their daily life activities are affected during this period. First, our findings showed that the age of migraine onset was low and the duration was long. Participants mostly described their pain as unilateral, prolonged, and severe, and reported that they experienced intense pain especially in the premenstrual period, even considering migraine pain as a warning that the menstrual period would begin. Menstrual migraine is a significant condition characterized by recurrent migraine attacks during the menstrual period. It is defined as migraine attacks occurring within a 5-day window, beginning 2 days prior to the onset of menstruation and continuing until the third day of bleeding. Studies indicate that migraine attacks occurring near menstruation tend to be more intense, persist for a longer duration, and are less responsive to treatment compared with those occurring at other times.<sup>[7,10]</sup> In their systematic review in 2021, Ornello et al.<sup>[11]</sup> showed that menstrual migraine affects 3% of young women, with a peak of 22% in women aged 30–34 years. In a case-control study involving 12,618 Danish individuals with migraine, a significant association was found between menstrual migraine and more severe migraine attacks.<sup>[12]</sup> In a migraine diary study conducted by van Casteren et al.<sup>[13]</sup> in 2021 with 500 participants, perimenstrual migraine attacks were shown to last longer and have a higher risk of recurrence compared with non-perimenstrual attacks. In a meta-analysis conducted by Wang et al.<sup>[14]</sup> in 2023 comparing the characteristics of menstrual and non-menstrual migraine attacks, menstrual migraine

**Table 3: Main themes and sub-themes derived from qualitative analysis**

Themes	Sub-themes (summary)	n	Sample expressions
Migraine pain characteristics	Unilateral/bilateral pain, continuous pain, pain severity related to menstruation	27	'Severe one-sided headache, more intense during menstruation'
Onset symptoms	Light, sound, odor sensitivity	25	Light and sound sensitivity before attacks
Physical accompanying findings	Nausea, vomiting, visual impairment, sleep disorder, fatigue	26	Nausea and blurred vision, severe fatigue
Psychosocial findings	Irritability, tension, despair, social isolation, perception disorder	35	Feelings of helplessness, avoiding communication
Impact on daily life	Loss of workforce, social life disruption, unhappiness, inability to perform tasks	13	Cancelling plans due to migraine pain
Coping strategies	Medication use, sleep, dark & quiet room, cold application, water intake	49	Taking medication and resting in a dark room

This table presents the main themes, sub-themes, frequencies (n), and sample expressions derived from the qualitative analysis of participants' experiences with migraine. Themes were categorized under six main headings: Migraine Pain Characteristics, Onset Symptoms, Physical Accompanying Findings, Psychosocial Findings, Impact on Daily Life, and Coping Strategies. Sub-themes reflect specific aspects of each theme, while frequencies indicate the number of participants who expressed opinions within that category. Sample expressions illustrate representative statements summarizing participants' experiences.

patients were shown to have more migraine attacks per month than non-menstrual migraine patients, a higher rate of migraine in family history, greater migraine aggravation with physical activity, a younger age at migraine onset, and a higher risk of concomitant symptoms. However, the quality of evidence was reported as low according to GRADE evaluation. Although our findings are consistent with the literature, further studies are needed to strengthen the level of evidence on migraine, especially in the perimenstrual period.

Our second finding showed that participants had prodromal symptoms such as sensitivity to light, sound, and smell at the onset of migraine. The International Headache Society defines migraine without aura as recurrent headache attacks lasting 4–72 hours that are unilateral, pulsating, and range from mild to severe. These attacks are aggravated by routine physical activity and are often accompanied by nausea, photophobia, and phonophobia. Menstrual-associated migraine is characterized as a type of migraine without aura occurring during the perimenstrual period.<sup>[15]</sup> van Casteren et al.<sup>[13]</sup> compared perimenstrual migraine attacks with those occurring at other times in the cycle and found that premenstrual migraine attacks were more sensitive to light and sound.

Our third finding showed that migraine was accompanied by symptoms such as nausea, vomiting, insomnia, visual disturbance, and fatigue. In the literature, there are few studies focusing specifically on the physical symptoms experienced by women with migraine during the premenstrual period. However, studies examining symptoms experienced during the premenstrual period report neurological and vascular conditions, including headache, dizziness, numbness, increased sensitivity of the arms and/or legs, palpitations, and gastrointestinal and ocular symptoms, all of which may disrupt daily life and functioning.<sup>[16]</sup> In a large survey of 238,114 Flo mobile application users from 140 countries aged 18–55 years, the most common premenstrual symptoms were food cravings

(85.28%), mood swings or anxiety (64.18%), and fatigue (57.3%). Symptoms such as absent-mindedness, low libido, sleep changes, gastrointestinal complaints, weight gain, headache, sweating or hot flushes, fatigue, hair changes, rashes, and swelling were shown to increase with age.<sup>[17,18]</sup> In a study conducted by Böttcher et al.,<sup>[18]</sup> which evaluated the relationship between pubertal status, menstrual cycle, migraine attacks, and accompanying symptoms in girls with migraine, a significant difference in migraine frequency was observed between pre- and post-pubertal girls, whereas no significant difference was found in headache characteristics. In light of these data, premenstrual syndrome appeared to be experienced more intensely in women diagnosed with migraine in our study, and visual impairment, which is rarely reported in the literature, was more common in our cohort.

Our fourth finding included irritability, tension, unhappiness, helplessness, communication disorders, perceptual disturbances, loneliness, loss of workforce participation, deterioration in social life, self-harm, feelings of violation, and impairment in daily life activities. Premenstrual syndrome (PMS) is a process in which mood changes include symptoms affecting the psycho-emotional, physical, and behavioral responses of women during menstruation. In the literature, psycho-emotional symptoms are reported as anger, irritability, and depression, whereas behavioral symptoms include social withdrawal, reduced social activity, absenteeism, poor work or academic performance, and increased libido.<sup>[19]</sup> In a study conducted by Fernández-Martínez et al.<sup>[20]</sup> in 2021 involving 269 female university students, nearly half of the participants reported experiencing menstrual migraine pain. A higher proportion of menstrual migraine was observed among women with dysmenorrhea, irritability, dizziness, oral contraceptive use, and daily cola consumption. Wang conducted a study in which a headache diary was kept by 75 women with menstrual migraine and 54 healthy women who underwent functional magnetic resonance imaging to investigate the pathophysiology of migraine pain, while also assessing migraine frequency, pain intensity,

and anxiety and depression levels using standardized scales. Structural and functional abnormalities in the right anterior cingulate cortex identified by magnetic resonance imaging were shown to be significantly associated with pain intensity and pain-related emotional disturbances in patients with menstrual migraine.<sup>[21]</sup> The Global Burden of Disease study conducted by GBD 2015 Disease and Injury Incidence and Prevalence Collaborators.<sup>[22]</sup> in 2016 classified migraine as the fourth leading cause of years lived with disability (YLD) among women. In another study using the Migraine Disability Assessment (MIDAS) questionnaire, women were 1.34 times more likely than men to report fourth-degree migraine-related disability within the previous 3 months. Women were also more likely to report inability to perform housework, participate in social or family activities, and reduce work or school activity by at least 50% for at least 1 day due to migraine. It was further reported that most women with migraine require an average of 2 hours of bed rest and are unable to fully resume daily activities for 3–6 days after a migraine attack, even if they continue work or school during this period.<sup>[23]</sup> In our study, in addition to findings consistent with the literature, participants' reports of self-harm and feelings of violation indicate that menstrual migraine should also be evaluated from this broader psychosocial perspective.

Our fifth finding showed that participants used various coping methods for perimenstrual and menstrual migraine, including taking medication, sleeping, staying in a dark and quiet room, adjusting ambient temperature, cold application, massage, drinking plenty of water, and postponing all plans. The literature indicates that the primary pharmacological approach to menstrual migraine involves acute therapies aimed at rapid relief of headache attacks and associated symptoms, with triptans being particularly prominent. Medical treatment strategies include daily use of a long-acting nonsteroidal anti-inflammatory drug or triptan for 5 days, starting 2 days before the expected onset of menstruation.<sup>[24,25]</sup> To avoid being directive, specific medications used by participants were not queried in this study. Non-pharmacological management strategies described in the literature include behavioral therapy, biofeedback, education, relaxation, mindfulness, and weight loss, while sleep hygiene, regular exercise, balanced nutrition without skipping meals, and stress management are emphasized as healthy lifestyle behaviors.<sup>[11]</sup> Behavioral interventions have been shown to significantly reduce headache frequency and positively influence patient-reported outcomes such as disability, quality of life, depression, anxiety, self-efficacy, and medication use.<sup>[26]</sup> Bagherzadi et al.<sup>[27]</sup> demonstrated that heat and cold therapy were effective in reducing nitroglycerin-induced migraine pain in a randomized controlled study involving 75 cardiac patients in 2021. In a study conducted in South India with 172 nursing students who reported headaches within the previous year, sleep, head massage, and taking breaks from work were identified as relaxing strategies.<sup>[28]</sup> Consistent with the literature, women in our study reported using similar coping methods while managing migraine.

## CONCLUSIONS

These findings emphasize the need for improved management of perimenstrual migraine attacks in all menstruating women. Patients' knowledge about the disease and its characteristics should be enhanced, and they should be informed that migraine is an incurable but controllable chronic condition and that its attacks can be prevented.

## Statement

**Ethics Committee Approval:** The Maltepe University Clinical Research Ethics Committee granted approval for this study (date: 01.02.2024, number: 2024/03-01).

**Informed Consent:** Participants provided written consent for involvement in the study.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

**Financial Disclosure:** The authors declare that they have not received any funding, grants, or other support during this study.

**Use of AI for Writing Assistance:** Not declared.

**Author Contributions:** Concept – AÖ, FA; Design – FA, AÖ; Supervision – FA, AÖ; Results – FA, AÖ; Materials – FA; Data Collection and/or Processing – AÖ; Analysis and/or Interpretation – FA, AÖ; Literature Search – FA, AÖ; Writing – FA, AÖ; Critical Reviews – AÖ, FA.






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

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# Exploring metabolic etiologies of MAFLD in children with normal BMI

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## ABSTRACT

**Objective:** Metabolic dysfunction-associated fatty liver disease (MAFLD) is increasingly recognized in children with a normal body mass index (BMI), and its etiology is generally associated with metabolic, genetic, and environmental factors. Although childhood obesity is a well-known cause of MAFLD, the condition can also develop in non-obese children, often due to underlying metabolic disorders.

**Material and Methods:** This retrospective, cross-sectional study was conducted over a three-year period at a Pediatric Gastroenterology Clinic. Initially, 253 pediatric patients diagnosed with hepatic steatosis by abdominal ultrasound were screened. After excluding overweight children and children with obesity, 20 non-obese patients with hepatic steatosis were included in the final analysis. The study focused on identifying secondary causes of hepatic steatosis in this cohort by collecting demographic, clinical, biochemical, and metabolic data.

**Results:** Of the 20 non-obese children evaluated by a pediatric metabolic specialist, two were diagnosed with a metabolic disease. Significant biochemical markers, such as elevated serum triglyceride, ALT, and AST levels, prompted further metabolic investigations, enabling early diagnosis and treatment.

**Conclusion:** This study highlights the critical role of metabolic and genetic screening in the evaluation of hepatic steatosis in non-obese children, particularly during infancy and early childhood. Early identification of underlying metabolic disorders may enable appropriate intervention and help prevent long-term complications. Non-obese pediatric MAFLD requires careful evaluation and targeted metabolic testing to achieve timely treatment and improved outcomes.

**Keywords:** Metabolic dysfunction, non-obese children, pediatric MAFLD, rare diseases.

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## INTRODUCTION

Fatty liver disease, also referred to as metabolic dysfunction-associated fatty liver disease (MAFLD), is an increasing health problem characterized by the accumulation of fat in the liver. Although obesity is one of the most common causes of this disease, fatty liver disease can also be observed in children with a normal body mass index (BMI).<sup>[1,2]</sup> It encompasses a spectrum of liver pathology ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and ultimately cirrhosis.<sup>[3]</sup>

While childhood obesity is widely recognized as the primary risk factor for fatty liver disease, recent studies emphasize that the condition can also develop in children with a normal BMI, often as a result of underlying metabolic, genetic, or environmental factors.<sup>[4]</sup> The global increase in childhood obesity parallels the rise in the prevalence of MAFLD. Schwimmer et al.<sup>[2]</sup> reported that MAFLD affects approximately 38% of obese children and approximately 10% of children with normal BMI. However, the etiology of fatty liver disease in non-obese children is often secondary and may include rare but clinically important disorders such as glycogen storage diseases (GSD), Wilson's disease, congenital disorders of glycosylation, and inherited lipid storage disorders such as Chanarin–Dorfman syndrome (CDS).<sup>[5–7]</sup>

Importantly, insulin resistance, the hallmark of metabolic syndrome, can occur independently of obesity and plays a significant role in the pathogenesis of MAFLD. Children with inborn errors of metabolism (IEMs) often present at a very early age and may develop fatty liver in the absence of common risk factors such as obesity. Therefore, early diagnosis of IEMs can be challenging. Fatty liver disease in this group may also result from certain medications, infections (e.g., HCV and CMV), and nutritional deficiencies.<sup>[8]</sup>

Clinical manifestations of MAFLD in non-obese children are often nonspecific, and routine liver function tests may fail to accurately identify the disease. Abdominal ultrasonography is commonly used for screening but lacks sensitivity for early or mild steatosis. Liver biopsy remains the gold standard for definitive diagnosis and for differentiating simple steatosis from MASH. Even in young patients with normal BMI, histopathological findings such as macrovesicular steatosis, portal inflammation, and varying degrees of fibrosis are frequently observed.<sup>[9,10]</sup>

A thorough investigation of the etiology of MAFLD in non-obese children is crucial, given the availability of targeted therapies for many underlying conditions and the potential for progression to severe liver disease. Early intervention, individualized management, and improved long-term outcomes are achievable through identification of these secondary causes.<sup>[10]</sup> In addition to obesity and insulin resistance, genetic factors affecting hepatic structure, dietary habits, and environmental influences play important roles in the development of fatty liver disease. In this context, determining the frequency of metabolic diseases in children with normal BMI but fatty liver disease will contribute to a better understanding of this condition.<sup>[11]</sup>

The aim of this study was to determine the frequency of secondary and metabolic causes of MAFLD and to characterize its clinical features in children with normal BMI who presented with hepatic steatosis.

## MATERIAL AND METHODS

### Study Design and Data Collection

This retrospective, cross-sectional study was conducted at the Department of Pediatric Gastroenterology and Hepatology, Göztepe Süleyman Yalçın City Hospital, and the Division of Inherited Metabolic Disease and Nutrition Clinic at Kartal Dr. Lütfi Kırdar City Hospital between April 2022 and April 2025. Children with a normal body mass index (BMI) who presented with hepatic steatosis during this period were evaluated by a pediatric gastroenterologist and a pediatric metabolic specialist. Clinical, laboratory, and radiological data were retrospectively collected from electronic medical records.

### Patient Selection and Inclusion Criteria

Patients with hepatic steatosis detected on ultrasonographic examination were retrospectively screened. To reduce confounding variables associated with obesity, patients with a BMI below the 85th percentile according to national growth reference standards for age and sex were included. Individuals classified as overweight or obese were excluded. Patients who were not evaluated by a pediatric metabolic disease specialist were also excluded from the study.

Although liver biopsy remains the gold standard for diagnosing MASH, histopathological confirmation was not feasible for all participants. Therefore, the diagnosis of hepatic steatosis in this study was based solely on ultrasonographic findings. Liver biopsy was performed in a limited number of patients; however, these data were not consistently documented and were not used as an inclusion criterion.

### Inclusion Criteria

- Ultrasonographic evidence of hepatic steatosis
- BMI below the 85th percentile for age and sex according to national growth reference standards
- Evaluation by a pediatric metabolic disease subspecialist

### Exclusion Criteria

- BMI  $\geq$ 85<sup>th</sup> percentile (classified as overweight or obese)
- Diagnosis of viral hepatitis (HBV, HCV)
- Diagnosis of autoimmune hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, or celiac disease
- History of prolonged use of medications known to cause hepatic steatosis (e.g., corticosteroids, valproic acid, methotrexate)
- Presence of known chronic systemic or genetic syndromes unrelated to MAFLD

### Comprehensive Clinical and Metabolic Assessment

The age, sex, height, weight, and body mass index (BMI) of all patients, as well as physical examination findings, abdominal ultrasound results, and metabolic and genetic test results, were retrieved from hospital medical records. Biochemical and metabolic assessments obtained from the hospital database included liver function tests (ALT, AST, ALP, GGT, bilirubin, albumin, INR); uric acid levels; lipid profile (cholesterol, LDL, HDL, triglycerides); HOMA-IR calculation based on serum insulin levels; serum amino acid chromatography; urine organic acid analysis

**Table 1: Patients' demographic data**

	Average	Median	SD	Minimum	Maximum	p
Age (years)	8.83	11.04	6.23	0.08	16.92	0.07
Weight (kg)	35.19	36.70	23.46	4.62	78.00	0.20
Weight (p)	58.90	68.72	29.04	2.22	95.35	0.10
Height (cm)	127.90	142.50	42.56	55.00	180.00	0.11
Height (p)	61.89	67.49	24.15	2.68	97.56	0.20
Waist circumference (cm)	51.18	53.50	5.77	37.00	57.00	0.02
Waist circumference (p)	45.89	49.41	25.49	2.22	91.92	0.20
BMI (kg/m <sup>2</sup> )	18.62	18.25	2.98	13.91	25.47	0.04
BMI (P)	51.71	53.59	27.97	4.95	91.77	0.20

p: Kolmogorov-Smirnov Normality Test; \*p>0.05: The data are normally distributed. SD: Standard deviation; p: percentile; BMI: Body mass index.

using gas chromatography/mass spectrometry (GC/MS); and plasma acylcarnitine profiling by tandem mass spectrometry.

This study was conducted in accordance with the Helsinki Declaration and was approved by the hospital's Institutional Ethics Committee (approval no: 2024/010.99/9/33). As this was a retrospective study, informed consent was not obtained from the patients' relatives.

### Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of variable distributions, and variables were considered to be normally distributed when p>0.05. Qualitative data were expressed as frequencies (%). Relationships between quantitative variables were analyzed using the Pearson correlation test for normally distributed data and the Spearman correlation test for non-normally distributed data. A p-value <0.05 based on two-tailed test results was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 25.00.

## RESULTS

A total of 253 pediatric patients who were diagnosed with hepatic steatosis by abdominal ultrasonography (USG) and who presented to the pediatric outpatient clinic within the last three years were screened. Of these, 20 patients with BMI values below the 85th percentile who were evaluated by a pediatric metabolic diseases specialist were included in the final analysis. Overweight and obese patients, as well as those not evaluated by a metabolic specialist, were excluded.

### Demographic and Anthropometric Characteristics

The study included 20 pediatric patients diagnosed with hepatic steatosis despite having a normal BMI. The mean age of the cohort was 8.83±6.23 years, ranging from infancy to adolescence. The mean body weight was 35.19±23.46 kg, and the mean height was 127.90±42.56 cm. The mean BMI was 18.62±2.98 kg/m<sup>2</sup>, and all values were within normal limits according to national growth

standards for age and sex. The mean waist circumference was 51.18±5.77 cm. No significant sex-related differences were observed in the cohort (Table 1).

### Biochemical and Metabolic Evaluation

Biochemical evaluation revealed that the mean serum alanine aminotransferase (ALT) level was 36.85±70.52 IU/L, while the mean aspartate aminotransferase (AST) level was 50.15±85.31 IU/L. The mean alkaline phosphatase (ALP) level was 252.70±125.61 IU/L, and the mean gamma-glutamyl transferase (GGT) level was 26.15±31.19 IU/L. Total bilirubin levels were below 1 mg/dL in all patients, and no cases of hyperbilirubinemia were observed. Coagulation parameters, including the international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT), were within normal limits, and no coagulation disorders were detected. The mean triglyceride level was 113.40 mg/dL, and triglyceride concentrations were within normal limits in all patients except those diagnosed with glycogen storage disease. The mean serum albumin level was 4.66±0.24 g/dL. The mean creatine kinase (CK) level was 150.65±100.65 IU/L. The mean serum uric acid level was 4.42±1.33 mg/dL, and the mean total bilirubin level was 1.06±1.26 mg/dL. Except for one patient, ALT, AST, CK, and triglyceride values were within reference limits (Table 2).

### Amino Acid and Carnitine Profiles

Furthermore, amino acid analysis, urinary organic acid screening, and plasma acylcarnitine profiling were within normal limits in all patients except one, who required further metabolic evaluation and was diagnosed with a fatty acid oxidation disorder. Free carnitine (C0) levels were also evaluated in all patients. The mean free carnitine concentration was 30.31±10.97 μmol/L, which falls within the reference range for the pediatric population.

### Radiological Findings

Liver steatosis was evaluated by ultrasonography in all patients. The severity of liver steatosis was predominantly mild (Grade 1), with moderate (Grade 2) steatosis reported in only two patients. No

**Table 2: Descriptive statistical information related to measurement values**

	Average	Median	SD	Minimum	Maximum	p
Glucose (mg/dl)	89.00	90.00	6.92	70.00	100.00	0.20
ALT (IU/L)	36.85	20.00	70.52	9.00	334.00	0.00
AST (IU/L)	50.15	26.00	85.31	12.00	405.00	0.00
ALP (IU/L)	252.70	230.50	125.61	70.00	618.00	0.20
GGT (IU/L)	26.15	15.50	31.19	10.00	143.00	0.00
Total bilirubin (mg/dl)	1.06	0.54	1.26	0.15	4.57	0.00
Direct bilirubin (mg/dl)	0.21	0.15	0.18	0.05	0.69	0.01
Protrombin time	13.12	12.55	1.53	10.90	16.20	0.05
INR	1.06	1.06	0.08	0.91	1.25	0.12
APTT	28.21	28.85	3.25	20.10	33.60	0.20
Creatinin kinase (IU/L)	150.65	118.00	100.65	60.00	431.00	0.00
Cholesterol (mg/dl)	152.80	151.50	27.80	95.00	203.00	0.20
Triglyceride (mg/dl)	113.40	94.50	89.41	29.00	419.00	0.01
HDL (mg/dl)	51.10	47.00	14.97	20.00	88.00	0.20
LDL (mg/dl)	75.20	82.50	32.00	0.00	127.00	0.20
Albumin (g/dl)	4.67	4.65	0.24	4.20	5.10	0.20
Uric asit (mg/dl)	4.42	4.10	1.33	2.50	7.10	0.16
Lactate ( $\mu$ mol/L)	1.46	1.30	0.66	0.90	3.70	0.02

p: Kolmogorov-Smirnov Normality Test, \* $p > 0.05$ : The data are normally distributed. SD: Standard deviation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; PT: Prothrombin time; INR: International normalized ratio; APTT: Activated partial thromboplastin time; CK: Creatine kinase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

patient was found to have severe (Grade 3) steatosis. The mean follow-up period was 12 months, during which complete resolution of liver steatosis was observed in five patients. No significant changes in steatosis severity were noted in the remaining patients.

When liver and spleen sizes were evaluated according to body size percentiles by abdominal ultrasonography, no hepatomegaly or splenomegaly was detected in any patient, except for the patient diagnosed with glycogen storage disease type 3.

### Case Studies and Diagnostic Insights

Notably, one patient was diagnosed with carnitine-acylcarnitine translocase (CACT) deficiency at the age of 2 months after presenting with hepatic steatosis. Fatty liver disease was detected on abdominal ultrasonography performed during evaluation for neonatal hypoglycemia. A diagnosis of CACT deficiency was established by genetic analysis in a patient suspected of having a fatty acid oxidation defect based on an increased C16+C18:1/C2 ratio identified in emergency acylcarnitine analysis. Following diagnosis, a low-fat diet enriched with medium-chain triglycerides (MCT), frequent feeding—particularly during nighttime—and regulated caloric intake were initiated.

Another case involved a 3-month-old female patient with elevated ALT, AST, CK, and triglyceride levels who was found to have Grade 2 fatty liver disease. Physical examination revealed

hepatosplenomegaly. Screening for inherited metabolic diseases and emergency carnitine profiling yielded normal results, and hypoglycemia was not detected. Genetic analysis identified a homozygous mutation in the AGL gene, leading to a diagnosis of glycogen storage disease type 3. The patient was advised to follow a high-carbohydrate diet with frequent feeding.

### Follow-up and Disease Progression

The mean follow-up duration for patients in this study was approximately 12 months under pediatric gastroenterology supervision. During this period, ultrasonographic resolution of hepatic steatosis was observed in five of the 20 patients, suggesting that hepatic steatosis may be transient or potentially overdiagnosed when based solely on imaging findings, particularly in patients with normal metabolic evaluations.

### DISCUSSION

In this study, we evaluated pediatric patients with ultrasonographically confirmed hepatic steatosis despite having a normal BMI, aiming to identify underlying metabolic or genetic causes. Although obesity remains the most well-known and prevalent cause of MAFLD, our findings support growing evidence that fatty liver disease in non-obese children is neither a benign nor an idiopathic condition but may indicate a significant underlying pathology, particularly in very young infants.

First, the majority of our patients exhibited normal liver enzyme levels and metabolic parameters, reinforcing the notion that incidental ultrasonographic detection of hepatic steatosis does not always reflect clinically significant metabolic pathology in non-obese children. Mean ALT and AST levels were mildly elevated but remained within reference ranges in all but one patient, suggesting that substantial hepatocellular injury is uncommon in this subgroup. Notably, the mean ALT ( $36.85 \pm 70.52$  IU/L) and AST ( $50.15 \pm 85.31$  IU/L) values demonstrated wide standard deviations, reflecting heterogeneity in hepatic involvement. Although elevated ALP and GGT levels were observed in some patients, no cases of hyperbilirubinemia or coagulopathy were documented, further supporting the generally benign biochemical profile of this cohort.

Our study highlights the critical role of metabolic investigations in non-obese children with hepatic steatosis. While most patients had normal amino acid, organic acid, and acylcarnitine profiles, two notable cases underscore the diagnostic value of a comprehensive metabolic workup. One patient was diagnosed with carnitine-acylcarnitine translocase (CACT) deficiency at 2 months of age following presentation with hepatic steatosis. CACT deficiency is a rare but severe disorder of mitochondrial long-chain fatty acid oxidation that may present with hypoglycemia, cardiomyopathy, and liver dysfunction during the neonatal period.<sup>[12,13]</sup> In this patient, hepatic steatosis was the sole initial finding prompting further metabolic evaluation, ultimately enabling early diagnosis and treatment. Similarly, another infant was diagnosed with glycogen storage disease (GSD) type III after presenting with elevated liver enzymes, hypertriglyceridemia, and fatty liver changes on ultrasonography. Genetic analysis revealed a homozygous mutation in the AGL gene, confirming the diagnosis. This finding is consistent with previous reports indicating that hepatomegaly and steatosis may represent early manifestations of GSD, often preceding overt clinical symptoms.<sup>[14]</sup> The absence of hepatosplenomegaly in most of our cohort, except in the patient with GSD type III, suggests that organomegaly remains an important clinical indicator for distinguishing metabolic hepatopathies from isolated or benign steatosis.

These two cases demonstrate that the earlier hepatic steatosis is detected in infants, the higher the likelihood of an underlying metabolic disorder. While fatty liver in an obese adolescent may suggest classic MAFLD, fatty liver in a non-obese infant or toddler should prompt a thorough metabolic and genetic evaluation. This concept is supported by prior literature. Vimalasvaran et al.<sup>[7]</sup> reported that in children younger than 10 years with biopsy-confirmed fatty liver disease, glycogen storage disease was the leading cause, accounting for more than 30% of cases.<sup>[2,7]</sup> Schwimmer et al.<sup>[2]</sup> also demonstrated that NAFLD may affect approximately 10% of non-obese children in autopsy-based studies and that histological features cannot be distinguished from those observed in obese patients.<sup>[2,7]</sup> Yıldız and Sivri<sup>[6]</sup> further emphasized that a substantial proportion of non-obese children undergoing liver biopsy for suspected NAFLD have underlying metabolic or genetic etiologies. This observation highlights that metabolic disorders may be misdiagnosed as idiopathic fatty liver disease in the absence of a comprehensive metabolic evaluation, underscoring the importance of early diagnosis. In our study, a patient diagnosed with carnitine-acylcarnitine translocase (CACT) deficiency exhibited elevated serum triglyceride, ALT, and AST levels.

These abnormalities served as the initial indicators prompting further diagnostic investigations. This case emphasizes the importance of early identification of rare metabolic disorders, as timely intervention can prevent long-term complications such as hypoglycemia, liver dysfunction, and cardiomyopathy in CACT deficiency.

Another important finding of our study is that lipid metabolism should be evaluated even in non-obese children. Particularly in the absence of obesity, elevated serum triglyceride and cholesterol levels may indicate underlying conditions such as familial combined hyperlipidemia, glycogen storage diseases, or fatty acid oxidation defects. Therefore, a routine metabolic work-up, including serum cholesterol, triglycerides, uric acid levels, and extended newborn screening panels (if not previously performed), should be considered in all non-obese children with hepatic steatosis. Ultrasonography remains a valuable, non-invasive tool for detecting hepatic steatosis; however, its ability to determine the underlying etiology is limited. Biochemical markers and enzyme panels alone may also fail to provide a complete assessment. In such cases, liver biopsy remains the gold standard, particularly in patients with unexplained or progressive liver dysfunction. In our cohort, biopsy findings further supported the presence of storage disorders in selected cases and reinforced the need for tissue-based diagnosis when clinically indicated.

Taken together, our findings suggest a paradigm shift in the evaluation of pediatric fatty liver disease. While obesity-related fatty liver disease is increasingly prevalent and well characterized, fatty liver disease in non-obese children—especially in infants—requires careful and early investigation for underlying, potentially treatable disorders. Early diagnosis not only guides appropriate management but also has important implications for genetic counselling, family screening, and long-term prognosis.

Importantly, two of the 20 patients were diagnosed with underlying metabolic diseases, and both were younger than one year at the time of diagnosis. This finding highlights the significance of age at diagnosis as a potential indicator of metabolic liver disease. In contrast, the remaining 18 patients exhibited normal or nonspecific metabolic profiles during the follow-up period.

This observation supports previous studies, such as that by Yıldız and Sivri, which emphasized that non-obese children with hepatic steatosis diagnosed at a younger age are more likely to have an underlying genetic or metabolic condition.<sup>[6]</sup> Conversely, older children with normal BMI and no significant metabolic abnormalities may have a more benign form of fatty liver disease that may resolve or remain stable without requiring invasive interventions. These findings suggest that early-onset steatosis in infants may warrant a more aggressive metabolic work-up, whereas a strategy of careful observation may be more appropriate in older children with normal BMI and unremarkable laboratory findings. This distinction may help avoid unnecessary anxiety, invasive testing, or overtreatment in a subset of patients while ensuring timely diagnosis in high-risk infants. Further prospective studies are needed to identify predictive factors for the persistence or resolution of steatosis in this population and to determine clinical or biochemical indicators that should prompt metabolic evaluation. Our findings contribute to the growing body of evidence supporting the need for age- and risk-stratified algorithms in the assessment of pediatric hepatic steatosis.

This study has several limitations. First, due to its retrospective design, the analysis was restricted to available clinical and laboratory data, and standardized assessment protocols could not be uniformly applied. Second, genetic testing and liver biopsy were not performed in all patients but were limited to selected cases based on clinical suspicion; therefore, some underlying metabolic or genetic conditions may have been underdiagnosed. Another limitation is that potential confounding factors, such as dietary habits, physical activity levels, and socioeconomic status, were not assessed in detail and thus could not be fully controlled. These variables are known to influence the development and progression of hepatic steatosis and may have affected the interpretation of our results. Finally, the relatively short follow-up period limited our ability to evaluate the long-term progression or resolution of hepatic steatosis in this population.

## CONCLUSION

Our findings emphasize the importance of considering underlying metabolic and genetic disorders, particularly in non-obese children presenting with hepatic steatosis during early infancy. When fatty liver is detected at a very young age, accompanied by significant biochemical abnormalities or associated with parental consanguinity, the likelihood of an inborn error of metabolism increases substantially. Therefore, patients with early-onset or severe hepatic steatosis—especially in the presence of parental consanguinity or hepatomegaly—should undergo comprehensive metabolic screening without delay. Referral to a pediatric metabolic specialist is essential to ensure accurate diagnosis, timely intervention, and improved clinical outcomes.

## Statement

**Ethics Committee Approval:** The Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee granted approval for this study (date: 25.10.2024, number: 2024/010.99/9/33).

**Informed Consent:** As this was a retrospective study, informed consent was not obtained from the patients' relatives.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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# Prevalence of postpartum depression after normal vaginal delivery and related variables

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## ABSTRACT

**Objective:** This study aimed to determine the prevalence of postpartum depression (PPD) in mothers after normal vaginal delivery (NVD) and to identify associated risk factors.

**Material and Methods:** Two hundred post-NVD mothers participated in this cross-sectional study. The Edinburgh Postnatal Depression Scale (EPDS; cutoff  $\geq 13$ ) and sociodemographic information were used. The chi-square test or Fisher's exact test was applied to assess categorical variables, while the Mann-Whitney U test and independent samples t-test were used to compare continuous variables. Logistic regression was performed to identify predictors of postpartum depression;  $p < 0.05$  was considered statistically significant.

**Results:** The prevalence of PPD was 15% ( $n=30$ ). Logistic regression revealed a significantly higher risk of PPD among mothers with comorbidities (OR=21.0), unplanned pregnancies (OR=83.5), smoking (OR=27.6), lack of a companion (OR=35.8), obstetric complications (OR=31.7), and formula use (OR=17.8) (all  $p < 0.001$ ).

**Conclusion:** PPD is a significant public health concern among mothers after NVD and is strongly associated with specific risk factors. Routine PPD screening and targeted support are crucial for mothers with these risk factors.

**Keywords:** Edinburgh postpartum depression scale, normal vaginal delivery, postpartum depression, risk factors.

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## INTRODUCTION

Pregnancy is an important period in a woman's life that requires physiological, psychological, and social changes, as well as adaptation to these changes. The changes that occur before and after birth may cause pregnant women to experience various problems and may negatively affect their health. For some mothers, emotional problems may arise, the most common and challenging of which is depression. Postpartum depression (PPD), which occurs through the interaction of depressive symptoms, anxiety, and increased irritability, is an important public health problem that affects the quality of life of new mothers, with a reported incidence of 17.2% worldwide, 27% in Middle Eastern countries, and 23.8% in Türkiye.<sup>[1–3]</sup>

The postpartum period, which is typically defined as the time from birth until the reproductive organs return to their pre-pregnancy state, is critical for both the mother and the child. Factors such as hormonal changes in the mother, breast milk production, postpartum pain, and neonatal care can lead to significant physiological and psychological changes.<sup>[4]</sup> These multifaceted changes make women particularly vulnerable to mental health disorders, with anxiety and depression emerging as the most common comorbidities.<sup>[5]</sup>

Postpartum depression is included among mood disorders in the DSM-IV and is defined by the “postpartum onset” specifier. Some studies have reported that it may occur at any time between 6–12 weeks postpartum and up to one year after delivery. Postpartum depression (PPD) is characterized by the presence of five or more diagnostic criteria for at least two weeks. These include insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of guilt or sadness, changes in appetite, decreased concentration, and suicidal ideation. According to the DSM, PPD is classified as a non-psychotic major depressive disorder.<sup>[6]</sup>

Many scales have been used to screen for postpartum depression. One of the most widely used and reliable screening tools for identifying women at risk of postpartum depression is the Edinburgh Postpartum Depression Scale (EPDS).<sup>[7,8]</sup> Although the EPDS is not a diagnostic instrument, a cutoff score of  $\geq 13$  has been reported to yield a sensitivity of 61.5% and a specificity of 77.4%.<sup>[9]</sup>

Inadequate rest, malnutrition, smoking, multiparity, exposure to violence or abuse by healthcare providers, a psychiatric history such as depression or anxiety, stressful life events including financial difficulties, relationship problems or the loss of a loved one, as well as difficult or traumatic childbirth experiences, may complicate both physical and psychological recovery and increase vulnerability to depression.<sup>[10,11]</sup> These findings underscore the need for targeted support during the postpartum period. Healthcare providers should proactively screen women for postpartum depression during both antenatal and postnatal visits. Depression may become chronic, recurrent, and/or treatment-resistant, and women who receive inadequate care are at increased risk of the consequences of untreated emotional illness, including suicide, which accounts for approximately 20% of postpartum maternal deaths.<sup>[12–15]</sup>

In light of these data, the present study aimed to determine the impact of the birth process and a postpartum follow-up care program on postpartum depression in a redesigned mother-friendly hospital, and to evaluate its role in the prevention and management of postpartum depression by identifying high-risk groups.

## MATERIAL AND METHODS

This study was conducted using a cross-sectional design at a tertiary care institution between January 2025 and March 2025.

### Study Population and Sample

The study population consisted of all mothers who had a normal vaginal delivery at Gazi Yaşargil Training and Research Hospital between January 2025 and March 2025. A total of 200 mothers who met the inclusion criteria and signed an informed consent form constituted the study sample. The inclusion criteria were as follows: having undergone a normal vaginal delivery, being 6–8 weeks postpartum, having the ability to read and speak Turkish, and agreeing to participate in the study by signing an informed consent form. The exclusion criteria included cesarean delivery, the presence of a physical or pre-existing psychiatric disorder, mental disability or difficulty in communication, and fetal anomalies.

### Data Collection Tools

The following tools were used in the data collection process:

#### 1. Sociodemographic Information Form

This form was developed by the researchers based on a review of the relevant literature and expert opinions. It included sociodemographic and obstetric characteristics such as age, height, weight, body mass index (BMI), education level, presence of comorbidities, pregnancy planning status, smoking and alcohol use, use of assisted reproductive techniques, mode of delivery, presence of a companion during delivery, access to healthcare personnel, use of epidural analgesia, previous history of depression, development of complications during pregnancy or delivery, breastfeeding status, and formula use.

#### 2. Edinburgh Postpartum Depression Scale (EPDS)

This scale was developed by Cox et al.<sup>[16]</sup> and later adapted into Turkish to ensure its validity and reliability. The EPDS consists of 10 items designed to identify depressive symptoms in women after childbirth. Each item is scored from 0 to 3, yielding a total score ranging from 0 to 30. In this study, a cutoff score of  $\geq 13$ , which is widely accepted in the literature, was used to identify individuals at risk for postpartum depression (PPD).

### Data Collection Process

Data were collected through face-to-face interviews conducted by the researchers during outpatient clinic visits at 6–8 weeks postpartum. The purpose and importance of the study were explained to the participants, and voluntary participation was emphasized. The sociodemographic information form and the EPDS were administered to mothers who provided written informed consent. Completion of the questionnaires took approximately 15–20 minutes.

### Ethical Considerations

This study was approved by the Ethics Committee of University of Health Sciences, Gazi Yaşargil Training and Research Hospital

(Decision No: 361, Date: 28.02.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Participants were informed about confidentiality and anonymity, and it was stated that the data would be used solely for research purposes.

### Statistical Analysis

Descriptive statistics were expressed as mean, standard deviation, median, and minimum–maximum values for continuous variables, and as frequencies (n) and percentages (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normality of data distribution. The independent samples t-test was applied when normality assumptions were met, while the Mann–Whitney U test was used for non-normally distributed data when comparing two groups. The chi-square test or Fisher's exact test, as appropriate, was used to evaluate associations between categorical variables. Logistic regression analysis was performed to identify factors associated with postpartum depression. A  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.

### RESULT

The mean age of the 200 mothers who participated in the study was  $27.83 \pm 5.73$  years (median=27, min=18, max=42), and the mean BMI was  $27.21 \pm 4.43$  (median=27.18, min=16.55, max=40.16). The mean number of children was  $2.50 \pm 1.41$  (median=2, min=1, max=7).

The mean Edinburgh score was  $9.37 \pm 4.75$  (median=10, min=0, max=26). Of the total 200 patients, 15% (n=30) had depression; 41.5% (n=83) were overweight; 41% (n=82) were primary school graduates; and 4% (n=8) had comorbidities. Pregnancy was planned in 89.5% (n=179) of patients; 85.5% (n=171) were non-smokers; none of the patients (n=200) used alcohol; 99% (n=198) had not used assisted reproductive techniques; and all patients (n=200) had a normal vaginal delivery. A total of 85.5% (n=171) had a companion during delivery; 97% (n=194) had access to health personnel; 77% (n=154) did not receive epidural anesthesia; 94.5% (n=189) had no prior history of depression; 91.5% (n=183) had no complications; 96% (n=192) breastfed their infants; and 93.5% (n=187) did not use formula.

Table 1 shows the sociodemographic characteristics of patients with and without postpartum depression according to the EPDS. The proportion of patients with comorbidities was significantly higher among patients with depression (20%) than among those without depression (1.2%) ( $p < 0.001$ ). The proportion of planned pregnancies was significantly lower in patients with depression (40.0%) than in those without depression (98.2%) ( $p < 0.001$ ). The proportion of smokers among patients with depression (63.3%) was significantly higher than among patients without depression (5.9%) ( $p < 0.001$ ). The proportion of patients with depression who had a companion during delivery (33.3%) was significantly lower than that of patients without depression (94.7%) ( $p < 0.001$ ). The proportion of patients with a history of depression was significantly higher in those with depression (36.7%) than in those without depression (0.0%) ( $p < 0.001$ ). The proportion of patients with complications was significantly higher among patients with depression (43.3%) than among those without depression (2.4%) ( $p < 0.001$ ). The proportion of breastfeeding among patients with depression (73.3%) was significantly lower than among patients without depression (100%) ( $p < 0.001$ ). The proportion of

formula use in patients with depression (30.0%) was significantly higher than among patients without depression (2.4%) ( $p < 0.001$ ).

Despite these findings, no significant relationship was observed between depression and the use of assisted reproductive techniques, access to health personnel, or epidural anesthesia ( $p > 0.05$ ).

Table 2 presents the sociodemographic characteristics of patients with and without the possibility of a postpartum depression diagnosis according to the EPDS, analyzed as continuous variables. No significant differences were found between groups in terms of the variables listed in Table 2 ( $p > 0.05$ ).

Table 3 shows the evaluation of variables associated with postpartum depression using logistic regression analysis. The probability of being diagnosed with postpartum depression was 21 times higher in mothers with comorbidities than in those without comorbidities ( $p < 0.001$ ; 95% CI: 4.007–110.057). The probability of postpartum depression was 83.5 times higher in mothers whose pregnancy was unplanned compared with those whose pregnancy was planned ( $p < 0.001$ ; 95% CI: 21.531–323.829). The probability of postpartum depression was 27.636 times higher in mothers who smoked than in non-smokers ( $p < 0.001$ ; 95% CI: 10.377–73.604). The likelihood of postpartum depression was 35.778 times higher in mothers without a companion during delivery than in those with a companion ( $p < 0.001$ ; 95% CI: 12.987–98.563). Mothers with complications were 31.735 times more likely to be diagnosed with postpartum depression than those without complications ( $p < 0.001$ ; 95% CI: 9.306–108.224). The probability of postpartum depression was 17.786 times higher in mothers who used formula than in those who did not ( $p < 0.001$ ; 95% CI: 5.034–62.843).

### DISCUSSION

This study investigated the prevalence of postpartum depression (PPD) and associated factors in a cohort of 200 mothers who underwent normal vaginal delivery. Our findings revealed a PPD prevalence of 15% using the Edinburgh Postnatal Depression Scale (EPDS) cutoff score of  $\geq 13$ , which is lower than the reported rates in Türkiye (23.8%) and the Middle East (27%) but within the global range of 17.2%.<sup>[17,18]</sup> This variation in prevalence may be attributed to differences in screening tools, cultural contexts, and specific characteristics of the study populations.

Our analysis identified several significant personal factors associated with an increased risk of PPD. Mothers with pre-existing medical conditions were 21 times more likely to experience PPD. This finding aligns with previous research indicating that physical health comorbidities can exacerbate physiological and psychological stressors during the postpartum period.<sup>[19]</sup> Unplanned pregnancy significantly increased the risk of PPD by 83.5 times, which is consistent with studies suggesting that unplanned pregnancies are associated with increased stress, lower social support, and poorer mental health outcomes in mothers.<sup>[20]</sup>

Furthermore, current smoking was found to increase the odds of PPD by more than 27-fold. This strong association corroborates existing evidence highlighting the detrimental effects of nicotine and other substances on maternal mental health during the postpartum period.<sup>[14]</sup> The absence of a companion during the postpartum period was also identified as a significant risk factor, with mothers lacking

**Table 1: Sociodemographic characteristics of the subjects with and without the possibility of receiving a diagnosis of postpartum depression according to EPDS analyzed as categorical variables**

	Depression no (n=170)		Depression yes (n=30)		Toplam (n=200)		p
	n	%	n	%	n	%	
BMI <sup>a</sup>							NA
Weak	2	1.2	1	3.3	3	1.5	
Normal	53	31.2	13	43.3	66	33.0	
Overweight	75	44.1	8	26.7	83	41.5	
I. degree obese	31	18.2	7	23.3	38	19.0	
II. degree obese	7	4.1	1	3.3	8	4.0	
III. degree obese	2	1.2	0	0.0	2	1.0	
Education level <sup>a</sup>							NA
No	14	8.2	0	0.0	14	7.0	
Primary school	65	38.2	17	56.7	82	41.0	
Middle school	42	24.7	9	30.0	51	25.5	
High school	37	21.8	2	6.7	39	19.5	
University	12	7.1	2	6.7	14	7.0	
Comorbidity*							<0.001
No	168	98.8	24	80.0	192	96.0	
Yes	2	1.2	6	20.0	8	4.0	
Planned pregnancy*							<0.001
Yes	167	98.2	12	40.0	179	89.5	
No	3	1.8	18	60.0	21	10.5	
Smoking*							<0.001
No	160	94.1	11	36.7	171	85.5	
Yes	10	5.9	19	63.3	29	14.5	
Alcohol using <sup>a</sup>							NA
Yes	170	100.0	30	100.0	200	100.0	
No	–	–	–	–	–	–	
Assisted reproductive technique*							0.278
No	169	99.4	29	96.7	198	99.0	
Yes	1	0.6	1	3.3	2	1.0	
Mode of delivery <sup>a</sup>							NA
Nvb	170	100.0	30	100.0	200	100.0	
Cs	–	–	–	–	–	–	
Patient with companion*							<0.001
Yes	161	94.7	10	33.3	171	85.5	
No	9	5.3	20	66.7	29	14.5	
Access to healthcare personnel*							0.222
Yes	166	97.6	28	93.3	194	97.0	
No	4	2.4	2	6.7	6	3.0	

**Table 1 (cont): Sociodemographic characteristics of the subjects with and without the possibility of receiving a diagnosis of postpartum depression according to EPDS analyzed as categorical variables**

	Depression no (n=170)		Depression yes (n=30)		Toplam (n=200)		p
	n	%	n	%	n	%	
	Epidural anesthesia**						
Yes	36	21.2	10	33.3	46	23.0	
No	134	78.8	20	66.7	154	77.0	
Lifetime history of depression*							<0.001
No	170	100.0	19	63.3	189	94.5	
Yes	0	0.0	11	36.7	11	5.5	
Complication*							<0.001
No	166	97.6	17	56.7	183	91.5	
Yes	4	2.4	13	43.3	17	8.5	
Current Breastfeeding status*							<0.001
Yes	170	100.0	22	73.3	192	96.0	
No	0	0.0	8	26.7	8	4.0	
Formula use*							<0.001
No	166	97.6	21	70.0	187	93.5	
Yes	4	2.4	9	30.0	13	6.5	

a: NA (Not Applicable); Chi-Square test assumptions were not met due to low expected cell counts.\*: Fisher's Exact test; \*\*: Chi-Square Test. EPDS: Edinburgh Postnatal Depression Scale; BMI: Body mass index.

**Table 2: Sociodemographic characteristics of the subjects with and without the possibility of receiving a diagnosis of postpartum depression according to EPDS analyzed as continuous variables**

	Depression no (n=170)	Depression yes (n=30)	Total (n=200)	p
	Age mother*			
Mean±SD	27.65±5.64	28.80±6.23	27.83±5.73	
Median (min-max)	27.00 (18–42)	29.00 (18–42)	27.00 (18–42)	
BMI**				0.281
Mean±SD	27.35±4.34	26.40±4.86	27.21±4.43	
Median (min-max)	27.25 (17.65–40.16)	26.31 (16.55–36.79)	27.18 (16.55–40.16)	
Parity*				0.486
Mean±SD	2.46±1.39	2.67±1.49	2.49±1.41	
Median (min-max)	2.00 (1–7)	2.00 (1–6)	2.00 (1–7)	

\*: Mann Whitney test; \*\*: Independent samples t test. SD: Standard deviation; BMI: Body mass index.

support being nearly 36 times more likely to develop PPD. This finding underscores the critical role of social support in buffering postpartum psychological distress.<sup>[21]</sup>

Consistent with the established literature, a history of prior depression emerged as a critical predictor of PPD. This finding was particularly striking in our cohort: while more than one-third

**Table 3: Logistic regression analysis of the data found significant by Chi-Square Test**

Variable	Odds ratio	%95 CI	p
Comorbidity			
No	Reference		
Yes	21.000	4.007–110.057	<0.001
Planned pregnancy?			
Yes	Reference		
No	83.500	21.531–323.829	<0.001
Smoking			
No	Reference		
Yes	27.636	10.377–73.604	<0.001
Patient with companion			
Yes	Reference		
No	35.778	12.987–98.563	<0.001
Lifetime history of depression <sup>a</sup>			
No	Reference		NA
Yes	–	–	
Complication			<0.001
No	Reference		
Yes	31.735	9.306–108.224	
Current breastfeeding status <sup>b</sup>			
Yes	Reference		NA
No	–	–	
Formula using*			
No	Reference		<0.001
Yes	17.786	5.034–62.843	

a: NA (Not Applicable): Analysis could not be performed due to zero cases in the reference group (no history of depression in the non-PPD group);

b: NA (Not Applicable): Analysis could not be performed as all patients in the non-PPD group were breastfeeding. \*: Fisher's exact test. CI: Confidence interval.

(36.7%) of mothers with PPD had a history of depression, none of the mothers in the non-PPD group reported such a history (0%). Although this complete separation precluded inclusion of this variable in the final regression model, this pronounced difference represents an important clinical warning sign. It strongly reinforces the necessity of thorough screening for past and current mental health conditions during antenatal care to identify and support high-risk individuals.<sup>[22]</sup> Moreover, the presence of complications during pregnancy or delivery increased the likelihood of PPD by nearly 32 times, suggesting that adverse obstetric events may have a substantial impact on maternal mental well-being.<sup>[23]</sup>

Interestingly, mothers who used formula were almost 18 times more likely to develop PPD than those who did not. Although causality cannot be inferred due to the cross-sectional design of the study, this association may reflect the emotional distress and challenges experienced by mothers with breastfeeding difficulties, which may lead to formula supplementation and an increased risk of PPD. In

contrast, exclusive breastfeeding has been associated with hormonal benefits and enhanced mother–infant bonding, potentially offering a protective effect against PPD.<sup>[15]</sup>

In contrast to some previous studies, no significant association was observed between PPD and factors such as access to healthcare professionals or the use of epidural anesthesia. The lack of association with healthcare access may be explained by the relatively high level of access within the study population. Similarly, the absence of a significant relationship between epidural anesthesia and PPD is consistent with recent evidence suggesting that the method of pain relief during labor may not be a primary determinant of postpartum depression.<sup>[24]</sup>

### Strengths and Limitations

This study benefited from a well-defined sample of mothers who underwent normal vaginal delivery and from a comprehensive

assessment of a wide range of sociodemographic and obstetric factors. However, the cross-sectional design limits the ability to establish causal relationships or determine the temporal sequence of events. In addition, reliance on self-reported data obtained via the EPDS, although a validated screening tool, does not constitute a clinical diagnosis of postpartum depression (PPD). Future longitudinal studies with larger and more diverse samples, incorporating structured clinical interviews, are needed to further elucidate the complex interplay of factors contributing to PPD in this population.

Additionally, the logistic regression analysis yielded some notably high odds ratios with wide confidence intervals (e.g., unplanned pregnancy, OR=83.5). Although these findings indicate strong associations, their magnitude should be interpreted with caution. This statistical instability is likely related to the skewed distribution of cases within certain subgroups. For example, the small number of participants with a specific risk factor in the non-depressed group (e.g., only three women with an unplanned pregnancy) compared with the depressed group may mathematically result in inflated odds ratios and wider confidence intervals.

### Implications for Practice and Research

Our findings underscore the importance of targeted interventions for women at higher risk of PPD, including those with pre-existing medical conditions, unplanned pregnancies, a history of smoking or depression, lack of social support, and obstetric complications. Healthcare providers should implement routine screening for PPD during both prenatal and postnatal visits and ensure appropriate support and referral mechanisms. Furthermore, promoting pregnancy planning, encouraging social support networks, and providing comprehensive breastfeeding support may contribute to lower rates of PPD.

Future studies should explore the underlying mechanisms driving these associations and develop culturally appropriate strategies for the effective prevention and treatment of postpartum depression. In addition, the relatively low prevalence of PPD observed in this study warrants further investigation. Comparative studies evaluating the impact of specific healthcare delivery models, such as the “Mother-Friendly Hospital” initiative implemented in our institution, on maternal mental health outcomes may provide valuable insights.

### CONCLUSION

This study identified a 15% prevalence of postpartum depression among mothers who underwent normal vaginal delivery and demonstrated significant associations with key personal risk factors, including pre-existing medical conditions, unplanned pregnancy, smoking, lack of a companion, history of depression, and obstetric complications. These findings highlight the importance of routine PPD screening and targeted supportive interventions for the early identification and management of at-risk mothers. Overall, this study provides valuable evidence to support the development of mother-centered healthcare services that prioritize the psychological well-being of women during the postpartum period.

### Statement

**Ethics Committee Approval:** The University of Health Sciences, Gazi Yaşargil Training and Research Hospital Ethics Committee granted approval for this study (date: 28.02.2025, number: 361).

**Informed Consent:** Informed consent was obtained from the patients.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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# Management and follow-up of congenital lung malformations

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## ABSTRACT

**Objective:** Congenital lung malformations (CLM)—including congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (PS), congenital lobar overinflation (CLO), bronchogenic cyst (BC), and isolated congenital bronchial atresia (BA)—have shown increased prenatal diagnosis rates with the more effective use of antenatal imaging methods such as ultrasound (US) and magnetic resonance imaging (MRI). However, the optimal management of these lesions remains unclear. We aimed to investigate the diagnostic processes and management approaches in patients with CLM diagnosed at our clinic.

**Material and Methods:** This retrospective, cross-sectional study included 46 patients aged 0–18 years who were diagnosed with CLM between April 2018 and March 2025. Data on the time and method of diagnosis, presenting complaints, whether surgery was performed, and imaging modalities were recorded.

**Results:** The median age of the patients was 60 months (IQR 62). In the prenatal diagnosis group, the median age at first presentation was 38 months (min–max=1–156) for asymptomatic patients and 6 months (min–max=0.2–132) for symptomatic patients. Sixty-three percent of cases were diagnosed prenatally, and 37% were diagnosed postnatally. Sixty-nine percent (20/29) of prenatally diagnosed cases were asymptomatic at birth. Most radiological lesions were unilobar and unilateral and did not show mediastinal shift. The most commonly affected lobe was the right lower lobe. CPAM (43.5%) was the most common diagnosis, followed by PS (17.8%). Advanced imaging, in addition to ultrasound and chest X-ray, was performed in 20% of the CPAM group and 37.5% of the PS group.

**Conclusion:** The majority of our CLM cases were diagnosed prenatally. In prenatally diagnosed cases that are asymptomatic postnatally, the types and timing of diagnostic tests vary on a case-by-case basis, and the timing of surgical treatment remains uncertain. We believe that further prospective studies and stronger scientific evidence are needed in this field and that management decisions should be based on an individualized benefit–risk assessment.

**Keywords:** Computed tomography, congenital lung malformations, diagnosis, surgical treatment.

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## INTRODUCTION

Congenital lung malformations (CLM) include congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (PS), congenital lobar overinflation (CLO), bronchogenic cyst (BC), and bronchial atresia (BA). These conditions develop from malformations of the lung parenchyma, airways, and vascular structures.<sup>[1]</sup>

Advancements in diagnostic methodologies, most notably prenatal ultrasound and fetal magnetic resonance imaging (MRI), have enabled the detection of the majority of congenital lung malformations prior to birth. Fetal MRI is a complementary imaging modality that provides clearer anatomical details of the lesion and aids in differential diagnosis from other thoracic anomalies. The management of CLM during the prenatal period is contingent upon the size of the lesion, its growth rate, and its effects on the fetus. Postnatal management depends on the symptomatology of the lesion and its dimensions. This is of great importance for planning postnatal management and preventing potential complications. Symptoms vary; therefore, lesions may be detected at birth with respiratory distress and cyanosis or incidentally in asymptomatic adults.<sup>[1]</sup> It is of paramount importance to diagnose and treat patients with severe respiratory distress in a timely manner, as this condition is often accompanied by high morbidity and mortality rates. Early diagnosis of CLM is imperative for optimal prenatal counselling and early perinatal and postnatal management.<sup>[2,3]</sup>

The enhanced efficacy of antenatal imaging techniques, such as ultrasonography (US) and, more recently, magnetic resonance imaging (MRI), has resulted in an increase in the prenatal diagnosis rate. Nevertheless, the optimal approach to the management of these lesions remains to be elucidated, given the heterogeneity of the lesions and the varied clinical presentations.<sup>[1,3]</sup>

The decision-making process can be challenging for clinicians because of the complex structure and diversity of these malformations. In our study, we examined the diagnostic processes and approaches used in patients diagnosed with CLM. The aim was to discuss ideal management strategies in the context of current healthcare conditions in our country.

## MATERIAL AND METHODS

This retrospective, cross-sectional study included 46 patients aged 0–18 years who were diagnosed with CLM and followed up between April 2018 and March 2025 at the Department of Paediatric Pulmonology, Güztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul Medeniyet University. Information regarding the participants' time of diagnosis, diagnostic method, presenting complaints, surgical history, imaging studies, and follow-up was obtained from the institutional patient information system and handwritten medical records.

Additionally, the following imaging studies were reviewed using the hospital database and the national online health monitoring system (e-Nabız): chest X-ray, ultrasound (US), chest computed tomography (CT), computed tomography angiography (CTA), and magnetic resonance imaging (MRI).

Patients were categorised into four groups based on the timing of diagnosis and symptom status: prenatal diagnosis with symptoms,

prenatal diagnosis without symptoms, postnatal diagnosis without symptoms, and postnatal diagnosis with symptoms.

This study was conducted in accordance with the principles of the 1964 Helsinki Declaration and its subsequent amendments, which establish ethical standards for research involving human subjects. Ethical approval was obtained from the Clinical Research Ethics Committee of İstanbul Medipol University on 22.05.2025 (decision number: 644).

## Statistical Analysis

Data were analysed using SPSS version 25.0 software. The normality of data distribution was assessed using the Shapiro–Wilk test. Owing to the descriptive nature of the study, only descriptive statistics were performed. Categorical variables were expressed as numbers and percentages. Continuous variables were presented as median (interquartile range (IQR), minimum–maximum) for non-normally distributed data. No inferential statistical analyses were performed.

## RESULTS

The median age of the 46 patients included in the study was 60 months (interquartile range [IQR] 62), and the median age at first presentation to the clinic was 17 months (minimum–maximum [min–max]=0.2–156.0 months). The median follow-up period at our clinic was 50 months (IQR 47.8). At the time of initial presentation, data according to diagnostic groups were as follows: for prenatally diagnosed asymptomatic patients, the median age was 38 months (range 1–156 months); for prenatally diagnosed symptomatic patients, the median age was 6 months (range 0.2–132 months); for postnatally diagnosed asymptomatic patients, the median age was 14 months (min–max=8–148 months); and for postnatally diagnosed symptomatic patients, the median age was 26 months (min–max=1–132 months).

The demographic profile of the cohort showed a predominance of males, accounting for 56.5% (n=26) of patients. The majority were born at term, and no parental consanguinity was documented in most cases. Parental consanguinity was present in 22.7% (n=10) of patients, while 9.3% (n=4) were born preterm. Overall, 63% of cases were diagnosed prenatally and 37% postnatally. Among prenatally diagnosed cases, 69% (20/29) were asymptomatic at birth, whereas 31% (9/29) were symptomatic. Most radiological lesions were unilobar and unilateral. Congenital heart malformations were present in 21.7% of cases. The most frequently affected lobe was the right lower lobe. Based on symptom status and timing of diagnosis, the most common groups were asymptomatic before birth (43.5%) and symptomatic after birth (30.4%). The most prevalent lesion type was CPAM (43.5%), with type 2 being the most common subtype (Table 1).

Operative age according to diagnostic group was as follows: asymptomatic patients with prenatal diagnosis had a median operative age of 18 months (IQR 51); symptomatic patients with prenatal diagnosis had a median operative age of 0.6 months (IQR 0.8); asymptomatic patients with postnatal diagnosis had a median operative age of 82 months (IQR 64); and symptomatic patients with postnatal diagnosis had a median operative age of 21 months (IQR 81).

**Table 1: Descriptive statistical information related to measurement values (n=46)**

	n	%
Classification by timing and symptom status		
i. Prenatal	29	63.0
Asymptomatic	20	69.0
Symptomatic	9	31.0
ii. Postnatal	17	37.0
Asymptomatic	3	17.6
Symptomatic	14	82.4
Type of CLM		
Bronchogenic cyst	3	6.5
CPAM	20	43.5
Type 3	1	4.3
Type 2	8	34.8
Type 1	6	26.1
N/A	8	34.8
PS	8	17.4
Intrapulmonary	3	30.0
Extrapulmonary	2	20.0
N/A	3	30.0
CLO	4	8.7
Hybrid lesion	2	4.3
CPAM type 1 + PS	1	50
CPAM type 1 + Bronchogenic cyst	1	50
Radiological features		
Anatomical location involved		
Right lower lobe	13	28.3
Right middle lobe	4	8.7
Mediastinum	3	6.5
Left upper lobe	10	21.7
Right upper lobe	4	8.7
Left lower lobe	7	15.2
More than. one lobe	5	10.9
Mediastinal shift	6	13
Extent of affected area		
Single lobe and/or confined to one hemithorax	41	89.1
Multilobar and/or involving both hemithoraces	5	10.9
Coexisting congenital malformations		
I. Gastrointestinal system (TOF)	1	9.1
II. Cardiovascular system (VSD, Dextroposition, ASD, PFO)	10	90.9

CLM: Congenital lung malformation; CPAM: Congenital pulmonary airway malformation; PS: Pulmonary sequestration; CLO: Congenital lobar overinflation; TOF: Tracheoesophageal fistula; VSD: Ventricular septal defect; ASD: Atrial septal defect; PFO: Patent foramen ovale; N/A: Not applicable.

**Table 2: Comparison of radiological preliminary and definitive diagnoses in operated patients (n=28)**

	n	%
Definitive diagnosis		
Bronchogenic cyst	3	10.7
CPAM	14	50
Pulmonary sequestration	7	25
Congenital lobar overinflation	2	7.1
Hybrid lesion	2	7.1
Radiological preliminary diagnosis		
Bronchogenic cyst	3	10.7
CPAM	7	25
Pulmonary sequestration	1	3.6
Air trapping	2	7.1
Cavitary lesion/ consolidation	2	7.1
Solid mass	2	7.1
CPAM	1	3.6
Pulmonary sequestration	4	14.3
Cavitary lesion	2	7.1
Air trapping	2	7.1
Cavitary lesion	1	3.6
Cystic lesion	1	3.6

CPAM: Congenital pulmonary airway malformation.

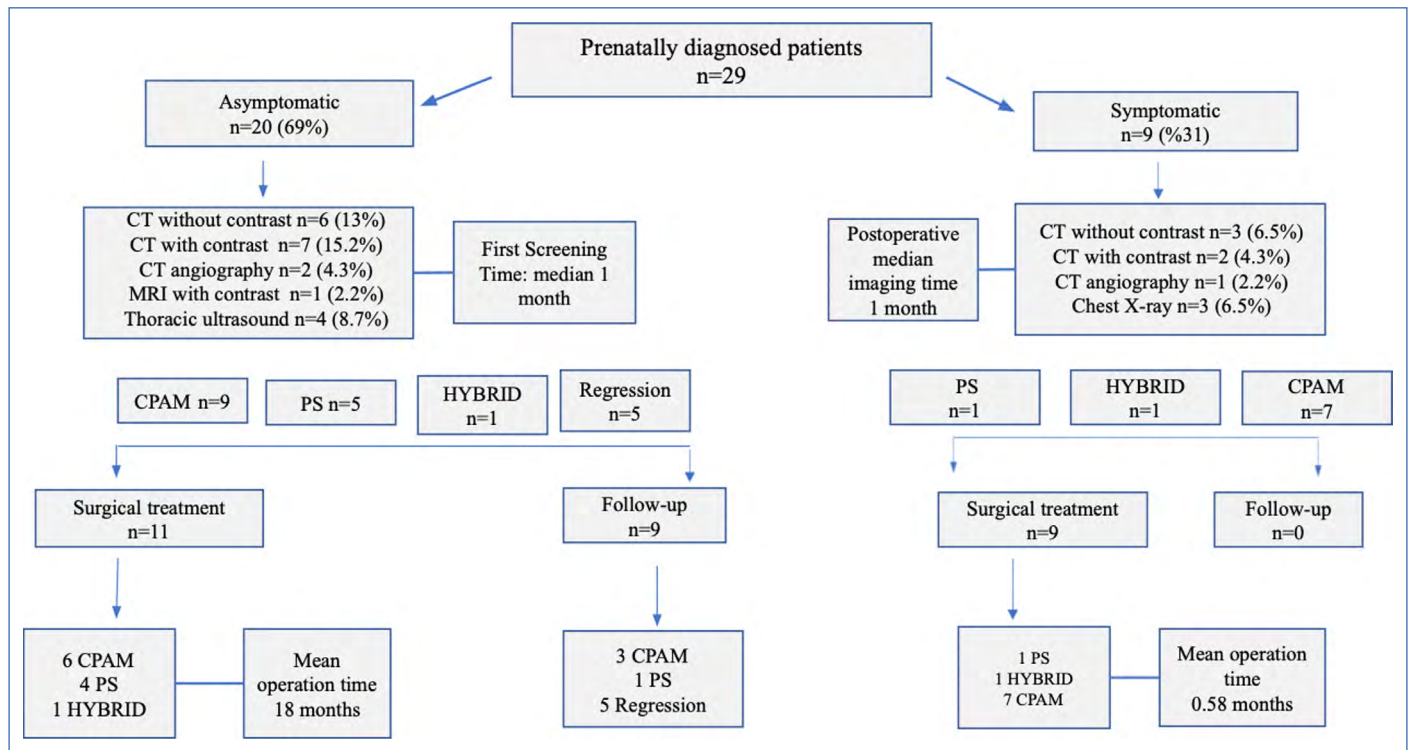
The timing of the first chest X-ray according to diagnostic groups was as follows: prenatally diagnosed asymptomatic patients had a median age of 1.0 month (IQR 29); prenatally diagnosed symptomatic patients had a median age of 1.0 month (IQR 0.5); and postnatally diagnosed asymptomatic patients had a median age of 4.2 months (IQR 3.7).

Among prenatally diagnosed asymptomatic patients, 17.2% (5/29) had a CLM diagnosis that could not be confirmed postnatally, suggesting possible lesion regression (Fig. 1).

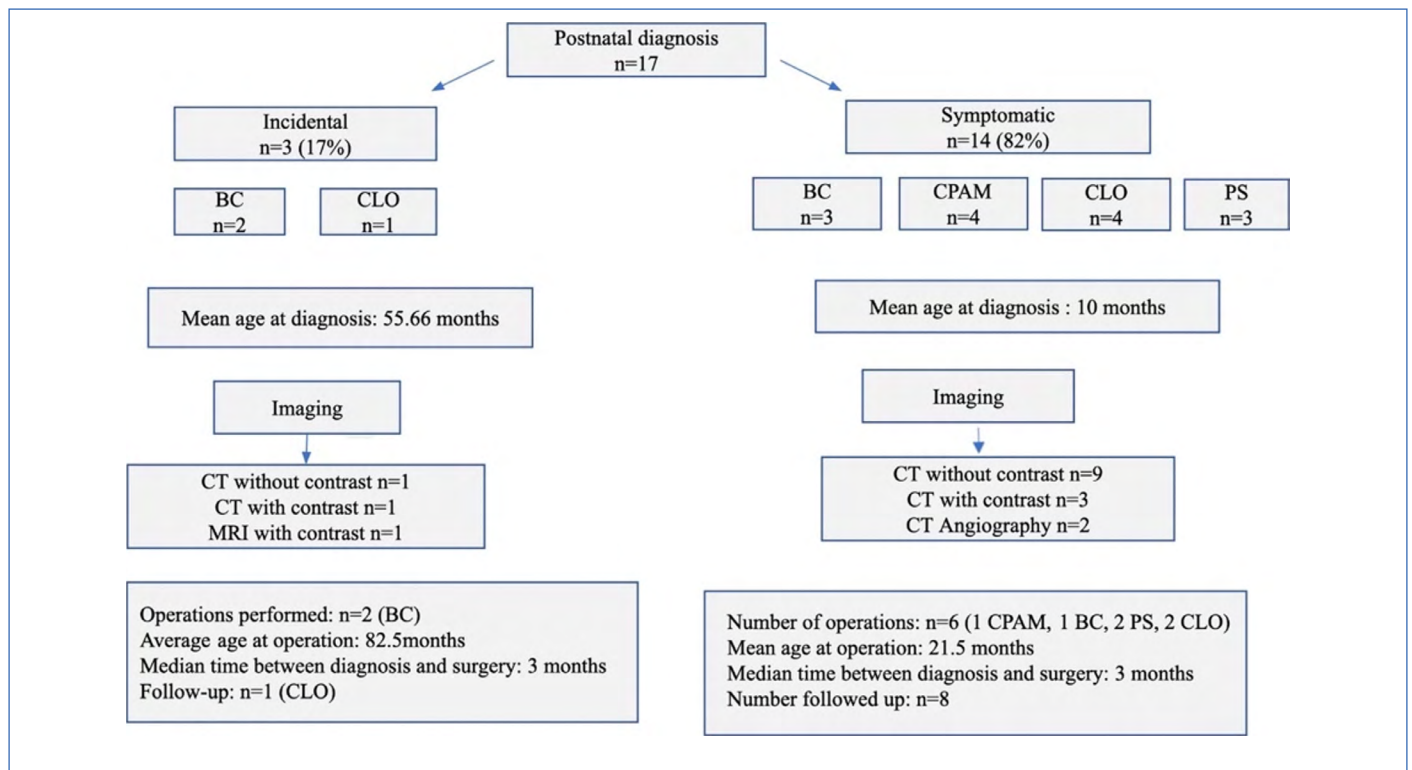
Similarly, 17.6% (3/17) of postnatally diagnosed patients were diagnosed incidentally. These incidental diagnoses included one case of CLO identified on a CT scan performed after trauma, one case detected on contrast-enhanced MRI during evaluation for neurofibromatosis type 1, and one case diagnosed on imaging performed for suspected foreign body aspiration (foreign body aspiration was not confirmed by bronchoscopy in this patient). The mean age at diagnosis in these cases was 55.6 years. Among postnatally diagnosed patients, 82.4% (14/17) were diagnosed based on imaging studies performed for recurrent respiratory symptoms, with a mean age at diagnosis of 10 months (Fig. 2).

### Imaging Findings

Lesions were confined to a single lobe and/or hemithorax in 89.1% of cases, involved multiple lobes and/or bilateral hemithorax in 10.9% of cases, and were associated with mediastinal shift in 13% of cases (Table 1).



**Figure 1:** Follow-up and management of our patients diagnosed with CLM during prenatal screening.



**Figure 2:** Follow-up and management of our patients diagnosed with CLM during postnatally screening.

Comparison of initial radiological diagnoses with final diagnoses showed that CPAM had the highest misdiagnosis rate. Among 14 cases with histopathologically confirmed CPAM after surgery, CPAM was

not considered in 7 cases (50%) during preoperative evaluation, and alternative preliminary diagnoses were made (Table 2). These included pulmonary sequestration, air trapping, cavitory lesion, solid mass, and

consolidation. Among patients who underwent advanced imaging in addition to ultrasound and chest X-ray, 20% of the CPAM group (two MRI and two CT scans) and 37.5% of the PS group (one MRI, one CT scan, and one CT angiography) received advanced imaging.

Surgical treatment was performed in 43.4% (20/46) of all cases, including 37.9% (11/29) of prenatally diagnosed patients and 47% (8/17) of postnatally diagnosed patients. Segmentectomy was performed in 15% (3/20) of cases, mediastinal cyst excision in 10% (2/20), and lobectomy in 75% (15/20), including one case that required additional vascular embolisation. At the time of data collection, eight patients were awaiting surgery as part of the planned surgical management, with follow-up close to their initial presentation.

## DISCUSSION

This article analyses the diagnostic processes of 46 CLM patients who were followed at our clinic for seven years. The majority of patients were diagnosed during the prenatal period (63%), were asymptomatic at birth (69%), and underwent surgery at a median age of 18 months.

The most common diagnostic groups were CPAM and PS, respectively. Regression of the lesion was observed in 10.9% of patients diagnosed IU in the postnatal period. CLMs exhibit diverse clinical characteristics; they may present with severe respiratory symptoms at birth, remain asymptomatic, or be detected incidentally at a later age.

Due to their wide clinical spectrum and albeit low risk of malignant transformation, CLMs require timely diagnosis and appropriate management. Therefore, early diagnosis, prenatal counselling, and early perinatal and postnatal management are essential.<sup>[2,3]</sup> In recent years, an increase in the frequency of prenatal diagnosis has been reported, with up to 4 in 10,000 pregnancies detected during the prenatal period. This increase is primarily attributed to technical advances in fetal ultrasound (US) and magnetic resonance imaging (MRI), as well as their more widespread use.<sup>[4]</sup>

Congenital thoracic malformations (CTMs) are frequently detected during routine antenatal ultrasonography and often encompass a spectrum of anomalies rather than isolated abnormalities. In addition, due to the similar appearance of various congenital lung and non-pulmonary lesions, a definitive antenatal diagnosis is usually not possible. Prenatal diagnosis is generally less reliable than postnatal diagnosis, as it typically relies on the cystic or solid appearance of lesions within the fetal thorax or abnormal lung size, which may result in displacement of the heart.<sup>[5]</sup>

Because our study included patients referred from different maternity clinics, we were unable to evaluate prenatal diagnostic characteristics in detail. Nevertheless, we found that 63% of all CLM cases had received a prenatal diagnosis. Prenatal CLM diagnosis should be confirmed postnatally, and the lesion type must be clearly defined. During fetal ultrasound follow-up, resolution (11–49%), regression (18–42%), or progression (33–44%) of lesions may be observed.<sup>[6]</sup> Cavoretto et al.<sup>[7]</sup> demonstrated that only 34 (44.7%) of 76 cases with prenatal sonographic resolution were confirmed postnatally. The reduction in CLM size appears to be related not only to fetal growth but also to the transition in lung development from

the canalicular to the sacular stage. In addition, in late pregnancy, lesions may become isoechoic with normal lung tissue, leading to the erroneous assumption that they have disappeared.<sup>[6]</sup>

Among prenatally diagnosed patients in our cohort, 17% had no detectable lesions on postnatal evaluation. A prospective study reported spontaneous regression in 17% of 29 cases diagnosed with prenatal CLM, with postpartum confirmation also performed. Prenatal and postnatal diagnoses were consistent in 37% of cases (with partial regression in 25%), whereas incorrect diagnoses, such as congenital diaphragmatic hernia or duplication cyst, were reported in 10% of cases.<sup>[8]</sup> As we were unable to review antenatal imaging, we hypothesised that regression may have occurred in this 17% subgroup, given the absence of detectable lesions and other anomalies. The reported accuracy of prenatal ultrasound in distinguishing lesion types ranges between 60% and 90%.<sup>[9]</sup> Therefore, caution is warranted to avoid unnecessary or inappropriate prenatal and/or postnatal interventions in every infant diagnosed with CLM before birth.

The average age of patients at our paediatric pulmonology centre was 17 months. The youngest patient was younger than 1 month, and the oldest was 156 months. This wide age range was attributable to diagnoses made both prenatally and postnatally. Asymptomatic patients diagnosed prenatally had a mean age of 38 months, whereas symptomatic patients had a mean age of 6 months. These ages were considered relatively late for the initiation of paediatric pulmonology follow-up. The most important contributing factor was referral from other clinics, resulting in delayed presentation. We would like to emphasise the importance of effective inter-clinic communication for timely diagnosis and management.

The group with the greatest uncertainty in management, for which standards are still being developed, consists of asymptomatic patients diagnosed prenatally. Advanced thoracic imaging should be performed to confirm the diagnosis and to evaluate the lesion more accurately in asymptomatic infants; however, the timing depends on individual risk factors. Even if they are asymptomatic postnatally, infants diagnosed prenatally should first undergo a chest X-ray. If a suspicious lesion is detected, chest computed tomography (CT) should be performed.<sup>[10]</sup>

Chest CT is recommended at approximately 6–9 months of age, even in asymptomatic patients, because of the risk of recurrent lung infections and malignant transformation. Chest magnetic resonance imaging (MRI) may also be used in centres with appropriate experience.<sup>[11]</sup> In addition, immediate advanced imaging evaluation is recommended for infants with features suggesting an increased risk of complications, such as large lesions on chest radiography, bilateral or multifocal cysts, or a family history of conditions associated with pleuropulmonary blastoma or pneumothorax. In infants without risk factors associated with poor prognosis, advanced thoracic imaging is recommended at 6–9 months postnatally.<sup>[12]</sup>

All infants in our cohort, whether asymptomatic or symptomatic, underwent chest X-ray evaluation within the first month after birth. Difficulties were encountered in postnatal management because of insufficient information regarding prenatal diagnostic methods. The largest diagnostic group consisted of asymptomatic patients diagnosed prenatally, with the first CT and/or MRI imaging performed

at a mean age of six months. Most patients had previously undergone non-contrast CT imaging. However, contrast-enhanced CT had to be repeated in patients requiring differential diagnosis of other congenital malformations, which occurred in six cases. Contrast-enhanced thoracic CT is recommended to definitively confirm the absence of pulmonary lesions within the first six months, and CT angiography (CTA) is recommended to evaluate associated hybrid lesions.<sup>[13]</sup>

Thoracic CT was the most frequently used imaging modality in our cohort, followed by CT angiography and MRI. Because of the high prevalence of CPAM and PS, advanced imaging was often required for differential diagnosis. The currently accepted view is that CT angiography is necessary to exclude or confirm PS, as the most common hybrid lesions involve the coexistence of CPAM and PS.<sup>[13]</sup>

In the postnatal period, children diagnosed due to respiratory symptoms are treated with early total surgical resection. Reported complications in patients who do not undergo surgery include cyst infection, dyspnoea, pneumothorax, bleeding, feeding difficulties, sudden respiratory failure (affecting approximately 20% of children younger than one year), and malignant transformation (reported in 1–3% of patients). Early surgical resection is also recommended when the lesion involves more than 20% of the hemithorax, in the presence of pneumothorax, bilateral or multifocal cysts, or a family history of pleuropulmonary blastoma. All of our patients diagnosed symptomatically in the postnatal period had recurrent lower respiratory tract infections and no history of malignancy. In most cases, lesions were unilateral and confined to a single lobe. Only one in ten patients had multilobar or bilateral involvement with mediastinal shift, and these cases underwent surgery at a median age of 21 months. Lobectomy was the most commonly applied surgical technique in our series. Following total resection, postoperative survival is generally high regardless of the timing of surgery.<sup>[14]</sup> The optimal timing of surgery in asymptomatic infants remains controversial; however, as anaesthetic and surgical risks decrease after the first few months of life, surgery is generally recommended between six months and two years of age.<sup>[15,16]</sup>

Half of the asymptomatic patients diagnosed prenatally in our cohort underwent surgical treatment, with a median operative age of 18 months. The remaining CLM cases currently under follow-up have not yet been classified as asymptomatic or high-risk lesions and are expected to reach one year of age.

As our study has shown, the most common type of CLM is CPAM, followed by PS. CPAM is characterised by the formation of one or more cysts within the lung parenchyma, typically involving a single lobe. It can be confused with many other malformations or cystic diseases.<sup>[17]</sup> In contrast, pulmonary sequestration can easily be overlooked or confused with other pathologies because it may appear as a solid nodule or mass, consolidation, or cystic lesion on chest X-ray.<sup>[18]</sup>

When we compared the initial radiological diagnoses of our patients with their final diagnoses, CPAM was found to have the highest misdiagnosis rate. Of the 14 cases in which CPAM was confirmed histopathologically after surgery, CPAM was not considered in 50% of preoperative evaluations, and alternative preliminary diagnoses, such as PS, cystic and cavitory lesions, or air trapping, were made. Among the cases in which the final diagnosis was PS, one case had previously been diagnosed as

CPAM and two cases as cavitory lesions. In a prospective study of fetuses with prenatally diagnosed CLM, 5% of lesions regressed spontaneously during the intrauterine period, 8% decreased in size, and 11% were associated with respiratory distress in the neonatal period. In addition, 83% of infants who underwent postnatal CT scanning proceeded to surgery. These infants were followed up until childhood, with a median follow-up period of five years. During follow-up, 5% developed symptoms, such as pneumonia, and underwent surgery between the ages of three and five years. In contrast, 81% remained asymptomatic, and 89% showed either a reduction in lesion size or complete resolution.<sup>[19]</sup>

Early and accurate diagnosis is essential for the appropriate management of patients with CLMs. A standardised, multidisciplinary approach is required for diagnosis, follow-up, and treatment. Close collaboration among obstetricians, neonatologists, paediatric surgeons, and paediatric pulmonologists facilitates optimal management.

### Limitations

Detailed diagnostic test results for patients with prenatal diagnoses were unavailable. As a tertiary care centre, we frequently manage patients who have already undergone multiple investigations at other institutions, which may contribute to delays in diagnosis.

### CONCLUSION

CLMs are most commonly diagnosed during the prenatal period, and the majority of affected infants remain asymptomatic at birth. In asymptomatic prenatal cases, the first postnatal investigation should be chest X-ray, and routine CT scanning immediately after birth is not necessary. The diagnosis and management of CLM are not yet clearly defined; therefore, further prospective studies and stronger scientific evidence are required in this field. Management decisions should be based on an individual benefit–risk assessment.

### Statement

**Ethics Committee Approval:** The Istanbul Medipol Clinical Research Ethics Committee granted approval for this study (date: 22.05.2025, number: 644).

**Informed Consent:** Not applicable. This is a retrospective study based on anonymized patient data, and informed consent was not obtained by the institutional ethics committee.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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**Use of AI for Writing Assistance:** We acknowledge that we employed ChatGPT 3.5 and 4 to assist us in refining the clarity of our writing while developing the draft of this original article. We always maintained continuous human oversight (editing and revising) and verified the artificial intelligence-generated output. We never used AI to find, locate, or review the literature or resources, summarize the articles, analyze the selected articles, or synthesize the findings. The authors completed all analyses with higher-level efforts.

**Author Contributions:** Concept – EG, SCO; Design – SCO, SG; Supervision – SG; Results – SG, EG; Materials – YÖ; Data Collection and/or Processing – EG, YÖ; Analysis and/or Interpretation – YÖ, EG; Literature Search – EG; Writing – EG, SG; Critical Reviews – SG.

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# Echocardiographic findings and clinical spectrum of pediatric Marfan syndrome

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## ABSTRACT

**Objective:** Marfan syndrome is more than a genetic diagnosis; it poses a significant cardiovascular risk, with critical structures such as the aortic root potentially affected before clinical symptoms appear. This study evaluated the echocardiographic profiles and characteristic clinical features of genetically confirmed pediatric Marfan syndrome patients in a tertiary center.

**Material and Methods:** Pediatric patients with confirmed Marfan syndrome who underwent transthoracic echocardiography between October 2018 and May 2025 were retrospectively reviewed. Aortic dimensions and valvular pathologies were assessed according to American Society of Echocardiography criteria. Clinical data, family history, and anthropometric features were also documented.

**Results:** Ten patients (8 females, 2 males; mean age 12.4±5.6 years) were included. Aortic root dilatation was observed in two patients, mitral valve prolapse in nine patients, and mitral regurgitation in six patients based on their most recent outpatient follow-up evaluations. Four patients received medical therapy; however, treatment adherence was inconsistent and outcomes varied. Most patients exhibited tall stature and had a positive family history. No cardiovascular surgeries were performed during the follow-up period.

**Conclusion:** In pediatric Marfan syndrome, severe cardiovascular complications may remain clinically silent until advanced stages. Our findings indicate that even in genetically confirmed cases, early echocardiographic evaluation frequently detects valvular abnormalities and aortic involvement before clinical deterioration. These results underscore the critical importance of early diagnosis and regular echocardiographic surveillance to optimize follow-up and prevent delayed recognition of potentially fatal complications.

**Keywords:** Aortic root dilatation, Marfan syndrome, pediatric cardiology.

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## INTRODUCTION

Marfan syndrome (MFS, MIM #154700) is an autosomal dominant connective tissue disorder affecting multiple organ systems. It is genetically caused by pathogenic variants in the FBN1 gene, which encodes the extracellular matrix protein fibrillin-1.<sup>[1–3]</sup> While the mutation exhibits high penetrance, its expression varies among individuals. As a result, clinical manifestations are heterogeneous and age-dependent. The most commonly affected systems are skeletal, ocular, and cardiovascular.<sup>[4]</sup>

Cardiovascular manifestations include mitral valve prolapse (MVP), mitral regurgitation (MR), left ventricular dilatation, aortic root dilatation, aortic regurgitation, and pulmonary artery dilatation. Among these, aortic root dilatation is the most critical complication, as it may lead to aortic dissection and sudden cardiac death.<sup>[1–3]</sup> These features may appear during childhood, and some cases may present with symptoms during the neonatal period, especially in severe phenotypes.<sup>[5,6]</sup>

This study aimed to evaluate the cardiovascular findings and follow-up of genetically confirmed pediatric MFS cases monitored at our Pediatric Cardiology outpatient clinic.

## MATERIAL AND METHODS

### Study Population and Echocardiographic Evaluation

This study included patients with genetically confirmed Marfan syndrome who underwent at least one transthoracic echocardiographic examination between October 2018 and May 2025 at our Pediatric Cardiology outpatient clinic. Data on age, sex, height, weight, percentiles, body mass index (BMI), family history of MFS, systemic manifestations, medical treatments, and surgical interventions were collected retrospectively from hospital records.

Echocardiographic assessments were performed using the Vivid 3 S26 (GE Medical Systems) device. Standard M-mode, 2D, and color Doppler techniques were used. Measurements and evaluations were based on criteria established by the American Society of Echocardiography (ASE). Aortic annulus and sinus of Valsalva dimensions were assessed, and Z-scores were calculated using a database-based tool according to age, sex, and body surface area. Z-scores  $\geq +2$  were considered diagnostic for annular or aortic root dilatation. Valve insufficiencies were classified as trace, mild, moderate, or severe.

### Statistical Analysis

The data were recorded in Microsoft Excel. Descriptive statistics were applied. Continuous variables are presented as mean  $\pm$  standard deviation, and categorical variables as frequencies and percentages. No inferential statistical tests were performed due to the limited sample size.

### Ethical Considerations

The study protocol was approved by the Ethics Committee of Zeynep Kamil Women and Children's Training and Research Hospital (approval number: 99, date: 25/12/2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

## RESULTS

Eighteen pediatric patients with genetically confirmed MFS were identified. Eight patients without echocardiographic data were excluded. The remaining ten cases were analyzed.

The mean age was  $12.4 \pm 5.6$  years; eight patients were female and two were male. Height percentiles were above the 95<sup>th</sup> percentile in eight cases, and weight percentiles were below the 50<sup>th</sup> percentile in two cases. BMI ranged from 12.6 to 30.8 kg/m<sup>2</sup>, with a mean of  $19.8 \pm 6.1$  kg/m<sup>2</sup>.

Among the ten patients, two were siblings and one was a cousin. A positive family history of MFS was identified in nine of ten patients. Parental consanguinity was reported in three of ten families.

Four of ten patients (40%) were prescribed enalapril therapy. In the first case, aortic root dilatation was present, and early initiation of medical therapy resulted in normalization of the aortic root Z-score during follow-up, with no subsequent increase observed. In the fifth case, enalapril therapy was initiated at the age of 9 years, continued for one year, and subsequently discontinued by the patient herself. In the seventh case, there was no consanguinity and no family history of Marfan syndrome, and the case was identified as a de novo mutation. In the eighth case, the patient's mother was diagnosed only after the patient was evaluated and had recently undergone both valvular and aortic surgery. The final findings of the cases are summarized in Table 1.

The most recent echocardiographic findings revealed Z-scores ranging from -1.2 to +3.28. During follow-up, two patients had an aortic root Z-score  $>+2$ , indicating aortic root dilatation. MVP was identified in nine cases, and MR was noted in six of these, four of which were graded as trace regurgitation. The 1-year-old infant had only a patent foramen ovale (PFO) without other abnormalities. The distribution of cardiac findings is presented in Table 2.

Three patients had undergone lens surgery, and one patient had undergone rhinoplasty. No cardiovascular surgeries were reported.

## DISCUSSION

Marfan syndrome affects 1 in 3,000 to 5,000 individuals, regardless of race or gender.<sup>[1–3]</sup> Clinical diagnosis is based on the Ghent criteria established by an international expert panel, but definitive diagnosis is genetic.<sup>[7]</sup>

In one striking case within our study, Patient 7 was identified as having a de novo mutation, consistent with the approximately 25% rate reported in the literature.<sup>[1–4]</sup> The mothers of Patients 5 and 6 had also been diagnosed with MFS. These observations highlight variable intrafamilial expression and emphasize the importance of early identification and screening of at-risk relatives.

Clinically, the cohort displayed classic Marfan features such as tall stature, long limbs, arachnodactyly, scoliosis, pectus deformities, and increased arm span.<sup>[1–3]</sup> Three patients had undergone lens surgery due to lens subluxation, aligning with the reported 40–56% prevalence in pediatric patients.<sup>[1]</sup>

Except for the infant, all cases demonstrated mitral valve prolapse, and most had associated mitral regurgitation. Aortic root dilatation was observed in 20% of cases, which may be underestimated due to

**Table 1: Summary of the demographic, medical history, echocardiographic findings and medication records**

Case number	G	Age	Weight	Height	BMI	Parental con.	Family Marfan history	EKO	Aortic annulus	Aortic sinus	LVDD	Medication
Case 1	F	10	72.6	183.7	21.5		Yes	MVP, MR (trace)	20.07	23.7	44.67	Enalapril
Case 2	F	18	62	180	19.1			MVP (mild)	20.3	24.7	41.75	
Case 3	F	8	24	138	12.6		Yes	MVP, MR (mild), aortic root dilatation	17	28	46.5	Enalapril
Case 4	F	18	100	180	30.8	Yes	Yes	MVP, Aortic root dilatation (mild)	22	33	48.5	
Case 5	F	13	55	172	18.5	Yes	Yes	MVP, MR (trace)	21	30	45.9	Enalapril for 1 year at age 9, discontinued
Case 6	F	15	58	170	20	Yes	Yes	MVP, MR (mild)	20.5	30.5	51	Enalapril
Case 7	F	7	23.4	130	13.6			MVP(mild)	15.5	17.5	38.8	
Case 8	F	1	11.6	84	16.4		Yes	PFO	12	15	25	
Case 9	M	17	112	195	29.4		Yes	MVP, MR (trace)	24	39	55	
Case 10	M	13	43.3	185	15.7		Yes	MVP, MR (trace)	24	29.7	48.6	

G: Gender; F: Female; M: Male; Con: Consanguinity; MVP: Mitral valve prolapse; MR: Mitral regurgitation; PFO: Patent foramen ovale; LVDD: Left ventricular end-diastolic diameter.

the younger age distribution. Across all patients, aortic root Z-scores ranged from -1.2 to +3.28 during follow-up. As age increases, the incidence of dilatation and related complications is known to rise.

Angiotensin-converting enzyme inhibitors, such as enalapril, have demonstrated efficacy in reducing the progression of aortic complications.<sup>[8–10]</sup> However, in our cohort, only four patients were receiving medical therapy, and adherence was suboptimal. One patient discontinued therapy prematurely on their own initiative, while others did not consistently adhere to the prescribed regimen.

Although inferential statistical analysis was limited by the small sample size, descriptive analyses were performed to illustrate trends among treated patients. In Patient 1, therapy was initiated when the aortic root Z-score was 1.14; during treatment, values fluctuated between -1.0 and +0.57, and at the last follow-up the Z-score was 1.71, without significant progression. In Patient 3, therapy began at a Z-score of 2.3; after 7 months, the Z-score increased to 3.28. This patient had previously received enalapril at an external center but discontinued the medication independently during the COVID-19 pandemic. Therapy was subsequently restarted at our center, and follow-up continued under treatment. In Patient 5, medical therapy was initiated at a Z-score of 2.31 but discontinued by the patient after one year; subsequent Z-scores ranged from -0.29 to +1.95, and

**Table 2: Distribution of cardiac findings**

Cardiac finding	n	%
Aortic root dilatation	2	20
Mitral valve prolapse	9	90
Mitral regurgitation	6 (4 trace, 2 mild)	60

clinical follow-up continued without medication. In Patient 6, therapy was initiated at a Z-score of 1.86, but the patient demonstrated poor adherence, with the most recent follow-up revealing a Z-score of 1.71. With the exception of Patient 5, all treated patients remain under ongoing medical therapy and surveillance.

Among the treated cases, follow-up Z-scores showed fluctuations rather than a consistent trend, reflecting both individual biological variability and inconsistent treatment adherence. These findings highlight the challenges of maintaining long-term therapy and follow-up in pediatric populations. Regular echocardiographic monitoring and multidisciplinary follow-up, including general pediatrics, ophthalmology, and orthopedics, remain essential for the optimal management of children with Marfan syndrome.

The 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease provided updated recommendations on surveillance intervals, medical therapy, and surgical thresholds, emphasizing individualized management and care at experienced centers.<sup>[11]</sup> It also highlighted the need for lifelong follow-up, earlier consideration of surgery in high-risk patients, and the use of  $\beta$ -blockers or angiotensin receptor blockers (ARBs) as first-line medical therapy.<sup>[10,11]</sup>

Building on these principles, the 2024 AHA Scientific Statement on Cardiovascular Management of Aortopathy in Children specifically addressed pediatric populations. It emphasized growth- and Z-score-based definitions of aortic dilatation, risk stratification by progression rate, and the role of genetic diagnosis in tailoring management.<sup>[12]</sup> In children, surgical decisions are not solely guided by absolute dimensions but also by rapid aortic enlargement, severity of regurgitation, and family history of dissection.<sup>[11,12]</sup> Furthermore, the statement introduced more individualized recommendations for lifestyle and exercise, advocating shared decision-making between clinicians and families.<sup>[12]</sup> These considerations are directly relevant to our cohort, given early aortic root dilatation, variable adherence to therapy, and heterogeneity of follow-up.

Kemna et al.<sup>[13]</sup> proposed a root-to-descending aorta ratio  $\geq 2$  as highly sensitive and  $\geq 2.3$  as highly specific. Gautier et al.<sup>[14]</sup> provided nomograms for Valsalva diameters. A French multicenter study reported a 7.6% cardiovascular event rate in pediatric Marfan patients, with 82.9% undergoing aortic surgery. Cumulative incidence increased from 5.3% at 18 years to 19.4% at 25 years.<sup>[6]</sup> Identified risk factors included an annual Z-score increase  $\geq 0.1$ , annual diameter growth  $\geq 5$ mm, aortic regurgitation  $\geq 2$ , and a Z-score  $\geq 3$  before the age of 16.<sup>[6]</sup> Recent studies have also suggested that the aortic sinus cross-sectional area-to-height ratio (5–7cm<sup>2</sup>/m) may aid surgical decision-making in children.<sup>[15]</sup>

No patients in our cohort underwent cardiovascular surgery, likely due to the outpatient and referral-based nature of our clinic. While moderate physical activity may be permitted, contact sports and intense physical exertion remain contraindicated in children with Marfan syndrome.<sup>[12]</sup>

## CONCLUSION

In this case series, the clinical and cardiovascular characteristics of pediatric Marfan syndrome were consistent with previously reported findings in the literature. Notably, the presence of aortic root dilatation at diagnosis in some children highlights the need for early and systematic surveillance. Although  $\beta$ -blockers or angiotensin receptor blockers (ARBs) are recommended as first-line therapy, our experience illustrates the challenges of long-term treatment adherence in pediatric patients. In our series, treatment outcomes varied, reflecting the impact of adherence and continuity of follow-up on aortic root progression.

In line with current guidelines,<sup>[12]</sup> children with Marfan syndrome should not only be followed by pediatric cardiology but also require a multidisciplinary approach, including general pediatrics, ophthalmology, and orthopedics. When necessary, collaboration with genetics and surgical specialties should also be considered to optimize individualized management.

Early recognition, sustained treatment adherence, and structured multidisciplinary follow-up remain the cornerstones for preventing major adverse outcomes in children with Marfan syndrome.

## Statement

**Ethics Committee Approval:** The Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 25.12.2024, number: 99).

**Informed Consent:** The authors declare that there is no conflict of interest.

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# Cytogenetic and Y chromosome microdeletion analysis in azoospermic patients: Insights into genetic causes of male infertility

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## ABSTRACT

**Objective:** Azoospermia, the most severe form of male infertility, is characterized by the absence of sperm in the ejaculate as a result of spermatogenesis failure. The aim of this study was to identify genetic anomalies associated with Y chromosome microdeletions and sex chromosomal aneuploidy.

**Material and Methods:** A total of 134 azoospermic patients were included in the study. Following a general clinical evaluation and laboratory testing, karyotype analysis and Y chromosome microdeletion screening were performed.

**Results:** The study included 134 infertile males with azoospermia. The overall rate of cytogenetic anomalies was 9.7%. Chromosomal abnormalities were detected in 7 of 134 cases (5.2%). The most common genetic abnormality was 47,XXY (Klinefelter syndrome), with a prevalence of 3.7%. Y chromosome microdeletions were identified in 5 patients (3.7%).

**Conclusion:** This study highlights the significant role of genetic factors, particularly chromosomal abnormalities and Y chromosome microdeletions, in the etiology of azoospermia. In addition, Y chromosome microdeletions were identified in a notable subset of cases. These findings emphasize the importance of comprehensive genetic screening, including both karyotype analysis and Y chromosome microdeletion testing, in the diagnostic evaluation of azoospermic men to guide clinical management and genetic counseling.

**Keywords:** Azoospermia, infertility, microdeletion, Y chromosome.

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## INTRODUCTION

Azoospermia, defined as the complete absence of spermatozoa in the ejaculate, affects approximately 1% of men. Around 35–40% of azoospermia cases result from various acquired conditions.<sup>[1]</sup> The congenital forms, on the other hand, are primarily attributed to genetic factors, many of which are routinely analyzed during the diagnostic evaluation of infertile males.<sup>[2]</sup> Genetic screening plays a critical role in guiding clinical decisions, providing effective genetic counseling, and improving diagnostic accuracy.<sup>[3]</sup> In clinical practice, patients with azoospermia due to primary testicular failure are typically assessed for chromosomal abnormalities and Y chromosome Azoospermia Factor (AZF) microdeletions.<sup>[4]</sup> The advent of Next Generation Sequencing (NGS) technologies—particularly Whole Exome Sequencing (WES) and targeted gene panels—has led to the identification of numerous novel monogenic causes of azoospermia. Among the most frequent genetic causes is Klinefelter syndrome (KFS), characterized by the presence of an extra X chromosome. This condition occurs in approximately 1 in 600 male newborns (0.1–0.2%), but its prevalence rises to 3–4% in infertile men and up to 10–12% among those with azoospermia.<sup>[5,6]</sup> Clinically, KFS is associated with features such as eunuchoid body habitus, hypergonadotropic hypogonadism, gynecomastia, small firm testes, azoospermia, and a range of neurocognitive impairments.<sup>[7]</sup>

Another common genetic cause of azoospermia involves deletions in the Y chromosome's long arm (Yq), specifically within the Azoospermia Factor (AZF) regions essential for normal spermatogenesis. Three major deletion patterns have been identified—AZFa, AZFb, and AZFc—located in the proximal, middle, and distal Yq11 regions, respectively.<sup>[8]</sup> Among these, AZFc deletions are the most frequent (approximately 80%), followed by AZFa (0.5–4%), AZFb (1–5%), and combined AZFbc deletions (1–3%). Because the AZF loci harbor multiple genes vital for spermatogenesis, microdeletions in these areas are well-established genetic causes of male infertility.<sup>[9]</sup> Determining the specific gene responsible for the clinical phenotype is challenging, as these regions contain multiple gene families. Within the 792 kb AZFa region, two single-copy genes—USP9Y and DDX3Y—are broadly expressed. The USP9Y gene encodes a ubiquitin C-terminal hydrolase that likely plays a regulatory role in protein turnover,<sup>[10]</sup> whereas DDX3Y encodes an ATP-dependent RNA helicase belonging to the conserved DEAD-box family. The loss of DDX3Y is thought to underlie the Sertoli Cell-Only Syndrome phenotype associated with complete AZFa deletions, characterized by small testicular volume and a total absence of germ cells in the seminiferous tubules.<sup>[11]</sup> Complete AZFb deletions, in contrast, remove approximately 6.2 Mb of DNA containing 32 gene copies and transcriptional units. Since their removal results in spermatogenic arrest, these genes are probably involved in germ cell maturation. There are 12 genes and transcription units in the AZFc area, each of which is present in a different number of copies, for a total of 32 copies. Complete AZFc deletion carriers have a wide range of clinical manifestations. Although sperm concentrations are usually <2 million/mL, spermatozoa can be found in the ejaculate.<sup>[12]</sup> In this study, we assessed the genetic reasons for azoospermia in male infertility patients.

## MATERIAL AND METHODS

This study was approved by the Ethics Committee of Umraniye Training and Research Hospital (Ethics No: B.10.1.TKH.4.34.H.GP.01/329, 30/09/2025), School of Medicine, University of Health Sciences, Istanbul, Türkiye. Following ethical approval, this study included 134 patients who were admitted to the Department of Medical Genetics at the University of Health Sciences Umraniye Training and Research Hospital between January 2021 and September 2025 for infertility. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was not required due to the retrospective design of the study and ethics committee regulations, and all records were kept confidential.

### Y Microdeletion

Peripheral blood samples were collected, and genomic DNA was extracted using standard methods. DNA extraction from blood samples was performed using a semi-automated robot as recommended by the manufacturer (Qiagen). DNA concentration and quality control (260/280 nm and 260/230 nm values) were determined by fluorometry (Qubit v3.0) and UV spectrophotometry. Disease-associated gene regions were amplified by polymerase chain reaction (PCR), and the samples were loaded onto the ABI SeqStudio 8 Flex instrument. Fragment analysis was performed using SeqStudio 8 Flex Software v6.0.

### Cytogenetics

For karyotype analysis, peripheral blood lymphocytes were cultured in special culture media. During the last 2 hours of the 72-hour culture period, colcemid was added to arrest the cells in mitosis. After colcemid treatment, trypsin-EDTA was used to detach the cells from the bottom of the flask. The cells were collected and transferred to tubes. For harvesting, the cells were treated with a hypotonic solution (potassium chloride or sodium citrate) for approximately 10–15 minutes after centrifugation. Immediately following the hypotonic treatment, the cells were fixed two to three times with a cold methanol:glacial acetic acid solution prepared at a 3:1 ratio. The prepared cell suspensions were dropped onto clean slides, and the aging process was carried out by air-drying or brief exposure to high temperatures. The aged preparations were banded and stained with trypsin and Giemsa for routine analysis. Karyotype analysis was performed using the Leica Biosystems Cytovision analysis system.

### Statistical Analysis

GraphPad Prism software version 8.4.2 was used for data analysis. Continuous variables are presented as mean±standard deviation. Statistical significance was considered when  $p < 0.05$ .

## RESULTS

The mean age of the 134 infertile men evaluated in this study was 30.9±7.0 years. Cytogenetic abnormalities were detected in 9.7% of cases overall. Chromosomal abnormalities were identified in 7 of 134 cases (5.2%). Structural and numerical chromosomal abnormalities are summarized in Table 1. Klinefelter syndrome

**Table 1: Karyotype and Y chromosome deletion information of the patients**

Patient no.	Age	Karyotype (peripheral blood)	Y Chromosome microdeletion
1	26	47, XXY	Not detected
3	28	46, Y, t(X;7) (q26; q11.22)	Not detected
5	26	46, XY, t (13;17) (p10; q10)	Not detected
29	24	46, XY, t (2;9) (q13; p24)	Not detected
30	29	47, XYY	Not detected
49	33	47, XXY	Not detected
69	32	46, XY, t (8;12) (q22; q24.1)	Not detected
92	39	46, X, inv (Y) (p11.2; q11.23)	Not detected
102	31	46, X, del (Y) (q12) [32] / 45, X [18]	Not detected
109	30	46, XY, t (3;14) (p10; q10)	Not detected
113	30	47, XXY	Not detected
117	44	47, XYY	Not detected
122	27	47, XXY	Not detected
127	29	47, XXY	Not detected
14	16	46, XY	Detected AZFa (SY82, SY83, SY88 & SY1065), AZFb (SY153, SY121, SY105 & SY143) AZFc gr/gr (SY1191 & SY1291)
41	37	46, XY	Detected AZFc (SY254 & SY255), AZFd (SY152 & SY153)
61	8	46, X, del(Y) (q11.21)	Detected AZFa (M259, SY84, SY86 & SY625), AZFb (SY127, SY130, SY131 & SY134), AZFc (SY157, SY254 & SY255), AZFd (SY152 & SY153).
80	33	46, X, der(Y)	Detected AZFc (SY157, SY254 & SY255), AZFd (SY152 & SY153).
86	36	46, XY	Detected AZFc (SY157, SY254 & SY255), AZFd (SY152 & SY153).

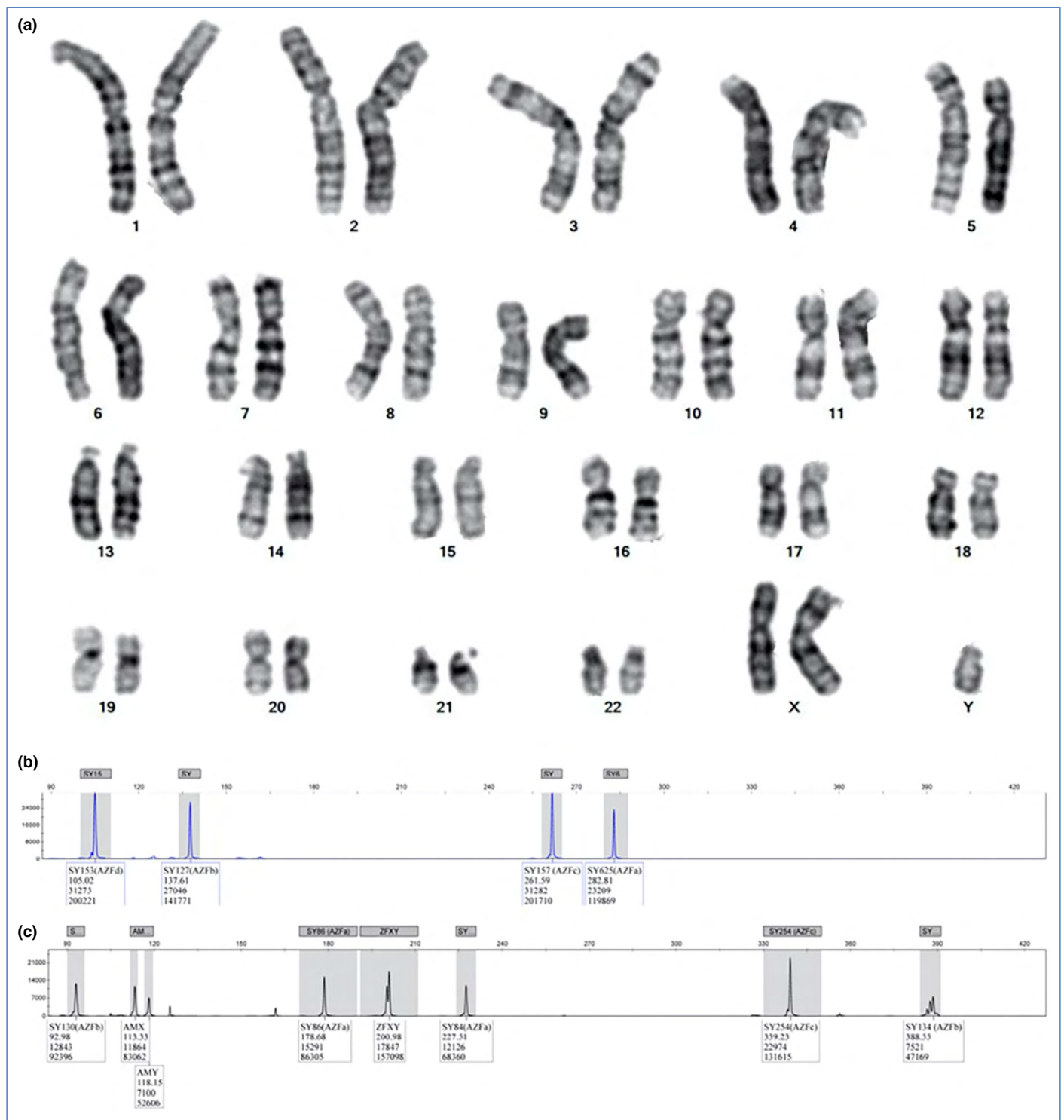
(47,XXY; KFS) was identified in five cases (3.7%) and represented the most common anomaly among all cases.

Y chromosome microdeletions were detected in 3.7% of cases overall, with the AZFc region being the most frequently deleted. Based on molecular screening of the AZF region, five AZF microdeletions were identified: one involving AZFa+b+c, one involving AZFa+b+c+d, and three involving AZFc+d (Table 1). Representative karyotype images and Y chromosome deletion images are shown in Figures 1–3.

## DISCUSSION

Male infertility is caused by genetic factors among many other etiologic contributors. Numerous genes on the Y chromosome that function at

various stages of germ cell development regulate spermatogenesis.<sup>[13]</sup> In the present study, the frequency of chromosomal abnormalities was determined to be 5.2%. These results closely resemble those reported in previous studies.<sup>[14]</sup> Numerous studies investigating the rate of chromosomal abnormalities from different countries have been published, with reported frequencies ranging from 6.2% to 12.6%.<sup>[15]</sup> KFS was identified as the most prevalent abnormality in this study, which is consistent with prior clinical findings.<sup>[16]</sup> In 50–60% of cases, the extra X chromosome is of paternal origin, whereas in 40–50% of cases it is maternal.<sup>[17]</sup> Epidemiological studies have shown that the incidence of KFS is gradually increasing and is thought to be associated with advanced paternal age.<sup>[18]</sup> In recent years, however, patients with KFS have been reported to experience

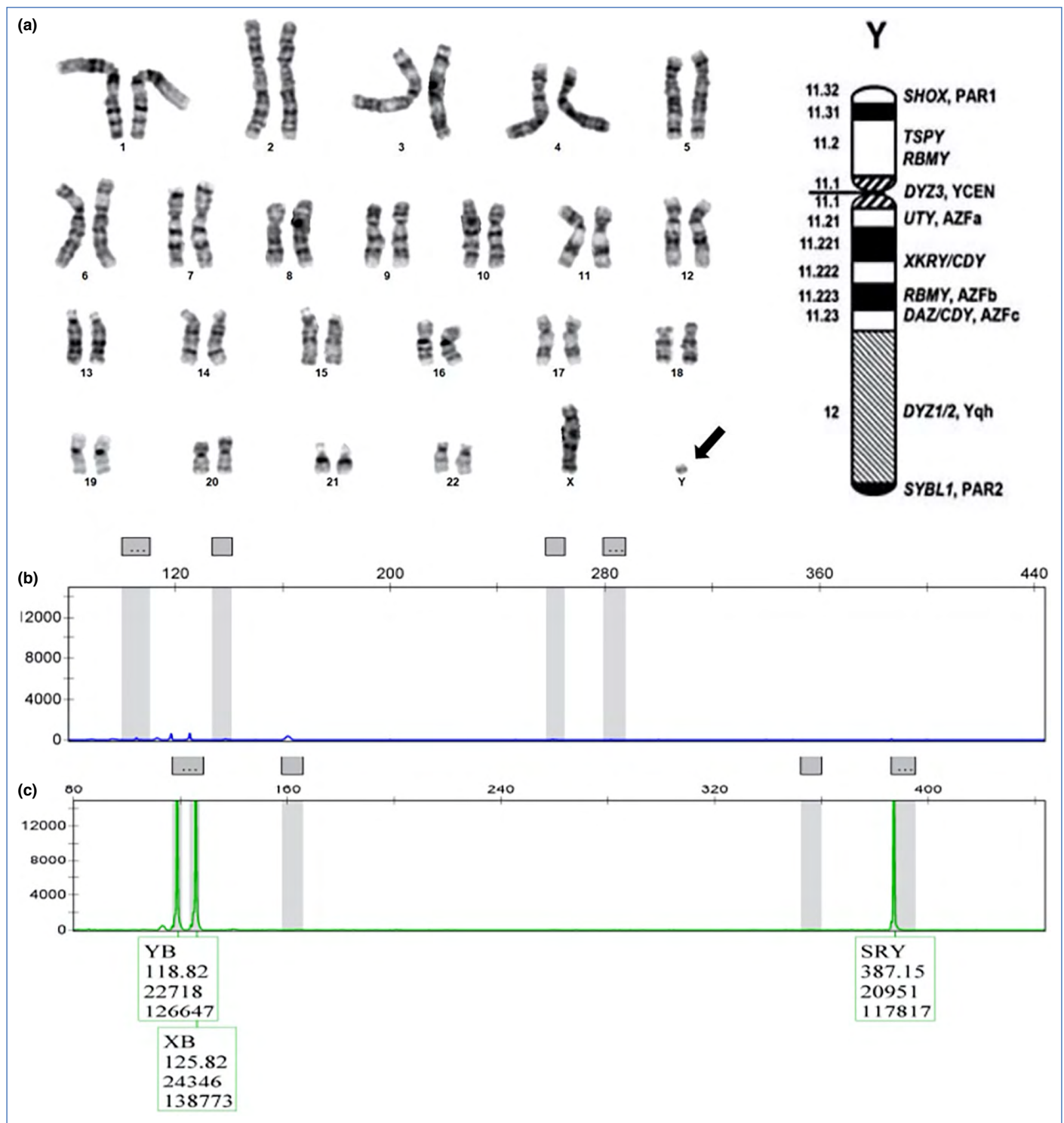


**Figure 1:** Case 113 (a) karyotype image (47, XXY), (b) Y microdeletion image (No deletion was detected), (c) Internal control DNA.

serious health problems, including substantial morbidity (70%) and mortality (50%), in addition to infertility.<sup>[19]</sup> Early diagnosis and timely initiation of disease management are therefore crucial, particularly during puberty. Testosterone replacement therapy promotes the development of secondary sexual characteristics in patients with KFS, alleviates depressive symptoms, and improves self-confidence.

Although patients with KFS are generally considered infertile, assisted reproductive techniques may enable fertilization in selected cases.

In addition, these patients may achieve parenthood through intracytoplasmic sperm injection (ICSI), testicular sperm extraction (TESE), micro-TESE, and sperm cryopreservation. Testicular tissue preservation and spermatogonial stem cell cryopreservation remain

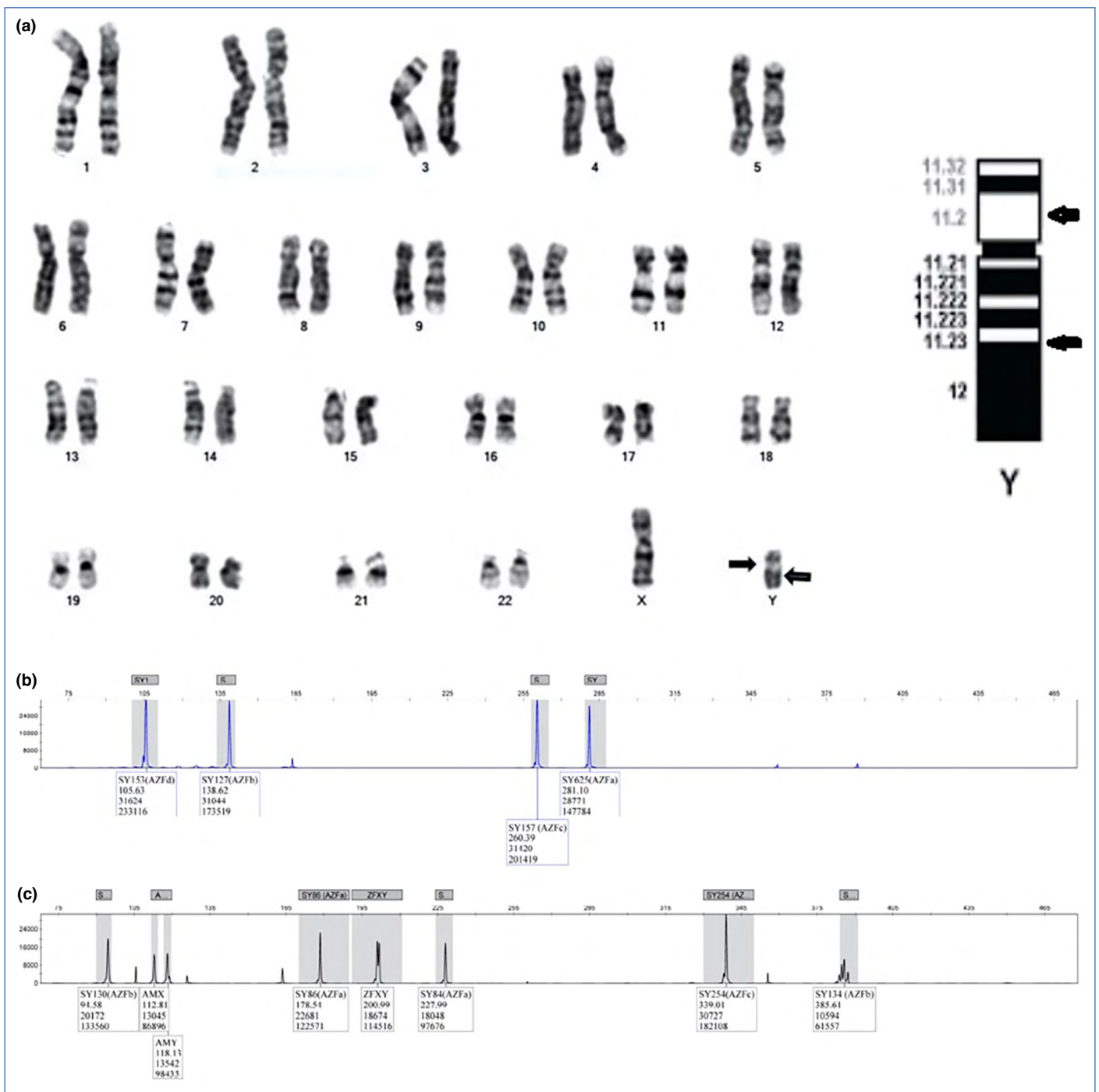


**Figure 2:** Case 61 (a) karyotype image [46, X, del(Y)(q11.21)], Y chromosome ideogram image on the right side. (b) Y microdeletion image (Deletions were detected in the AZFa, AZFb, AZFc, and AZFd regions). (c) Internal control DNA.

experimental approaches.<sup>[20]</sup> Y chromosome microdeletions are among the most common genetic causes of male infertility.<sup>[21]</sup> Ethnic and regional characteristics have been identified as major factors influencing the variability and prevalence of these microdeletions. An international study based on a large dataset reported Yq

microdeletion rates ranging from 7% to 10%.<sup>[22]</sup> Several studies have investigated the incidence of Y chromosome microdeletions in the Türkiye population, reporting frequencies between 1.3% and 9.6%.<sup>[23]</sup>

In the present study, the prevalence of Y chromosome microdeletions was found to be 3.7%. Variations in reported



**Figure 3:** Case 92 (a) karyotype image (46, X, inv[Y] [p11.2 q11.23]), Y chromosome ideogram image on the right side (b) Y microdeletion image (No deletion was detected). (c) Internal control DNA.

frequencies may be attributed to differences in genetic background, environmental factors, primer sets used for AZF microdeletion analysis, and genetic heterogeneity among populations, particularly with respect to Y chromosome-specific haplotypes. Population size, regional differences, and patient selection based on the etiology and severity of spermatogenic impairment may also contribute to these discrepancies. In the Iranian population, Akbarzadeh et al.<sup>[24]</sup> reported a higher frequency of AZFb microdeletions (66.67%)

compared with AZFc deletions (41.67%). It has been suggested that although AZFc deletions impair spermatogenesis, they do not invariably result in complete infertility.

Sperm retrieval by TESE may be possible in azoospermic men with AZFc deletions, allowing fertilization. In contrast, complete deletions of the AZFa and AZFb regions lead to total germ cell loss, rendering TESE and ICSI ineffective. Reports indicate that sperm retrieval by TESE is possible in approximately 50% of cases with partial AZFb deletions.

<sup>[25]</sup> Couples with Yq microdeletions who undergo assisted reproductive procedures should be informed that male offspring may also develop spermatogenic abnormalities due to transmission of the microdeletion.

Comprehensive genetic screening plays a crucial role in the diagnostic evaluation of azoospermic men, as it enables identification of underlying genetic abnormalities that directly affect clinical management and reproductive counseling. Karyotype analysis is essential for detecting chromosomal aneuploidies and structural rearrangements, such as KFS, which are major contributors to male infertility. In parallel, Y chromosome microdeletion analysis provides critical information on deletions within the AZF regions that are strongly associated with spermatogenic failure.<sup>[2]</sup> The combined use of these diagnostic modalities allows more accurate etiological classification of azoospermia, facilitates assessment of the feasibility of sperm retrieval for assisted reproductive techniques, and supports informed genetic counseling regarding inheritance risks and reproductive options. The limitations of this study include its retrospective design and the lack of data on patient treatment strategies and paternity outcomes during follow-up.

## CONCLUSION

Incorporating both karyotype analysis and Y chromosome microdeletion testing into the diagnostic workflow for azoospermic men ensures a comprehensive genetic evaluation. This integrated approach not only clarifies the underlying cause of infertility but also provides essential guidance for personalized clinical management and accurate genetic counseling of affected individuals.

## Statement

**Ethics Committee Approval:** The Umraniye Training and Research Hospital Ethics Committee granted approval for this study (date: 30.09.2025, number: B.10.1.TKH.4.34.H.GP.0.01/329).

**Informed Consent:** Written informed consent was not required due to the retrospective design and ethics committee regulations.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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# Hyperbilirubinemia in Gilbert syndrome and hepatitis B infection: Two confusing clinical cases accompanied by hereditary spherocytosis

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## ABSTRACT

Gilbert's syndrome (GS) is a benign disorder that causes chronic jaundice and unconjugated hyperbilirubinemia. When it occurs in conjunction with hereditary spherocytosis (HS), it can lead to an elevated risk of severe hyperbilirubinemia and associated complications. However, acute pancreatitis is a rare complication in this setting. This study explores complex etiologies in severe hyperbilirubinemia and pancreatitis through two acute pancreatitis cases. One case involves a patient with HS and hepatitis B, and the other is of GS with HS contributing to the condition. Two pediatric patients with severe hyperbilirubinemia and acute pancreatitis, managed at different time points in our pediatric gastroenterology clinic, were presented. GS in one case and hepatitis B infection in the other were considered contributing factors but did not fully explain the disease's severity. A systematic review of clinical, laboratory, and imaging findings identified hereditary spherocytosis as the common underlying condition. A 16-year-old boy with consanguineous parents presented with recurrent abdominal pain and jaundice. Laboratory and imaging findings indicated acute pancreatitis due to gallstones, extreme hyperbilirubinemia, and HS with GS. Genetic testing confirmed GS (UGT1A polymorphism). ERCP relieved the obstruction, and the patient was referred for cholecystectomy and splenectomy. The other boy, a 14-year-old with chronic hepatitis B, presented with acute abdominal pain. Imaging revealed gallstones, splenomegaly, and acute pancreatitis. Laboratory findings suggested HS, confirmed by osmotic fragility testing. MRCP excluded bile duct obstruction. Following stabilization, laparotomic cholecystectomy and splenectomy were performed without complications. We present two pediatric cases with distinct etiologies who developed severe hyperbilirubinemia and acute pancreatitis in the presence of hereditary spherocytosis. These cases highlight the complex interplay of underlying conditions contributing to disease severity. By adding to the limited literature on this association, we aim to enhance understanding of the diverse etiologies of severe hyperbilirubinemia and acute pancreatitis.

**Keywords:** Acute pancreatitis, Gilbert syndrome, hepatitis, hereditary spherocytosis, hyperbilirubinemia.

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## INTRODUCTION

Gilbert's Syndrome (GS) is an autosomal dominant (AD) disorder characterized by chronic jaundice episodes and unsevere or chronic unconjugated hyperbilirubinemia without the existence of hepatocellular disease or hemolysis. GS is the most common hereditary bilirubin glucuronidation defect. When the level of UDP-glucuronosyltransferase 1-1 (UGT-1A), the glucuronidation enzyme, decreases to under 30% of its normal level, this leads to an increase in monoconjugated bilirubin. GS is frequently diagnosed incidentally, and its incidence is 3-10% in the West, whereas it is 3% in the East.<sup>[1–3]</sup>

Hereditary spherocytosis (HS) is the most common inherited hemolytic disorder, characterized by the loss of membrane surface area due to defects in membrane spectrin, ankyrin, band 3, or protein 4.2, leading to reduced deformability. Its incidence is 1/2000 in Europe and North America. Approximately 75% of cases follow an autosomal dominant inheritance pattern and present with varying degrees of anemia, jaundice, and splenomegaly. The most common complications are hemolytic crises and cholelithiasis.<sup>[4,5]</sup>

Acute pancreatitis can occur at any age in childhood, although its incidence is not as high as in adults, with an incidence of 30-50/100,000. In previous publications, major pediatric clinics reported 2-10 cases of acute pancreatitis per year; it is claimed that this number has been increasing in recent years, and the cause of this increase is multifactorial. Acute pancreatitis is diagnosed more frequently, especially in children with systemic disease. Along with systemic diseases, other frequent causes include obesity, infections, gallstones, and metabolic diseases.<sup>[6–10]</sup>

Coexistence of spherocytosis, thalassemia, or cystic fibrosis with GS leads to extremely increased bilirubin levels, and the likelihood of developing cholelithiasis increases fivefold. In the literature, a few cases with the coexistence of these two diseases show a complicated pattern.<sup>[11–15]</sup> However, acute pancreatitis episodes following gallstones and severe hyperbilirubinemia in cases with the coexistence of GS and HS have not been reported.

Hepatitis B infection can also cause acute pancreatitis. Non-fulminant hepatitis can significantly increase morbidity and mortality when associated with acute pancreatitis. Therefore, it is of great importance to recognize pancreatic involvement in hepatitis virus infections in a timely manner, modify treatment accordingly, and prevent adverse impacts on the outcome.<sup>[16]</sup>

In this report, we investigate the coexistence of HS with GS and chronic hepatitis B infection in two different cases with the same clinical condition of acute pancreatitis, gallstones, and severe hyperbilirubinemia, who presented with complaints of jaundice and abdominal pain. The literature is reviewed after obtaining informed consent from their families.

## CASE REPORT

The first case involves a 16-year-old boy who presented with recurrent abdominal pain for six months and jaundice for fifteen days. His parents were consanguineous, and he had no known diseases. He had experienced intermittent scleral icterus since age 9, worsening with fatigue and insomnia from age 12.

On physical examination, the patient was conscious and exhibited scleral icterus. His body temperature was 37°C, blood pressure 110/60 mmHg, and heart rate 80 beats per minute with a regular rhythm. His respiratory examination was unremarkable. Cardiovascular examination revealed a grade 1/6 systolic murmur at the apex. Abdominal examination revealed generalized tenderness and guarding, with hepatomegaly (liver palpable 2 cm below the right midclavicular line) and splenomegaly (spleen palpable 4 cm below the left midclavicular line).

Laboratory tests revealed a leukocyte count of 7800 10<sup>3</sup>/uL, hemoglobin 12.8 g/dL, hematocrit 34.4%, platelet count 292,000/mm<sup>3</sup>, mean corpuscular volume (MCV) 79 fL, mean corpuscular hemoglobin concentration (MCHC) 36.5%, corrected reticulocyte ratio 3%, total bilirubin 5.7 mg/dL, indirect bilirubin 5.3 mg/dL, total lipid 285 mg/dL, cholesterol 62 mg/dL, calcium 9.6 mg/dL, IgA 190 mg/dL (47-249 mg/dL), IgG 941 mg/dL (716-1711 mg/dL), and IgM 34.3 mg/dL (15-188 mg/dL). Liver and kidney function tests were within normal limits; however, amylase was elevated at 2063 U/L, lipase at 2711 U/L, and amylase clearance at 6.5%. Abdominal ultrasonography revealed a slightly enlarged liver with homogeneous parenchymal echogenicity, a significantly enlarged spleen, a homogeneous but mildly edematous pancreas, and a thickened gallbladder wall measuring 5 mm with signs of inflammation. Multiple gallstones, the largest measuring 6 mm in diameter, were detected. The common bile duct measured 5.7 mm, but no apparent dilation of the extrahepatic bile ducts was observed.

The patient was diagnosed with acute pancreatitis secondary to gallstones. Enteral nutrition was withheld, and intravenous fluids and broad-spectrum antibiotic therapy were initiated. Further investigations revealed negative serologic markers for hepatitis A, B, and C, negative autoimmune hepatitis antibodies, and normal levels of alpha-1 antitrypsin, copper, and ceruloplasmin. On the second day of hospitalization, abdominal pain, tenderness, and jaundice worsened. Laboratory tests showed hemoglobin 10 g/dL, hematocrit 27%, MCV 77 fL, corrected reticulocyte ratio 9%, total bilirubin 34.6 mg/dL, direct bilirubin 23.7 mg/dL, indirect bilirubin 10.9 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 58 U/L, serum glutamic pyruvic transaminase (SGPT) 30.2 U/L, alkaline phosphatase (ALP) 184 U/L, gamma-glutamyl transferase (GGT) 101 U/L, and lactate dehydrogenase (LDH) 273 U/L. Repeated abdominal ultrasonography demonstrated mild hepatomegaly, significant splenomegaly, intrahepatic bile duct dilatation, a notably distended gallbladder with thickened walls (4 mm), multiple gallstones, and dense sludge formation. The common bile duct was slightly dilated at 7 mm, but no stones were detected within it. Magnetic resonance cholangiopancreatography (MRCP) confirmed acute pancreatitis, significant splenomegaly, multiple gallstones in the gallbladder, and a suspected calculus in the common bile duct.

Severe abdominal pain and worsening jaundice persisted despite acute pancreatitis treatment, prompting repeated laboratory tests, which revealed a total bilirubin of 45 mg/dL, direct bilirubin of 36 mg/dL, SGOT of 58 U/L, SGPT of 30.2 U/L, ALP of 184 U/L, GGT of 106 U/L, amylase of 1004 U/L, and lipase of 817 U/L. A repeat MRCP showed intrahepatic bile duct dilation and a newly detected stone in the common bile duct, leading to a decision for therapeutic endoscopic retrograde cholangiopancreatography (ERCP). During

**Table 1: Initial clinical and laboratory findings in two patients**

	Case 1	Case 2
Age / Gender	16 yo / Male	14 yo / Male
Total bilirubin (mg/dL)	34.6	4.6
Direct bilirubin (mg/dL)	23.7	3.4
Hemoglobin (g/dL)	10.0	11.2
MCHC (g/dL)	37.0	33.9
Corrected reticulocyte ratio (%)	9.0	1.4
SGPT / SGOT (U/L)	30 / 36	45 / 56
Amylase / Lipase (U/L)	2063 / 2711	1187 / 1542
HBs Ag (S/CO)	0.547 (negative)	100 (positive)
Peripheral blood smear	Acanthocytes and spherocytes	Acanthocytes and spherocytes
Osmotic fragility test	Increased	Increased
Abdominal USG	HSM, edematous pancreas, multiple gallstones, CBD ectasia	HSM, edematous pancreas, CBD dilation
Treatment	Folic acid, cholecystectomy and splenectomy	Folic acid, cholecystectomy and splenectomy

yo: Year-old; MCHC: Mean corpuscular hemoglobin concentration, SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; Hbs Ag S/CO: 0-0.98\_negative, >=0.90-<0.1\_borderline, >=1\_positive; HSM: Hepatosplenomegaly; CBD: Common bile duct.

ERCP, sphincterotomy was performed, and 4–5 small black gallstones (<0.5 cm) were extracted. A 10F, 10 cm plastic stent was placed in the common bile duct. The patient's clinical condition improved, and enteral nutrition was resumed. Follow-up laboratory tests showed a total bilirubin of 16.3 mg/dL, direct bilirubin of 6.6 mg/dL, GGT of 47 U/L, ALP of 86 U/L, amylase of 603 U/L, and lipase of 578 U/L. Although there was no family history of hereditary spherocytosis (HS), the persistently elevated total bilirubin in the absence of pain, the presence of reticulocytosis, and the identification of acanthocytes and spherocytes on peripheral blood smear prompted further investigation. Osmotic fragility testing returned positive results. Genetic testing for Gilbert's syndrome (GS) revealed a TA repeat polymorphism (rs8175347) in the promoter region of the UGT1A gene, confirming the diagnosis of GS. Ultimately, the patient was diagnosed with extreme hyperbilirubinemia, gallstones, and acute pancreatitis, secondary to the concurrent presence of hereditary spherocytosis and Gilbert's syndrome. Upon discharge, the total bilirubin was 11.3 mg/dL, indirect bilirubin was 8.7 mg/dL, and hemoglobin was 10 g/dL. Follow-up abdominal ultrasonography revealed splenomegaly, multiple gallstones in the gallbladder, and mild intrahepatic bile duct dilatation, while the pancreas and extrahepatic bile ducts appeared normal. The patient was subsequently referred to the pediatric surgery department for planned cholecystectomy and splenectomy.

The second case involves a 14-year-old boy who presented to the pediatric emergency department with a sudden onset of severe abdominal pain. His history revealed that he had been followed with a diagnosis of chronic hepatitis B since the age of six and had no complaints other than yellowing of the eyes when very tired. Physical examination revealed body temperature 37°C, respiratory rate 20 per minute, heart rate 78 per minute, blood pressure systolic 110/70 mmHg, and slightly jaundiced sclera. The respiratory and cardiovascular examinations were normal, and the abdomen was

slightly tender to palpation but there were no signs of defense or rebound. The liver was two centimeters below the ribs and the spleen three centimeters below the costal margin.

Laboratory investigations were as follows: leukocytes 8400 10<sup>9</sup>/uL, hemoglobin 11.2 g/dL, hematocrit 33%, platelet count 324,000/mm<sup>3</sup>, reticulocyte 2%, total bilirubin 4.6 mg/dL, indirect bilirubin 3.4 mg/dL, SGOT 56 U/L, SGPT 45 U/L, GGT 34 U/L, ALP 131 U/L, amylase 1187 U/L, lipase 1542 U/L, triglycerides 197 mg/dL, cholesterol 124 mg/dL, IgA 167 mg/dL, IgM 121 mg/dL, IgG 1123 mg/dL. Among the indicators of hepatitis, HBs Ag, Anti-HBe, Anti-HBc total were positive, HBe negative, HBV DNA 34,200 IU/mL, anti-HAV IgG positive, and Anti-HCV negative were detected.

Abdominal ultrasonography showed a slightly enlarged liver with homogeneous parenchymal echogenicity, significantly enlarged spleen, homogeneous and slightly edematous pancreas parenchyma. The biliary vesicle wall thickened to 4.5 mm with inflammation, and numerous calculi with a maximum diameter of 6.2 mm were detected. The common bile duct diameter was 5.5 mm, and extrahepatic bile ducts appeared normal.

Intravenous hydration treatment was initiated, and on the second day of follow-up, jaundice on the skin and increased serum bilirubin levels were observed. A magnetic resonance cholangiopancreatography (MRCP) was performed, and no pathology was observed, except for millimetric stones in the gallbladder. Acanthocytes and spherocytes were seen in the peripheral smear, raising the possibility of a secondary illness that could worsen hyperbilirubinemia. The diagnosis was considered to be hereditary spherocytosis with a positive osmotic fragility test result. When the patient was stable, laparoscopic cholecystectomy and splenectomy were performed, and there were no issues in the postoperative follow-up.

The clinical features of the two cases are summarized in Table 1.

## DISCUSSION

Gilbert Syndrome (GS) is the most common form of hereditary unconjugated hyperbilirubinemia metabolic disorder. Plasma bilirubin concentration is usually below 3 mg/dL and increases up to two to three times this level during fasting and illness.<sup>[2]</sup> GS incidence increases due to inhibition of bilirubin glucuronidation by endogenous steroid hormones during puberty and accelerated hemoglobin turnover.<sup>[17,18]</sup> Clinical findings are nonspecific, and patient complaints are mostly weakness and abdominal pain. GS does not cause hepatic damage, and therefore, it usually does not require treatment. GS has a decreasing effect on both the uptake of bilirubin by hepatocytes and uridine diphosphate glucuronosyltransferase (UDP) activity. The UDP enzyme is encoded by the UGT1A1 gene. Since the gene's promoter region does not have a DNA sequence composed of thymine (T) and adenine (A), mutations in this region affect not the enzyme structure but its activity, causing Gilbert Syndrome.<sup>[19]</sup> Total serum bilirubin levels in GS are usually below 3 mg/dL; however, due to increased bilirubin production, this level sometimes reaches up to 6 mg/dL, but it does not exceed this value.<sup>[3]</sup> Our first case presented with complaints of weakness and abdominal pain intermittently, and the maximum serum bilirubin level was determined as 2.5 mg/dL. No treatment was administered due to the absence of any liver disorder, although the complaints in our case became more severe after the age of ten.

Hereditary spherocytosis (HS) results in spherocytic erythrocytes that undergo premature hemolysis within the acidic and anoxic milieu of the splenic sinusoids, causing hemolytic anemia. Typical findings of this disorder can occur at any age, from birth to older ages. Hereditary spherocytosis has a very wide range of clinical severity, e.g., symptom-free carrier or severe hemolysis.<sup>[5,19,20]</sup> The most common findings in childhood are varying degrees of anemia, splenomegaly, and jaundice. In some patients, anemia may not be detected, but in most cases, well-compensated hemolytic anemia is present.<sup>[20]</sup> The most common complications are hemolytic crises and cholelithiasis. In carefully selected cases, splenectomy can result in a significant increase in hemoglobin and a reduction in transfusion requirements.

HS typically presents with gallstones and episodes of hemolytic or aplastic crisis. In cases with moderate or severe HS, splenectomy is the most appropriate treatment. With splenectomy, hemoglobin levels increase, while the frequency of blood transfusions, reticulocyte count, and bilirubin levels decrease.<sup>[5,20]</sup> Likely, along with splenomegaly, anemia, reticulocytosis, and increased osmotic fragility present in our cases, gallstones were found in the gallbladder.

Acute pancreatitis is characterized by acute abdominal pain with elevated pancreatic enzyme levels in serum and/or urine. Acute pancreatitis is self-limiting in 80% of the cases. In recent years, it has been reported that the incidence of acute pancreatitis is increasing in all childhood age groups. Systemic diseases, biliary tract diseases, trauma, and infectious agents account for fewer than 1% of cases of acute pancreatitis; these include viruses (mumps, coxsackie, hepatitis B, cytomegalovirus, herpes simplex, varicella zoster virus), and autoimmune diseases as the main causes of acute pancreatitis. Acute biliary pancreatitis is the cause

of childhood acute pancreatitis in 10–30% of cases. Gallstones or calculus in the choledochus and congenital anomalies of the gallbladder are the most common causes of biliary pancreatitis in childhood.<sup>[6,7,10]</sup> Abdominal pain and nausea are very common and important symptoms, while clinical findings are related to the causes of the disease.<sup>[6,7,9]</sup>

There is no certain evidence of a causal relationship between HS and GS; it is stated that the coexistence of these two disorders can be coincidental. The coexistence of GS and HS leads to an increased incidence of hemolytic crises, which causes increased gallstone development, thus making the course of diseases more complicated. Bilirubin levels in patients who have both GS and HS concurrently are five times higher than in patients who have only one of these two diseases.<sup>[21]</sup> Acute pancreatitis was suspected based on the biochemical tests and imaging results of the first case with severe abdominal pain and jaundice complaints. The total serum bilirubin (TSB) level was initially 5 mg/dL when the patient presented to our clinic; however, this level dramatically increased to 43 mg/dL. In this condition, the cause of biliary acute pancreatitis is thought to be numerous stones in the gallbladder and choledochus caused by GS and HS. After calculus in the choledochus was removed via ERCP, both clinical findings and laboratory results showed improvement. Splenectomy, which is the appropriate treatment for cases with moderate/severe HS and severe hyperbilirubinemia, and removal of the gallbladder due to the presence of symptomatic gallstones, were decided upon to prevent the case, who had acute pancreatitis episodes caused by the coexistence of GS and HS, from experiencing a similar clinical condition.

Although acute hepatitis B virus (HBV) infections have been linked to acute pancreatitis, there is no information on the relationship between acute exacerbation of chronic HBV infection and acute pancreatitis.<sup>[22]</sup> When we look at the literature, the occurrence of acute pancreatitis with chronic hepatitis B infection appears as an extrahepatic finding of acute exacerbation.<sup>[23,24]</sup> The integration of viral DNA in pancreatic tissue in the case of HBV, a DNA virus, and the chronic inflammation of pancreatic tissue brought on by viral infection provide a reasonable explanation for this connection.<sup>[16]</sup> However, in our second case, there was no elevated transaminase level that would suggest exacerbation.

## CONCLUSION

Although the formation of gallstones secondary to hemolysis in patients with GS coexisting with HS has been frequently reported, occurrences of acute pancreatitis in such cases remain rare in the literature. When biliary acute pancreatitis episodes are present, performing ERCP to remove calculus in the choledochus before splenectomy and cholecystectomy is crucial to improving the clinical condition of the cases. Furthermore, it is important to consider the possibility of severe hyperbilirubinemia as a hematological sign of acute pancreatitis without worsening during chronic hepatitis B infection.

In cases of severe pancreatitis and icterus, a detailed examination for a hematological cause of hyperbilirubinemia should be considered, regardless of the underlying disease.

## Statement

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Informed consent has been obtained from the families.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

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**Author Contributions:** Concept – NU; Design – SÖ; Supervision – NU, SÖ; Materials – CAA; Data Collection and/or Processing – SÖ; Analysis and/or Interpretation – NU; Literature Search – SÖ; Writing – NU, SÖ; Critical Reviews – NU.

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# Early diagnosis and treatment of tracheoesophageal fistula in a newborn: A case report

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## ABSTRACT

Tracheoesophageal fistula (TEF) is an extremely rare congenital anomaly in newborns. In this case, we emphasize the role of contrast tube esophagography in diagnosing TEF and highlight how intraoperative guidewire placement facilitated fistula localization during surgical exploration. A female newborn was admitted to the neonatal intensive care unit due to respiratory distress and wheezing. Her condition deteriorated on day 4, necessitating endotracheal intubation and mechanical ventilation. Despite treatment for congenital pneumonia, intermittent respiratory distress persisted. On day 23, TEF was confirmed via contrast esophagography. At 25 days of age, the patient underwent rigid esophagoscopy, which confirmed the presence of TEF. A guidewire was advanced through the fistula to aid in its localization, allowing for precise surgical repair. This case underscores the challenges associated with diagnosing H-type TEF in neonates and highlights the crucial role of contrast esophagography and intraoperative guidewire placement in optimizing surgical management.

**Keywords:** Esophageal atresia, esophagogram, neonatal surgery, newborn, tracheoesophageal fistula.



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## INTRODUCTION

Congenital tracheoesophageal fistula (TEF) is a rare anomaly, with an estimated incidence of approximately 1 in 2,500 live births.<sup>[1]</sup> TEFs are classified into five distinct types based on their anatomical characteristics. Types I and IV are associated with esophageal atresia and are typically diagnosed immediately after birth due to feeding difficulties and respiratory distress. In contrast, Type V, also known as H-type TEF, is the rarest variant and occurs without esophageal atresia, constituting approximately 4% of all TEF cases.<sup>[2]</sup> Due to its isolated nature and the absence of esophageal atresia, the diagnosis of H-type TEF is often challenging, particularly in the neonatal period.

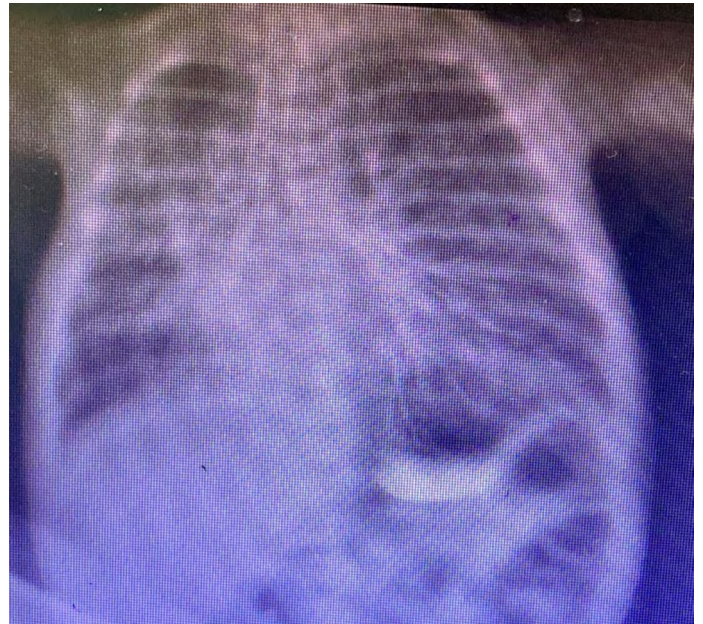
H-type TEF frequently presents with nonspecific and subtle clinical manifestations, leading to delayed recognition. Symptoms such as persistent aspiration, recurrent pneumonia, tracheomalacia, and bronchiectasis may develop over time, potentially resulting in significant morbidity and even mortality if left undiagnosed.<sup>[3]</sup> Neonates with TEF often exhibit feeding difficulties characterized by coughing, choking, and cyanosis during feeding, which may be misinterpreted as gastroesophageal reflux disease (GERD).<sup>[3]</sup> Diagnostic modalities include contrast esophagography, computed tomography (CT), bronchoscopy, and esophagoscopy; however, even with these techniques, diagnosis may be delayed.<sup>[4,5]</sup> Critically ill neonates who require prolonged mechanical ventilation pose an additional diagnostic challenge, as persistent respiratory distress may obscure the underlying TEF.

In this report, we present a neonate diagnosed with H-type TEF on day 25 of life. We emphasize the critical role of contrast tube esophagography in early detection and highlight how intraoperative guidewire placement facilitated precise fistula localization, ultimately optimizing surgical exploration and repair.

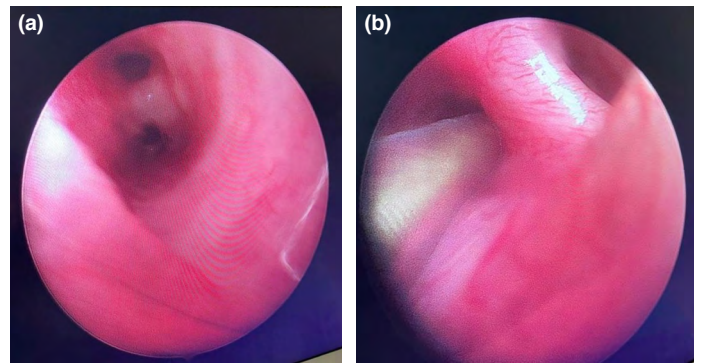
## CASE REPORT

A female infant, born via cesarean section at 39+4 weeks of gestation with a birth weight of 3015 g, was admitted to the neonatal intensive care unit (NICU) due to respiratory distress accompanied by excessive mucus. Antenatal history and the initial physical examination were unremarkable. The patient was initially fed maternal milk via the oral route and received nasal oxygen support. However, on the fourth day of hospitalization, her condition deteriorated with worsening respiratory distress, necessitating intubation and mechanical ventilation. A chest X-ray revealed diffuse infiltrates, leading to a diagnosis of congenital pneumonia. Further evaluation with cardiac ultrasonography identified pulmonary stenosis, a small patent ductus arteriosus, and a secundum atrial septal defect. Cranial ultrasonography findings were within normal limits. Laboratory tests showed a C-reactive protein (CRP) level of 1 mg/L, a white blood cell (WBC) count of 17,000/ $\mu$ L with neutrophil predominance, and a hemoglobin (Hb) level of 20.5 g/dL.

By the eighth day, the patient demonstrated clinical improvement on mechanical ventilation and was successfully extubated, transitioning to nasal oxygen support. However, during follow-up, she developed recurrent respiratory distress accompanied by increased subcostal and intercostal retractions and nasal flaring, necessitating



**Figure 1:** Water soluble radiopaque contrast swallow study on the 23<sup>rd</sup> day of life showing contrast reflux from the esophagus into the trachea, confirming TEF.



**Figure 2:** (a) Rigid esophagoscopy confirming the presence of the fistula. (b) Guidewire advanced through the fistulous tract.

reintubation and mechanical ventilation. Given the persistent respiratory instability, two doses of 6cc surfactant were administered. As oxygen requirements escalated, thoracic ultrasonography and computed tomography (CT) were performed, revealing findings consistent with aspiration pneumonia. Blood cultures later identified vancomycin-resistant *Enterococcus* (VRE).

Following extubation, recurrent respiratory distress was noted particularly during oral feeding, raising suspicion of an underlying TEF. On the 23<sup>rd</sup> day of life, a water-soluble radiopaque contrast swallow study was performed, which confirmed the presence of TEF, as water-soluble radiopaque contrast was observed refluxing upward from a catheter advanced into the stomach (Fig. 1).

The patient was scheduled for surgery on day 25. During the operation, rigid esophagoscopy confirmed the presence of the fistula, and a guidewire was advanced through the fistulous tract. Simultaneous flexible bronchoscopy verified the position of the guidewire (Fig. 2a, b).

Surgical exploration via a left presternal incision identified the fistula, which was meticulously dissected, separated from the trachea, and sutured. The procedure was completed in 55 minutes. Postoperatively, the patient was successfully weaned from mechanical ventilation and extubated on the third postoperative day. A gradual transition to oral feeding was well tolerated, and the patient was discharged on postoperative day eight.

During a one-year follow-up period, the patient exhibited no signs of respiratory distress or feeding difficulties, demonstrating a favorable clinical outcome. Consent for publication was obtained from the patient's family.

## DISCUSSION

Due to the anatomical characteristics of congenital H-type TEF, its diagnosis remains a significant challenge.<sup>[6]</sup> In cases in which the fistula has a narrow diameter, diagnosis is often delayed, as these patients are frequently misdiagnosed with gastroesophageal reflux disease or recurrent aspiration pneumonia.<sup>[4,5]</sup> The true incidence of H-type TEF is difficult to determine because of its low morbidity and the high rate of misdiagnosis during the neonatal period. Most cases presenting in the neonatal period are rarely identified within the first month of life. In infants with recurrent pulmonary infections, as in our case, chest computed tomography may be performed under suspicion of an underlying pulmonary pathology, further complicating the clinical picture, particularly after oral feeding.<sup>[7]</sup>

H-type TEFs are typically located more cephalad on the tracheal side and lower on the esophageal side, forming an anatomical configuration that resembles an "N" rather than an "H." This structure makes complete visualization of the fistula challenging on computed tomography imaging. In our case, thoracic computed tomography did not directly reveal the fistula but contributed to the diagnosis of an H-type TEF anomaly. A water-soluble radiopaque contrast swallow study (tube esophagogram), when performed using a specialized technique, can successfully visualize the fistula, as demonstrated in our case. In neonates suspected of having H-type TEF, bronchoscopy and esophagoscopy under anesthesia are valuable diagnostic tools for identifying the fistula.<sup>[8]</sup> Li et al.<sup>[9]</sup> reported the use of methylene blue dye during esophagoscopy to aid in the diagnosis of TEF anomalies in neonates. Similarly, Wong et al.<sup>[10]</sup> demonstrated that flexible bronchoscopy with guidewire cannulation facilitated anatomical localization of the fistula in H-type TEF cases and contributed to increased rates of early diagnosis.

As is well known, TEF represents a subtype of esophageal atresia, and their pathophysiologies share common embryological origins. However, both the diagnostic process and therapeutic approach to TEF exhibit distinct characteristics, making it a separate clinical entity from esophageal atresia. The clinical differences and diagnostic considerations have been discussed above. In the management of esophageal atresia, traditional thoracotomy has gradually been replaced by thoracoscopic repair.<sup>[11]</sup> With the development of smaller thoracoscopic instruments, many centers are now able to perform minimally invasive repair of esophageal atresia. However, due to the cervical location of many TEFs, the adoption of minimally invasive techniques for their repair has been slower and less widespread.<sup>[12]</sup>

## CONCLUSION

Early diagnosis and prompt surgical intervention are crucial in the management of TEF. Delays in diagnosis often arise because of the nonspecific nature of its symptoms. Reported early clinical manifestations include coughing, choking, vomiting, cyanosis, stridor during feeding, hemoptysis, regurgitation, dyspnea, tachypnea, and recurrent pneumonia. In our case, the predominant findings were respiratory distress following oral feeding, paroxysmal cyanosis without coughing, and aspiration pneumonia. Although coughing is a common symptom in older children with TEF, the cough reflex is not fully developed in neonates, leading to prolonged requirements for mechanical ventilation and further diagnostic challenges. In our patient, TEF was identified using a tube esophagogram performed without anesthesia. The diagnosis was subsequently confirmed through esophagoscopy-assisted guidewire placement, which effectively delineated the anatomical localization of the fistula and facilitated surgical planning.

A water-soluble radiopaque contrast esophagogram performed by an experienced radiologist is a rapid and effective early diagnostic method. The use of a guidewire passed through the fistula during confirmation with esophagoscopy and bronchoscopy facilitates surgical intervention and shortens the procedure time.

## Statement

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**Author Contributions:** Concept – ABK, GE; Design – ABK, GE, SK; Supervision – ABK, GE, SK; Results – ABK, GE, SK; Materials – ABK, GE; Data Collection and/or Processing – ABK, GE; Analysis and/or Interpretation – GE; Literature Search – ABK, GE, SK; Writing – SK; Critical Reviews – ABK, GE, SK.

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

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