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Turkish Journal of Pediatric Disease

Original Article

Experience with peripherally inserted central catheters in very low birth weight neonates: Indications, complications, and clinical outcomes

Mehtap Durukan Tosun[1], Şefika Aldaş[2], Emine Sultan Yıldız[1], Hüseyin Şimşek[1], Mustafa Akçalı[1], Mustafa Yıldırım[1], Berfin Özgökçe Özmen[3]

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ABSTRACT

Objective: Vascular access is a critical factor in the monitoring and treatment of neonates requiring intensive care. In this context, peripherally inserted central catheters (PICCs) are one of the primary methods for safely and for extended periods in neonates, compared to traditional central vascular access routes. This study aimed to evaluate the indications and complications of PICC placement and to raise awareness of the development and implementation of protocols to prevent complications.

Materials and Methods: In this study, after obtaining approval from the Ethics Committee, the indications, compositions, and clinical outcomes of patients born at Mersin City and Education Hospital between 01.01.2024-01.10.2025, weighing ≤1500 g and those who had peripheral central catheters left in place, were evaluated retrospectively.

Results: A total of 89 patients were included in the study. Forty-nine cases were male (44.9 %). Forty-nine of the cases were 28 weeks of gestation or less. Thirty-three cases were inserted due to prematurity, forty-two due to feeding difficulties, and three due to pre/post-operative complications. The median PICC placement day was 5 d (4-12.5), and the median weight was 1020 g (780-1310). Nineteen cases developed complications related to PICCs. Among the complications, phlebitis was the most common (47.4%). Four patients required catheter removal due to infection. Nine patients (10.1%) died. Eighty patients (89.9%) were discharged after recovery.

Conclusion: Peripherally inserted central catheters play a crucial role in neonatal intensive care by providing reliable, long-term venous access in neonates. When used with appropriate indications, strict aseptic technique, and standardized care protocols, they provide a healthy and safe vascular pathway for newborns with low complication and infection rates. A specialized team approach, guided by protocols, can enhance the quality of care in the neonatal intensive care unit.

Keywords: Mortality, newborn, PICC, NICU, sepsis

Introduction

Peripherally inserted central venous catheters (PICCs) are a reliable method of central venous access widely used in neonatal intensive care units for infants requiring prolonged intravenous therapy. Intravenous access is essential for the administration of fluids, medications, and parenteral nutrition in many hospitalized patients. These catheters can be inserted at the bedside without general anesthesia and may remain in place for extended periods. By providing safe and durable vascular access, peripherally inserted central catheters play a life-saving role in the management of neonates (1, 2).

A peripherally placed central catheter can be inserted into a deep vein of the upper or lower extremities. Scalp veins are also a safe and alternative site for PICC placement. Numerous veins, including the cephalic, basilic, saphenous, or superficial temporal vein, are suitable for PICC cannulation (3).

Placement of a PICC in an infant prevents repeated venous punctures, thereby minimizing pain and discomfort. By reducing the need for repeated invasive procedures, it may also decrease the risk of infection and provide prolonged, reliable vascular access. In addition, PICCs help preserve peripheral veins and, by lowering infection risk, may contribute to shorter hospital stays and reduced hospitalization costs (4).

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Although PICCs offer significant advantages in clinical practice, certain complications may occur related to their insertion and use. The most common complications include catheter-related infections, phlebitis, catheter fracture, leakage, rupture, and abnormal catheter positioning or migration (5, 6).

The aim of this study was to investigate the clinical characteristics, incidence of infections, and outcomes of very low birth weight neonates admitted to our neonatal intensive care unit who required peripherally inserted central catheter placement during the postnatal period.

Materials and Methods

The study was designed as a retrospective analysis of patients born at ≤1500 g and admitted to the neonatal intensive care unit at Mersin City and Education Hospital between 01.01.2024-01.10.2025. Data related to peripherally inserted central catheters were collected and recorded accordingly.

The following data were retrospectively retrieved from the hospital database: gestational age, birth weight, mode of delivery, gender, day of peripherally inserted central catheter placement, body weight on the day of catheter insertion, anatomical site of insertion, number of insertion attempts, catheter size, duration of catheterization, presence of catheter-related complications, occurrence of catheter-related infection and the isolated pathogen, as well as patient outcome data.

Peripherally inserted central catheter placement procedure

In this study, all PICCs were performed by a neonatologist and three PICC-specialized nurses who had received both theoretical and hands-on training. VYGON® GmbH & Co. KG 1F (24G) and 2F (28G) catheters were used for catheter placement. The basilic vein and median cubital vein in the antecubital region were selected as the primary insertion sites.

PICC was carried out at the bedside within the neonatal intensive care unit under laminar airflow conditions, and all procedures were performed in accordance with established standard protocols. Following catheterization, the catheter tip position was confirmed by radiographic (X-ray) evaluation. For neonatal blood culture sampling, BACT/ALERT® pediatric blood culture bottles were used. Blood samples of no less than 1 mL were obtained, and the VITEK® 2 (bioMérieux) automated culture system was utilized for microbiological analysis of neonatal specimens.

In this study, clinical sepsis was defined as the presence of general clinical deterioration, apnea, tachycardia, bradycardia, and elevated acute-phase reactants, or the isolation of a causative microorganism from sterile body fluids. Culture-proven bloodstream infection was defined as the growth of a pathogenic organism in blood culture. Colonization was defined as microbial growth without accompanying clinical signs of infection (7). Catheter-related bloodstream infection (CRBSI) was defined as the isolation of the same microorganism from both peripheral blood and the tip of the PICCs within 48 hours after catheter placement (7).

Statistical analysis

Data were analyzed using IBM SPSS version 26.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY) software. Descriptive statistics were expressed as numbers, percentages (%), median, mean, and standard deviation.

Results

A total of 89 patients were included in the study. Infants with a birth weight above 1500 g and those outside the specified study period were excluded. Forty-nine patients were female (55.1%), and 40 were male (44.9%). Forty-nine infants were born at or below 28 weeks of gestation. Peripherally inserted central catheters were placed in 33 infants due to prematurity, in 42 due to feeding intolerance, in three for pre- or postoperative management, in seven for sepsis treatment, and in four because of difficult vascular access. Patients with difficult vascular access were those who had not yet transitioned to full enteral nutrition without nutritional intolerance. The median day of PICCs placement was 5 days (4-12.5), and the median body weight at the time of placement was 1020 g (780-1310). A 2F catheter was inserted in three patients, whereas a 1F catheter was used in all other cases. Successful catheterization was achieved on the first attempt in 69 patients; 18 required two attempts, one required three attempts, and one required four attempts. In 53 cases (59.6%), the catheter was inserted via the left antecubital region.

The PICCs remained in place for a median dwell time of 16 (10-25) days. While 76 patients required only a single catheter placement, 10 patients required two insertions at different time points, and three patients required a total of three PICCs placements.

Complications associated with PICC were observed in 19 cases, with phlebitis being the most common complication among these 19 cases (47.4%). In four patients, the catheter had to be removed due to infection. Two cases presented with clinical sepsis, and *Staphylococcus aureus* was isolated in two cases.

When infection rates were evaluated, only two patients (2.2%) had culture-proven bloodstream infections. No catheter-related bloodstream infections (CRBSIs) were identified in our cohort.

The mean length of hospital stay was 60±28.5 days. Nine patients (10.1%) died, while 80 patients (89.9%) were discharged in good health. Detailed patient data are presented in Table I.

Discussion

The use of peripherally inserted central catheters has increased worldwide in parallel with advances in neonatal care. Owing to their ability to provide secure vascular access, allow prolonged use, and maintain a relatively low risk of infection, PICCs are increasingly preferred over umbilical venous catheters in current practice.

Particularly in preterm and very low birth weight infants, as well as in cases of feeding intolerance, necrotizing enterocolitis, sepsis, and in preoperative or postoperative management, the use of PICCs has steadily expanded. By providing reliable and relatively comfortable vascular access, PICCs have established a crucial role in modern neonatal intensive care units.

Table I: Demographic and clinical characteristics of the study population

Variables	Values
Gestational age (weeks)*	28.3±1.2
Gender†	
Male	40 (44.9)
Female	49 (55.1)
Birth weight (g)‡	1080 (680-1420)
Weight at PICC placement‡	1020 (780-1310)
Day of PICC placement‡	5 (4-12.5)
PICC size†	
1F (28G)	86 (96.6)
2F (24G)	3 (3.4)
Clinical diagnosis†	
Prematurity	77 (86.5)
IUGR	7 (7.9)
NEC	2 (2.2)
Gastroschisis	2 (2.2)
Intestinal Atresias	1 (1.1)
Indication for PICC placement†	
Prematurity	33 (37)
Nutritional deficiency	42 (47.2)
Pre/post-operative	3 (3.4)
Infection treatment	7 (7.9)
Difficult vascular access	4 (4.5)
Number of insertion attempts†	
1	69 (77.5)
2 or more	20 (22.5)
Number of PICC placements per patient†	
1	76 (85.4)
2	10 (11.2)
3 or more	3 (3.4)
PICC insertion site†	
Right antecubital	34 (38.2)
Left antecubital	53 (59.6)
Upper right-hand	2 (2.2)
Catheter dwell time (days)‡	16 (10-25)
Catheter complications†	
None	70 (78.6)
Phlebitis (swelling, redness)	9 (10.1)
Leaking	5 (5.6)
Catheter rupture	1 (1.1)
Occlusion	4 (4.5)
Systemic infection†	
Clinical sepsis	2 (2.2)
Culture-positive sepsis	2 (2.2)
Duration of hospitalization (days)‡	60 (45-78.5)
Outcome†	
Discharge	80 (89.9)
Exitus	9 (10.1)

: mean±SD, †: n(%), ‡: median (IQR),* ***IUGR:* *Intrauterine growth restriction,* ***NEC:*** *Necrotizing enterocolitis*

Our NICU is a tertiary-level neonatal intensive care unit with a capacity of 66 beds and an average annual admission volume of approximately 2000 patients. In our center, catheter insertions are performed by a neonatologist and three nurses who have completed formal training and certification in PICC placement.

Taylor T. et al.(8) reported that, following the establishment of a dedicated PICC team in the neonatal intensive care unit, the incidence of catheter-related bloodstream infections was reduced by nearly half among extremely low birth weight infants requiring long-term central venous access. The fact that only two of our patients developed culture-positive infections may be attributed to the placement of PICCs by trained and experienced healthcare professionals, with strict adherence to hygienic and aseptic conditions. In addition, regular catheter care and dressing changes performed by the same dedicated team may have contributed to the low rate of infection observed (9).

Standardization of PICC line is essential and constitutes a prerequisite for improving catheter-related bloodstream infection rates. The use of a unified approach and language in catheter care by the team performing the insertion, together with their experience and expertise, may have contributed to the absence of catheter-related infections in our patients (10).

There are no definitive data regarding the optimal duration of PICCs placement in patients hospitalized in the neonatal intensive care unit. Several studies have suggested that the risk of catheter-related complications increases as the catheter dwell time lengthens. In particular, the risk of catheter-related infection rises with increasing PICC duration. A study conducted in neonates reported that for PICCs remaining in place for more than 35 days, the risk of catheter-related infection increased by 33% for each additional day the catheter remained in situ (1).

The anatomical characteristics of neonates allow access to multiple potential sites for PICCs placement (11). The veins of the upper extremities are longer and narrower than the femoral vein, whereas the femoral vein has a larger diameter and is located more deeply. Theoretically, frequent limb movements may lead to intimal injury and phlebitis, which are more commonly observed in the upper extremities compared to the lower extremities. Therefore, complications such as phlebitis, occlusion, or catheter fracture and breakage may occur more frequently in catheters inserted through the lower extremities (12, 13).

When the timing of peripheral central catheter placement was evaluated, the median insertion day in our study was 5 (4-12.5 d). In our clinical practice, initial vascular access is established via standard methods following admission to the unit, and PICC is performed only when conventional vascular access is no longer feasible.

The rationale for this approach is to ensure adequate thermal and pain control in the newly born neonate and to protect edematous infants—who have not yet achieved sufficient diuresis during the first days of life—from repeated invasive attempts.

The statistically high variability observed in PICCs days may be attributed to repeated PICC requirements, as well as to the presence of patients requiring PICCs for conditions other than prematurity, such as sepsis and preoperative or postoperative management.

Hu Y. et al.(4) reported that a birth weight ≤1500 g, a PICCs dwell time ≥21 days, and PICC via the femoral vein were significant risk factors for catheter-related bloodstream infection in neonates with PICCs.

To prevent PICCs–related bloodstream infections, the necessity of the PICC line should be reviewed on a daily basis, catheter care practices should be optimized, and targeted

infection-prevention strategies should be implemented, particularly for catheters with prolonged dwell times.

In a multicenter study conducted by Milstone et al. (14), which evaluated 4797 PICC lines inserted in a total of 3967 neonates, 149 cases of catheter-related bloodstream infections occurred over 89946 catheter days, corresponding to an incidence rate of 1.66 per 1000 catheter days. The lowest infection rates were observed in catheters with a dwell time of fewer than seven days. In contrast, PICC lines remaining in place for 8–13 days, 14–22 days, and ≥23 days were each associated with a significantly higher risk of infection compared to those with a dwell time of ≤7 days ($p<0.050$). The authors further reported that during the first two weeks following PICC placement, the risk of CRBSI increased with each additional day the catheter remained in situ. Moreover, they noted a higher frequency of gram-negative CLABSIs (Central Line–Associated Bloodstream Infections) cases in catheters with a dwell time exceeding 50 days (14).

In our study, although the median catheter dwell time was 16 (10-25) days, no catheter-related bloodstream infections were observed.

In addition to proper PICC and maintenance practices, clinicians should exercise careful judgment regarding catheter retention or removal, taking into account the increased risk of infection associated with prolonged catheter duration. Such measures are essential for reducing catheter-related infection rates and for supporting quality improvement initiatives in the neonatal intensive care unit (15).

In neonates and children, optimization of PICCs and maintenance practices to prevent CLABSIs, as well as the establishment of dedicated catheter teams within each institution, has been supported by previous studies. In our unit, the presence of a specialized catheter insertion and maintenance team has played a pivotal role in the favorable catheter-related outcomes observed (16, 17).

The microorganisms responsible for CLABSIs and bacteremia may vary according to the duration of catheter dwell time. Smith et al. (18) reported that the mean time to the development of gram-positive bacteremia was eight days after catheter insertion, whereas gram-negative bacteremia occurred at a mean of 13.5 days following insertion. Similarly, Sengupta et al.(9) found that coagulase-negative *Staphylococci* (55.6%) were the predominant pathogens during the first two weeks after PICC, while Gram-negative bacteria (58.3%) became the dominant organisms beyond the initial two-week period.

In our study, both isolated microorganisms were *Staphylococcus aureus*. One case occurred in a 1420 g neonate in whom the catheter was inserted on postnatal day eight due to difficult vascular access and remained in place for only four days. The other case involved an infant born at 27 weeks of gestation with a birth weight of 910 g; the catheter was inserted on postnatal day 64 for the treatment of sepsis and was used for 14 days. Similarly, Yan Hu et al.(4) reported *Staphylococcus aureus* (23.92%) as the second most frequently isolated pathogen in their study.

When catheter insertion sites were evaluated, the right and left antecubital veins were the most commonly used sites in our study. In a study assessing the relationship between catheter insertion site and CLABSI incidence, a higher risk was identified in catheters inserted via the femoral vein (4). Another study published in 2024 evaluated PICC placement sites, ease of use, and complication rates, and concluded that the saphenous vein in the right lower extremity may represent the most suitable site for PICC in neonates (19). Another study reported no significant difference between upper and lower extremity PICC sites with respect to complications requiring catheter removal (20).

In a meta-analysis investigating whether placement of PICCs in neonates via upper versus lower extremity veins differed in terms of ease of use, reduced infection risk, and complication rates, PICC through the lower extremity veins was found to be easier compared with insertion through the upper extremity veins (21).

When the findings of our clinical study are evaluated in conjunction with the existing literature, it should be acknowledged that the selection of the PICCs site in neonates depends on the quality of the infant's available veins, the suitability of the insertion site, and the skill and experience of the practitioner performing the procedure.

When PICC placement and complications are evaluated, it is observed that complications resulting in mortality are encountered (22). None of the nine patients who lost their lives in our study died due to PICC complications.

Limitations

Our study has several notable strengths as well as certain limitations. The single-center design may be considered a methodological limitation; however, given the number of cases and the duration of the study period, the dataset is numerically substantial.

One of the key strengths of our study is that catheter insertions in neonates were performed according to a standardized protocol by the same dedicated team. We believe that the establishment of specialized interventional teams in neonatal care may lead to meaningful improvements in both short- and long-term follow-up and treatment outcomes.

Conclusion

Peripherally inserted central catheters play an important role in neonatal intensive care, particularly in neonates with a birth weight ≤1500 g, by providing reliable long-term venous access. When used with appropriate indications, strict aseptic technique, and standardized care protocols, PICC can be performed safely with low complication and infection rates.

Although prolonged catheter dwell time may increase the risk of infection, daily assessment of catheter necessity, adherence to aseptic principles, correct catheter positioning, and proper maintenance can help reduce adverse outcomes. The choice of insertion site should be individualized based on vascular access, the infant's clinical condition, and the operator's experience.

The presence of an experienced and dedicated catheter team plays a key role in reducing catheter-related complications. Therefore, a protocol-based and specialized team approach

may improve the quality of care in the neonatal intensive care unit.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Mersin City Hospital (20/10/2025, reference number: 2025/05).

Contribution of the authors

MDT: Primarily responsible for protocol development, patient screening, registration, outcome assessment, preliminary data analysis, and manuscript writing. He planned the study design and supervised its implementation. HS, MY, MA: Responsible for developing the protocol and evaluating the results. ESY,SA,BOÖÖ: performed protocol development, patient screening, outcome assessment and statistical analysis, and was primarily responsible for the registration procedures.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Ferritin/erythrocyte sedimentation rate ratio in macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis: A single center experience

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ABSTRACT

Objective: Systemic juvenile idiopathic arthritis (JIA) is a subgroup of JIA that can involve multiple systems other than the joints. Macrophage activation syndrome (MAS) is a life-threatening condition that can be observed in patients with systemic JIA. The aim of this study was to evaluate the performance of the ferritin/erythrocyte sedimentation rate (ESR) ratio, a diagnostic parameter for MAS, in our cohort.

Materials and Methods: Children with systemic JIA who were followed in our hospital's pediatric rheumatology department and diagnosed with MAS were retrospectively recorded for the presence or absence of MAS. The performance of the ferritin/ESR ratio between these patient groups was analyzed.

Results: The study included 45 patients with systemic JIA without MAS and 11 patients with systemic JIA with MAS. No differences were observed between the two groups in terms of age, gender, and follow-up duration ($p = 0.121$, $p = 0.547$, and $p = 0.495$, respectively). The JADAS-27 score, which includes rash, hepatomegaly, splenomegaly, and disease activity score, was significantly higher in the systemic JIA group with MAS (all $p<0.050$). The ferritin/ESR ratio was significantly higher in systemic JIA patients who developed MAS [247.71 (36.23-886.66) vs. 31.47 (0.39-555.55); $p<0.001$]. A ferritin/ESR ratio of >38.84 had 100% sensitivity and 73.3% specificity for the development of MAS in patients with systemic JIA.

Conclusion: A ferritin/ESR ratio of (>)38.84 had high sensitivity and specificity for predicting the development of MAS in patients with systemic JIA in our cohort.

Keywords: Erythrocyte sedimentation rate, ferritin, macrophage activation syndrome

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is a distinct category of JIA defined by the International League of Associations for Rheumatology (ILAR) criteria, characterized by quotidian fevers, arthritis, and extra-articular manifestations such as lymphadenopathy, serositis, hepatosplenomegaly, and an evanescent rash (1, 2). A severe and life-threatening complication of sJIA is macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis (HLH). MAS arises from a dysregulated immune response involving uncontrolled T-lymphocyte and macrophage activation, culminating in a profound cytokine storm. Precipitating factors include infections or modifications to immunomodulatory therapy (3, 4). While the documented prevalence of overt MAS in sJIA is 10–24%, subclinical manifestations may be present in 30–40% of patients (5). The clinical presentation of MAS includes persistent fever, hepatosplenomegaly, lymphadenopathy, hemorrhagic diathesis, and central nervous system (CNS) dysfunction (6-8). Characteristic laboratory findings comprise hyperferritinemia, cytopenias, elevated liver transaminases, hypofibrinogenemia, hypertriglyceridemia, coagulopathy, and a paradoxically decreased erythrocyte sedimentation rate (ESR) (4). Although MAS is most commonly associated with sJIA, it can also complicate other inflammatory conditions such as juvenile systemic lupus erythematosus and Kawasaki disease (4, 9). While often appearing spontaneously or in response to triggers, a genetic predisposition is implicated in cases of recurrent MAS (4, 6).

Various diagnostic guidelines and methods have been proposed to better differentiate MAS from other diagnoses; these include the HLH-2004 criteria (originally for familial HLH), the 2016 EULAR/ACR/PRINTO classification criteria for MAS in sJIA, the more recent MS score, and the ferritin-ESR ratio (5, 10-12). The MS score, developed by Minoia et al., helps distinguish MAS from an sJIA disease flare, and this score

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includes assessment of the central nervous system involvement, hemorrhagic manifestations, active arthritis, platelet count, plasma levels of lactate dehydrogenase, fibrinogen and ferritin (11). Concurrently, Eloseily et al. (12) proposed the ferritin/ESR ratio, leveraging the observation that ferritin rises dramatically in MAS while ESR falls due to fibrinogen consumption, creating a high ratio indicative of MAS. Differentiating MAS from active sJIA is clinically challenging due to overlapping features, yet it is critical as early, aggressive treatment is essential for survival.

This study aimed to evaluate the performance of the 2016 MAS classification criteria for the early identification of MAS in a single-center cohort of sJIA patients and to compare its diagnostic utility with other available tool, including the ferritin/ESR ratio.

Materials and Methods

This retrospective study was conducted on 56 children diagnosed with sJIA according to ILAR criteria, who were followed at the Pediatric Rheumatology Clinic of Ankara Bilkent City hospital between August 2019 and September 2025. Demographic and clinical data were extracted from electronic medical records, including demographic details (gender, date of birth, age at sJIA onset, age at MAS onset) and clinical manifestations (fever, hepatosplenomegaly, hemorrhagic manifestations, lymphadenopathy, active arthritis, CNS involvement, serositis). A comprehensive laboratory workup was performed, including ESR, C-reactive protein (CRP), complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fibrinogen, D-dimer, ferritin, triglycerides, and immunologic parameters (antinuclear antibodies and rheumatoid factor). Patients were stratified into two groups based on the 2016 classification criteria: “sJIA with MAS” and “sJIA without MAS.” MAS 2016 criteria include fever and ferritin > 684 µg/L plus 2 of 4 criteria: platelets 181×10^9/L, AST > 48 U/L, triglycerides > 156 mg/dl, and fibrinogen ≤360 µmol/L. Ferritin/ESR ratio 21:5 considered as a screening tool for the diagnosis of MAS.

The final version of the Juvenil Arthritis Disease Activity Score (JADAS) included 4 measures; physician global assessment of disease activity 10-cm visual analog scale (VAS) where 0= no activity and 10= maximum activity; parent/patient global assessment of well-being, measured on a 10-cm VAS where 0= very well and 10 = very poor; count of joints with active disease; and erythrocyte sedimentation rate. JADAS-27 includes the following joints: cervical, spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles 1.

The ferritin/ESR ratio was calculated using the first available ferritin and coincident ESR values upon hospital admission.

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive data are presented as requency, percentage, median (interquartile range), or mean and standard deviation. Normality of continuous variables was assessed visually (histograms, probability plots) and analytically (Kolmogorov-Smirnov test). Group comparisons for categorical variables used the Chi-square or Fisher’s exact test, while the Student’s T-test or Mann-Whitney U test was used for continuous variables, as appropriate. The sensitivity and specificity of the 2016 criteria were analyzed using Pearson’s chi-square test. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the diagnostic accuracy of the ferritin/ESR ratio and to determine an optimal cut-off value for our cohort using the Youden index. Area under the curve (AUC) values > 0.8 were considered indicative of good diagnostic performance. Sensitity and specificity values were derived from the ROC curve analysis, while group comparisons were prformed using Pearson’s chi-square test. A p-value <0.050 was considered statistically significant, with a 95% confidence interval (CI).

Results

A total of 56 children with sJIA were included into this retrospective, cross-sectional study included 11 children with sJIA accompanied by MAS and 45 children with sJIA without MAS. There were no differences in age, follow-up duration, or gender between the two groups (p=0.121, p=0.547, and p = 0.495, respectively). Rash was the most common clinical finding in the MAS group (11/11, 100%, p=0.042), while hepatomegaly and splenomegaly were significantly more common than in the children with sJIA without MAS (p=0.026 and p=0.002, respectively). The disease courses (monocyclic, polycyclic, etc.) of both groups were similar (p=0.639). However, the JADAS-27 score was significantly higher in children with MAS compared to without (35.92±9.15 vs. 30.63±6.61; p=0.032). When the 2016 MAS classification criteria were examined, ferritin vs. triglyceride values were significantly higher in children with MAS (3666.55±1830.13 µg/L vs.1655.68±1112.38 µg/L, p<0.001; 234.36±163.67 mg/dl vs. 142.21±101.87 mg/dl, p=0.022, respectively). Platelet counts were significantly lower in children with MAS (282.7±195.2 $x10^9$/L vs. 484.5±231.9 $x10^9$/L, p=0.010). No significant difference was observed in fibrinogen and AST values (p=0.523 vs. p=0.399, respectively). The ferritin/ESR ratio, which is among the MAS diagnostic criteria, was significantly higher in sJIA patients with MAS than in those without MAS [247.71 (36.23-886.66) vs. 31.47 (0.39-555.55), p<0.001] (Table I).

As shown in Table II, when the 2016 MAS classification criteria were analyzed individually within our cohort, ferritin >684 µg/L had a sensitivity of 100% and a specificity of 66.7%, with a negative predictive value (NPV) of 100%. When examined for PLT ≤181 × 109/L, it had a sensitivity of 45.5% and a specificity of 91.1%, with a negative predictive value (NPV) of 87.2%. Fibrinogen ≤10.6 g/L had a sensitivity of 100% and a specificity of 2.2%, with a negative predictive value (NPV) of 100%.

In the ROC analysis performed for the ferritin/ESR ratio in our cohort for the prediction of MAS defined by the 2016 MAS classification criteria, the ferritin/ESR ratio > 38.84 (area under curve [AUC]: 0.917, [95% CI (0.84-0.99)], p<0.001) with a 100% sensitivity and 73.3% specificity in MAS (Figure 1). Additionally, as shown in Table III, a ferritin/ESR ratio cut-off point of >38.84 had a positive predictive value of 50% and a negative predictive value of 97.2%.

Table I: Demographic characteristics and laboratory data in children with active SJIA with and without MAS according to the 2016 MAS classification criteria.

	MAS (n=11)	Non-MAS (n=45)	p
Clinical findings			
Age (months)*	61.8±55.72	90.46±55.18	0.121
Duration of follow up days*	1292.36±1014.70	1307.96±1583.29	0.495
Gender (f/m)	6/5	20/25	0.547
Fever†	11 (100)	45 (100)	1.000
Rash	11 (100)	32 (71.1)	0.042
Hepatomegaly†	8 (72.7)	16 (35.5)	0.026
Splenomegaly†	9 (81.8)	14 (31.1)	0.002
Arthritis†	9 (81.8)	36 (80)	0.892
Lymphadenopathy†	8 (72.7)	19 (42.2)	0.070
Oligoarticular presentation†	4 (36.3)	22 (48.8)	0.455
Poligoarticular presentation†	5 (45.4)	14 (21.1)	0.368
Serositis†	4 (36.3)	6 (13.3)	0.074
Pleural effusion†	3 (27.2)	3 (6.6)	0.048
Pericardial effusion†	2 (18.2)	3 (6.6)	0.230
Peritoneal effusion†	0 (0)	2 (4.4)	0.476
Uveitis†	0 (0)	2 (4.4)	0.476
Disease course†			
Monocyclic	6 (54.5)	21 (46.7)	0.639
Polycyclic	0 (0)	8 (17.8)	
Polyarticular	5 (45.5)	16 (35.5)	
JADAS-27 score*	35.92±9.15	30.63±6.61	0.032
Laboratory findings			
Ferritin µg/L*	3666.55±1830.13	1655.68±1112.38	<0.001
Platelets*	282727.27±195210.70	484488.9±231894.63	0.010
Fibrinogen g/L*	4.32±2.44	5.99±3.12	0.523
Triglyserides mmol/L*	234.36±163.67	142.21±101.87	0.022
AST U/L*	60.73±28.44	46.49±25.66	0.399
LDH U/L*	777.55±489.04	425.22±264.58	0.002
WBC x10^9/L*	20160.91±14560.97	14445.33±6327.90	0.050
Neutrophils x10^9/L*	14678.18±13615.86	10509.33±6202.63	0.312
Lymphocytes x10^9/L*	2929.09±2131.57	2503.56±1311.09	0.402
ESR mm/hr *	72.45±30.42	66.36±33.50	0.584
CRP mg/L*	86.47±65.96	93.35±66.76	0.760
Hb gr/dL*	9.89±2.37	10.43±1.38	0.106
Ferritin/ESR ratio‡	247.71 (36.23-886.66)	31.47 (0.39-555.55)	<0.001

:** *mean±SD,*†**:** *n(%),* ‡**:** *median (min-max),* ***ALT: *Alanine aminotransferase,* ***LDH:*** *lactate dehydrogenase,* ***WBC:*** *white blood cells,* ***ESR:*** *erythrocyte sedimentation rate,* ***CRP:*** *C-reactive protein,* ***Hb:*** *hemoglobin.*

Discussion

The absence of a gold standard for diagnosing sJIA-associated MAS underscores the importance of validated diagnostic tools. The 2016 MAS classification criteria and the ferritin/ESR ratio were both derived from large multinational cohorts. This study represents a single-center, external validation of two different approaches for the early detection of MAS in sJIA.

Kostik et al. (14) , found comparable rates of lymphadenopathy between MAS and non-MAS patients. In contrast, a larger study by Kelly et al. (15) reported significantly higher frequencies of hepatosplenomegaly, lymphadenopathy, CNS dysfunction, and hemorrhage in MAS patients). In our study, rash, hepatomegaly, and splenomegaly were observed more frequently in children with sJIA who developed MAS, while lymphadenopathy was observed at similar rates in children with sJIA who developed MAS, unlike previous studies.

The hallmark laboratory features of MAS are a sharp decline in platelet count and ESR, coupled with elevated ferritin, triglycerides, and lactate dehydrogenase (LDH) (15,16). Hoeg et al. (17) who found significantly higher levels of ferritin, triglycerides, ALT, and LDH in patients with MAS compared to the group without MAS. In addition, the levels of platelets and fibrinogen were significantly lower in MAS patients. Kostik et al. (14) found similar differences in patients with active sJIA with and without MAS. Zeng et al. (18) collected clinical and laboratory data from thirteen sJIA patients with MAS and found elevated levels of triglycerides, ALT, and LDH. In our cohort, children who developed MAS had significantly higher ferritin, triglyceride, and LDH levels, while platelet levels were significantly lower. No significant changes were observed in AST and fibrinogen levels, which are components of the 2016 MAS criteria. According to similar studies, the differing results may depend on factors such as early disease stage, sampling timing, and small sample size.

Although a ferritin level >684 µg/L is a mandatory criterion in the 2016 guidelines, its specificity has been questioned. Hoeg et al. (17) revealed that 56% of non-MAS patients had ferritin levels above this threshold. In our cohort, ferritin levels >684 µg/L were present in 100% of children with MAS, compared with one-third of children with sJIA who did not

Table II: Sensitivity and specificity of components of 2016 MAS classification criteria

	Cut off	MAS*	Non-MAS*	p†	Sensitivity	Specificity	PPV	NPV
Ferritin µg/L	> 684	11 (100)	15 (33.3)	<0.001	100	66.7	42.3	100
PLT×10⁹/L	≤ 181	5 (83.3)	4 (8.9)	0.452	45.5	91.1	55.6	87.2
Fibrinogen g/L	≤ 10. 6	11 (100)	44 (97.8)	0.618	100	2.2	20.0	100
Triglycerides mg/dl	> 156	5 (83.3)	15 (33.3)	0.003	45.5	66.7	25	83.3
AST U/L	> 48	5 (83.3)	10 (22.2)	0.119	45.5	77.8	33.3	85.4

: n (%), †: Pearson chi-square test, **PLT: platelets, **AST:** alanine aminotransferase, **PPV:** Positive predictive value, **NPV:** Negative predictive value*

Table III: The performances of Ferritin/ ESR ratio for diagnosing macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA) patients

	Cut off	Sensitivity	Specificity	PPV	NPV
Ferritin/ESR	≥21.5	100	68.9	44	100
	>38.84	100	73.3	50	97.2

***ESR:** Erythrocyte sedimentation rate, **PPV:** Positive predictive value, **NPV:** Negative predictive value*

develop MAS. This had a sensitivity of 66.7%, a specificity of 100%, and a negative predictive value of 100%.

Individual laboratory parameters showed high specificity for MAS. A platelet count ≤181×10⁹/L and AST >48 U/L demonstrated specificities of 91.1% and 77.8%, respectively, identifying them as potentially useful markers for distinguishing MAS from an sJIA flare in hyperferritinemic patients. Since AST, ALT, and triglycerides in general are normal in patients with sJIA, a simple increase above the upper limits of these parameters in combination with other criteria and clinical signs may be adequate to indicate the development of MAS (4). This aligns with Ravelli et al.'s (19) earlier finding that thrombocytopenia (≤ 262×10⁹/L) is a highly sensitive (100%) and specific (92%) indicator of MAS. For the patients in our study, the 2016 MAS classification criteria of PLT ≤ 181×10⁹/L had a specificity of 91.1% and an NPV of 87.2%. Another criterion, AST > 48 U/L, had a specificity of 77.8% and an NPV of 85.4% in children who developed MAS.

The optimal hemophagocytic syndrome diagnostic score (HScore) cut-off value was proposed as 190.5, revealing a sensitivity of 96.7% and specificity of 98.4% (20). MS-score is a new tool for differentiating MAS from disease activation in sJIA patients. This score also has weighted values for each parameter, and patients with a score above -2.1 points were defined as having MAS (11).

The ferritin/ESR ratio demonstrated the highest sensitivity but lower specificity among the MAS diagnostic tools evaluated. Hoeg et al. (17) showed that the best cut-off value of the ferritin/ESR ratio was ≥19.4. This is compatible with the cut-off value of ≥21.5 in the original paper by Eloseily et al. (12). In our study, a ferritin/ESR ratio cut-off point of ≥21.5, as documented by Eloseily et al. (12) had 100% sensitivity, 68.9% specificity, and 100% NPV. In our cohort, a ferritin/ESR ratio cut-off point of >38.84, which we found after ROC analysis, had similar 197.2% sensitivity, 73.3% specificity, and

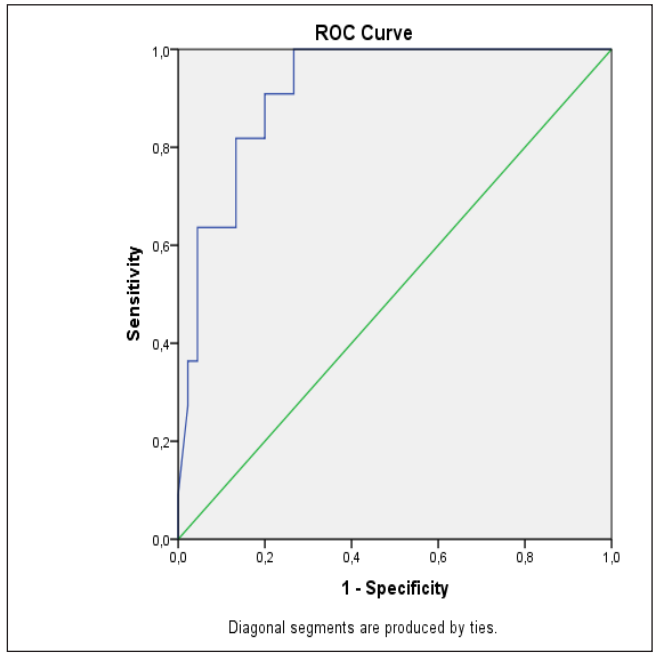


Figure 1: Receiver operating characteristics (ROC) plots illustrating the area under the curve (AUC) model for the prediction of MAS defined by the 2016 MAS classification criteria.

100% NPV (area under curve [AUC]: 0.917, [95% CI (0.84-0.99)], p<0.001).

Limitations

This study has several limitations. Its single-center, retrospective design and small sample size limit statistical power and generalizability. The absence of some laboratory data, particularly from patients transferred from other institutions, may have introduced bias. Furthermore, using the 2016 classification criteria as the reference standard may have missed subclinical MAS forms, potentially leading to an underestimation of the tools' diagnostic capabilities. One of the most important limitations of our study is that the necessary validation analyses for these criteria, such as the ferritin/ESR ratio, could not be performed because the HLH criteria and MS score criteria components, which are among the other diagnostic criteria, could not be obtained retrospectively.

Conclusion

The ferritin/ESR ratio is a valuable, readily available tool to differentiate MAS from active sJIA. In our cohort, a cut-

off value of ≥38.84 provided an optimal balance of sensitivity and specificity. To refine and validate these diagnostic scoring systems, large-scale, prospective, multi-center studies with comprehensive data collection are essential which may facilitate earlier recognition and treatment of MAS in children with sJIA.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (08.10.2025, reference number: 25-1771).

Contribution of the authors

Conceptualization: ŞE, BÇA; Methodology: ŞE, BÇA, EE, Formal analysis and investigation: EÖ, MIE, SNY, DÖ, YUE, ŞET; Writing - original draft preparation: ŞE, ,CK, BÇA; Writing - review and editing: ŞE, BÇA; Supervision: BÇA

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Germinal matrix-intraventricular hemorrhage in very preterm infants: Frequency, associated factors, and the role of postnatal clinical course

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ABSTRACT

Objective: Germinal matrix-intraventricular hemorrhage (GMH-IVH) remains one of the most important complications associated with prematurity and is a major cause of neonatal morbidity and mortality. This study aimed to determine the frequency of GMH-IVH and to evaluate prenatal, natal, and postnatal factors associated with its development in preterm infants.

Materials and Methods: This retrospective study included preterm infants with a gestational age between 24 and 32 weeks and a birth weight ≤1500 g who were followed in the neonatal intensive care unit of a tertiary referral center. Cranial ultrasonography, performed within the first 72 hours of life and repeated at the end of the first week, was used to diagnose and grade GMH-IVH according to the Volpe classification. Demographic characteristics, maternal factors, delivery characteristics, and early postnatal clinical and laboratory parameters were analyzed. Infants were grouped according to the presence of GMH-IVH and the severity of hemorrhage.

Results: A total of 312 preterm infants were included in the study. GMH-IVH was detected in 49.7% of the infants. Among these, 83 (53.5%) had mild hemorrhage (Grade 1–2) and 72 (46.5%) had severe hemorrhage (Grade 3–4). Lower gestational age, lower birth weight, absence of antenatal steroid use, lower Apgar scores, requirement for invasive mechanical ventilation, presence of patent ductus arteriosus, and abnormalities in coagulation parameters were significantly associated with GMH-IVH.

Conclusion: GMH-IVH in preterm infants is a multifactorial condition associated with several prenatal and postnatal factors. However, the retrospective design precludes establishing causality. Our findings highlight the strong association with postnatal clinical instability, particularly invasive mechanical ventilation and PDA treatment, suggesting that these are critical markers of illness severity. Identification of modifiable factors and optimization of perinatal and neonatal care may contribute to reducing the incidence and severity of GMH-IVH in this vulnerable population.

Keywords: Associated factors, germinal matrix hemorrhage, neonatal intensive care prematurity, intraventricular hemorrhage

Introduction

Prematurity is defined by the World Health Organization (WHO) as birth occurring before 37 weeks of gestation (1). Of the approximately 135 million live births worldwide each year, nearly 15 million are preterm births (2). Prematurity is considered one of the leading causes of neonatal morbidity and mortality globally (1).

In recent years, a significant increase in preterm birth rates has been observed. A substantial portion of this increase is attributed to the rise in late preterm births due to medically indicated early deliveries and increasing cesarean section rates. In addition, maternal risk factors, the widespread use of assisted reproductive technologies, and the increase in multiple pregnancies have contributed particularly to the growing number of preterm infants born with a birth weight below 1500 grams (3).

Advances in perinatal care, the expansion of neonatal intensive care units, antenatal steroid administration, surfactant therapy, and mechanical ventilation have played major roles in improving survival rates among preterm infants. Although mortality among preterm infants monitored in neonatal intensive care units has decreased, prematurity-related complications remain a significant concern. These complications include sepsis, respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). Germinal matrix--intraventricular hemorrhage (GMH-IVH), one of the major complications observed in preterm infants, may lead to adverse long-term neurodevelopmental outcomes (4,5). The incidence of GMH-IVH increases as gestational age decreases. In particular, the frequency of GMH-IVH may reach approximately 45% in preterm neonates born at or below 26 weeks of gestation, whereas

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this rate has been reported to range between 5% and 10% in preterm infants born before 32 weeks of gestation (5). One of the principal mechanisms involved in the development of GMH-IVH in preterm neonates is fluctuation in cerebral blood flow accompanied by impaired cerebral autoregulation. Due to the structurally fragile and highly vascular nature of the germinal matrix region, hemorrhages most commonly originate from this area. Approximately 50% of cases are detected within the first 24 hours of life, and 90% within the first 72 hours (4,6).

The aim of this study was to determine the frequency of GMH-IVH in preterm infants born between 24 and 32 weeks of gestation with a birth weight of 1500 grams or less and to evaluate the prenatal, natal, and postnatal clinical characteristics of infants who developed GMH-IVH. Since GMH-IVH in preterm infants is a serious cause of mortality and morbidity, identifying the factors associated with this condition is of great importance. Determination of these factors will contribute to increasing opportunities for early intervention, eliminating preventable factors, and improving both survival rates and long-term quality of life in these infants.

Materials and Methods

Study design and population

This retrospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of Ankara Bilkent City Hospital, a tertiary referral center, between September 2019 and March 2023. The study included preterm infants born at 24–32 weeks of gestation with a birth weight ≤1500 g who were either delivered at the study center and admitted to the NICU within the first 24 hours of life or transferred from another center within the same time frame. To clarify the study population's baseline risk, we have added stratified data on gestational age and birth weight in the Results section. Infants who underwent transfontanel cranial ultrasonography within the first 72 hours of life and whose complete medical records were accessible were included. Exclusion criteria were discharge or death within the first 72 hours, presence of major congenital anomalies, congenital-metabolic diseases, chromosomal abnormalities, or incomplete medical records.

During the study period, 312 eligible preterm infants were identified. Of these, 155 infants with GMH-IVH constituted the study group, and 157 infants without hemorrhage formed the control group. The hemorrhage group was further stratified according to hemorrhage severity.

Data collection

Clinical data were obtained retrospectively from electronic medical records. Prenatal variables included maternal age, multiple pregnancy, antenatal magnesium sulfate administration, antenatal steroid use, smoking during pregnancy, gestational hypertension, gestational diabetes, thyroid dysfunction, preeclampsia, placental anomalies, oligohydramnios or polyhydramnios, prolonged premature rupture of membranes (PPROM), urinary tract infection, other maternal infections, chronic maternal diseases, medication use during pregnancy, and chorioamnionitis. Natal and postnatal variables included mode of delivery, gestational age, birth weight, sex, 1st- and 5th-minute APGAR scores, need for resuscitation, presence of respiratory distress syndrome (RDS), early neonatal sepsis (ENS), development and treatment of patent ductus arteriosus (PDA), surfactant administration within the first 24 hours, invasive or non-invasive mechanical ventilation in the first 24 hours, cardiopulmonary resuscitation (CPR), inotropic support, blood product transfusion, daily fluid intake, first-day body weight, and weight change. The timing of PDA treatment relative to GMH-IVH diagnosis was not consistently documented, a limitation that is addressed in the discussion.

Laboratory and clinical definitions

Cord blood gas parameters (pH, PCO_2, HCO_3, base excess [BE], and lactate) were evaluated, and perinatal asphyxia was defined as cord pH <7.0 or BE <–12 (7). Hemoglobin (HGB), hematocrit (HCT), and platelet (PLT) levels measured within the first 24 hours were recorded, and thrombocytopenia was defined as PLT <150.000/mm³ (8). Coagulation parameters (INR, APTT, PT) measured within the first 72 hours were analyzed. Acid–base disturbances were defined as pH <7.35 for acidosis and pH >7.45 for alkalosis. Hypoglycemia was defined as blood glucose <50 mg/dL, hyperglycemia as >150 mg/dL, hyponatremia as sodium <135 mEq/L, and hypernatremia as sodium >145 mEq/L (9). Blood culture results obtained within the first 24 hours were recorded. Clinical diagnoses including RDS, PDA, GMH-IVH, and transfusion indications were defined according to Turkish Neonatology Society (TNS) guidelines (7,8). Maternal infection was defined as any infection occurring during pregnancy. Preeclampsia was defined as hypertension and proteinuria occurring after mid-gestation (1). Chorioamnionitis was diagnosed based on clinical criteria including maternal fever >37.5°C, uterine tenderness, foul-smelling vaginal discharge, maternal or fetal tachycardia, and leukocytosis >15.000/mm³ (1). Prolonged membrane rupture ≥18 hours was accepted as PPROM. Antenatal steroid exposure was defined as administration of at least one dose between $23^0/_7$ and $34^6/_7$ weeks of gestation. Inotropic support was defined as administration of dopamine, dobutamine, adrenaline, or noradrenaline within the first 24 hours (10). Early neonatal sepsis was defined as clinically and/or microbiologically confirmed infection within the first three days of life.

Neuroimaging and hemorrhage classification

The diagnosis of GMH-IVH was established through cranial ultrasonography performed via the anterior fontanelle. Imaging procedures were conducted by experienced pediatric radiologists; however, they were not blinded to the infants' clinical status, and interobserver variability was not assessed—a limitation inherent to the retrospective design. Cranial ultrasonography was performed within the first 72 hours of life and repeated at the end of the first week. The highest grade of hemorrhage recorded during the first week of life was used for analysis. The presence and grade of germinal matrix--intraventricular hemorrhage (GMH-IVH) were recorded. Hemorrhages were classified according to the Volpe classification system (4,5). Grades I–II were considered mild hemorrhage, whereas Grades III–IV or periventricular hemorrhagic infarction (PVHI) were classified as severe hemorrhage. Infants were analyzed both according

to the presence or absence of hemorrhage and according to hemorrhage severity.

Statistical analysis

Descriptive statistics were presented as mean and standard deviation, median (min-max), and frequency (percentage). The Shapiro–Wilk test was used to assess the normality of continuous variables. Categorical variables were compared using the chi-square test. For continuous variables, the Independent Samples t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Multivariate logistic regression analysis was performed to identify factors independently associated with GMH-IVH, with results presented as odds ratios (OR) and 95% confidence intervals. Statistical analyses were conducted using IBM SPSS Statistics 21.0, and a p-value <0.050 was considered statistically significant. A post-hoc power analysis was performed using G*Power software (version 3.1.9.7). With a sample size of 312 patients (155 with GMH-IVH, 157 without), an effect size of 0.3, and α=0.05, the study achieved a statistical power of 0.94 (94%). For subgroup analyses comparing Grade 1-2 (n=83) vs. Grade 3-4 (n=72) GMH-IVH, the power was 0.82 (82%). These results indicate that the sample size was adequate to detect clinically meaningful differences.

Results

Infants with GMH-IVH constituted the study group, while those without GMH-IVH formed the control group. Of the participating infants, 50.3% (n=157) had no GMH-IVH, while 49.7% (n=155) were diagnosed with GMH-IVH. Among the 155 infants with GMH-IVH, grade distribution was as follows: Grade 1: 43 (27.7%), Grade 2: 40 (25.8%), Grade 3: 35 (22.6%), Grade 4: 37 (23.9%). This sums to 155, consistent with the subgroup counts (Grade 1–2: n=83; Grade 3–4: n=72). Stratified data on gestational age and birth weight are as follows: In the entire cohort, 28.2% (n=88) of infants were <26 weeks GA, and 71.8% (n=224) were 26-32 weeks GA. In the <26 weeks GA subgroup, the incidence of GMH-IVH was 68.2% (60/88), compared to 42.4% (95/224) in the 26-32 weeks GA subgroup. Regarding birth weight, 58.3% (n=182) of infants had a birth weight <1000 g, and 41.7% (n=130) had a birth weight between 1000-1500 g. The incidence of GMH-IVH was 62.1% (113/182) in the <1000 g subgroup and 32.3% (42/130) in the 1000-1500 g subgroup. Furthermore, 31.1% (n=97) of the infants were outborn (transferred from another center).

Maternal and Pregnancy Characteristics were shown in Table I. Infants with GMH-IVH had significantly lower mean gestational age (26.48±2.22 vs. 27.36±2.39 weeks, p=0.001) and lower maternal age (28.68±6.26 vs. 29.82±5.09 years, p=0.031). Although the maternal age difference was statistically significant, it is likely not clinically meaningful and should not be overemphasized. Gestational age decreased as hemorrhage grade increased (Grade 3-4: 25.68±1.57 vs. Grade 1-2: 27.18±2.45 weeks, p<0.001). Multiple pregnancy rate was significantly associated with GMH-IVH presence (p=0.034) and severity, with higher rates in Grade 3-4 group (p=0.046). Antenatal steroid use was associated with lower GMH-IVH frequency (p=0.020) and lower grade (p=0.018). Polyhydramnios was associated with reduced GMH-IVH occurrence (p=0.019) but not with grade (p=0.535). No significant associations were found with magnesium sulfate treatment, smoking, gestational diabetes, hypothyroidism, hypertension, preeclampsia, infections, PPROM, chorioamnionitis, amniotic fluid abnormalities, or placental anomalies (all p>0.050). These non-significant variables are presented in the tables for transparency.

Table II represents Perinatal and Early Neonatal Characteristics. Cesarean delivery rate was lower in the GMH-IVH group (84.5% vs. 91.7%, p=0.049) but not associated with grade (p=0.947). Both 1-minute and 5-minute Apgar scores were significantly lower in infants with GMH-IVH (p=0.002 and p=0.004), with the lowest scores in Grade 3-4 GMH-IVH (p=0.014 and p=0.003). Birth weight was significantly lower in the GMH-IVH group (895.4±267.4 g vs. 990.4±320.6 g, p=0.016), particularly in Grade 3-4 GMH-IVH (821.5±205.4 g vs. 959.5±298.1 g, p=0.003). A similar pattern was observed for postnatal day 1 weight (p=0.028 for GMH-IVH presence; p=0.004 for grade).

Table I: Maternal and pregnancy characteristics according to GMH-IVH presence and severity

Variable	No GMH-IVH	GMH-IVH	p	Grade 1–2	Grade 3–4	p
Total number of patients	157	155	-	83	72	-
Gestational age weeks*	27.36±2.39	26.48±2.22	0.001	27.18±2.45	25.68±1.57	<0.001
Maternal age years*	29.82±5.09	28.68±6.26	0.031	29.30±6.75	27.96±5.61	0.254
Multiple pregnancy†	58 (36.9)	40 (25.8)	0.034	16 (19.3)	24 (33.3)	0.046
Antenatal steroid use†	145 (92.4)	130 (83.9)	0.020	75 (90.4)	55 (76.4)	0.018
Polyhydramnios†	8 (5.1)	1 (0.6)	0.019	1 (1.2)	0 (0.0)	0.535
Antenatal magnesium sulfate†	35 (22.3)	32 (20.6)	0.720	18 (21.7)	14 (19.4)	0.739
Smoking during pregnancy†	12 (7.6)	10 (6.5)	0.683	5 (6.0)	5 (6.9)	0.822
Gestational diabetes†	18 (11.5)	15 (9.7)	0.599	8 (9.6)	7 (9.7)	0.986
Hypothyroidism†	11 (7.0)	13 (8.4)	0.649	7 (8.4)	6 (8.3)	0.984
Gestational hypertension†	9 (5.7)	11 (7.1)	0.621	6 (7.2)	5 (6.9)	0.949
Preeclampsia†	15 (9.6)	12 (7.7)	0.558	7 (8.4)	5 (6.9)	0.731
PPROM†	24 (15.3)	20 (12.9)	0.545	11 (13.3)	9 (12.5)	0.887
Chorioamnionitis†	6 (3.8)	5 (3.2)	0.777	3 (3.6)	2 (2.8)	0.775
Urinary tract infection†	14 (8.9)	12 (7.7)	0.704	6 (7.2)	6 (8.3)	0.796

**: mean±SD, †: n(%), Although maternal age difference was statistically significant, it is likely not clinically meaningful. Non-significant variables are included here for transparency as recommended by reviewer.*

Table II: Perinatal and early clinical characteristics according to GMH-IVH presence and severity

Variable	No GMH-IVH	GMH-IVH	p	Grade 1–2	Grade 3–4	p
Total number of patients	157	155	-	83	72	-
Mode of delivery (C/S*)	144 (91.7)	131 (84.5)	0.049	70 (84.3)	61 (84.7)	0.947
1-min Apgar score†	4.33±1.70	3.75±1.75	0.002	4.08±1.84	3.38±1.56	0.014
5-min Apgar score†	6.27±1.59	5.82±1.58	0.004	6.17±1.58	5.42±1.51	0.003
Birth weight g†	990.4±320.6	895.4±267.4	0.016	959.5±298.1	821.5±205.4	0.003
Day 1 weight g†	966.9±315.1	882.1±258.2	0.028	941.4±286.6	813.7±202.2	0.004
Weight change day 1 g†	−28.7±33.8	−17.7±39.6	0.006	−22.3±42.5	−11.9±35.2	0.131
Invasive ventilation*	89 (56.7)	115 (74.2)	0.001	48 (57.8)	67 (93.1)	<0.001
Surfactant therapy*	121 (77.1)	137 (88.4)	0.008	65 (78.3)	72 (100)	<0.001
PDA*	88 (58.3)	110 (73.8)	0.004	53 (65.4)	57 (83.8)	0.011
PDA treatment*	53 (35.1)	90 (60.4)	<0.001	42 (51.9)	48 (70.6)	0.020
Inotrope support*	34 (21.7)	44 (28.4)	0.170	17 (20.5)	27 (37.5)	0.019
RDS*	148 (94.3)	149 (96.1)	0.442	77 (92.8)	72 (100)	0.022

***:** *n(%),* **†:** *mean±SD*

Table III: Comparison of hematological and biochemical parameters according to the presence and severity of GMH-IVH

Variable	No GMH-IVH*	GMH-IVH* *	p	Grade 1–2*	Grade 3–4*	p
Total number of patients	157	155	-	83	72	-
Hemoglobin (g/dL)	16.29 ± 2.38	15.29 ± 2.20	<0.001	15.90 ± 2.12	14.59 ± 2.10	<0.001
Hematocrit (%)	52.37 ± 7.67	48.99 ± 7.01	<0.001	50.79 ± 6.63	46.91 ± 6.89	<0.001
INR	1.61 ± 0.73	2.09 ± 1.20	0.002	1.99 ± 1.68	2.14 ± 0.87	0.042
PT (sec)	18.12 ± 7.79	23.67 ± 15.10	0.002	23.34 ± 22.65	23.85 ± 9.18	0.039
APTT (sec)	44.23 ± 17.21	53.87 ± 23.95	0.032	44.40 ± 18.80	58.96 ± 25.05	0.014
First sodium (mEq/L)	141.76 ± 6.07	141.29 ± 7.26	0.435	142.27 ± 6.80	140.14 ± 7.65	0.018
Cord blood PCO_2 (mmHg)	42.56 ± 9.78	39.23 ± 12.34	0.003	40.39 ± 13.86	37.45 ± 9.42	0.185
Cord blood HCO_3 (mmol/L)	21.79 ± 3.22	20.35 ± 4.05	0.010	20.03 ± 4.44	20.84 ± 3.36	0.704
Cord lactate (mmol/L)	3.59 ± 1.95	3.79 ± 2.76	0.888	4.25 ± 3.14	3.09 ± 1.86	0.010

***:** *mean±SD, Although a statistical difference was observed between severity groups, the mean value was higher in Grade 1–2 than in Grade 3–4. This finding should not be overinterpreted as higher lactate being associated with more severe hemorrhage; it merely indicates a difference between groups.*

Table IV: Comparison of GMH-IVH according to maternal chronic diseases

Maternal Disease	No GMH-IVH*	GMH-IVH*	Grade 1–2*	Grade 3–4*
Hypothyroidism	11 (45.8)	13 (54.2)	7 (53.8)	6 (46.2)
Hypertension	8 (47.1)	9 (52.9)	4 (44.4)	5 (55.6)
Hypertension + Hypothyroidism	5 (71.4)	2 (28.6)	1 (50.0)	1 (50.0)
Asthma	1 (25.0)	3 (75.0)	3 (100.0)	0 (0.0)
Other	12 (60.0)	8 (40.0)	4 (50.0)	4 (50.0)

***:** *n(%), p-value (GMH-IVH presence): 0.501; p-value (grade comparison): 0.394**

Early weight loss differed between groups (p=0.006) but was not associated with grade (p=0.131). Invasive mechanical ventilation was more frequent in the GMH-IVH group (74.2% vs. 56.7%, p=0.001), especially in Grade 3-4 GMH-IVH (93.1% vs. 57.8%, p<0.001). Surfactant therapy was more common in the GMH-IVH group (88.4% vs. 77.1%, p=0.008), and all infants with severe GMH-IVH received surfactant (100% vs. 78.3%, p<0.001). PDA was more frequent in the GMH-IVH group (73.8% vs. 58.3%, p=0.004), with higher rates in Grade 3-4 GMH-IVH (83.8% vs. 65.4%, p=0.011). PDA treatment was also more common in the GMH-IVH group (60.4% vs. 35.1%, p<0.001) and in severe GMH-IVH (70.6% vs. 51.9%, p=0.020). Inotrope support was not associated with overall GMH-IVH (p=0.170) but was more frequent in severe GMH-IVH (37.5% vs. 20.5%, p=0.019). RDS was associated with severe GMH-IVH (100% vs. 92.8%, p=0.022) but not with overall GMH-IVH presence (p=0.442).

Laboratory Parameters were summarized in Table III. Hemoglobin and hematocrit levels were significantly lower in the GMH-IVH group (p<0.001 for both), with further decreases in Grade 3-4 GMH-IVH (p<0.001). INR, PT, and APTT were significantly higher in the GMH-IVH group (p=0.002, p=0.002, and p=0.032, respectively) and in severe GMH-IVH (p=0.042, p=0.039, and p=0.014). Acidosis was not associated with overall GMH-IVH (p=0.587) but was significantly related to grade (p=0.004). Initial sodium level was lower in severe GMH-IVH (p=0.018) but not associated with GMH-IVH presence (p=0.435). Cord blood PCO_2 and HCO_3 were significantly lower in the GMH-IVH group (p=0.003 and p=0.010) but not associated with grade. Cord lactate was significantly different only in severe GMH-IVH (p=0.010). Of note, cord lactate values appeared higher in the Grade 1–2 group than in the Grade 3–4 group; therefore, we do not conclude that higher lactate is associated with more severe hemorrhage, but merely that a difference exists. No significant associations were found with thrombocytopenia, platelet count, admission blood gas parameters (pH, PCO_2, HCO_3, BE, lactate), initial glucose, or cord blood pH (all p>0.050).

Maternal Chronic Diseases and Medication Use are Tables IV-V. No significant associations were found between GMH-IVH presence or grade and maternal chronic diseases

Table V: Comparison of GMH-IVH presence and grade according to medications used during pregnancy

Medication Used During Pregnancy	GMH-IVH Absent*	GMH-IVH Present*	p	Grade 1-2*	Grade 3-4	p
Total number of patients	56	61	-	35	26	-
Alphamed	12 (63.2)	7 (36.8)	-	5 (71.4)	2 (28.6)	-
Antibiotics	8 (38.1)	13 (61.9)	-	9 (69.2)	4 (30.8)	-
Coraspin	4 (50.0)	4 (50.0)	-	2 (50.0)	2 (50.0)	-
LT4	9 (40.9)	13 (59.1)	0.694	6 (46.2)	7 (53.8)	0.448
Oxapar	2 (40.0)	3 (60.0)	-	3 (100.0)	0 (0.0)	-
Alphamed + Coraspin	4 (44.4)	5 (55.6)	-	2 (40.0)	3 (60.0)	-
Insulin	1 (25.0)	3 (75.0)	-	1 (33.3)	2 (66.7)	-
Other	16 (55.2)	13 (44.8)	-	7 (53.8)	6 (46.2)	-

: n(%)

Table VI: Univariate and multivariate logistic regression analysis of factors associated with GMH-IVH

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Gestational week	0.849 (0.768-0.937)	0.001	1.365 (0.712-2.617)	0.349
Maternal age	0.965 (0.928-1.004)	0.080	0.877 (0.721-1.068)	0.192
Multiple pregnancy	0.594 (0.366-0.964)	0.035	0.485 (0.051-4.619)	0.530
Antenatal steroid	0.430 (0.208-0.891)	0.023	1.059 (0.044-25.735)	0.972
Polyhydramnios	0.121 (0.015-0.979)	0.048	0.033 (0.000-11.071)	0.250
Apgar 1st minute	0.824 (0.723-0.940)	0.004	0.501 (0.139-1.806)	0.291
Apgar 5th minute	0.837 (0.726-0.965)	0.014	1.436 (0.386-5.350)	0.589
Birth weight	0.999 (0.998-1.000)	0.005	0.992 (0.923-1.066)	0.830
Postnatal day 1 body weight	0.999 (0.998-1.000)	0.010	1.010 (0.940-1.085)	0.782
Day 1 body weight change	1.008 (1.001-1.015)	0.023	0.961 (0.888-1.039)	0.314
Invasive mechanical ventilation	2.197 (1.361-3.545)	0.001	32.451 (1.095-961.402)	0.044
Surfactant administration	2.264 (1.223-4.194)	0.009	1.315 (0.050-34.737)	0.870
PDA presence	2.019 (1.240-3.289)	0.005	0.098 (0.005-1.753)	0.114
PDA treatment	2.821 (1.766-4.506)	<0.001	35.366 (1.837-680.798)	0.018
Hemoglobin	0.824 (0.744-0.913)	<0.001	0.807 (0.233-2.788)	0.734
Hematocrit	0.939 (0.909-0.969)	<0.001	0.902 (0.593-1.372)	0.631
INR	1.992 (1.128-3.518)	0.018	0.001 (0.001-253.458)	0.234
PT	1.067 (1.011-1.127)	0.018	2.399 (0.600-9.596)	0.216
APTT	1.024 (1.003-1.046)	0.024	0.918 (0.817-1.030)	0.146
Umbilical cord blood PCO_2	0.973 (0.949-0.997)	0.026	1.042 (0.941-1.154)	0.431
Umbilical cord blood HCO_3	0.894 (0.827-0.965)	0.004	0.729 (0.511-1.038)	0.080

***MV:** Mechanical ventilation, **PDA:** Patent ductus arteriosus, **GMH-IVH:** Germinal matrix–intraventricular hemorrhage, Bold ORs and p-values indicate statistical significance (p<0.05). These associations should be interpreted with extreme caution due to the risk of reverse causality inherent to the retrospective design, as well as the very wide confidence intervals suggesting model instability.*

(hypothyroidism, hypertension, asthma, etc.) (p=0.501 and p=0.394) or medications used during pregnancy (alphamed, antibiotics, coraspin, LT4, oxapar, insulin, etc.) (p=0.694 and p=0.448).

Table VI presents univariate and multivariate logistic regression analyses of factors associated with GMH-IVH in preterm infants. In univariate analysis, significant factors included lower gestational week (OR: 0.849), absence of antenatal steroids (OR: 0.430), lower Apgar scores, lower birth weight, invasive mechanical ventilation (OR: 2.197), surfactant administration (OR: 2.264), PDA presence (OR: 2.019), PDA treatment (OR: 2.821), lower hemoglobin/hematocrit, and elevated INR, PT, and APTT (all p<0.05). In multivariate analysis, invasive mechanical ventilation (OR: 32.451, p=0.044) and PDA treatment (OR: 35.366, p=0.018) remained independently associated with GMH-IVH. However, the very wide confidence intervals (e.g., 1.095–961.402 for mechanical ventilation) suggest model instability and possible collinearity; these findings should be interpreted with caution and do not imply causation.

Discussion

In this study, the frequency of GMH-IVH and the prenatal, natal, and postnatal factors affecting its development were evaluated in premature infants with a gestational age of 24–32 weeks and a birth weight ≤1500 g. In our study population, the incidence of GMH-IVH was found to be 49.7%. Approximately half of the infants with hemorrhage had mild-stage hemorrhage (Grade 1–2), while the remaining half had severe-stage hemorrhage (Grade 3–4). This high incidence is likely explained by the high-risk nature of our cohort, which included a large proportion of infants <26 weeks GA (28.2%), extremely low birth weight (<1000 g, 58.3%), and outborn neonates (31.1%), all of whom are at

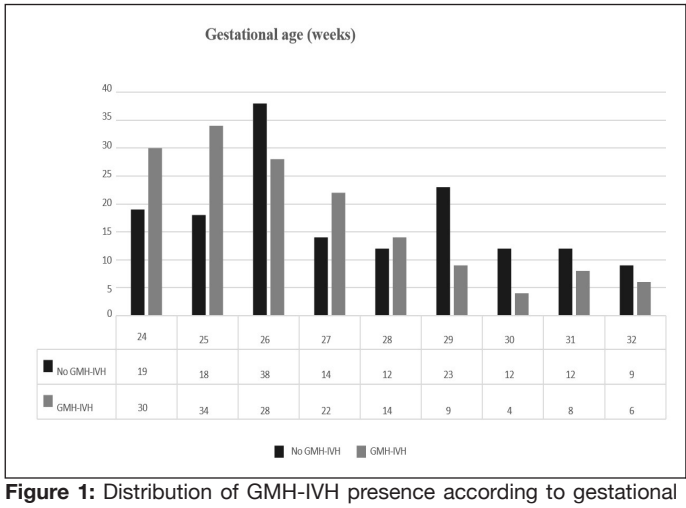


Figure 1: Distribution of GMH-IVH presence according to gestational week. A statistically significant difference was observed between gestational weeks and GMH-IVH presence (p=0.004). The frequency of GMH-IVH decreased as gestational week increased.

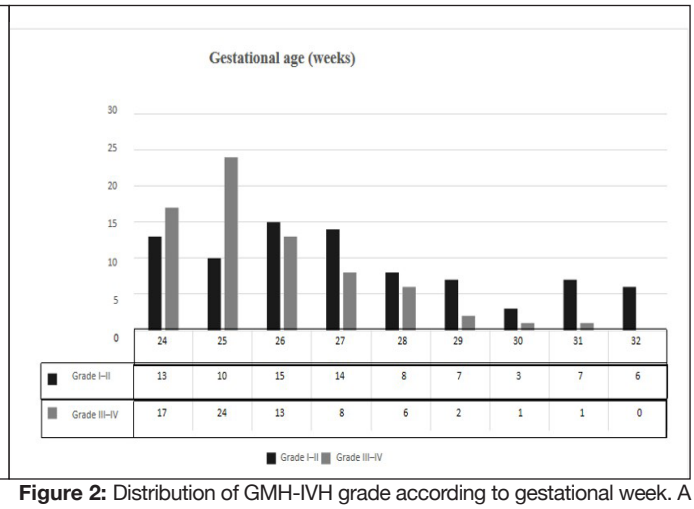


Figure 2: Distribution of GMH-IVH grade according to gestational week. A statistically significant difference was observed between gestational weeks and GMH-IVH grade (p=0.001). The severity of GMH-IVH decreased as gestational week increased.

increased baseline risk for GMH-IVH. Our findings suggest that the development of GMH-IVH in preterm infants is a multifactorial process and that gestational age, birth weight, antenatal steroid use, postnatal adaptation indicators, the need for respiratory support, the presence of PDA, and certain hematological parameters are associated with this condition.

Gestational age is one of the most important factors associated with the development of GMH-IVH in premature infants. The immature vascular structure of the germinal matrix region and the insufficient development of cerebral autoregulation mechanisms increase the risk of hemorrhage, particularly at lower gestational ages (11,12). As described by Volpe, the germinal matrix contains a dense capillary network, and these vessels are structurally thin-walled and fragile (11). In the classical study conducted by Papile et al. (13), the incidence of GMH-IVH was also reported to increase significantly with decreasing gestational age. In our study, the mean gestational age was significantly lower in infants who developed GMH-IVH, and gestational age was even lower in cases with severe-stage hemorrhage. These findings are consistent with the data reported in the literature.

Birth weight is another important factor closely associated with the development of GMH-IVH. In particular, the fragility of germinal matrix vessels and instability in cerebral blood flow are more pronounced in very low birth weight (<1500 g) and extremely low birth weight (<1000 g) infants. In a comprehensive review conducted by Ballabh, it was demonstrated that the immature structure of germinal matrix vessels and hemodynamic fluctuations play a critical role in the pathogenesis of GMH-IVH in premature infants (14). Recent epidemiological studies have also reported a strong association between low birth weight and the development of GMH-IVH (15). Similarly, in our study, the birth weight of infants with GMH-IVH was significantly lower, and birth weight was even lower in infants with severe-stage hemorrhage.

Antenatal steroid administration is one of the most important obstetric interventions that improves neonatal outcomes in pregnancies at risk for preterm birth. In addition to accelerating fetal lung maturation, antenatal steroids may reduce the risk of GMH-IVH by improving cerebral vascular stability. Recent meta-analyses have shown that antenatal steroid use significantly reduces both mortality and the risk of GMH-IVH in premature infants (16). In our study, a significant association was observed between antenatal steroid use and the development of GMH-IVH, and the rate of hemorrhage was higher in pregnancies that did not receive steroids. These findings further support the importance of antenatal steroid administration in pregnancies at risk of preterm delivery.

Perinatal adaptation indicators also provide important markers for the development of GMH-IVH. In our study, the 1st- and 5th-minute Apgar scores were significantly lower in infants who developed GMH-IVH. Low Apgar scores may indicate hypoxia and hemodynamic instability occurring during delivery. It is known that sudden changes in cerebral blood flow in premature infants may lead to rupture of the fragile vessels within the germinal matrix (11). Therefore, maintaining hemodynamic stability in the early postnatal period may play an important role in reducing the development of GMH-IVH.

The need for respiratory support was another factor associated with GMH-IVH in our study. The requirement for invasive mechanical ventilation was significantly higher among infants with GMH-IVH. Changes in intrathoracic pressure during mechanical ventilation may affect cerebral venous return and lead to fluctuations in cerebral blood flow. Recent studies have suggested that aggressive ventilation strategies may negatively affect cerebral hemodynamic stability in premature infants (17). In addition, the need for ventilation generally reflects a more severe clinical condition, which may further increase the risk of GMH-IVH.

Patent ductus arteriosus (PDA) is a common cardiovascular condition in premature infants and may have significant effects on systemic circulation and cerebral perfusion. The presence of PDA may contribute to the development of GMH-IVH by causing fluctuations in cerebral blood flow

(14). Recent clinical studies have also demonstrated that the presence of PDA may increase the risk of GMH-IVH, particularly in very low birth weight infants (18). In our study, both the presence of PDA and the need for PDA treatment were found to be significantly associated with GMH-IVH.

When hematological parameters were evaluated, hemoglobin and hematocrit levels were significantly lower in infants with GMH-IVH. In addition, coagulation parameters, including INR, PT, and APTT, were higher in infants who developed GMH-IVH. The immaturity of the coagulation system and incomplete development of platelet function in premature infants may increase the tendency for bleeding. Recent studies have indicated that abnormalities in coagulation parameters may be associated with the development of GMH-IVH (19,20).

When metabolic parameters were evaluated, the presence of acidosis was not directly associated with the development of GMH-IVH; however, it was observed more frequently in severe-stage hemorrhages. Electrolyte disturbances and metabolic instability may adversely affect cerebral circulation in premature infants (21-23).

The multicenter cohort study conducted by Poryo et al. (24) supports the findings of our study. After controlling for maternal factors, the researchers demonstrated that the factors significantly associated with GMH-IVH were predominantly related to the postnatal period. In our study, no significant association was found between GMH-IVH and maternal factors such as gestational diabetes, hypertension, preeclampsia, maternal infections, and PPROM. This finding suggests that the degree of prematurity and the postnatal clinical condition may be more decisive than maternal factors in the development of GMH-IVH.

The most striking finding of our study is that invasive mechanical ventilation (OR: 32.451) and PDA treatment (OR: 35.366) emerged as factors independently associated with GMH-IVH. However, these associations should not be interpreted as causal. The retrospective design introduces a critical risk of reverse causality. Infants with severe prematurity and hemodynamic instability are more likely to require both invasive ventilation and PDA treatment. Furthermore, it is plausible that an infant who develops a severe GMH-IVH may subsequently experience hemodynamic instability, leading to the diagnosis and treatment of a PDA. Without precise documentation of the timing of these events, our multivariate analysis cannot establish whether PDA treatment preceded GMH-IVH or vice versa. In our study, the exact temporal relationship between PDA treatment and the diagnosis of GMH-IVH could not be determined due to the retrospective design. Therefore, it remains unclear whether PDA treatment preceded hemorrhage or occurred as a consequence of hemodynamic instability following hemorrhage. This is a major limitation that must be considered when interpreting our results. Our findings align with recent meta-analyses. Chen et al. (25) identified mechanical ventilation (OR: 2.09) and PDA (OR: 1.86) as significant factors associated with IVH in very low birth weight infants. The substantially higher odds ratios in our study may reflect the severity of illness in our cohort, highlighting that infants requiring invasive ventilation and PDA treatment represent a particularly vulnerable population requiring heightened surveillance to mitigate GMH-IVH risk.

Limitations

Our study has several limitations. The retrospective, single-center design may limit the generalizability of our findings and introduces potential for selection bias. The tertiary referral center setting, with a high proportion of outborn and extremely preterm infants, may not reflect the outcomes of lower-risk populations. Excluding infants who died or were discharged within the first 72 hours may have introduced selection bias, as the sickest and most immature infants at highest risk for severe hemorrhage were not included. The absence of blinding for radiologists, lack of interobserver reliability assessment, and the lack of standardized timing for interventions like PDA treatment relative to GMH-IVH diagnosis are significant limitations. Residual confounding from unmeasured variables (e.g., exact severity of respiratory illness, minute-to-minute hemodynamic fluctuations) is also possible. Furthermore, we did not use MRI for confirmation of hemorrhagic lesions, and long-term neurodevelopmental outcomes were not assessed. The inborn/outborn status was recorded (31.1% outborn), but differences in transport conditions and early stabilization could not be fully controlled for. Several findings, such as those related to multiple pregnancy and polyhydramnios, are based on very small subgroup numbers and should be interpreted cautiously. These points should be considered when interpreting the results.

Conclusion

Our study demonstrates that the development of GMH-IVH in premature infants is a multifactorial process. Lower gestational age, lower birth weight, absence of antenatal steroid use, lower Apgar scores, the need for invasive mechanical ventilation, the presence of PDA, and abnormalities in coagulation parameters were found to be associated with the development of GMH-IVH. However, the associations with mechanical ventilation and PDA treatment should be interpreted with caution due to the risk of reverse causality. Early identification of these factors and the implementation of appropriate clinical management strategies, with careful attention to hemodynamic and respiratory stability, may contribute to reducing the incidence and severity of GMH-IVH in this vulnerable population. Future prospective studies are needed to clarify the temporal relationship between clinical interventions and GMH-IVH.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City (01.11.2023, reference number: E2-23-5429).

Contribution of the authors

Study conception and design: İZA, CT; data collection: İZA; analysis and interpretation of results: İZA, CT; draft manuscript preparation: İZA, CT. All authors reviewed the results and approved the final version of the article

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Beyond the threshold of viability: Mortality, morbidity, and critical prognostic cut-offs in infants born at 22–26 weeks of gestation

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ABSTRACT

Objective: The aim of this study was to evaluate mortality, early morbidities, and critical prognostic thresholds in extremely preterm infants born at 22–26 weeks of gestation at the limit of periviability.

Materials and Methods: This retrospective single-center study included live-born infants between 22+0 and 26+6 weeks of gestation who were admitted to a tertiary 194-bed neonatal intensive care unit between June 1, 2021, and March 31, 2023. Prenatal, natal, and postnatal characteristics were analyzed. The primary outcome was mortality. Receiver operating characteristic (ROC) analysis was performed to determine optimal gestational age and birth weight cut-off values for predicting mortality.

Results: Among 11038 neonatal admissions during the study period, 263 (2.38%) were extremely preterm infants within the specified gestational age range. Overall mortality was 70.7%. Gestational age and birth weight were identified as the strongest independent predictors of survival. ROC analysis demonstrated significant cut-off values of 24.2 weeks for gestational age and 740 g for birth weight in predicting mortality. The most common early morbidities were patent ductus arteriosus (54.6%), culture-proven sepsis (38.7%), and osteopenia (28%). Survival improved markedly beyond 24 weeks of gestation, highlighting the critical prognostic importance of even small increments in maturity.

Conclusion: Biological immaturity remains the principal determinant of outcome in infants born at the threshold of viability. However, identification of clinically relevant gestational age and birth weight thresholds may guide prenatal counseling, individualized resuscitation decisions, and intensive care strategies to improve survival in this vulnerable population. Ultimately, achieving “quality survival” – survival without major disability – requires long-term neurodevelopmental follow-up beyond hospital discharge.

Keywords: Birth weight, extremely preterm infants, fetal viability, gestational age, mortality, neonatal intensive care

Introduction

Preterm birth is one of the most important causes of perinatal mortality and morbidity (1). In particular, extremely preterm birth is closely associated with high rates of disease and death. According to the World Health Organization, preterm birth refers to births occurring before 37 weeks of gestation. Prematurity is subdivided into late preterm (34–36 weeks 6 days), moderate preterm (32–33 weeks 6 days), very preterm (<32 weeks), and extremely preterm infants (<28 weeks) (1).

Approximately 15 million preterm infants are born each year worldwide. With advances in perinatal and neonatal intensive care, survival has increased, particularly among infants born before 32 weeks (1). Although extremely preterm infants constitute only 0.73% of all preterm births, they represent a significant burden in terms of complications and healthcare costs (2).

Survival rates of extremely preterm infants vary widely by country, ranging from around 10% in high-income settings to up to 90% in resourcelimited ones (2). Even in developed countries, survival without neurological sequelae is very low at <23 weeks, and no marked improvement has been reported at 22–23 weeks (3). Despite increased survival, poor longterm quality of life has raised ethical debates (4). Decisions regarding delivery and resuscitation remain controversial due to uncertain prognosis and practice differences (3).

Over the past 50 years, advances in perinatology and neonatology have improved survival, but serious comorbidities, prolonged hospital stays, and rising costs remain major concerns (5,6). Recent studies show improved survival particularly at 25 weeks (7). Periviability (22–26 weeks) represents a gray zone: survival probability is high at ≥26 weeks, whereas births below 22 weeks usually result in death, making 22 weeks the lower limit of periviability (8).

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In studies of delivery room management, "gray zone infants" are often defined as those weighing 500–600 g and/or born at 23–24 weeks (9). Parental request is a key determinant of resuscitation decisions; without such request, intervention is often initiated at 25 weeks, whereas with request it may start at 23 weeks (10).

As prognosis changes rapidly with increasing gestational age, potential benefits and risks must be discussed in detail during parental counseling (11).

In this study, we aimed to evaluate mortality, early morbidity rates, and risk factors in extremely preterm infants born at 22–26 weeks, and to identify factors associated with survival. Secondary aims included examining prematurity related complications and emphasizing the importance of prenatal and postnatal care.

Materials and Methods

In this retrospective study, the medical records of preterm infants born alive between 22 and 26 weeks of gestation and hospitalized in the Neonatal Intensive Care Unit (NICU) of Ankara Bilkent Şehir Hastanesi between June 1, 2021, and March 31, 2023, were reviewed. Mortality and early neonatal morbidities were evaluated.

Selection of cases

Inclusion Criteria: Infants born alive at ≥22 and <26 weeks of gestation, followed in the NICU, with complete data available. Gestational age was determined based on the mother's last menstrual period, first trimester ultrasonography, and, when necessary, by neonatal examination using the Ballard scoring system (12).

Exclusion Criteria: Patients with insufficient or inaccessible medical records and those diagnosed with syndromic diseases prenatally were excluded.

Recording of case data

Prenatal, natal, and postnatal data were recorded retrospectively from NICU files, discharge summaries, physician notes, and maternal follow up records.

Prenatal Characteristics: Maternal age, parity, birth order, multiple pregnancy, chronic diseases, risk factors for preterm birth, presence of infection, history of previous preterm birth, gestational weight gain, preterm labor, premature rupture of membranes (PROM), and antenatal steroid and magnesium administration.

Natal Characteristics: Mode of delivery, gestational age, gender, birth weight, 1st and 5thminute APGAR scores, and need for postnatal resuscitation.

Postnatal Characteristics: Surfactant administration, respiratory support, intubation timing, mechanical ventilation duration, oxygen therapy, inotropic support; body weights and fluid intake on days 1 and 7; time to enteral feeding; hypothyroidism; patent ductus arteriosus (PDA) – diagnosed by echocardiography and considered hemodynamically significant (hsPDA) if it required medical or surgical treatment; osteopenia; intraventricular hemorrhage (IVH); hydrocephalus; periventricular leukomalacia; seizures; necrotizing enterocolitis (NEC); retinopathy of prematurity (ROP); bronchopulmonary dysplasia (BPD); sepsis; duration of intensive care and hospital stay; and day of death.

Morbidities were evaluated according to internationally accepted criteria

NEC diagnosis and staging were based on Bell criteria (13). IVH classification was assessed according to Papile staging (14). BPD diagnosis was made according to National Institutes of Health (NIH) consensus criteria (15). Diagnoses of ROP, PDA, and sepsis were made according to relevant international guidelines. Osteopenia of prematurity: diagnosed when at least two of the following were present – serum phosphorus <1.8 mmol/L, serum alkaline phosphatase >500 IU/L, or radiographic evidence of osteopenia/rickets (e.g., fraying, cupping, or fractures) (16).

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Normality was assessed with the Kolmogorov–Smirnov test. For continuous variables with normal distribution, comparisons between two independent groups used Student's t test, and comparisons among more than two groups used oneway ANOVA. For nonnormally distributed variables, the Mann–Whitney U test was used for two groups and the Kruskal–Wallis test for more than two groups. Categorical variables were compared using the chi square test. When ANOVA or Kruskal–Wallis tests were significant, post hoc comparisons were performed using Tukey's HSD (for ANOVA) or Dunn's test with Bonferroni correction (for Kruskal–Wallis). Continuous variables are presented as mean and SD or median (IQR), categorical variables as number and percentages. Logistic regression analysis was performed to identify independent risk factors using a forward stepwise (likelihood ratio) variable selection method. Multicollinearity was assessed using variance inflation factors (VIF <2.5). Model fit was evaluated with the Hosmer–Lemeshow goodness of fit test (p>0.050). ROC curve analysis was used to evaluate diagnostic performance. A p value <0.050 was considered statistically significant.

Power analysis was conducted to determine the sample size. The total study population consisted of 263 infants distributed across five gestational age groups (22 weeks, n=46; 23 weeks, n=51; 24 weeks, n=65; 25 weeks, n=53; 26 weeks, n=48). Based on the observed overall mortality rate of 70.7% and an assumed effect size corresponding to an absolute mortality difference of 15% between gestational age subgroups (approximately n≈45 per group), the estimated statistical power was 82% at a two sided alpha level of 0.05. Power calculations were performed using G*Power version 3.1.9.7. Accordingly, the sample size was considered adequate for the primary outcome analysis and certain subgroup analyses.

Results

Between June 1, 2021, and March 31, 2023, 263 extremely preterm infants born at 22+0–26+6 weeks were included. During the study period, 11038 neonates were admitted to our 194 bed tertiary NICU; infants born at 22–26 weeks accounted for 2.38% of total admissions. Distribution by

Table I: Comparison of basic clinical characteristics and mortality according to gestational age

Variables	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	p
Total number of patients	46	51	65	53	48	-
Male gender*	27 (58.7)	28 (54.9)	34 (52.3)	31 (58.5)	25 (52.1)	0.689
Birth weight (g)†	537.5±145.4	634.8±138.4	660.3±145.8	737.5±148.4	883.5±210.6	<0.001 / $<0.001_{cdgij}$
APGAR 1 min‡	1 (2)	2 (3)	2 (2.5)	3 (3)	4 (3)	<0.001 / $<0.01_{dgi}$
APGAR 5 min‡	3 (3)	5 (3)	5 (3)	5 (2)	6 (2)	<0.001 / $<0.05_{dgi}$
Resuscitation performed*	18 (39.1)	13 (25.5)	15 (23.1)	13 (24.5)	2 (4.2)	0.006 / $<0.01_{dgij}$
Death*	44 (95.6)	42 (82.4)	46 (70.8)	34 (64.1)	20 (41.7)	<0.001 / 0.003_b 0.001_c/ $<0.001_d$ 0.002_g

***:** n(%) (Pearson Chi-Square, post-hoc pairwise z-test with Bonferroni correction), **†:** mean±SD (ANOVA, Post-hoc Tukey HSD), **‡:** median(IQR) (Kruskal-Wallis, Post-hoc Dunn's test with Bonferroni correction), **a:** 22 vs. 23 week, **b:** 22 vs. 24 week, **c:** 22 vs. 25 week, **d:** 22 vs. 26 week, **e:** 23 vs. 24 week, **f:** 23 vs. 25 week, **g:** 23 vs. 26 week, **h:** 24 vs. 25 week, **i:** 24 vs. 26 week, **j:** 25 vs. 26 week*

Table II: Maternal prenatal and obstetric characteristics

Variables	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	p
Total number of patients	46	51	65	53	48	-
Maternal age (years)*	28.6±4.9	28.9±5.7	29.4±5.6	28.2±6.6	28.9±5.1	0.624
Parity†	2 (1-3)	2 (1-3)	2 (1-4)	2 (1-3)	2 (1-3)	0.781
Magnesium use‡	20 (43.5)	24 (47.1)	35 (53.8)	28 (52.8)	26 (54.2)	0.742
Infection during pregnancy‡	13 (28.3)	15 (29.4)	24 (36.9)	11 (20.8)	16 (33.3)	0.012 / 0.008_h
Smoking during pregnancy‡	3 (6.5)	3 (5.9)	5 (7.7)	0 (0)	2 (4.2)	0.394
Chronic disease‡	19 (41.3)	14 (27.5)	20 (30.8)	17 (32.1)	20 (41.7)	0.429
PPROM‡	12 (26.1)	15 (29.4)	20 (30.8)	12 (22.6)	12 (25.0)	0.032 / 0.020_h / 0.040_i
Bleeding during pregnancy‡	16 (34.8)	13 (25.5)	17 (26.2)	10 (18.9)	11 (22.9)	0.043 /0.030_c
Multiple pregnancy‡	12 (26.1)	11 (21.6)	20 (30.8)	10 (18.9)	13 (27.1)	0.563
Antenatal steroids‡	27 (58.7)	39 (76.5)	52 (80.0)	39 (73.6)	37 (77.1)	0.002 / 0.001_b/ 0.003_c / 0.002_d

***:** mean±SD (ANOVA, Post-hoc Tukey HSD), **†:** median(IQR) (Kruskal-Wallis, Post-hoc Dunn's test with Bonferroni correction), **‡:** n(%) (Pearson Chi-Square, post-hoc pairwise z-test with Bonferroni correction), **a:** 22 vs. 23 week, **b:** 22 vs. 24 week, **c:** 22 vs. 25 week, **d:** 22 vs. 26 week, **e:** 23 vs. 24 week, **f:** 23 vs. 25 week, **g:** 23 vs. 26 week, **h:** 24 vs. 25 week, **i:** 24 vs. 26 week, **j:** 25 vs. 26 week, **PPROM :** preterm premature rupture of membranes.*

Table III: Postnatal morbidities and hospital course (n=263)

Variables	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	p
Total number of patients	46	51	65	53	48	-
Duration of mechanical ventilation (days)*	2 (4.25)	2 (7)	5 (17.5)	13 (45.5)	5 (14.75)	<0.001/ $<0.001_c$/0.002_f
Sepsis†	24 (52.2)	25 (49.0)	33 (50.8)	21 (39.6)	21 (43.8)	$0.015/0.010_c$
PDA†	13 (28.3)	22 (43.1)	39 (60.0)	34 (64.2)	34 (70.8)	<0.001/0.001_b/$<0.001_{cd}$
hsPDA†	8 (17.4)	18 (35.3)	23 (35.4)	18 (34.0)	24 (50.0)	<0.001/0.001_d/0.040_b
NEC†	2 (4.3)	3 (5.9)	5 (7.7)	7 (13.2)	5 (10.4)	<0.001/0.020_c/0.040_f
Osteopenia†	5 (10.9)	11 (21.6)	19 (29.2)	21 (39.6)	17 (35.4)	<0.001/0.004_c/0.010_d/0.020_b/0.040_f
Hypothyroidism†	2 (4.3)	5 (9.8)	7 (10.8)	6 (11.3)	8 (16.7)	$0.012/0.040_d$
Length of hospital stay in deceased infants (days)‡	5.2±7.6	13.4±35.4	14.1±32.2	27.7±34.8	11.3±29.4	$0.029/0.020_c$
NICU stay in discharged infants (days)‡	153±131.5	126.9±100.8	96.3±48.0	101.1±56.8	88.1±42.4	<0.001/0.010_b/0.020_c/0.008_d/0.040_g

***:** median (IQR) (Kruskal-Wallis, Post-hoc Dunn's test with Bonferroni correction),**†:** n(%) (Pearson Chi-Square, post-hoc pairwise z-test with Bonferroni correctio), **‡:** mean±SD (ANOVA, Post-hoc Tukey HSD), **a:** 22 vs. 23 week, **b:** 22 vs. 24 week, **c:** 22 vs. 25 week, **d:** 22 vs. 26 week, **e:** 23 vs. 24 week, **f:** 23 vs. 25 week, **g:** 23 vs. 26 week, **h:** 24 vs. 25 week, **i:** 24 vs. 26 week, **j:** 25 vs. 26 week **PDA:** patent ductus arteriosus, **hsPDA:** hemodynamically significant PDA, **NEC:** necrotizing enterocolitis, **NICU:** neonatal intensive care unit*

gestational age: 22 weeks (n=46, 17.5%), 23 weeks (n=51, 19.4%), 24 weeks (n=65, 24.7%), 25 weeks (n=53, 20.2%), and 26 weeks (n=48, 18.3%). Overall mortality was 70.7% (186/263); 29.3% (77/263) survived to discharge.

Baseline neonatal characteristics are summarized in Table I. Gender distribution did not differ significantly (p=0.689). Birth weight increased with gestational age (p<0.001). Apgar scores improved significantly (p<0.001). Resuscitation need decreased from 39.1% at 22 weeks to 4.2% at 26 weeks (p=0.006). Mortality showed a strong inverse relationship with gestational age (p<0.001).

Maternal characteristics are presented in Table II. Maternal age, smoking, chronic disease, and multiple pregnancy rates were similar across groups (p>0.050). Prenatal infection rates differed

Table IV. Comparison of prenatal characteristics between deceased and surviving infants (n=263)

Variables*	Deceased	Surviving	p
Total number of patients	186	77	
Antenatal steroid use	139 (71.6)	55 (28.4)	<0.001
Magnesium use	97 (67.8)	46 (32.2)	<0.001
Preeclampsia	21 (61.8)	13 (38.2)	0.039
GDM	12 (75.0)	4 (25.0)	0.026
Infection during pregnancy	51 (64.6)	28 (35.4)	0.012
Smoking during pregnancy	10 (76.9)	3 (23.1)	0.028
Presence of chronic disease	68 (75.4)	22 (24.6)	0.033
Bleeding during pregnancy	52 (77.6)	15 (22.4)	0.008
PPROM	49 (69.0)	22 (31.0)	0.025
Oligohydramnios	35 (77.8)	10 (22.2)	0.036
Polyhydramnios	7 (70.0)	3 (30.0)	0.034

***:** *n(%),* ***GDM:** Gestational diabetes mellitus,* ***PPROM:** Preterm premature rupture of membranes. Percentages are row percentages (within each variable).*

Table V: ROC analysis for predictors of mortality

Variable	Cutoff	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	p
Gestational age	>24.2 weeks	0.733 (0.675–0.785)	76.62 (65.6–85.5)	62.37 (55.0–69.3)	<0.001
Birth weight (grams)	>740 g	0.786 (0.731–0.835)	66.23 (54.6–76.6)	80.11 (73.6–85.6)	<0.001

***AUC:** Area under the curve,* ***CI:** Confidence interval. Cut off values were selected based on the Youden index*

significantly (p=0.012). PPROM (p=0.032) and antepartum bleeding (p=0.0430) also differed. Antenatal steroid exposure increased with gestational age (p=0.002).

Postnatal outcomes are summarized in Table III. Mechanical ventilation duration differed significantly (p<0.001). Sepsis occurred in 39.6 to 52.2% (p=0.015). The incidence of PDA increased with gestational age, from 28.3% at 22 weeks to 70.8% at 26 weeks (p<0.001). hsPDA showed a similar trend (p<0.001). NEC rates ranged from 4.3% to 13.2% (p<0.001). Osteopenia also increased with gestational age (p<0.001). Among infants who died, hospital stay increased with gestational age (p=0.029); among survivors, NICU stay decreased (p<0.001).

Prenatal risk factors associated with survival are shown in Table IV. Nonsurvivors had significantly higher rates of antenatal steroid exposure, magnesium therapy, preeclampsia, gestational diabetes, maternal infection, smoking, chronic disease, antepartum bleeding, PPROM, oligohydramnios, and polyhydramnios (all p<0.050).

ROC Analysis were performed for the mortality predictors ROC analysis results are presented in Table V and Figures 1 and 2. Gestational age predicted survival with an AUC of 0.733 (95% CI 0.675–0.785, p<0.001). A cut off of >24.2 weeks yielded 76.6% sensitivity and 62.4% specificity. Birth weight predicted survival with an AUC of 0.786 (95% CI 0.731–0.835, p<0.001). A cut off of >740 g yielded 66.2% sensitivity and 80.1% specificity. Logistic regression confirmed that gestational age >24.2 weeks increased survival odds 1.45 fold (95% CI 1.10–1.90, p<0.001) and birth weight >740 g increased survival odds 1.20 fold (p=0.007).

Discussion

In this study, the mortality rate among extremely preterm infants born at 22–26 weeks was 70.7%, consistent with high mortality ranges reported for periviable infants. Gestational age and birth weight were the strongest determinants of mortality; cut off values of 24.2 weeks and 740 g demonstrated that prognosis is markedly influenced by small weekly or gram level increases. These thresholds are largely consistent with large international cohorts (e.g., NICHD, EPICure) (17,21). They may provide clinically useful guidance for prenatal counseling, delivery room resuscitation, and intensive care planning. The high frequency of PDA, sepsis, and osteopenia indicates that cardiovascular, immunological, and metabolic immaturity plays a decisive role. The observed increase in PDA incidence with advancing gestational age (from 28.3% at 22 weeks to 70.8% at 26 weeks) is likely influenced by survival bias: mortality is extremely high (95.6%) at 22 weeks, so many infants in that group do not survive long enough for PDA to become clinically diagnosed or hemodynamically significant. In contrast, more mature infants survive longer, providing a wider clinical window for PDA and other morbidities to manifest. The observed increase in osteopenia with advancing gestational age may be explained, at least in part, by longer survival and prolonged hospitalization. Taken together, biological immaturity is the principal determinant of prognosis; however, appropriate prenatal care, experienced tertiary level intensive care, and early targeted therapies may improve outcomes.

Periviability (22–26 weeks) remains a period where survival strongly depends on gestational age and birth weight. Recent national cohort studies show progressive survival increases with each week: approximately 50–60% at 23 weeks and 60–70% at 24 weeks, while survival at 22 weeks, though still limited, has improved with proactive management (17,21). Our 24.2 week cutoff supports 24 weeks as a critical prognostic threshold. Center experience, antenatal steroids, and active resuscitation significantly influence survival (22). Our 70.7% mortality is consistent with the 60–80% range in NICHD and EPICure cohorts (17,20,21,22). The marked survival improvement after 24 weeks matches literature reports (17,23,24). Frequent PDA, sepsis, and osteopenia underscore the key role of cardiovascular and immune immaturity (19,25).

At 22–23 weeks, survival and neurodevelopmental outcomes remain controversial. NICHD and other multicenter studies show wide center to center variation in survival at 22 weeks, but significant increases at 23 weeks (22–24). Antenatal steroids and active resuscitation may improve survival even at 22–23 weeks (25). Centers with active care policies report substantially higher survival at 22 weeks (21,23). Our 24.2 week cut off is consistent with the literature and supports individualized care, particularly at 23–24 weeks.

In our cohort, the most common early morbidities were PDA (54.6%), culture positive sepsis (38.7%), and osteopenia (28%). Previous studies similarly report PDA, sepsis, BPD, ROP, and NEC as frequent complications (21,25). The paradoxical increase

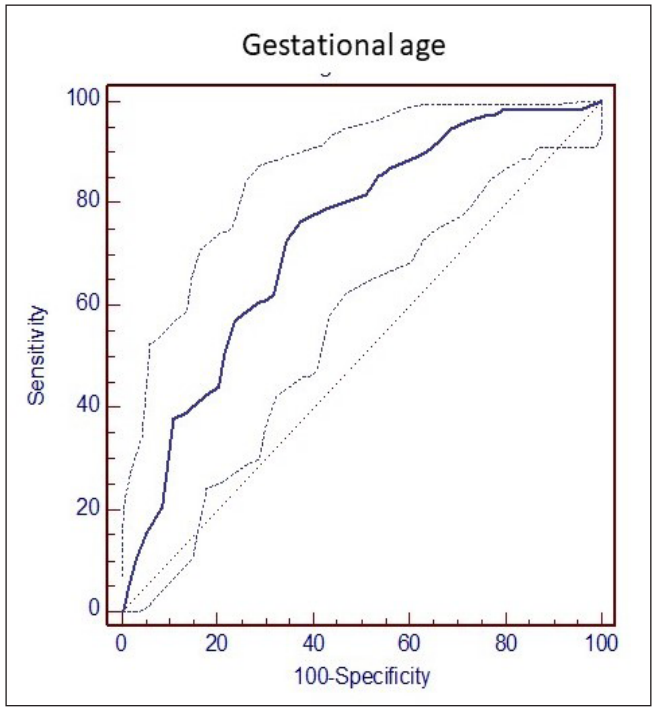


Figure 1: Receiver operating characteristic (ROC) curve showing the predictive performance of gestational age for survival in infants born at 22–26 weeks of gestation. A gestational age cut off value of >24.2 weeks predicted survival with 76.6% sensitivity and 62.4% specificity (AUC=0.733, 95% CI 0.675–0.785; p<0.001).

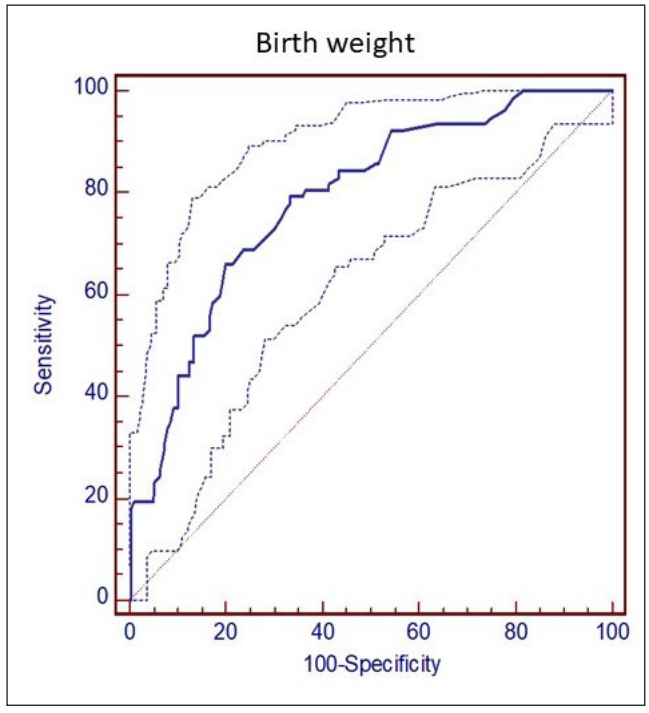


Figure 2: Receiver operating characteristic (ROC) curve demonstrating the predictive value of birth weight for survival among infants born at 22–26 weeks of gestation. A birth weight cut off value of >740 g predicted survival with 66.2% sensitivity and 80.1% specificity (AUC=0.786, 95% CI 0.731–0.835; p<0.001).

in PDA incidence with gestational age is best explained by survival bias, as noted above. As survival increases, persistent severe comorbidities underscore the need for care strategies targeting not only survival but also neurodevelopmental and functional quality of life (27).

Maternal infection, preeclampsia, PPROM, and multiple pregnancy are known contributors to prematurity (28). Antenatal steroids improve survival and reduce IVH risk (25). The limited observed effect of antenatal steroids on mortality in our study may relate to the dominant influence of gestational age and sample size; Larger international cohorts (e.g., NICHD, EPICure) have demonstrated more pronounced survival benefits with antenatal steroids, particularly at 23–24 weeks' gestation; the lack of a strong signal in our data may reflect the play of chance in a smaller sample or differences in the timing or completeness of steroid administration (29). This again supports the concept that biological immaturity is the principal determinant of prognosis in the periviability group.

Over the past 50 years, advances in neonatal care have substantially improved survival among extremely preterm infants (21). Nevertheless, neurodevelopmentally intact survival remains low, especially at 22–23 weeks (27). Periviability management is thus not only a medical but also an ethical and sociocultural process. Realistic prognostic counseling, individualized active care decisions, and improved center experience are paramount.

Clinically, individualized intensive care, strict infection control, and early cardiovascular stabilization are critical in reducing mortality, particularly for infants born before 24 weeks or weighing <750 g. Antenatal steroids and magnesium sulfate, and delivery in experienced tertiary centers, may improve prognosis. Strengths of our study include detailed prenatal ,natal and postnatal data focused on the periviability group and the determination of clinically relevant thresholds using ROC analysis.

Limitations

Limitations include its retrospective, single center design, the relatively small number of infants in the 22–23 week subgroup, and the absence of long term neurodevelopmental outcome assessment.

Three key clinical messages emerge. First, active care decisions for infants born at 23–24 weeks should be made jointly by a multidisciplinary team and the family. Second, in infants weighing <750 g, individualized ventilation, infection control, and cardiovascular stabilization may be critical for reducing mortality. Third, broader implementation of antenatal steroids and magnesium, and delivery in experienced tertiary centers, may improve survival (26,30). However, increasing survival must be evaluated alongside neurodevelopmental outcomes, with the goal of achieving "quality survival" (23,27).

Conclusion

In conclusion, although biological immaturity remains the principal determinant of prognosis in extremely preterm infants at the periviability threshold, appropriate prenatal care, experienced center management, and targeted intensive care strategies may achieve meaningful improvements in survival and morbidity. Given that survival without major disability –

"quality survival" – is the ultimate goal, future studies should incorporate longterm neurodevelopmental follow up beyond hospital discharge. Multicenter studies including longterm outcomes will make an important contribution to clinical decisionmaking.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (March 15, 2023, reference number: E2 23 3612).

Contribution of the authors

Study conception and design: CT; data collection: MHEM; analysis and interpretation of results: CT, MHEM; draft manuscript preparation: MHEM. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of neutrophil-to-lymphocyte, platelet-to-lymphocyte and eosinophil-to-lymphocyte ratios in childhood atopic dermatitis: Association with disease severity and treatment response

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ABSTRACT

Objective: Atopic dermatitis (AD) is a common chronic, inflammatory skin disease in childhood, characterized by pruritus and recurrent exacerbations. AD may impair daily functioning and negatively affect quality of life, psychosocial status, and personal development. In recent years, hematologic inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and eosinophil-to-lymphocyte ratio (ELR) have been investigated as potential biomarkers in chronic inflammatory diseases.

The aim of this study was to evaluate the relationship between disease severity assessed by the Eczema Area and Severity Index (EASI) and inflammatory biomarkers (NLR, PLR, and ELR), and to determine whether these markers can predict prognosis and treatment response in children with AD.

Materials and Methods: This prospective observational study included pediatric patients diagnosed with AD based on standard diagnostic criteria. Demographic characteristics, clinical findings, laboratory parameters, and quality of life scores (Infants' Dermatitis Life Quality Index, IDLQI) were recorded. EASI scores were calculated at diagnosis and after treatment. Receiver operating characteristic (ROC) analyses were performed to determine whether hematologic inflammatory parameters predicted ≥50% improvement in EASI score.

Results: Seventy patients without additional chronic disease were included; 41 (58.6%) were boys. The mean age was 9.4 ±14.4 months. ROC analysis demonstrated that the neutrophil-to-lymphocyte ratio (NLR) significantly differentiated patients who achieved ≥50% reduction in EASI score from those who did not (AUC = 0.648, p =0.041; 95% CI: 0.50–0.70). The optimal cutoff value for NLR was 0.3.

Conclusion: NLR is a rapid, inexpensive, and widely accessible biomarker that may help predict disease prognosis and treatment response in pediatric AD. Incorporating NLR into routine follow-up may assist clinicians in monitoring inflammation and optimizing treatment strategies.

Keywords: Atopic, biomarkers, blood cell count, dermatitis, pediatrics

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in children, characterized by itching and recurrent intermittent flare-ups. Its prevalence has reportedly increased approximately 2-3 times in industrialized countries with a high socioeconomic level in recent years (1,2).

In the development of AD, environmental factors such as lifestyle changes, increased environmental pollution, and exposure to smoking interact with genetic predisposition, immunological dysregulation, and epidermal barrier dysfunction. Although the exact steps in its pathophysiology are not fully understood, it is thought to develop as a result of triggering immune events in genetically predisposed individuals (3,4).

Additionally, the chronic course of the disease, the characteristic morphology and distribution of dermatitis, and a history of atopic diseases are key factors used in the diagnostic process. Clinical scoring systems, which include a detailed evaluation of the entire skin, are used to assess disease activity and the effectiveness of treatment (5,6). In patients with atopic dermatitis, eosinophilic and neutrophilic inflammation has been shown to be associated with immune and inflammatory mechanisms. Over the years, various inflammatory markers have been used to better assess inflammation and more accurately reflect disease activity. Recently, white blood cell counts and their subtypes in complete blood count have been identified as potential biomarkers of inflammation in various diseases (7-9).

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In our study, we aimed to evaluate the relationship between disease severity and simple complete blood count parameters such as Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Eosinophil-to-Lymphocyte Ratio (ELR). Additionally, we aimed to determine the impact of these inflammatory markers on predicting prognosis and treatment response.

Materials and Methods

Participant selection: A total of 70 patients aged 1–42 months who presented to the Pediatric Allergy and Immunology Outpatient Clinic of Ankara Bilkent City Hospital, were diagnosed with AD according to the diagnostic criteria, and voluntarily agreed to participate were included in the study. Patients with chronic comorbidities such as obesity, chronic liver disease, kidney disease, cardiovascular disease, diabetes, malignancy, or systemic inflammatory disorders were excluded. Additionally, those with abnormal blood test results (including anemia/polycythemia, leukopenia/leukocytosis, thrombocytopenia/thrombocytosis), patients receiving topical corticosteroid treatment, and those experiencing an active infection at the time of blood sampling were not included in the study. Before the study, informed consent forms were obtained from the parents of the patients. The study was carried out over a six-month period starting on 21 February 2024.

Atopic dermatitis diagnosis: The diagnosis was made in accordance with the diagnostic criteria established by Hanifin and Rajka in 1980, which were last revised in 2003, based on history and physical examination findings (10).

Atopic dermatitis severity: The Eczema Area and Severity Index (EASI) was used to assess disease severity.

EASI (Eczema Area and Severity Index); The area involved in four different body regions (upper extremities, head and neck, trunk, and lower extremities) is visually assessed and an area score is calculated; 1 (1%–9%), 2 (10%–29%), 3 (30%–49%), 4 (50%–69%), 5 (70%–89%), and 6 (90%–100%). The feet and buttocks are considered part of the lower extremities, while the groins and armpits are counted as part of the trunk.

Lesion severity: Each site is individually assessed for 4 clinical symptoms (erythema, edema/papulation, excoriation, and lichenification): Each symptom is assigned a severity score from 0 to 3, with 0 being absent; 1 being mild; 2 being moderate; and 3 being severe.

Area score: Each area is associated with an adult (>8 years) or pediatric multiplier that reflects the relative contribution of that area to the total body surface area. The area score is calculated for each area separately by multiplying the area density score by the area score and the area-specific multiplier.

Total Score: The final EASI score is the sum of 4 regional scores ranging from 0 to 72. A score of 0 indicates no eczema, 0.1 to 1.0 indicates almost clear, 1.1 to 7 indicates mild AD, 7.1 to 21 indicates moderate AD, 21.1 to 50 indicates severe AD, and greater than 51 indicates very severe AD (11).

Since this index has a subjectivity that is dependent on the person, the score was calculated and evaluated by the same person throughout the study. EASI was evaluated twice, at the initial application and one month after the appropriate treatment.

Data collection tools

Sociodemographic data form: Age, gender, medical history, family history, accompanying atopic diseases, initial symptoms, medications used, and the presence of familial allergic diseases were evaluated.

Clinical evaluation form: The characteristics, distribution, and severity of AD lesions were recorded. The presence of accompanying food allergies was also assessed.

Laboratory data and diagnostic tests: Neutrophil, Lymphocyte, White blood cell, Eosinophil and Platelet counts, Neutrophil to Lymphocyte count ratio (NLR), Platelet to Lymphocyte count ratio (PLR), Eosinophil to Lymphocyte count ratio (ELR) of the patients at the time of admission were recorded. Specific IgE levels (Siemens immulite 2000) of the patients at the time of admission were recorded and 0.35 kU/L was determined as the cut-off.

Quality of life assessment: For patients aged 0-3 years, the Infants Dermatitis Quality of Life Index (IDQOL) was completed by their parents. Permission to use both scales was obtained via email from the researchers who conducted the Turkish validity studies.

Infants dermatitis quality of life index (IDQOL): The IDQOL is designed as a parent-completed questionnaire to assess the impact of AD on the quality of life of children aged 0-3 years. It consists of 10 questions that evaluate various aspects, including the child's mood, itching, sleep patterns, ability to play, participation in family activities, discomfort during dressing or undressing, difficulties during mealtime, problems related to treatment, and challenges during bath time. Each question assesses the impact over the past week and is scored 0, 1, 2, or 3 based on severity. The total index score ranges from 0 to 30 and is categorized as follows: 0-1 points: not affected, 2-6 points: mildly affected, 7-12 points: moderately affected, 13-18 points: severely affected, and 19-30 points: very severely affected.

Statistical analysis

The SPSS 25 (IBM Corp., Armonk, NY, USA) program was used for the evaluation of the results. The normality of data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics were presented as mean and standard deviation for normally distributed variables, and as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were expressed as number (n) and percentage (%). Continuous variables was compared between two independent groups using the the Mann–Whitney U test for non-normally distributed data. For comparisons among three or more independent groups, the Kruskal–Wallis test was used. Categorical variables were compared using the chi-square test. Potential risk factors associated with AD severity and treatment resistance were examined using univariable logistic regression analysis.

ROC curve analysis was performed to test the overall discriminative ability of NLR, ELR, and PLR values for a significant decrease in EASI score. The optimal cut-off point was determined as the value at which the Youden index is highest. A p-value of <0.050 was considered statistically significant.

Results

A total of 70 infant patients diagnosed with AD were included in the study. The study population consisted of 41 (58.6%) males and 29 (41.4%) females. The median age of the patients was The median age of the patients was 6.0 months (IQR, 4.0–9.0). A family history of allergic disease was present in 29 patients (41.4%).

When evaluating the characteristics of AD-related skin lesions, it was found that 7 patients (10%) had lesions that had never regressed since their initial appearance, while 64 patients (91.4%) showed a tendency for lesion expansion compared to the initial stage. A change in lesion size was observed in 65 patients (92.9%). Itching was present in 57 patients (81.4%), and 40 patients (57.1%) experienced nighttime awakenings due to itching. All patients had dry skin. Additionally, 51 patients (72.9%) exhibited crusting, while 33 patients (47.1%) had oozing, peeling, or scaling.

The socio-demographic and clinical characteristics of the patients are summarized in Table I. Food sensitivity detected by skin prick test was present in 11 patients (15.7%), with egg sensitivity in 6 patients and milk sensitivity in 5 patients. When evaluating the EASI score results, which were used as the AD severity scale, the mean EASI score at diagnosis was 7.07±5.61, while after one month of treatment, it decreased to 4.09±4.13. A 50% significant reduction in EASI scores was observed in 32 patients after treatment. At the time of diagnosis, 41 patients had mild, 26 patients had moderate, and 3 patients had severe AD. After one month of treatment, 19 patients were almost clear, 40 patients had mild, 10 patients had moderate, and one patient had severe AD.

Table I: Sociodemographic characteristics of patients diagnosed with atopic dermatitis

Demographic characteristics	Values
Total number of patients	70
Gender*	
Male	41 (58.6)
Age (Month)†	6 (4-9)
Age at symptom onset (Monthly)‡	3.06±2.39
Method of birth*	
Caesarean	46 (65.7)
Vaginal delivery	24 (34.3)
Birth weight (Gram)‡	3258.2±539.72
Gestational age*	
Mature	65 (92.9)
Premature	5 (7.1)
Complementary feeding*	
5th month	6 (8.5)
6th month	31 (44.3)
After 6 Months	1 (1.4)
Prenatal maternal smoking*	7 (10)
Family history of allergic disease*	29 (41.4)

**: n(%), †: median (IQR), ‡: mean ± SD*

Table II: Laboratory data and EASI skore results of patients diagnosed with atopic dermatitis

Laboratory Data*	Values
Total number of patients	70
Diagnostic WBC (10^6/L)	10060±2714
Diagnostic ALC (10^6/L)	6179±1971
Diagnostic ANC (10^6/L)	2342±1186
Diagnostic EOS (10^6/L)	543.4±298.8
Diagnostic PLT (10^6/L)	419642±97062
Diagnostic NLR	0.42±0.32
Diagnostic ELR	0.09±0.05
Diagnostic PLR	73.7±25.7
Mean EASI skore	7.07±5.61
EASI skore after treatment	4.09±4.13

****:** mean ± SD, **WBC:** white blood cell count, **ALC:** absolute lymphocyte count, **ANC:** absolute neutrophil count, **EOS:** eosinophil count, **PLT:** platelet count, **NLR:** neutrophil-to-lymphocyte ratio, **ELR:** eosinophil-to-lymphocyte ratio, **PLR:** platelet-to-lymphocyte ratio, **EASI:** eczema area and severity index*

Laboratory data and EASI score results are summarized in Table II.

Comparisons of laboratory parameters according to disease severity and treatment response are presented in Table III. Based on EASI scores, 41 patients were classified as having mild disease and 29 as having moderate-to-severe disease. No statistically significant differences were found between these two groups in NLR, PLR, ELR, white blood cell count, absolute lymphocyte count, absolute neutrophil count, eosinophil count, or platelet count. Regarding treatment response, 38 patients showed no significant improvement in EASI scores, whereas 32 showed significant improvement. Although the median NLR was higher in the group without significant improvement than in the group with significant improvement, this difference was not statistically significant [0.401 (IQR: 0.267–0.515) versus 0.299 (IQR: 0.223–0.422), respectively; p=0.109]. No statistically significant differences were found between the treatment response groups in the other laboratory parameters.

In the logistic regression model applied to identify potential risk factors associated with moderate-to-severe EASI scores at diagnosis, the following variables were analyzed using a univariate logistic regression model: gender, maternal smoking, maternal history of thyroid disease, family history of allergic diseases, mode of delivery, and time of birth. However, none of these factors were found to be statistically significant risk factors. Detailed results of the univariate logistic regression analysis for these risk factors are presented in Table IV.

The ability of the NLR value to distinguish between groups with and without a 50% reduction in EASI score was evaluated, yielding an AUC of 0.648 (95% CI: 0.51–0.78, p=0.041). The optimal cutoff value for differentiating these groups was determined to be 0.32, yielding a sensitivity of 65.6%, a specificity of 61.1% (Figure 1). In contrast, ROC analysis for ELR and PLR values did not identify a statistically significant cutoff point for distinguishing between groups with and without a 50% reduction in EASI score (p = 0.190 and p=0.620, respectively).

Table III: Comparison of laboratory parameters according to disease severity and treatment response in patients with atopic dermatitis

Parameter	Mild EASI*	Moderate-Severe EASI*	p	No significant improvement EASI score*	Significant improvement EASI score*	p
Total number of patients	41	29	-	38	32	-
NLR	0.309 (0.224–0.424)	0.420 (0.280–0.508)	0.067	0.401 (0.267–0.515)	0.299 (0.223–0.422)	0.109
PLR	65.78 (56.20–85.17)	71.32 (54.52–88.58)	0.882	63.29 (52.01–77.75)	74.34 (55.37–101.16)	0.199
ELR	0.075 (0.053–0.098)	0.087 (0.067–0.107)	0.331	0.080 (0.062–0.108)	0.073 (0.054–0.099)	0.629
WBC	10010 (7900–11270)	10000 (8430–12170)	0.368	10075 (8400–12080)	9725 (7930–11325)	0.458
ALC	6290 (4880–7190)	5620 (4900–7600)	0.725	6130 (4930–7600)	5865 (4665–7410)	0.592
ANC	2050 (1540–2280)	2570 (1460–3640)	0.099	2170 (1580–3420)	2070 (1345–2515)	0.173
EOS	520 (250–690)	470 (400–720)	0.849	525 (420–720)	470 (335–710)	0.440
PLT	401000 (342000–483000)	394000 (339000 -473000)	0.957	394000 (339000–460000)	445000 (345500–502500)	0.447

:** *median (IQR) (Mann-Whitney U test),* ***EASI: *eczema area and severity index,* ***WBC:*** *white blood cell count,* ***ALC:*** *absolute lymphocyte count,* ***ANC:*** *absolute neutrophil count,* ***EOS:*** *eosinophil count,* ***PLT:*** *platelet count,* ***NLR:*** *neutrophil-to-lymphocyte ratio,* ***ELR:*** *eosinophil-to-lymphocyte ratio,* ***PLR:*** *platelet-to-lymphocyte ratio*

Table IV: Univariable logistic regression analysis of factors associated with treatment response and decrease in EASI score

Variable	OR	95% Confidence Interval	p
Gender	1.06	0.40-2.76	0.900
Maternal smoking	0.17	0.02-1.51	0.110
Family history of allergic disease	1.51	0.58-3.94	0.390
Mode of delivery	0.99	0.36-2.67	0.980
Maternal thyroid disease	1.57	0.38-6.43	0.520
Time of birth	3.64	0.38-34.4	0.250

Table V: Infants Dermatitis Quality of Life Index (IDQOL) scores stratified by EASI severity categories

EASI Severity Category	Values*	IDQOL Score†	p‡
Mild (EASI 0.1–7.0)	41 (58.6)	4.17±2.87	
Moderate (EASI 7.1–21.0)	26 (37.1)	9.65±4.54	<0.001
Severe (EASI >21.0)	3 (4.3)	15.70±5.61	
Total	70 (100)	7.07±5.61	-

**:n(%), †:mean±SD, ‡: Kruskal–Wallis test*

In the logistic regression model applied to identify potential risk factors associated with treatment response, the variables gender, maternal smoking, maternal history of thyroid disease, family history of allergic disease, mode of delivery, and birth timing were analyzed using a univariate logistic regression model. No significant risk factors were identified.

Since all patients were under the age of four, the Infants Dermatitis Quality of Life Index (IDQOL) was administered at diagnosis, completed by the parents to assess the impact of atopic dermatitis (AD) on quality of life. It was found that 37.1% (n=26) of the patients were moderately affected, 12.9% (n=9) were severely affected, and 18.6% (n=13) were very severely affected. Only one patient (1.4%) had no impact on their quality of life. When evaluating the effect of AD severity on quality of life at diagnosis, patients whose quality of life was moderately or more affected were compared to those who were not or minimally affected. It was found that the EASI scores at diagnosis were significantly higher in the more affected group, with mean IDQOL scores of 4.17±2.87 for mild, 9.65±4.54 for moderate, and 15.70±5.61 for severe AD groups, respectively ($p<0.001$). The detailed distribution of IDQOL scores stratified by EASI severity categories is presented in Table V.

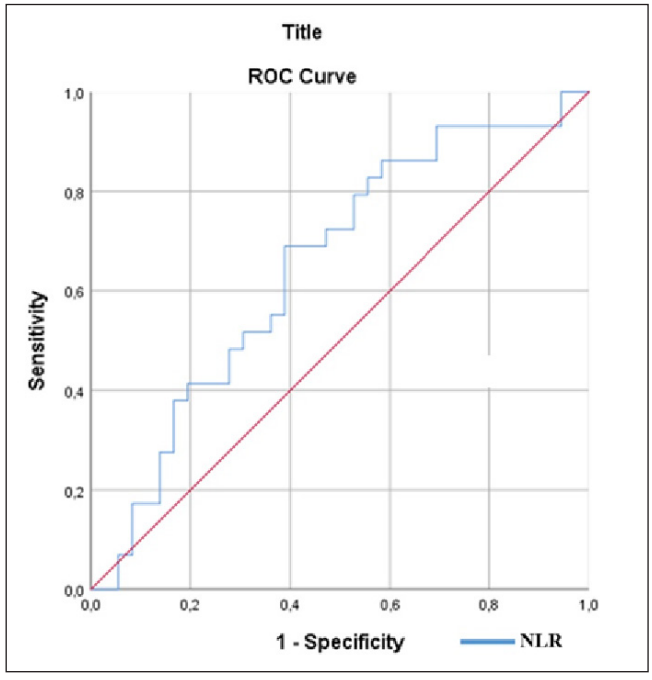


Figure 1: ROC curve of NLR values for groups with and without a 50% reduction in EASI score

Discussion

This study aimed to investigate the role of an easily accessible, inexpensive, and objectively assessable marker in evaluating disease severity and treatment response. In our

study, no significant differences in NLR, ELR, or PLR were observed between the mild and moderate-to-severe atopic dermatitis groups. Comparisons according to treatment response also revealed no significant differences in these markers. However, ROC analysis showed that pretreatment NLR had limited discriminatory ability to identify an inadequate treatment response, defined as failure to achieve a 50% reduction in EASI score (AUC=0.648; p=0.041). The NLR cutoff of 0.32 yielded a sensitivity of 65.6% and a specificity of 61.1%, whereas no statistically significant cutoff was identified for ELR or PLR.

In recent years, studies have been conducted on the prognostic importance of the NLR in chronic inflammatory diseases such as inflammatory cardiovascular diseases, hypertension, diabetes, malignancies, familial Mediterranean fever, and liver cirrhosis. NLR is considered a cost-effective and easily calculated marker for assessing inflammation (14). Building on this, studies have suggested that in AD, the most common inflammatory skin disease, not only local but also systemic inflammation may be present. Research has been conducted on the potential use of inflammatory markers in assessing this condition. However, the relationship between AD and peripheral blood leukocyte profiles has yielded conflicting results in the literature. AD is characterized by T-helper-2-driven inflammation in the acute phase and both T-helper-1 and T-helper-2-type inflammation in the chronic phase. Neutrophilic inflammation accompanies eosinophilic inflammation in AD. Studies indicate a correlation between allergic inflammation and blood eosinophil count, and while neutrophils alone may not fully reflect inflammation, NLR is increasingly considered a potential marker of inflammation (15). In their study including 66 AD patients and an equal number of control subjects, Doğru and colleagues did not find a significant difference in NLR values between the patient and control groups. However, when they classified the patients based on disease severity using the SCORAD index into mild, moderate, and severe groups, they observed that NLR was higher in patients with severe AD compared to those with mild and moderate AD. Both NLR and ELR were found to correlate with disease severity (16).

Hagino and colleagues conducted a study to evaluate treatment response in AD patients, including 65 patients over the age of 12 diagnosed with moderate-to-severe AD. They assessed the relationship between NLR, PLR, and ELR values and EASI and pruritus scores (PP-NRS) at baseline and at weeks 4, 12, and 24 of treatment. The authors found a positive correlation between baseline ratios and both EASI and pruritus scores. They observed that NLR and ELR decreased in parallel with EASI and pruritus scores at week 4, and this reduction was maintained until week 24. However, PLR showed a temporary decrease at week 4 but returned to baseline levels by week 12. The authors found that the percentage reduction in ELR was significantly associated with the percentage reduction in EASI and pruritus scores at weeks 4, 12, and 24, suggesting that ELR may serve as an indicator of clinical improvement and itch relief in AD treatment (15).

In another study including 252 AD patients and 75 healthy controls, the mean NLR and PLR values were found to be higher in the patient group compared to the control group. Additionally, a positive correlation was observed between NLR and PLR values and disease duration. The study emphasized that, due to their easier accessibility compared to other expensive inflammatory markers, NLR and PLR could be more preferable as biomarkers (17).

In another study conducted by Jiang et al. (9) in China (80 patients / 45 controls), it was reported that NLR was higher in AD patients compared to the control group. Additionally, when grouped according to the severity of the SCORAD index, a positive correlation was observed between disease severity and NLR. In our study, unlike other studies, we examined the relationship between inflammatory markers (ELR / PLR / NLR) and treatment response, represented by a decrease in the EASI score before and after treatment. Pre-treatment high NLR was found to be associated with inadequate treatment response. However, no significant cutoff point was found in evaluating the ability of ELR and PLR values to distinguish between groups with and without a 50% reduction in the EASI score. In our study, the AUC value of 0.648 for NLR indicates a modest discriminative performance in predicting treatment response. We acknowledge that this predictive capacity is moderate and suggests that NLR should not be viewed as a standalone gold-standard diagnostic tool. However, the potential clinical applicability of NLR remains noteworthy. Its primary strength lies in being a cost-effective, non-invasive, and universally accessible biomarker derived from a routine complete blood count. In clinical practice, particularly in resource-limited settings, such a ‘modest’ marker can still provide valuable ancillary information. Rather than providing a definitive prognosis, NLR can serve as a supplementary screening tool to help clinicians identify patients who may require closer monitoring or a more aggressive treatment approach from the outset

There are also similar studies evaluating inflammatory chronic airway diseases such as asthma and allergic rhinitis. In a study conducted by Yıldız and colleagues, which included a total of 600 adult participants with a diagnosis of allergic rhinitis (AR) and/or asthma and a control group, the NLR and ELR values were found to be significantly higher in the patient group compared to the control group. The authors emphasized that these markers could serve as potential indicators for prognostic processes and early diagnosis (18). Radhapyari and colleagues, in their study evaluating a total of 90 pediatric patients aged 5 to 18 years diagnosed with asthma, found a significant relationship between NLR and asthma severity. They emphasized the potential of NLR as an inflammatory marker (19).

In a study evaluating the relationship between AR severity and NLR and PLR, including 200 AR patients and 160 healthy controls (aged 3-18 years), NLR and PLR values were found to be higher in the AR group compared to the control group. When AR patients were categorized as intermittent and persistent, NLR and PLR were found to be higher in the persistent group. A positive correlation was observed between higher NLR and PLR values and AR severity. The authors suggested that these markers could be used at the initial diagnosis stage to determine disease severity in pediatric patients (20). In another

study comparing 140 AR patients with a control group, the mean NLR and PLR values were found to be significantly higher in the patient group than in the control group. Additionally, when the cases were classified as mild, moderate, and severe, NLR and PLR were higher in severe cases. These markers were identified as indicators of disease severity (21).

In recent years, as a requirement of a holistic approach to patients, the concept of "quality of life" has emerged alongside the assessment of physical well-being, incorporating psychological and social evaluations. In our study, quality of life assessment using IDQOL showed that, except for one patient, all patients experienced an impact on their quality of life, ranging from mild to very severe. Furthermore, when evaluating the effect of disease severity on quality of life, patients whose quality of life was moderately or severely affected had higher baseline EASI scores compared to those who were not or only slightly affected. Similarly, in a study assessing the quality of life in children with AD, Siafaka et al. (22) found that disease duration and severity negatively impacted quality of life.

AD can negatively impact quality of life due to severe itching, sleep disturbances triggered by itching—especially during infancy—frequent night awakenings, dietary restrictions recommended upon identifying allergens, difficulties in adhering to dietary regimens, and changes in eating habits. Additionally, in adolescence, when physical appearance is particularly important, altered body image due to skin lesions can further affect quality of life. Therefore, treatment should be planned in a multidisciplinary manner, and psychosocial support mechanisms should be activated for both the patient and their family when necessary. Due to ethical considerations, routine blood tests are not performed on healthy infants, making it impossible to include a control group in our study. This can be considered a limitation of our research. Additionally, there is no established cut-off value for NLR, as there is for other inflammatory parameters. However, in our study, we were able to determine a cut-off value for NLR that could predict a 50% reduction in pre-treatment EASI scores. This suggests that NLR may serve as a simple biomarker for predicting treatment response. A similar evaluation was conducted for ELR and PLR, but no significant differences were found. This may be related to both the limited sample size and the insufficient number of patients classified as having severe atopic dermatitis.

Limitations

There are several limitations to our study that should be considered. First, the evaluation of treatment response was conducted at a one-month follow-up. Given that atopic dermatitis is a chronic condition characterized by periodic fluctuations and flare-ups, this relatively short observation period limits our ability to assess the long-term sustainability of the clinical improvement and the predictive stability of the investigated hematologic markers. Additionally, our study was conducted in a single center and lacked a healthy control group due to ethical constraints regarding blood sampling in the infant population. Further multi-center, longitudinal studies with extended follow-up durations are warranted to validate the long-term prognostic value of NLR, PLR, and ELR in pediatric AD management.

Conclusion

NLR is a subcomponent of the complete blood count, is an inexpensive, reliable, and easily measurable parameter, even in primary healthcare settings. It may serve as an economical and useful biomarker for assessing disease severity and activity in conditions associated with systemic inflammation. Given that AD is prevalent in the pediatric population, utilizing NLR in clinical practice could provide healthcare providers with significant practicality in evaluating disease prognosis and treatment response. Further large-scale, controlled pediatric studies are needed to guide future applications in this field.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (14.02.2024, reference number: E2-23-5190).

Contribution of the authors

Study conception and design: PY, ZŞE, AS, MT, EDM, Data collection: PY, AS,Analysis and interpretation of results: PY, ZŞE, AS, MT, EDM, Draft manuscript preparation: PY, ZŞE, AS, All authors reviewed the results and approved the final version of the manuscript

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Original Article

Maternal iron status in mothers of infants with ventricular septal defect: A retrospective case–control study

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ABSTRACT

Objective: Maternal nutrition is increasingly recognized as a modifiable determinant of fetal cardiovascular development. Experimental and epidemiological studies suggest that iron deficiency may contribute to congenital heart disease, but data focusing on ventricular septal defect (VSD) remain limited. This study aimed to evaluate the association between maternal iron status and isolated perimembranous VSD in offspring.

Materials and Methods: This single-center retrospective case–control study included mothers of 41 infants younger than one year with isolated perimembranous VSD and 38 control mothers whose infants had no structural heart disease after echocardiographic evaluation. Maternal laboratory parameters were retrieved from electronic medical records, and the earliest available results were used for analysis. Evaluated parameters included hemoglobin, ferritin, vitamin B12, folate, and 25-hydroxyvitamin D. Group comparisons were performed using the Mann–Whitney U test or chi-square test, as appropriate. Binary logistic regression was used to assess independent associations with VSD, and receiver operating characteristic analysis was performed for ferritin.

Results: Maternal ferritin levels were significantly lower in the VSD group than in controls (median 25.8 [IQR 15.5–52.0] vs 57.9 [IQR 21.3–79.3] ng/mL, p=0.012), whereas maternal hemoglobin, vitamin B12, folate, and vitamin D levels did not differ significantly. In multivariable logistic regression adjusted for maternal age, hemoglobin, vitamin B12, and folate, ferritin remained independently associated with VSD (OR 0.83 per 10-ng/mL increase, 95% CI 0.72–0.96, p=0.012). Ferritin showed moderate discriminative ability for VSD (AUC 0.665, 95% CI 0.537–0.781).

Conclusion: Lower maternal ferritin levels were associated with isolated perimembranous VSD in offspring, independent of hemoglobin levels. These findings suggest that reduced maternal iron stores may be relevant to fetal septal development and warrant confirmation in prospective studies with measurements obtained during early pregnancy.

Keywords: Congenital heart disease, ferritin, iron deficiency, perimembranous ventricular septal defect

Introduction

Congenital heart disease (CHD) represents the most common congenital anomaly worldwide, affecting around 1–2% of live births and remaining a leading cause of infant morbidity and mortality. Within the broad spectrum of CHD, ventricular septal defect (VSD) is consistently reported as the most frequently observed subtype (1). The etiology of CHD is multifactorial, arising from complex interactions between genetic predisposition and environmental influences, among which maternal factors during early gestation are increasingly recognized as critical determinants of risk (1–4). Recent systematic review data also suggest that maternal micronutrient deficiencies may contribute to fetal CHD risk, including VSD, although the quality and consistency of the available evidence vary across nutrients and study designs (5).

Maternal nutrition is a key modifiable determinant of fetal development. Pregnancy has been described as a state of impending or existing iron deficiency, and commonly used biomarkers such as hemoglobin and ferritin may not always fully reflect tissue iron sufficiency during gestation (6). During pregnancy, iron requirements rise markedly to support maternal erythropoiesis, placental function and fetal growth, and a large proportion of pre-pregnant and pregnant women have inadequate iron stores or iron deficiency anemia worldwide (2,7). Iron deficiency is the leading cause of anemia in pregnancy and remains highly prevalent worldwide, particularly where dietary diversity and intake of animal-source foods are low (2,8). Maternal iron deficiency anemia has been linked to adverse perinatal outcomes and impaired offspring development, underscoring the need for systematic screening and treatment in pregnancy (2,8,9). Importantly, iron deficiency

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may be present even before overt anemia develops, making ferritin-based assessment particularly relevant when evaluating maternal iron stores (5,10).

Experimental work in mice demonstrates that maternal iron deficiency perturbs embryonic cardiovascular morphogenesis, producing ventricular septal defects and outflow tract anomalies through mechanisms involving premature differentiation of cardiac progenitors and increased retinoic acid signaling; early iron repletion can rescue these defects (1). This biological plausibility is supported by developmental studies showing that retinoic acid signaling and second heart field regulation are essential for normal cardiac septation and outflow tract development (11,12). Emerging human data suggest that maternal anemia and low iron status may be associated with an increased risk of congenital heart defects, including ventricular septal defect, indicating that maternal iron deficiency could represent a potentially modifiable factor in VSD development (13,14).

Şırnak is one of the provinces with the highest fertility rates in Türkiye, and the Southeastern Anatolia region, where Şırnak is located, has a high proportion of households in the lowest socioeconomic welfare category (15). In clinical practice, children with congenital heart disease in this region frequently come from families with limited socioeconomic resources, and maternal nutritional deficiencies may therefore represent a potentially underrecognized risk factor. The aim of this study was to evaluate the association between maternal iron status, assessed by ferritin levels, and the presence of VSD in their children.

Materials and Methods

This study was designed as a single-center retrospective case–control study conducted at the pediatric cardiology clinic of Şırnak State Hospital, including infants evaluated between April 2022 and January 2025. The aim of the study was to evaluate the association between maternal biochemical parameters and the presence of VSD in infants younger than one year of age. The VSD group consisted of infants younger than one year of age with a confirmed diagnosis of isolated perimembranous VSD who were followed in the pediatric cardiology clinic. The diagnosis of VSD was confirmed by transthoracic echocardiography performed by a pediatric cardiologist. The control group consisted of infants younger than one year of age who were referred to the pediatric cardiology clinic for evaluation of a cardiac murmur but were subsequently confirmed to have no structural heart disease after clinical examination and echocardiographic assessment.

Infants with additional major congenital heart defects, major extracardiac anomalies, or insufficient maternal laboratory data were excluded from the study. A small number of infants in the VSD group had Down syndrome, reflecting the known association between trisomy 21 and septal defects.

Maternal laboratory parameters were retrieved retrospectively from the hospital's electronic medical record system. The earliest available maternal laboratory results were used for analysis. Because of the retrospective nature of the study, maternal laboratory measurements were not uniformly obtained during pregnancy. In most cases, the available laboratory measurements were obtained during the postpartum period, whereas first-trimester laboratory data were available for only two mothers. Among mothers with postpartum laboratory data, the median interval between delivery and maternal blood sampling was 123 days.

The evaluated maternal biochemical parameters included:

- Complete blood count
- Ferritin
- Vitamin B12
- Folic acid
- 25-hydroxyvitamin D

Maternal demographic and obstetric characteristics, including maternal age at delivery, gravidity, and interpregnancy interval, were obtained from obstetric outpatient clinic records. Information on parental consanguinity was available only for the VSD group and was recorded when accessible.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using visual (histograms and probability plots) and analytical methods. Non-normally distributed variables were expressed as median with interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Comparisons between the VSD group and the control group were performed only for variables available in both groups, including maternal age at delivery, maternal hemoglobin level, ferritin level, vitamin B12 level, folate level, and vitamin D level. Since several biochemical parameters showed non-normal distribution, comparisons between groups were conducted using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Variables considered clinically relevant based on previous literature and available in both study groups, including maternal age at delivery, hemoglobin, ferritin, vitamin B12, and folate levels, were entered into a multivariable binary logistic regression model to evaluate their independent association with the presence of VSD. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative ability of maternal ferritin levels for identifying VSD. The area under the curve (AUC) was calculated. The optimal cut-off value was determined using the Youden index, and corresponding sensitivity and specificity values were reported. A p-value <0.050 was considered statistically significant.

Results

A total of 79 participants were included in the study, consisting of 41 mothers in the VSD group and 38 mothers in the control group. Among the infants in the VSD group, five patients had Down syndrome.

Baseline characteristics

Maternal age at delivery was comparable between the two groups (median 27.45 years [IQR 23.67–33.33] in the VSD group vs 29.46 years [IQR 23.70–34.67] in the control group, p=0.346). Similarly, maternal hemoglobin levels did not differ

Table I: Baseline maternal and infant characteristics

Variable	VSD	Control	p
Total number of patient	41	38	-
Maternal age at delivery (years)*	27.45 (23.67–33.33)	29.46 (23.70–34.67)	0.346
Maternal hemoglobin (g/dL)*	12.70 (11.90–13.30)	12.65 (11.50–13.38)	0.864
Maternal ferritin (ng/mL)*	25.80 (15.50–52.03)	57.85 (21.33–79.25)	0.012
Vitamin B12 (pg/mL)*	282.00 (236.00–426.00)	339.00 (287.00–398.25)	0.197
Folate (ng/mL)*	6.73 (4.10–10.11)	5.64 (4.79–11.00)	0.757
Vitamin D (ng/mL)*	11.05 (8.80–14.20)	13.30 (8.95–15.73)	0.407
Infant gender (Female/Male)	18 / 23	15 / 23	0.865†

**: median (IQR) (Mann–Whitney U test), †:chi-square test*

Table II: Logistic regression analysis for the presence of VSD

Variable	OR	95% CI	p
Maternal age at delivery	0.97	0.90–1.05	0.460
Maternal hemoglobin	1.15	0.80–1.66	0.459
Maternal ferritin (per 10-ng/mL increase)	0.83	0.72–0.96	0.012
Vitamin B12	0.999	0.996–1.003	0.731
Folate	1.02	0.92–1.13	0.662

Binary logistic regression analysis was performed to evaluate the association between maternal biochemical parameters and VSD. The Hosmer-Lemeshow goodness-of-fit test indicated adequate model fit (Chi-square = 9.204, df = 8, p = 0.325), and the Nagelkerke R square was 0.151.

significantly between the groups (median 12.70 g/dL [IQR 11.90–13.30] vs 12.65 g/dL [IQR 11.50–13.38], p=0.864).

The distribution of infant gender was also similar between the groups (female/male: 18/23 vs 15/23, p=0.865). The baseline maternal and infant characteristics of the study population are summarized in Table I.

Maternal ferritin levels were significantly lower in the VSD group compared with the control group (median 25.80 ng/mL [IQR 15.50–52.03] vs 57.85 ng/mL [IQR 21.33–79.25], p=0.012). The distribution of maternal ferritin levels is illustrated in Figure 1.

No significant differences were observed between the groups in terms of vitamin B12 levels (median 282 pg/mL [IQR 236–426] vs 339 pg/mL [IQR 287–398], p=0.197), folate levels (median 6.73 ng/mL [IQR 4.10–10.11] vs 5.64 ng/mL [IQR 4.79–11.00], p=0.757), or vitamin D levels (median 11.05 ng/mL [IQR 8.80–14.20] vs 13.30 ng/mL [IQR 8.95–15.73], p=0.407).

Logistic regression analysis

Binary logistic regression was used to examine the relationship between maternal biochemical parameters and the occurrence of VSD, as presented in Table II.

The multivariable logistic regression model included maternal age at delivery, hemoglobin level, vitamin B12 level, folate level, and ferritin level. Maternal ferritin remained independently associated with VSD. Specifically, the odds of VSD decreased by 17% for every 10 ng/mL increase in ferritin (OR 0.83, 95% CI 0.72–0.96, p=0.012), while other maternal biochemical parameters were not independently associated with VSD. A subgroup analysis was performed within the VSD cohort to evaluate whether maternal ferritin levels differed between infants requiring surgical intervention and those managed

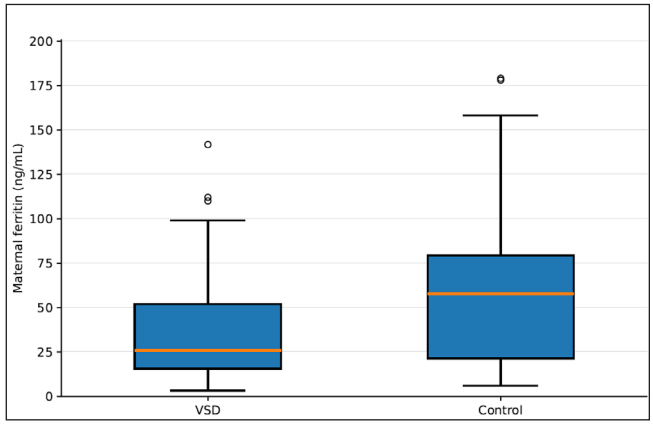


Figure 1: Distribution of maternal ferritin levels in mothers of children with ventricular septal defect (VSD) and controls. Maternal ferritin levels were significantly lower in mothers of children with VSD than in controls (median 25.8 ng/mL vs 57.9 ng/mL, p = 0.012).

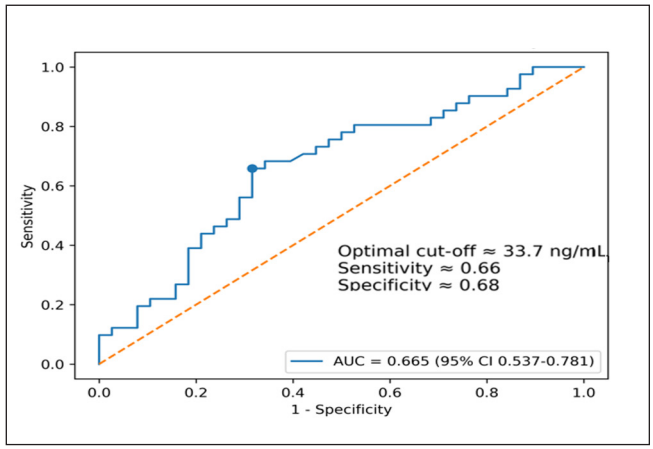


Figure 2: Receiver operating characteristic (ROC) curve of maternal ferritin levels for discrimination of ventricular septal defect (VSD). Maternal ferritin demonstrated moderate discriminative ability with an area under the curve (AUC) of 0.665 (95% CI 0.537–0.781). The optimal ferritin cut-off value determined using the Youden index was 33.7 ng/mL, yielding a sensitivity of 65.9% and specificity of 68.4%.

conservatively. Among the 41 patients with VSD, 13 required surgical repair. Maternal ferritin levels were numerically lower in the surgical group compared with the non-surgical group (median 19.7 ng/mL vs 27.3 ng/mL); however, this difference did not reach statistical significance (Mann–Whitney U test, p=0.230).

ROC curve analysis

ROC curve analysis was conducted to evaluate the capacity of maternal ferritin levels to differentiate VSD cases, as depicted in Figure 2. Maternal ferritin exhibited a moderate level of discriminative power, evidenced by an area under the curve (AUC) of 0.665 (95% CI 0.537–0.781). Using the Youden index, the best ferritin cut-off value was found to be 33.7 ng/mL. This value showed a sensitivity of 65.9% and a specificity of 68.4%.

Discussion

In this retrospective case–control investigation, mothers of infants diagnosed with VSD exhibited significantly reduced ferritin concentrations compared to mothers of infants without VSD. Nevertheless, hemoglobin levels and other micronutrient concentrations were comparable across both cohorts. Maternal ferritin concentrations, notably, remained independently associated with VSD, even when accounting for potential confounding factors. This observation suggests a potential association between diminished maternal iron reserves and VSD, rather than a direct causal relationship. These findings may suggest that ferritin could serve as a more sensitive marker of maternal iron status in this context. This distinction is clinically relevant because iron depletion may precede changes in hemoglobin concentration, particularly in pregnancy, where biochemical iron deficiency can exist despite apparently normal hemoglobin values (7,10).

While our study focused on isolated perimembranous VSD, whether maternal iron status is similarly associated with other VSD subtypes, such as muscular defects, remains to be determined and warrants further investigation. Receiver operating characteristic analysis demonstrated that maternal ferritin had a moderate discriminative ability for identifying VSD. However, its modest performance (AUC: 0.665) suggests that its clinical applicability as a standalone predictive biomarker may be limited and should be interpreted within a broader clinical context.

An additional consideration is the presence of Down syndrome in a subset of patients within the VSD group. Trisomy 21 is strongly associated with congenital heart defects, with approximately 40–60% of affected individuals having structural cardiac anomalies, and ventricular septal defect representing one of the most frequently observed lesions. This association has been consistently demonstrated both in large population-based cohorts and in regional studies, including data from Türkiye, where congenital heart defects are reported in nearly half of individuals with Down syndrome (16,17). Although the number of such patients in our cohort was limited, their inclusion may represent a potential source of confounding and should be considered when interpreting the observed association between maternal ferritin levels and VSD. Therefore, our findings should be interpreted with caution, and future studies incorporating detailed genetic or chromosomal stratification are warranted to better distinguish the relative contributions of maternal and genetic factors.

Experimental and clinical data together suggest that maternal iron deficiency may disrupt embryonic heart development through converging metabolic and signaling pathways. In experimental models, iron is required as a cofactor for CYP26 enzymes that regulate retinoic acid (RA) metabolism; iron deficiency may reduce CYP26 activity, leading to excess RA signaling and altered differentiation and migration of second heart field progenitors. These changes have been associated with structural heart defects, including VSD. Maternal iron deficiency may also contribute to embryonic hypoxia and altered vascular development. These mechanisms provide biologically plausible pathways that may help explain the observed association, although they do not establish causality (1,14,18).

An important consideration when interpreting our results is the timing of maternal biochemical assessment. In our cohort, most iron parameters were measured in the postpartum period and therefore cannot be assumed to capture iron status during the critical window of early cardiac morphogenesis. While iron deficiency in pregnancy is often part of a broader, chronic imbalance between increased physiological demand and insufficient intake or absorption, postpartum ferritin levels cannot be considered a precise proxy for early gestational iron status (19). In addition, postpartum ferritin levels may be influenced by delivery-related factors such as mode of delivery and peripartum blood loss, which were not systematically accounted for in this study. Furthermore, ferritin is an acute-phase reactant and may be affected by inflammatory processes, and pregnancy-specific diagnostic thresholds remain an area of ongoing refinement (10,19,20). Clinical guidelines further emphasize that a low serum ferritin is diagnostic of iron deficiency in pregnancy, and that ferritin levels <30 ng/mL are indicative of iron deficiency, although higher levels do not fully exclude iron depletion (21). Taken together, these factors warrant cautious interpretation of postpartum ferritin levels. Nevertheless, lower ferritin concentrations observed in mothers of infants with VSD may still reflect an underlying, longer-standing maternal iron vulnerability.

In line with this interpretation, population-based data have shown that maternal anemia in the first 100 days of pregnancy is associated with a higher odds of congenital heart defects in offspring, which may also be relevant to VSD (13). Complementary evidence from the Generation R cohort indicates that dysregulated maternal iron status in early pregnancy is associated with persistent alterations in cardiac structure and function in childhood, with higher maternal haemoglobin relating to smaller ventricular end-diastolic volumes in boys and maternal anemia predicting larger LV volumes and reduced systolic function, while higher ferritin in girls was associated with increased left ventricular mass (22). A recent systematic review of observational studies similarly concluded that maternal micronutrient deficiency may be relevant to fetal CHD risk, including VSD, although the available evidence remains heterogeneous and insufficient for nutrient-specific causal inference (5). Together, these findings may indicate that both iron deficiency and iron overload could be associated with long-term, gender-specific differences in cardiovascular development. These observations are broadly in line with our findings, although causal relationships cannot be inferred. The regional context may also be relevant for interpreting our findings. Şırnak is in the Southeastern Anatolia region, which has some of the highest fertility rates in Türkiye but also some of the worst

socioeconomic indicators (15). Repeated pregnancies, limited dietary diversity, and restricted access to nutritional resources may increase the risk of maternal micronutrient deficiencies, including iron deficiency. In daily pediatric cardiology practice in this region, children with CHD are frequently observed to come from families facing nutritional challenges. Although our study was not designed to directly evaluate socioeconomic determinants, our findings raise the possibility that maternal nutritional status may represent an important and potentially modifiable factor in regions with similar demographic and social characteristics.

Limitations

One important limitation of this study is the timing of maternal biochemical measurements. Maternal ferritin levels were not uniformly obtained during pregnancy, and most measurements were obtained during the postpartum period. Therefore, these values cannot be considered a direct representation of maternal iron status during early cardiac morphogenesis. In addition, the relatively small sample size and single-center design may limit the generalizability of the findings. Residual confounding factors, including dietary habits, iron supplementation during pregnancy, and broader socioeconomic variables, could not be fully accounted for. Given the retrospective design, limited sample size, and timing of measurements, these findings should be considered hypothesis-generating rather than confirmatory. Consequently, our results suggest a possible association between diminished maternal ferritin concentrations and VSD, rather than a causal relationship. Further prospective studies with measurements obtained during early pregnancy are needed to better clarify the timing and nature of this association, as well as to determine whether optimization of maternal iron status may contribute to the prevention of VSD.

Conclusion

In conclusion, lower maternal ferritin levels were associated with the presence of VSD in offspring, independent of hemoglobin levels. These findings suggest that maternal iron stores, rather than overt anemia, may be relevant for fetal cardiac development. Further prospective studies are needed to clarify causality and to determine whether optimization of maternal iron status may contribute to the prevention of congenital heart defects.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Sirnak University (07.12.2023, reference number: 83711).

Contribution of the authors

Study conception and design: MMA, VT; data collection: MMA, VÇ, ED; analysis and interpretation of results: MMA, VÇ, VT; draft manuscript preparation: MMA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Assessing the training needs of pediatric healthcare professionals in communication, risk management, and psychosocial resilience

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ABSTRACT

Objective: The quality of pediatric healthcare is closely tied to the communicative and psychosocial capacities of healthcare professionals. This study aimed to quantitatively determine the training needs of staff working in a tertiary pediatric hospital focusing on communication, management of violence-related risks, and psychosocial resilience.

Materials and Methods: A cross-sectional descriptive design was employed using the Hennessy-Hicks Training Needs Analysis approach. Data were collected via an online questionnaire from 133 healthcare professionals. The training need for each specific skill was calculated using discrepancy scores, which represent the difference between the perceived importance of the skill for professional duties and the participant's self-assessed current competence.

Results: Positive discrepancy scores were observed across all 16 items, although the magnitude of these differences was modest in absolute terms. At the domain level, relatively higher training needs were identified in the management of violence-related risks (M=0.44) and the psychosocial resilience/organizational dimension (M=0.42). Communication skills presented a relatively lower but still positive need (M=0.24). The training topics ranked highest included recognizing and coping with burnout, achieving competency in "White Code" (a national emergency response protocol for workplace violence) procedures, and exhibiting safe behaviors during threats.

Conclusion: Training needs in pediatric hospital settings extend beyond individual knowledge gaps to represent structural requirements driven by professional roles and high-stress environments. In-service training policies should prioritize risk management and psychosocial resilience as core components, embedding communication skills as a foundational layer rather than an isolated module. Training designs must be sensitive to specific professional roles, unit intensities, and shift schedules.

Keywords: Communication, health personnel, inservice training, pediatric hospitals, psychological resilience, workplace violence

Introduction

The quality of healthcare extends beyond technical skills and physical infrastructure, heavily relying on the communicative competencies, emotional self-regulation, and psychosocial resilience of professionals. In clinical settings requiring intensive patient contact, limitations in these skills compromise both service quality and staff well-being. Therefore, cultivating a healthy work environment is a holistic process that requires reinforcing employees' individual competencies alongside structural arrangements.

This necessity emerges much more prominently in pediatric healthcare. The developmental vulnerabilities of pediatric patients and the acute anxiety of their parents transform care into an emotionally intense interaction. Combined with heavy workloads and time pressure, this continuous empathic demand creates an exhausting climate that rapidly depletes the emotional resources of healthcare professionals (1-6). Consequently, the stress, burnout, and psychosocial strain prevalent among staff are largely linked to high emotional labor and inadequate coping strategies. Creating sustainable work environments, therefore, requires moving beyond physical security measures to foster individual skills such as stress management, anger control, and situational awareness (7-9). The World Health Organization also highlights enhancing employees' psychosocial capacity as fundamental to safe work environments (10).

Despite this, foundational medical education predominantly focuses on biomedical knowledge, leaving communicative and psychosocial skills secondary. Entering complex clinical environments without adequate preparation in these areas predisposes professionals to emotional difficulties and

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interpersonal tensions early in their careers. While in-service training aims to bridge this gap, standardized programs lacking context-sensitivity yield limited impact (11). Analyzing training needs at a micro-level (reflecting the specific dynamics of a single institution rather than broad macro-level assumptions) provides measurable improvements in service delivery (12). Accordingly, the Hennessy-Hicks Training Needs Analysis Model utilized in this study provides a robust foundation for developing contemporary, role-sensitive training strategies by objectively revealing the structural gap between healthcare professionals' occupational expectations and current competencies (13).

While health policy documents increasingly emphasize organizational climate and communication, translating this awareness into field practice requires measurable, context-sensitive data. Empowering psychosocial support professionals, such as social workers, to actively shape this environment necessitates accurately identifying the staff's actual training needs. This study aimed to quantitatively determine the training needs of healthcare professionals working in a tertiary pediatric hospital across three domains: (i) communication skills, (ii) management of violence-related risks, and (iii) psychosocial resilience and the organizational dimension. Training need was operationalized within a descriptive and comparative framework based on discrepancy scores, representing the gap between the perceived importance of a specific skill for professional duties and the participant's self-assessed current competence. The specific objectives were to identify the relative priority structure among these domains and to examine how training needs differ across contextual variables, including professional group, unit type, work schedule, seniority, and volume of daily patient interactions. By investigating the interrelationships among domains, this study sought to determine whether these needs were perceived as an integrated professional experience, thereby informing the development of targeted, role-sensitive in-service training modules.

Materials and Methods

This cross-sectional, descriptive field study aimed to reveal the individual training needs of healthcare professionals within their current work context. The scope, intensity, and patterns of self-perceived educational requirements were delineated without establishing causal relationships or intervening on variables. Instead, perceived needs in communication, violence-related risk management, and psychosocial resilience were evaluated contextually. Training need was conceptualized not as absolute deficiency, but as the relative discrepancy between the perceived importance of specific skill areas for professional duties and current self-perceived competence. This approach avoids reducing needs to individual deficits, making the gap between professional expectations and perceived capacity visible, and facilitating the identification of patterned training requirements across the work context.

The target population comprised approximately 1,900 healthcare professionals working in a well-established tertiary pediatric hospital in Turkey (Ankara Bilkent City Hospital, Children's Hospital). This pediatric setting, characterized by continuous patient-relative interactions, presents a work environment with prominent communicative and psychosocial burdens. The inclusion criteria for the study required participants to be actively employed full-time and to have direct, face-to-face contact with patients or their relatives. The target group included physicians, nurses, midwives, medical technicians, allied health professionals and support staff. Due to the intense and unpredictable shift schedules inherent in pediatric care, convenience sampling based on voluntary participation was utilized. Data from 133 employees who fully completed the questionnaire were analyzed. This heterogeneous sample, while limited in size, enabled comparative analyses across distinct professional groups, unit types, and work schedules.

Data were collected using a 16-item structured questionnaire developed by the researchers. The items were drafted based on clinical field experience and a review of relevant literature. To establish content validity, the drafted questionnaire was reviewed and refined by the research team, which consists of academicians with expertise in medical social work and pediatric care. The tool is grounded in the Hennessy-Hicks (15) Training Needs Analysis Model, whose importance-performance discrepancy approach was itself developed and psychometrically validated through thematic literature analysis, focus groups, and semi-structured interviews with health care professional. This model identifies educational requirements by calculating the discrepancy between the perceived importance of a professional task (A) and the individual's self-assessed current competence in that task (B).

The items were categorized into three distinct functional domains based on the specific psychosocial demands of pediatric care. The Communication Skills domain (5 items) focused on clinical interactions (encompassing empathic engagement, active listening, and the ability to explain medical processes clearly to anxious parents). The Management of Violence-Related Risks domain (6 items) addressed safety and legal security (including the recognition of early warning signs, de-escalation of tense encounters, and proficiency in "White Code" emergency procedures). Finally, the Psychosocial Resilience and Organizational Dimension (5 items) targeted the staff's coping mechanisms and institutional connectivity (specifically measuring needs related to managing workplace stress, recognizing burnout symptoms, and utilizing institutional support channels).

The internal consistency of the instrument (evaluated via Cronbach's α coefficient based on the importance ratings) was found to be 0.954 for the entire scale, indicating excellent reliability for the study context. Subscale reliability was likewise excellent to good (Management of Violence-Related Risks, α =0.930; Psychosocial Resilience and Organizational Dimension, α = 0.897; Communication Skills, α = 0.872). For each item, participants provided two independent ratings on a 5-point Likert scale (1 = very low, 5 =very high), where the resulting discrepancy score (A–B) served as the primary quantitative indicator of training priority.

Following the acquisition of ethical committee approval and necessary institutional permissions, the questionnaire was administered online via Google Forms between 23 and 27 February 2026. The survey link was distributed through

internal WhatsApp groups and direct messaging to enhance data saturation across professional groups. Voluntary participation, anonymity, and data confidentiality were explicitly emphasized, and participants could withdraw at any time. Only fully completed forms were included in the analysis.

Statistical analysis

Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS), version 27.0 (IBM Corp., Armonk, NY, USA). An AI-based tool (Gemini Pro) was utilized strictly for linguistic refinement and the technical formatting of raw survey data (e.g., restructuring text responses into numerical columns for SPSS entry) during data preprocessing. No statistical calculations, data manipulation, or analytical interpretations were automated. Training needs were evaluated using descriptive statistics (frequencies, means, standard deviations) for item- and domain-based discrepancy scores. The Friedman test, with Bonferroni correction, was used for cross-domain comparisons. Due to violations of the homogeneity of variances assumption, Welch's t-test was used for comparing two independent groups, and Welch's ANOVA (F_Welch) was employed for comparisons involving more than two groups. The Mann-Whitney U test was used to assess seniority differences within the physician subgroup. Statistical significance was set at $p<0.050$.

Results

A total of 133 healthcare professionals employed at a tertiary pediatric hospital participated in the study. The demographic profile indicated a predominantly female workforce (78.2%), with age clusters concentrated in the young adult (20–29 years, 34.6%) and middle-aged (40–49 years, 33.8%) groups. In terms of professional distribution, the sample was weighted towards frontline clinical staff; nurses, midwives, and medical technicians comprised 45.1%, while physicians accounted for 24.8%.

Table I: Demographic and professional characteristics of the participants

Characteristics	n (%)
Gender	
Female	104 (78.2)
Male	29 (21.8)
Age Groups	
20–29 years	46 (34.6)
30–39 years	27 (20.3)
40–49 years	45 (33.8)
≥ 50 years	15 (11.3)
Job Title	
Nurse / Midwife / Medical Technician	60 (45.1)
Physician	33 (24.8)
Medical Secretary / Clinical Support	21 (15.8)
Administrative / Technical Support	13 (9.8)
Allied Health Professional (Physiotherapist, Psychologist, Social Worker, etc.)	6 (4.5)
Unit	
Inpatient Unit	43 (32.3)
Outpatient Clinic	32 (24.1)
Intensive Care Unit (ICU)	18 (13.5)
Administrative Unit	9 (6.8)
Emergency Department	6 (4.5)
Operating Room	4 (3.0)
Imaging / Diagnostic	2 (1.5)
Other	19 (14.3)
History of Violence Exposure	
Yes	69 (51.9)
No	64 (48.1)

Table II: Assessment of training needs by domain and item

Training domains and items	mean±SD
Domain 1: Management of Violence-Related Risks	0.44 ± 0.63
Being familiar with the "White Code" procedure and relevant legal rights	0.54 ± 0.84
Exhibiting safe behaviors in situations involving assault or threat	0.48 ± 0.83
Applying de-escalation techniques	0.44 ± 0.87
Maintaining a calm and professional attitude in tense or conflicting situations	0.41 ± 0.69
Recognizing and managing one's own anger level	0.38 ± 0.70
Recognizing early warning signs of violence	0.37 ± 0.74
Domain 2: Psychosocial Resilience and Organizational Dimension	0.42 ± 0.62
Recognizing burnout symptoms and applying coping strategies	0.56 ± 0.95
Using institutional support mechanisms effectively	0.44 ± 0.79
Recognizing and managing stress sources in the work environment	0.43 ± 0.80
Developing organizational belonging and adopting corporate identity	0.39 ± 0.75
Using organizational communication channels and working with team spirit	0.26 ± 0.61
Domain 3: Communication Skills	0.24 ± 0.43
Communicating with difficult or angry patients and their relatives	0.32 ± 0.75
Using active listening and body language techniques	0.29 ± 0.60
Using empathic communication skills	0.23 ± 0.64
Strengthening intra-team communication and cooperation	0.21 ± 0.49
Explaining medical processes clearly and understandably to patients/relatives	0.16 ± 0.59

Values represent the difference scores (A-B) between perceived importance (A) and current competence (B). Positive values indicate a training need.

The distribution of work settings reflected the hospital's acute care focus, with the majority of participants working in inpatient clinics (32.3%) and outpatient units (24.1%). A notable characteristic of the sample was the high prevalence of violence exposure; 51.9% of the participants reported having been subjected to violence at some point in their careers. Detailed demographic and professional characteristics are presented in Table I.

The primary aim of the study was to identify the gap between perceived importance and current competence. The analysis revealed positive mean difference scores across all 16 items, indicating a universal training deficit where professional demands consistently exceeded the participants' self-assessed capacity.

When evaluated by domain, a clear hierarchy of needs emerged. Participants identified the Management of Violence-Related Risks (0.44±0.63) and Psychosocial Resilience and

Table III: Mean training need scores by domain and professional groups

Training Domain	Physician	Nursing & Care Staff*	Medical Secretary†	Allied Health Prof.	Admin. & Tech. Support	Welch's F (η^2)	p
Communication Skills	0.39	0.27	0.07	0.27	0.02	8.70 (0.09)	< 0.001
Violence-Related Risks	0.73	0.41	0.21	0.56	0.17	3.02 (0.09)	0.035
Psychosocial Resilience	0.74	0.42	0.10	0.43	0.09	6.23 (0.14)	0.001

Post-hoc pairwise comparisons (Games-Howell) indicated that the differentiation in Communication Skills was driven mainly by physicians scoring higher than medical secretaries (p=0.010) and administrative/technical support staff (=0.001), and by nursing & care staff scoring higher than administrative/technical support staff (p=0.001). For Violence-Related Risks, the only significant pairwise difference was physicians versus medical secretaries (p=0.021). For Psychosocial Resilience, physicians scored higher than medical secretaries (p=0.002) and administrative/technical support staff (p=0.001), and nursing & care staff scored higher than both of these groups (p=0.035–0.040).

Table IV: Comparison of training needs by unit type

Training Domain	Outpatient Clinic	Inpatient Unit	OR & ICU	Emergency & Diagnostic	Admin. & Support	Welch's F (η^2)	p
Communication Skills	0.37 ± 0.51	0.29 ± 0.35	0.17 ± 0.46	0.20 ± 0.32	-0.02 ± 0.34	3.44 (0.10)	0.016
Violence-Related Risks	0.60 ± 0.71	0.56 ± 0.64	0.28 ± 0.50	0.08 ± 0.49	0.23 ± 0.54	3.20 (0.10)	0.021
Psychosocial Resilience	0.63 ± 0.80	0.45 ± 0.57	0.39 ± 0.53	0.05 ± 0.37	0.14 ± 0.33	4.56 (0.10)	0.003

Post-hoc pairwise comparisons (Games-Howell) indicated that, for Communication Skills, the difference was driven by the Administrative & Support group scoring lower than the Inpatient Unit (p=0.019) and the Outpatient Clinic (p=0.013). For Violence-Related Risks, although the omnibus test was significant, no individual pairwise comparison reached significance, which can occur with unequal group sizes and variances. For Psychosocial Resilience, the Outpatient Clinic scored higher than both the Administrative & Support group (p=0.021) and the Emergency & Diagnostic group (p=0.016).

Table V: Comparison of training needs by history of violence exposure

Training Domain	Mean (Yes)	Mean (No)	Welch t (df)	p	Cohen's d
Communication Skills	0.32	0.16	2.22 (130.94)	0.028	0.39
Violence-Related Risks	0.57	0.30	2.45 (129.10)	0.015	0.42
Psychosocial Resilience	0.57	0.25	3.05 (122.02)	0.003	0.52

Welch's t-test was used for between-group comparisons; degrees of freedom (df) are provided in parentheses. Effect sizes are reported using Cohen's d coefficient. The sizes of the groups with and without a history of violence exposure are presented in the Participant Profile section.

Organizational Dimension (0.42±0.62) as the domains with relatively higher, though modest in absolute magnitude, discrepancy scores. In contrast, the need for technical Communication Skills, while present, was comparatively lower (0.24±0.43) than the other two domains (Table II).

Item-level analysis provided deeper insights into these priorities. The highest training needs were not related to routine tasks but to crisis management and emotional survival. Specifically, "recognizing burnout symptoms and applying coping strategies" (0.56±0.95) and "knowledge of White Code procedures and legal rights" (0.54±0.84) were the top-ranked items. This underscores that the staff's primary concerns are centered on legal security and psychological well-being.

To statistically verify the hierarchy of needs observed in descriptive statistics, a Friedman test was conducted. The results confirmed a significant difference in how participants prioritized the training domains (χ^2 =18.81, p<0.001). Post-hoc comparisons revealed that Psychosocial Resilience (Mean Rank: 2.43) and Management of Violence-Related Risks (Mean Rank: 2.00) were prioritized significantly higher than Communication Skills (Mean Rank: 1.57). This finding suggests that for pediatric healthcare workers, safety and resilience are prerequisite needs that supersede standard communication training.

The analysis of training needs by professional roles revealed a significant stratification. Physicians reported the highest training needs across all three domains, distinguishing them clearly from other groups (Table III). The disparity was most pronounced in the Psychosocial Resilience domain (F =6.23, p=0.001), where physicians reported a mean need score of 0.74, compared to 0.10 for medical secretaries. Notably, Allied Health Professionals also reported high needs in violence-related risks (0.56), diverging significantly from administrative staff. The effect sizes (partial η^2) for these group differences ranged from 0.09 to 0.14, indicating a moderate to large practical significance in how various professional roles experience training deficits.

Work setting also played a determining role. Participants working in direct patient care units (outpatient clinics and inpatient units) reported significantly higher needs in Risk Management (p=0.021) and Communication (p=0.016) compared to administrative staff. Interestingly, staff in high-intensity units such as the Intensive Care Unit (ICU) and Operating Room reported moderate to high needs in psychosocial resilience, reflecting the stressful nature of these environments (Table IV). The partial η^2 values of 0.10 across all three domains denote a moderate effect size, confirming that the physical and clinical environment of the unit substantially influences the perceived need for psychosocial training.

A critical determinant of training needs was the history of exposure to workplace violence. Participants who had previously experienced violence from patients or their relatives reported significantly higher training deficits across all three domains compared to those with no such history. This difference was most striking in the Psychosocial Resilience and Organizational Dimension (t=3.05, p=0.003), where the effect size was moderate-to-large (Cohen's d= 0.52). Significant differences were also observed in the Management of Violence-Related

Table VI: Comparison of specific psychosocial training items by job title

Training domain	Physician	Nursing & Care Staff	Medical Secretary	Allied Health Prof.	Admin. & Tech. Support	Kruskal-Wallis H (η^2)	p
Coping with Burnout	0.88±1.14	0.62±0.90	0.24±0.89	0.50±0.55	0.08±0.49	11.70 (0.09)	0.020
Anger Management	0.67±0.89	0.33±0.54	0.24±0.89	0.50±0.55	0.08±0.28	11.98 (0.09)	0.018
Stress Management	0.70±0.92	0.45±0.77	0.24±0.89	0.17±0.41	0.08±0.28	12.49 (0.09)	0.014

Values in this table represent mean ± SD difference scores (A-B), consistent with the other tables; the previously reported values reflected Kruskal-Wallis mean ranks rather than raw discrepancy scores and have been corrected accordingly. Dunn's post-hoc test with Bonferroni correction indicated that, for Anger Management, physicians scored significantly higher than medical secretaries (p=0.047); for Stress Management, physicians likewise scored higher than medical secretaries (p=0.040). For Coping with Burnout, no pairwise comparison remained significant after Bonferroni correction, despite the significant omnibus test.

Risks (t=2.45, p=0.015, d=0.42) and Communication Skills (t=2.22, p=0.028, d= 0.39) (Table V). These findings indicate that the experience of violence exacerbates the training need within a holistic framework encompassing communication and psychosocial processes, extending far beyond mere security and risk management.

Further analysis of specific psychosocial items showed that training needs regarding recognizing and coping with burnout, managing anger, and managing stress differed significantly among professional groups (Kruskal-Wallis H test; p=0.014-0.020). As presented in Table VI, these needs were particularly pronounced among physicians and allied health professionals, while they were expressed at relatively lower levels by medical secretaries and administrative/technical support staff. The effect sizes for these specific item differences (partial η^2 = 0.09) indicate a moderate practical significance. These findings suggest that the educational requirement regarding psychosocial coping domains is dictated by the professional role and the emotional burden of clinical responsibility, rather than merely the quantitative workload.

In summary, the findings demonstrate that pediatric healthcare professionals experience significant training deficits, particularly in managing violence-related risks and maintaining psychosocial resilience. These identified needs are not uniform; they are instead intricately tied to high-stress work settings, prior exposure to workplace violence, and the specific emotional and clinical burdens inherent to different professional roles. The intersection of these factors highlights a complex landscape of educational requirements that extends significantly beyond basic communication or routine clinical skills.

Discussion

The findings consistently highlight training needs across three axes: communicative competencies, management of violence-related risks, and psychosocial resilience. The predominantly positive discrepancy scores across all domains indicate an expectation-capacity gap. Participants perceive these competencies as crucial, yet their self-assessed proficiency lags behind. Validating the fundamental premise of the Hennessy-Hicks approach, this pattern demonstrates that educational requirements should be conceptualized through the gap between perceived importance and current performance rather than absolute deficiency (14,15). Thus, the chosen measurement logic directly articulates the professional demands generated by the pediatric hospital climate.

Domain-based averages reveal that training needs are intensely concentrated in managing violence-related risks and psychosocial resilience, while communication skills present a lower, yet positive, need. This implies two dynamics. First, communication is likely experienced as a routinized repertoire within daily practice, whereas risk management and resilience are fragile domains interwoven with workplace uncertainties. Second, the continuous nature of communication in pediatric settings may normalize the need, reducing its visibility. Conversely, threshold experiences like risk and burnout signal educational requirements much more sharply. The high discrepancy scores for items such as recognizing burnout, achieving competence in White Code procedures, and exhibiting safe behaviors suggest that employees construct their training needs as a necessity for security and sustainability. Recent meta-analyses confirm that workplace violence prevention training programs significantly increase healthcare professionals' confidence and their capacity to act during incidents (16). This aligns with frameworks emphasizing that healthcare environments must be comprehended through employee safety and psychosocial well-being rather than solely communication quality (7,17,18).

The significant differentiation in priority structure, confirmed by the Friedman test, indicates that training needs are organized hierarchically. In environments with high emotional burden, skills addressing critical incidents naturally elevate the educational demand over communication. However, this lower priority does not imply communication is unnecessary; rather, it is accepted as an embedded, obligatory clinical practice. Marginalizing communication content in educational planning would be risky, as it serves as a foundational layer for early risk recognition, de-escalation, and utilizing institutional support (19, 20).

Significant stratification at the professional group level demonstrates that needs are constructed relative to role expectations and responsibility burdens. Physicians reported the highest needs across all domains, a finding that can be attributed to several structural dynamics inherent in the medical hierarchy. As primary clinical decision-makers, physicians bear the ultimate legal and medical accountability for patient outcomes, which structurally positions them as direct targets of parental anxiety and frustration. Furthermore, during incidents of workplace violence, they are implicitly expected to assume a leadership role in de-escalating conflicts, a responsibility that frequently transcends their clinical expertise. However, traditional biomedical education structurally underprepares them for these complex organizational and psychosocial demands. Recent systematic reviews confirm that the high cognitive load

and chronic emotional exhaustion inherent in modern medical practice significantly deplete physicians' psychosocial reserves and career engagement (21). This structural vulnerability necessitates a role-sensitive training design rather than a uniform format. Similarly, contextual variables like patient circulation and care intensity shape needs across unit types. The high communication and risk management needs in outpatient and inpatient clinics correspond to the continuous, tension-generating nature of face-to-face interactions. Meanwhile, the prominent need for psychosocial resilience in operating rooms and intensive care units reflects the wearing effect of high-risk decisions, uninterrupted attention, and exposure to severe illness.

The variation in communication needs according to work schedules highlights that training efficacy depends on delivery rhythm as much as content. Elevated needs among employees on mixed schedules may be associated with irregular time organization complicating intra-team coordination and rapidly depleting emotional regulation resources. Because educational demand fluctuates with context, methods like shift-compatible short modules and micro-learning gain importance. Organizational training literature has long emphasized the necessity of aligning training design with the work context (11). Furthermore, recent pedagogical reviews in healthcare strongly support this alignment, demonstrating that continuous digital micro-learning interventions effectively bypass the time constraints of rotating shifts (22).

Conversely, the absence of significant differentiation across quantitative variables like seniority and daily direct interactions demonstrates that needs cannot be explained by the reductionist assumption that "less experience equals more need." Experience may strengthen skills, but it simultaneously increases cumulative burdens like chronic stress and emotion regulation difficulties. Thus, seniority alone is not distinguishing; training needs are more tightly coupled with specific roles and environments. Similarly, the quality of contact is often more decisive than quantity. A high volume of routine contacts versus fewer highly tense contacts shapes the perception of need differently, indicating that crude targeting strategies based solely on interaction volume will be insufficient.

Within the physician subgroup, the significance of the resident-senior distinction in psychosocial resilience reflects how institutional positioning impacts perceived needs. Residents operate under heavy workloads, ambiguous boundaries, and limited autonomy. Contemporary literature confirms that this lack of structural autonomy leaves medical residents highly vulnerable to systemic burnout and moral injury, elevating their need for targeted organizational support (23). Consequently, topics like utilizing support mechanisms and coping with burnout generate higher discrepancy scores. This underscores that training must not be confined to increasing individual resilience; organizational components (such as in-house counseling, supervision, and accessible support lines) must also be fortified to target holistic environmental conditions (7).

The strong correlations among the three domains suggest that training needs are perceived as an integrated professional experience rather than fragmented skills. A curriculum advancing through interconnected skill sets and shared scenarios would be highly functional. For instance, de-escalation techniques resonate more realistically when combined with early warning recognition, self-regulation, and institutional procedures. Likewise, White Code training should link pre-incident risk awareness, safe behavior during the incident, and post-incident psychosocial reporting processes.

Limitations

While these findings offer a context-sensitive roadmap for reconstructing training design in high-stress pediatric environments, certain limitations must be acknowledged. First, the cross-sectional design and the relatively small sample size from a single tertiary hospital limit the generalizability of the findings to all pediatric settings. Relying on self-reported data evaluates training needs through participants' perceptions, precluding validation with objective performance indicators. Therefore, future research should incorporate objective metrics (such as actual incident reporting rates, absenteeism data, or simulated performance evaluations) to validate these self-reported training needs. Furthermore, while content validity was established via expert consensus and internal consistency was excellent, the absence of construct validity testing (e.g., factor analysis) due to sample size constraints constitutes a methodological limitation. Despite these constraints, the study provides a critical baseline for developing psychosocially-oriented training policies in pediatric care.

Conclusion

This study offers an original contribution to the literature by evaluating the training requirements of pediatric healthcare professionals not through assumed knowledge gaps, but through the structural expectation-capacity imbalance shaped by their high-stress work context. By revealing that employees perceive their greatest educational needs in areas critical to their psychological survival and physical safety, rather than in routine clinical or standard communication skills, this research highlights a critical blind spot in traditional biomedical education. This finding underscores the necessity of repositioning in-service training from a mandatory administrative routine to a strategic, psychosocially informed tool designed to meticulously manage the equilibrium between professional demands and workforce capacity.

Consequently, an effective institutional training policy must transcend a narrow framework centered solely on communication. Instead, violence-related risk management and psychosocial resilience must constitute the core curriculum. Communication skills should be systematically embedded within this curriculum as a foundational integrative framework for risk awareness, tension de-escalation, and team coordination, rather than being taught as an isolated theme. Comprehensive training curricula in pediatric settings that integrate both communication and safety protocols across all staff roles have been shown to directly improve patient care experiences (24). In practice, this entails restructuring in-service training into brief, shift-compatible modules embedded in institutional support structures (e.g., peer-supervision circles led by psychosocial

professionals), with programme impact monitored through objective indicators such as incident reports and burnout metrics.

Ethics committee approval
This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (18/02/2026, reference number: TABED 2-26 - 1956).

Contribution of the authors
Study conception and design: HCİ, TT, CK; data collection: HCİ, CK; analysis and interpretation of results: HCİ; draft manuscript preparation: HCİ; critical revision of the manuscript: TT. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

Generative AI Statetment
During data preprocessing, an AI-based tool (Gemini Pro) was used strictly for linguistic refinement and for the technical formatting of raw survey text responses into numerical columns for SPSS entry. No statistical calculations, data manipulation, or analytical interpretations were performed by the tool. All authors have reviewed and take full responsibility for the content of this manuscript.

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Original Article

How many suspected drug allergies in children are true allergies? A stepwise diagnostic evaluation from a single center

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ABSTRACT

Objective: The aim of this study was determine the rate of confirmed drug allergy using a stepwise diagnostic algorithm in children with a suspected or previously labeled drug allergy, to assess the proportion of patients in whom an incorrect drug-allergy label could be safely removed (delabeling rate), and to evaluate the diagnostic tests applied.

Materials and Methods: In this retrospective cross-sectional study, children presenting with suspected drug allergy to our pediatric allergy clinic between April 2023 and January 2025 were evaluated retrospectively. A stepwise protocol comprising detailed history, drug-specific IgE, skin tests (prick and intradermal), and drug provocation testing (oral or, when clinically indicated, subcutaneous or intravenous) was applied. Of 127 patients initially assessed, 41 were excluded and 86 who completed the clinically indicated diagnostic evaluation were analyzed.

Results: The mean age was 10.5±4.6 years. True drug allergy was confirmed in 16 patients (18.6%), whereas the incorrect drug-allergy label was safely removed in 70 (81.4%). Beta-lactams were the most common culprit group (12/16; 75.0%). Parental atopy, parental drug allergy, and personal atopy were significantly more frequent in the true-allergy group (p=0.004, p=0.028, and p=0.006, respectively), whereas no significant difference was found for age, sex, or laboratory parameters. In 10 confirmed patients, the diagnosis was established only by OPT. Anaphylaxis occurred in two of the 74 OPTs performed (2.7% per test).

Conclusion: In the majority of children presenting with suspected drug allergy, true allergy can be safely excluded through comprehensive diagnostic evaluation. Under appropriate patient selection and safe conditions, OPT is the gold-standard method for confirming or excluding true drug allergy, while specific IgE and skin tests support a stepwise evaluation for selected drugs; referral of these children to a pediatric allergist is important for both individual patient safety and antimicrobial stewardship.

Keywords: Anti-bacterial agents, beta-lactams, child, drug hypersensitivity, immunoglobulin E, skin tests

Introduction

Drug hypersensitivity reactions (DHRs) are dose-independent, unpredictable reactions that arise through immunological or non-immunological mechanisms and occur only in susceptible individuals (1). Frequently encountered in clinical practice, these reactions pose substantial diagnostic and management challenges, particularly in the pediatric population. Although the prevalence of drug allergy in childhood is reported to be high, a considerable proportion of these data rely on patient or parental reports and do not accurately reflect true immunological reactions confirmed by detailed allergological evaluation (2,3).

Recent studies have shown that the great majority of reported drug allergies cannot be confirmed after comprehensive diagnostic work-up (2,3). This indicates that the “drug-allergy label” is frequently applied incorrectly and over-diagnosed in clinical practice. Labels assigned in childhood in particular often persist throughout life and substantially restrict treatment options. Indeed, individuals carrying a drug-allergy label are frequently directed to more expensive, more toxic, or broader-spectrum alternative treatments, which both reduces treatment efficacy and increases the risk of adverse effects (4,5).

Incorrect drug-allergy labeling has important consequences not only at the individual level but also at the societal level. These include acceleration of antimicrobial resistance due to unnecessary antibiotic use, increased healthcare costs, and prolonged hospital stays (6,7). The widespread prevalence of incorrect allergy labels for beta-lactam antibiotics in particular further complicates clinical management by restricting the use of effective, narrow-spectrum treatment options (6-8).

Accurate diagnosis of DHRs is critical for preventing unnecessary labeling and determining appropriate treatment strategies. In this process, a detailed clinical history, in vitro tests (drug-specific IgE), and in vivo tests (skin prick and intradermal tests) play important roles, while the oral drug provocation test (OPT) is accepted as the gold-standard method (9-11). Performing OPT under safe conditions with

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appropriate patient selection constitutes a fundamental step in confirming true drug allergy and removing incorrect labels. In contrast, current data on the true frequency of DHRs in childhood and the clinical efficacy of diagnostic tests are limited, and data from our country in particular are scarce (12). This leads to a lack of standardization in the management of drug allergy in pediatric patients.

In this study, we aimed to determine the rate of true drug allergy by applying a stepwise diagnostic algorithm in pediatric patients who had been labeled as drug allergic at various outpatient clinics or referred to our clinic with suspected drug allergy, to determine the delabeling rate—the proportion of children in whom an incorrect drug-allergy label could be safely removed—and to demonstrate the clinical value of the diagnostic tests used (13).

Materials and Methods

Study design and population

This study was designed as a retrospective cross-sectional descriptive investigation. Patients who presented with suspected drug allergy to the pediatric immunology and allergy clinic of Şanlıurfa Training and Research Hospital between April 2023 and January 2025 were reviewed retrospectively. The records of all consecutive patients who presented with suspected drug allergy or who had previously been given a "drug-allergy label" at other centers were reviewed. Diagnostic tests were performed within routine clinical practice after obtaining patient/parental consent; ethics committee approval was obtained for the retrospective use of data.

Inclusion and exclusion criteria

Patients meeting the following criteria were included: pediatric patients (0-18 years) with a history of DHR or carrying a drug-allergy label; those who completed the diagnostic evaluation steps planned according to the suspected drug and clinical indication; and those able to attend the clinic regularly.

Patients were excluded in the following situations: those who declined to complete the diagnostic test protocol; those who were lost to follow-up and could not attend the stepwise testing program regularly; those for whom oral provocation testing was not performed because a reliable alternative drug was available; and those whose diagnostic evaluation could not be completed for any other reason. The number of patients at each stage, together with the reasons for exclusion, is reported in the Results and summarized in the patient flow diagram (Figure 1).

Diagnostic algorithm

A diagnostic protocol comprising applicable steps according to the suspected drug and clinical risk assessment was applied.

The diagnostic pathway was tailored to the suspected drug and to a risk assessment based on the index reaction. In line with current EAACI recommendations, patients were stratified as low or high risk according to the phenotype, severity, and timing of the index reaction (10,14,15). Low-risk reactions were defined as benign, delayed-onset cutaneous

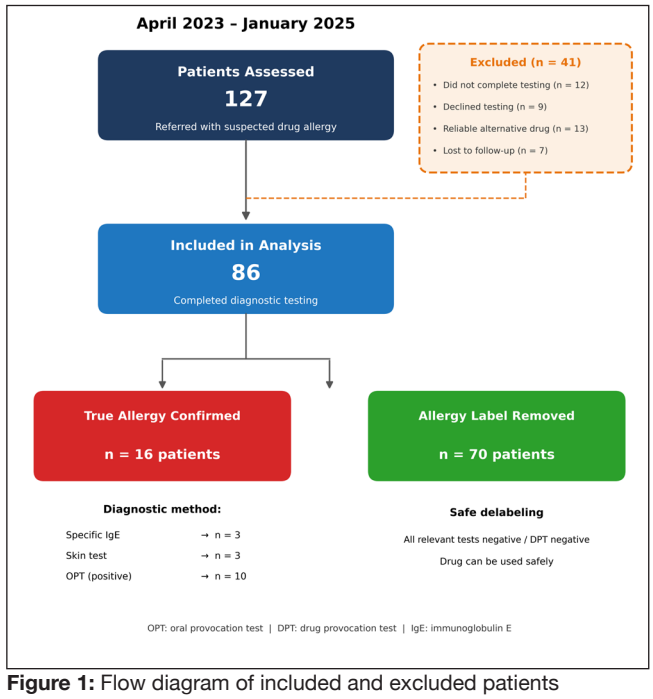


Figure 1: Flow diagram of included and excluded patients

manifestations without systemic involvement (e.g., a mild maculopapular exanthem or mild non-immediate urticaria) occurring in a child without significant comorbidity, whereas high-risk reactions included immediate-type reactions, anaphylaxis, severe or systemic reactions, and reactions suggestive of a severe cutaneous adverse reaction. For culprit drugs with validated test material—principally beta-lactams—drug-specific IgE and/or skin testing were performed before provocation in all patients for whom such testing was applicable. Patients proceeded directly to oral provocation testing, without prior skin testing, when no validated skin test or specific IgE was available for the culprit drug (e.g., non-steroidal anti-inflammatory drugs, macrolides, and antiepileptics) or when a low-risk reaction justified direct provocation, in accordance with current recommendations (10,14,15).

Step 1 – Detailed drug allergy history: The implicated drug, the time of reaction onset, clinical findings, the presence of concomitant disease, and atopic history were recorded using a standardized form.

Step 2 – In vitro tests: For the beta-lactam group, specific IgE levels for ampicillin, amoxicillin, penicillin V, and penicillin G were measured. A drug-specific IgE level of ≥0.35 kU/L was accepted as positive. Positive results were interpreted together with a clinically compatible reaction history. In patients with positive specific IgE, a diagnosis of beta-lactam allergy was made without further testing.

Step 3 – Skin tests: When specific IgE was negative or could not be measured, skin prick and intradermal (ID) tests were performed in accordance with the ENDA/EAACI guidelines (9,11,12). Skin tests were performed at the non-irritant drug concentrations recommended in the ENDA/EAACI position paper (9). For amoxicillin-clavulanate, test solutions were prepared at these non-irritant concentrations from the injectable (parenteral) formulation; because no separate test

material was available for clavulanic acid, discrimination between the amoxicillin and clavulanic acid components could not be made.

Step 4 – Oral drug provocation test (OPT): In patients with negative skin tests, in whom skin testing was not applicable, or who were classified as low risk, an open oral drug provocation test was performed under continuous medical supervision in a setting equipped for the management of anaphylaxis (9,10,15). In our protocol, the full age- and weight-appropriate therapeutic dose was administered in successive, increasing portions (approximately 20%, 30%, and 50% of the total dose) at 30-minute intervals, with observation for at least 2 hours after the final dose, consistent with current recommendations (15). When no immediate reaction occurred but a non-immediate (delayed) reaction was suspected from the index history, the drug was continued at therapeutic doses at home for 5 days, and the family was contacted by telephone to record any delayed reaction. A test was regarded as positive when objective, reproducible signs developed during or after provocation—such as urticaria, angioedema, erythema or a measurable exanthem, rhinoconjunctivitis, wheezing or dyspnea, laryngeal edema, gastrointestinal symptoms accompanied by objective findings, hypotension, or anaphylaxis—whereas isolated subjective symptoms in the absence of objective findings were not accepted as a positive result (10,15). If any systemic reaction developed, the test was terminated immediately and appropriate treatment was administered. Because no validated skin test or specific IgE was available for azithromycin, diagnostic evaluation in that patient was performed directly by OPT (10). Although provocation was performed orally in most patients, a non-oral route was used when appropriate for the drug: subcutaneous provocation for local anesthetics and graded intravenous provocation for parenterally administered drugs (ceftriaxone, amikacin, and paracetamol).

Definitions

Reactions were characterized both by the organ system(s) involved and by overall severity. Anaphylaxis was defined according to the EAACI and World Allergy Organization criteria as either (i) an acute reaction with involvement of the skin and/or mucosal tissue together with at least one of respiratory compromise, reduced blood pressure or associated end-organ symptoms, or severe gastrointestinal symptoms; or (ii) the acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient, even in the absence of typical skin involvement (16,17). For the description of organ-system involvement, each affected system was recorded separately, and patients who met the criteria for anaphylaxis were additionally counted in the anaphylaxis category. Consequently, a patient with multisystem involvement could be represented both under the relevant individual organ systems and under anaphylaxis, so the sum of organ-system counts may exceed the number of patients. Overall reaction severity was graded as mild, moderate, severe, or anaphylaxis.

Statistical analysis

Data were analyzed using SPSS v26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation (SD) or median (min-max); categorical variables were expressed as number and percentage (n,%). Normality of distribution was assessed with the Kolmogorov-Smirnov test. For between-group comparisons, the Student t-test or Mann-Whitney U test was used for continuous variables, and the chi-square or Fisher exact test for categorical variables. A p value <0.050 was considered statistically significant. Because a large number of variables were examined in the between-group comparisons, these analyses are exploratory (hypothesis-generating); no correction for multiple comparisons was applied, and the significant associations obtained should be interpreted with caution. For the categorical variables that differed significantly between the groups, unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the logit (Woolf) method. Multivariable logistic regression was not performed because only 16 outcome events were observed among three candidate predictors, resulting in approximately five events per variable. Simulation studies have suggested that a low number of events per variable may increase the risk of biased parameter estimates, inaccurate variance estimates, and inadequate confidence interval coverage. Therefore, multivariable analysis was considered unlikely to provide sufficiently reliable estimates (18). Penalized (Firth) approaches were also considered; however, with only 16 outcome events and three clinically inter-related predictors, the resulting estimates would remain too imprecise to support inference about independent effects, as is already apparent from the width of the univariable confidence intervals. The associations identified in the univariable comparisons are therefore reported as exploratory and hypothesis-generating.

Results

Patient flow

During the study period, 127 patients were assessed for suspected drug allergy. Of these, 41 (32.3%) were excluded: 12 whose diagnostic evaluation could not be completed, 9 who declined testing, 13 for whom oral provocation testing was not performed because a reliable alternative drug was available, and 7 who were lost to follow-up. The remaining 86 patients (67.7%) completed the full stepwise diagnostic protocol and were included in the analysis (Figure 1).

Demographic and clinical characteristics of the whole study group

The mean age of the 86 patients included was 10.5±4.6 years (range: 2-18 years); 41 were girls (47.7%) and 45 were boys (52.3%). A parental history of atopy was present in 25.6% (n=22) and a parental history of drug allergy in 12.8% (n=11). Among accompanying allergic diseases, asthma was found in 8.1% (n=7), allergic rhinitis in 11.6% (n=10), atopic dermatitis in 4.7% (n=4), and food allergy in 3.5% (n=3) (Table I).

The suspected drugs were most frequently antibiotics (n=64; 68.1%), followed by non-steroidal anti-inflammatory drugs (NSAIDs; n=25; 26.6%), local anesthetics (n=3; 3.2%), and antiepileptics (n=2; 2.1%). The most frequently suspected antibiotic group was beta-lactams (n=47), and the most frequently suspected NSAID/analgesic agent was paracetamol (n=19); paracetamol, a weak COX-1 inhibitor, was evaluated within the NSAID/analgesic group in accordance with the

Table I: Demographic, clinical, and laboratory characteristics of the study group and comparison according to confirmed drug allergy status

Variable	Total	Confirmed drug allergy	Allergy excluded	p
Total number of patients	86	16	70	-
Age (years)*	10.5±4.6 (2-18)	10.2±5.0	10.6±4.5	0.772
Sex - female†	41 (47.7)	7 (43.8)	34 (48.6)	0.787
Parental history of atopy†	22 (25.6)	9 (56.2)	13 (18.6)	0.004
Parental drug allergy†	11 (12.8)	5 (31.2)	6 (8.6)	0.028
Personal atopy†	19 (22.1)	8 (50.0)	11 (15.7)	0.006
Comorbid asthma†	7 (8.1)	3 (18.8)	4 (5.7)	0.116
Comorbid allergic rhinitis†	10 (11.6)	4 (25.0)	6 (8.6)	0.085
Comorbid atopic dermatitis†	4 (4.7)	2 (12.5)	2 (2.9)	0.156
Comorbid food allergy†	3 (3.5)	1 (6.3)	2 (2.9)	0.465
Absolute eosinophil count (/mm³)*	364±238 (0-1350)	380±240	360±235	0.766
Eosinophil (%)‡	4.7±2.3 (0-16.8)	5.0±2.4	4.6±2.2	0.138
Total IgE (IU/mL)‡	310±197 (1-1103)	325±205	307±195	0.236

***:** *mean±SD (min-max) (Student t-test),* **†:** *n (%) (chi-square or Fisher exact test),* **‡:** *mean±SD (min-max)(Mann-Whitney U test)*

Table II: Clinical characteristics of the 16 patients with confirmed drug allergy

Patient	Culprit drug (group)	Sex / Age	Atopy (parental / personal)	Presenting reaction (onset)	Diagnostic test	Reaction during test / outcome
P1	Amoxicillin-clavulanate (beta-lactam)	F / 12	Yes / Asthma	Urticaria at hour 3	Sp IgE / Skin / OPT	Anaphylaxis during OPT
P2	Amoxicillin-clavulanate (beta-lactam)	M / 8	No / —	Angioedema at hour 2	Skin / OPT	MPE at min 10 of OPT
P3	Valproic acid (antiepileptic)	M / 11	No / —	Maculopapular exanthem at hour 3	OPT	Transient maculopapular rash during OPT
P4	Amoxicillin-clavulanate (beta-lactam)	F / 16	No / Asthma	Urticaria at hour 3	Sp IgE	Sp IgE positive (skin test and OPT not performed)
P5	Amoxicillin-clavulanate (beta-lactam)	F / 13	Yes / Allergic rhinitis	Urticaria at hours 3-4	Sp IgE / Skin / OPT	Urticaria during OPT
P6	Amoxicillin-clavulanate (beta-lactam)	M / 17	Yes / Urticaria	Urticaria + angioedema at hour 2	Sp IgE / Skin	Urticaria on ID test (OPT not performed)
P7	Ibuprofen (NSAID/analgesic)	M / 3	Yes / Atopic dermatitis	Urticaria at hour 2	OPT	Anaphylaxis at step 1 of OPT
P8	Amoxicillin-clavulanate (beta-lactam)	M / 5	No / —	Maculopapular exanthem at hour 2	Sp IgE / Skin / OPT	MPE at min 20 of OPT
P9	Penicillin (beta-lactam)	F / 17	Yes / Allergic rhinitis	Syncope at min 15	Sp IgE / Skin	Prick test positive (OPT not performed)
P10	Amoxicillin-clavulanate (beta-lactam)	F / 11	Yes / Allergic rhinitis, food allergy	Angioedema at hour 3	Sp IgE	Sp IgE positive (OPT not performed)
P11	Paracetamol + Penicillin (NSAID/ analgesic + beta-lactam)	M / 13	No / —	Urticaria at hour 5 / urticaria on day 1	Sp IgE / Skin / OPT	MPE at min 15 of OPT with paracetamol; urticaria at step 2 of OPT with penicillin
P12	Amoxicillin-clavulanate (beta-lactam)	F / 17	No / Allergic rhinitis, asthma	Angioedema at hour 4	Sp IgE	Sp IgE positive (OPT not performed)
P13	Ampicillin-sulbactam (beta-lactam)	M / 4	Yes / Atopic dermatitis, food allergy	Urticaria at hour 1	Sp IgE / Skin	Positivity on ID test (OPT not performed)
P14	Paracetamol (NSAID/analgesic)	M / 4	Yes / —	Urticaria at min 30	OPT	Urticaria at first dose of OPT
P15	Cefixime (beta-lactam)	F / 6	No / —	Urticaria at hour 2	OPT	Urticaria at min 30 of OPT
P16	Azithromycin (macrolide)	M / 7	Yes / —	Urticaria at hour 1	OPT	Urticaria at min 45 of OPT

***Sp IgE:** drug-specific IgE,* ***OPT:** oral provocation test,* ***ID:** intradermal,* ***MPE:** maculopapular exanthem/rash,* ***M:** male,* ***F:** female. In patient P11, two different drug allergies were confirmed in the same patient*

EAACI classification of hypersensitivity to NSAIDs (19). Because 8 patients had a history of allergy to more than one drug, the drug-group percentages given above were calculated over the total number of drug records (n=94). In 75 patients (87.2%), the reaction had developed within the first 6 hours; the most frequently affected system was the skin (90.7%, n=78), with respiratory involvement in 3 patients, gastrointestinal in 2, cardiovascular in 2, and anaphylaxis in 2 (because more than

Table III: Distribution of culprit drug groups in patients with confirmed drug allergy

Drug group	n (%)
Beta-lactam (alone)	11 (68.8)
NSAID/analgesic (alone)	2 (12.5)
Beta-lactam + NSAID/analgesic (P11)	1 (6.3)
Antiepileptic	1 (6.3)
Macrolide	1 (6.3)
Total	16 (100)

In patient P11, both beta-lactam and NSAID/analgesic allergy were confirmed, so this patient is included in two groups; therefore, the patient-based total is 16 while the number of confirmed allergens/drugs is 17. All beta-lactam-involving cases: 12/16 (75.0%).

one system was affected in some patients, the sum of system counts exceeds the number of patients).

Rate of true drug allergy

As a result of the stepwise diagnostic evaluation, true drug allergy was confirmed in only 16 of the 86 patients (18.6%); the incorrect drug-allergy label was safely removed in the remaining 70 patients (81.4%). A total of 203 diagnostic tests were performed: 56 specific IgE tests, 59 skin tests (prick and intradermal), and 88 drug provocation tests (DPTs), of which 74 were oral (OPT), 3 subcutaneous, and 11 graded intravenous. By diagnostic method, 3 patients were diagnosed by positive specific IgE (beta-lactam allergy; P4, P10, P12), 3 patients by positive skin test (beta-lactam allergy; P6, P9, P13), and 10 patients by positive oral provocation (beta-lactam alone in 5, NSAID/analgesic alone in 2, antiepileptic in 1, macrolide in 1, and both beta-lactam and NSAID/analgesic in 1 [P11]). For culprit drugs without a validated in vitro or skin test (NSAIDs/analgesics, non-beta-lactam antibiotics, and antiepileptics) or in the case of a low-risk reaction, 52 of the 88 provocations were performed directly, without prior specific IgE or skin testing (25 NSAID/analgesic, 16 non-beta-lactam antibiotic, 2 antiepileptic, and 9 low-risk beta-lactam). Thus, only a minority of the diagnostic work-up served to establish a true allergy, whereas the large majority served to safely exclude it and remove the incorrect label.

In patients evaluated for a suspected non-immediate reaction who had a negative in-hospital oral provocation, the culprit drug was continued at home for 5 days; no additional delayed reactions were reported during this period.

Characteristics of the 16 patients with confirmed allergy

The mean age of the 16 patients with confirmed true drug allergy was 10.2±5.0 years (median: 11.0; range: 3-17 years). The distribution by age group was: ≤5 years, 4 patients (25.0%); 6-11 years, 5 patients (31.2%); and 12-18 years, 7 patients (43.8%). A parental history of atopy was present in 9 patients (56.2%) and a personal atopic disease in 8 patients (50.0%). When reaction severity was assessed, anaphylaxis was observed in 2 patients (12.5%), a severe reaction in 1 (6.3%), a moderate reaction in 8 (50.0%), and a mild reaction in 5 (31.2%) (Table II).

Distribution of culprit drug groups

The distribution of culprit drug groups among the 16 patients with confirmed allergy is presented in Table III. Beta-lactams accounted for the majority of confirmed allergies (Table III).

Comparison of groups with and without drug allergy

When the groups with confirmed (n=16) and excluded (n=70) drug allergy were compared, a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were significantly higher in the true drug allergy group (p=0.004, p=0.028, and p=0.006, respectively). The corresponding unadjusted ORs were 5.64 (95% CI 1.77-17.93) for a parental history of atopy, 4.85 (95% CI 1.26-18.67) for a parental history of drug allergy, and 5.36 (95% CI 1.66-17.32) for personal atopy; the width of these intervals reflects the small number of patients with confirmed allergy. No significant difference was found with respect to age, sex, asthma, allergic rhinitis, atopic dermatitis, food allergy, absolute eosinophil count, eosinophil percentage, or total IgE level (Table I).

Discussion

Our study demonstrated that the great majority (81.4%) of children evaluated for suspected drug allergy did not in fact have a drug allergy. This rate is consistent with the global literature; although approximately 10% of parents report suspected drug allergy in their children, confirmation rates of true allergy after comprehensive evaluation generally remain between 1% and 20% (12,13,20). Indeed, the prevalence of confirmed drug allergy in the general pediatric population has been shown to be approximately 0.05%, and only a small proportion of reported drug reactions can be confirmed by comprehensive testing (21,22).

One of the most original findings of our study is that a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were significantly higher in the true-allergy group.These findings suggest that these three parameters may be associated with true drug allergy. However, these odds ratios are unadjusted; because the three characteristics are clinically inter-related and only 16 patients had confirmed allergy, we could not determine whether any of them is an independent predictor. Given the limited sample size (n=16), the wide confidence intervals, and the large number of comparisons, these associations are hypothesis-generating and require confirmation in larger, prospectively designed studies. Nevertheless, the absence of a significant difference between the two groups in terms of age, sex, laboratory values, and other clinical parameters suggests that drug-allergy decisions based solely on history and laboratory parameters may be insufficient, and supports the importance of the stepwise diagnostic algorithm and especially OPT (9-11).

Beta-lactams stood out as the most frequent cause of true allergies; calculated per patient, beta-lactam allergy was confirmed in 12/16 (75.0%) cases (21,203). This finding is consistent with the international literature showing that the majority of drug allergies reported in children are attributed to beta-lactams (12,24). Nevertheless, it is known that up to 90% of beta-lactam allergy labels are incorrect; this arises particularly from the frequent interpretation of maculopapular rashes accompanying infection in children as beta-lactam allergy (11,24). In patient P11, the simultaneous confirmation of both penicillin and paracetamol allergy demonstrates that

each suspected drug must be evaluated separately in cases of multiple-agent sensitization (10).

In the diagnostic process, OPT played a key role both in confirming and in safely excluding drug allergy; in 10 of the patients with confirmed true allergy, the diagnosis could be established only by OPT. Current literature showing that direct OPT can be safely applied in children with mild symptoms and negative skin test results supports our approach (14). Because no validated skin test or specific IgE was available for azithromycin, diagnostic evaluation was performed directly by OPT and the reaction was confirmed; this once again demonstrates the importance of developing a separate diagnostic protocol for each agent (10). In the NSAID group, ibuprofen and paracetamol allergies could be proven only by OPT; the diagnostic value of specific IgE and skin tests for these drugs is quite limited, and OPT remains the primary approach (22,23).

Anaphylaxis occurred in two of the 74 OPTs performed in our study (2.7% per test), underscoring that these tests must be conducted only by an experienced team with full resuscitation facilities available (9,10). Because of the small denominator and the inclusion of different drug classes and risk profiles, this center-specific rate should be interpreted with caution and not directly compared with cohorts limited to low-risk beta-lactam challenges. Both anaphylaxis episodes were promptly recognized and successfully treated in a center equipped for resuscitation, and the patients were safely discharged; this supports the view that, when performed under appropriate patient selection and safe conditions, OPT is a reliable diagnostic method. Removing an incorrect drug-allergy label not only enhances individual patient safety but also, by enabling the use of first-line antibiotics, both reduces antimicrobial resistance and contributes to health economics (6-8).

Limitations

This study should be interpreted in light of the following limitations:

- Retrospective cross-sectional design: Data were obtained retrospectively from patient records, which entails the possibility that some clinical information was recorded in a non-standardized or incomplete manner and does not permit causal inference.
- Single center: The study is based on data from a single center. Because our hospital is a regional referral center, more severe and complex cases may have presented preferentially, which may have made the proportion of patients with confirmed allergy appear relatively high compared with the general population.
- Sample size: Because the study had a retrospective cross-sectional design, a prospective power analysis could not be performed before data collection. Nonetheless, the sample of 86 patients is comparable to the sample sizes reported in international single-center studies on this subject (30–120 patients) (12,13,20,25). The relatively limited number of patients with confirmed true drug allergy (n=16) restricts the statistical power of subgroup analyses in particular, so these findings should be confirmed in larger, prospectively designed studies.
- Limited in vitro test infrastructure for non–beta-lactam drugs: The lack of validated specific-IgE and skin-test protocols for NSAIDs, macrolides, and antiepileptics made the diagnostic process for these drugs largely dependent on OPT, raising the possibility that some cases in which a skin test could theoretically have been positive were missed.
- Absence of long-term follow-up data: Long-term follow-up data on whether delabeled patients subsequently tolerated the relevant drugs are not available.
- Exclusion of patients for whom an alternative drug was available: In 13 patients, provocation testing was not performed because a reliable and effective alternative agent was available and the culprit drug was not immediately required; considering the small but real risk of provocation, these patients were not challenged and were therefore not delabeled. This represents a pragmatic, risk-based clinical decision intended to avoid unnecessary provocation in children who did not need the specific drug. We nevertheless acknowledge that the availability of an alternative is not, in itself, a sufficient reason to forgo provocation, since confirming or excluding a suspected allergy has value independent of current treatment options and the label may persist throughout life. As these patients were not part of the analyzed cohort and retained an unverified drug-allergy label, we recognize this as a limitation: it may introduce a degree of selection bias and limits the generalizability and completeness of delabeling, although it does not alter the calculations performed within the analyzed cohort of 86 patients.

Multicenter, prospective studies with larger samples are needed to address these limitations.

Conclusion

In the great majority (81.4%) of pediatric patients presenting with suspected drug allergy, true drug allergy can be excluded through comprehensive diagnostic evaluation. History, clinical findings, and basic laboratory parameters alone were insufficient to predict the patient with true allergy; in contrast, a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were higher in the true-allergy group, although prospective studies are needed to confirm these associations. For confirming or safely excluding true drug allergy, OPT—under appropriate patient selection and safe conditions—is the principal diagnostic method and gold standard, while specific IgE and skin tests support a stepwise evaluation for selected drugs. Structured evaluation and, when clinically appropriate, referral of children with suspected drug allergy to a pediatric allergist will benefit both individual patient safety and antimicrobial stewardship at the societal level (4,5,26).

Presented

Preliminary results of this study, based on a smaller sample, were presented as an oral presentation at the 59th Turkish Pediatric Congress (Türk Pediatri Kongresi, TPK), held on 22–26 May 2024 in the Turkish Republic of Northern Cyprus.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Harran University (27.01.2025, reference number: HRÜ/25.02.43).

Contribution of the authors

Study conception and design: MŞK; data collection: MŞK, APS; analysis and interpretation of results: MŞK, APS; draft manuscript preparation: MŞK, APS. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

Generative AI Statement

During the preparation of this manuscript, the authors used a generative AI-assisted tool (ChatGPT, OpenAI) in August 2026 for English-language checking, the correction of spelling and typographical errors, formatting, and preparation of the flow diagram (Figure 1). No AI-assisted tool was used for data collection, statistical analysis, interpretation of results, or the generation of original scientific content. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Original Article

Enhancing diagnostic accuracy in acute scrotum in the pediatric emergency department: A combined diagnostic model integrating the TWIST score and systemic inflammatory markers

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ABSTRACT

Objective: Timely and accurate differentiation of testicular torsion (TT) from epididymo-orchitis (EO) in pediatric patients presenting with acute scrotum is crucial to prevent testicular loss. The Testicular Workup for Ischemia and Suspected Torsion (TWIST) score is widely used, but lacks laboratory markers. We aimed to evaluate whether combining systemic inflammatory markers with the TWIST score improves diagnostic accuracy.

Materials and Methods: We retrospectively evaluated 99 pediatric patients diagnosed with TT (n=50) or EO (n=49). Clinical findings, TWIST scores, and inflammatory markers (NLR, SII, PLR) were recorded. Receiver operating characteristic (ROC) analysis was used to assess diagnostic performance. Multivariable logistic regression was performed to build a combined diagnostic model using TWIST score and the single most predictive inflammatory marker (NLR) to avoid potential collinearity between collinear biomarkers.

Results: A total of 99 pediatric patients were included in the study; TT was diagnosed in 50 (50.5%) and EO in 49 (49.5%) of them. Patients with TT had significantly higher TWIST scores, NLR, and SII values compared to those with EO. While individual ROC analyses demonstrated high discriminatory performance for both NLR (AUC: 0.871) and SII (AUC: 0.866), the model combining the TWIST score and NLR yielded a higher AUC (0.915) than the TWIST score alone (AUC: 0.795), suggesting improved diagnostic discrimination.

Conclusion: Integrating NLR with the clinical TWIST score may enhance diagnostic accuracy in pediatric acute scrotum, providing a simple and robust clinical decision-support tool to guide early surgical decision-making.

Keywords: Epididymitis, inflammation, spermatic cord torsion, testicular torsion, TWIST score

Introduction

Acute scrotum is usually characterized by sudden onset of scrotal redness, swelling, and pain associated with inflammatory processes (1,2). The main causes of acute scrotum include torsion of the testis and its appendages, epididymitis and orchitis, incarcerated inguinal hernia, hydrocele, trauma, testicular laceration, scrotal edema, acute varicocele, testicular tumor, Henoch-Schönlein purpura, and scrotal abscess (3). Epididymo-orchitis (EO) is inflammation of the epididymis and testicles and is the most common cause of acute scrotum in prepubertal boys and is usually treated conservatively (4). Testicular torsion (TT) occurs as a result of the spermatic cord twisting around itself and requires urgent surgical intervention. Among the two most common etiologies, delay in TT diagnosis can lead to permanent testicular damage and infertility (2,5-7).

In the literature, the Testicular Workup for Ischemia and Suspected Torsion (TWIST) scoring system has been shown to be useful in the diagnosis of testicular torsion (8). Although the TWIST score helps to practically estimate TT risk at the bedside, it has some limitations, especially in cases of intermittent torsion. The most commonly used method for diagnosing testicular torsion is Color Doppler Ultrasonography (CDUS). However, in some cases of testicular torsion, it has been shown that testicular blood flow continues (9). Additionally, among the disadvantages of CDUS are that it is not always accessible and that it depends on the radiologist's experience (10).

In recent years, studies have been conducted on systemic inflammatory markers such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) that evaluate laboratory tests in the diagnosis of TT (11). However, these parameters

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have not yet been integrated into a validated clinical scoring system.

The aim of this study was to evaluate a combined diagnostic model integrating clinical TWIST Score with systemic inflammatory markers for the differential diagnosis of TT and EO in the pediatric emergency department, and to develop a new clinical decision support tool that could increase diagnostic accuracy in early diagnosis.

Materials and Methods

Study design and setting

In this retrospective observational study, the medical records of patients aged 0-18 years who presented to the pediatric emergency department of Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital, a tertiary pediatric referral center in Ankara, with acute scrotal pain between July 1, 2017, and July 31, 2022, were reviewed.

Patient selection

The definitive diagnosis of TT was confirmed through surgical exploration by a pediatric surgeon, whereas the diagnosis of EO was established by pediatric emergency and pediatric surgery specialists based on clinical and CDUS findings. Trauma history, previous scrotal surgery, and other causes of acute scrotum were exclusion criteria. A total of 99 patients meeting the inclusion criteria were analyzed: 50 were diagnosed with TT and 49 with EO. The flow chart of patient selection and exclusion criteria is shown in Figure 1.

Clinical and laboratory data collection

From medical records; patients' age, the time between symptom onset and hospital presentation, and physical examination findings at presentation were recorded. The TWIST Score was calculated for each patient using the scale: testicular swelling (2 points), firm testicle (2 points), absence of cremasteric reflex (1 point), nausea or vomiting (1 point), and high-riding testis (1 point). Patients with a score of ≥5 were categorised as high risk for testicular torsion.

The white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count (PLT), NLR, PLR, and SII were recorded at presentation. SII was calculated using the formula: platelets × neutrophil/lymphocyte count.

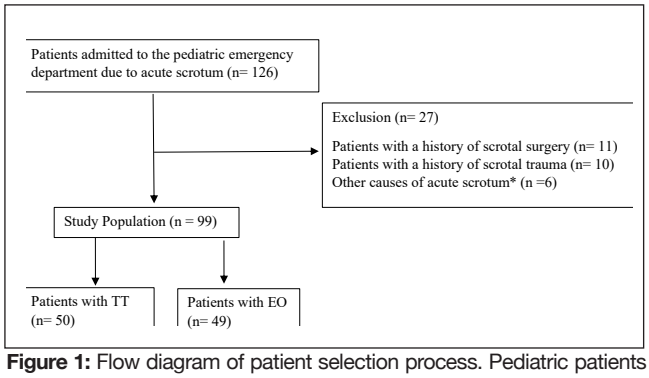


Figure 1: Flow diagram of patient selection process. Pediatric patients presenting with acute scrotal pain were evaluated between July 2017 and July 2022. A total of 99 patients (50 testicular torsion, 49 epididymo-orchitis) were included in the final analysis. ***:** Hydrocele, Inguinal Hernia, Henoch-Schönlein Purpura, Varicocele, **TT:** Testicular Torsion, **EO:** Epididymo-orchitis

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The distribution of variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as medians and interquartile ranges (IQRs) due to non-normal distribution, and categorical variables were summarized as counts and percentages (n, %). Categorical variables were analyzed using the chi-square or Fisher's exact test, while continuous variables were compared using the Mann–Whitney U or independent t-test, depending on data distribution. ROC analysis was used to evaluate the diagnostic value of TWIST Score, NLR, PLR, and SII, and to calculate the area under the curve (AUC) for each parameter. The optimal cut off values were determined using the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the TWIST Score, individual biomarkers and the combined model. Multivariable logistic regression analysis was performed to identify independent predictors of TT and to generate predicted probabilities for the combined model (TWIST + NLR). A p-value of less than 0.050 was considered statistically significant.

Results

A total of 99 pediatric patients were included in the study; TT was diagnosed in 50 (50.5%) and EO in 49 (49.5%) of them. The median age of patients was 144 (IQR: 111–177) months, and the median age of patients in the TT group was significantly higher than that in the EO group [162.5 months (IQR: 138–183) vs. 124.0 months (IQR: 85–150), p<0.001]. The symptom duration was significantly shorter in TT patients [6 hours (IQR: 3–8)] compared to EO patients [24

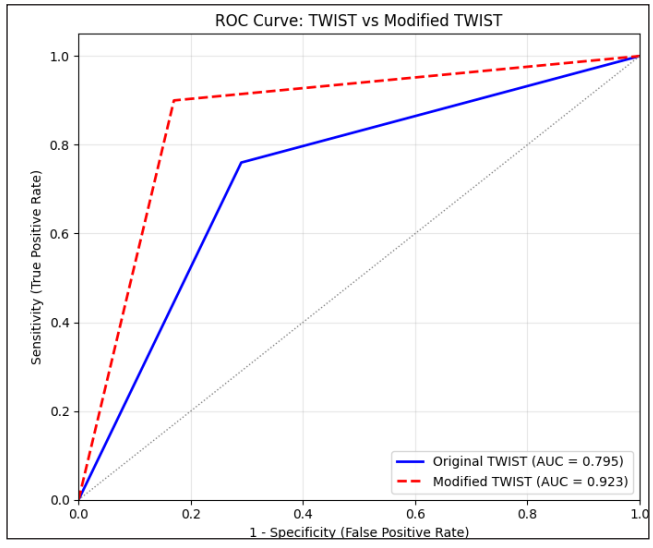


Figure 2: ROC curves illustrating and comparing the diagnostic accuracy of the original clinical TWIST score (AUC: 0.795) and the Combined Diagnostic Model integrating TWIST score with NLR (AUC: 0.915).

Table I: Demographicand clinical characteristics of the patients

	Total	Testicular Torsion	Epididymo orchitis	p
Total number of patients	99	50	49	-
Age,month*	144 (111-177)	162.5 (138-183)	124 (85-150)	<0.001
Side†				
Right	52 (52.5)	24 (48)	28 (57.1)	0.353
Left	46 (46.4)	26 (52)	20 (40.8)	
Bilateral	1 (1.01)	-	1 (2.04)	
TWIST Score*	-	4.0 (2.0-5.0)	2.0 (2.0–3.25)	<0.001
TWIST Category†				
Low Risk	40 (40.4)	3 (6)	37 (75.5)	<0.001
Middle Risk	32 (32.3)	22 (44)	10 (20.4)	
High Risk	27 (27.2)	25 (50)	2 (4.9)	
Scrotal Swelling†	77 (77.7)	42 (86)	35 (71.4)	0.103
Hard Testis†	4 (4.04)	2 (4)	2 (4.08)	0.684
Absence of cremasteric reflex†	55 (55.5)	43 (86)	12 (24.4)	<0.001
High riding testis†	34 (34.3)	32 (64)	2 (4.08)	<0.001
Nausea / vomiting†	32 (32.3)	29 (58)	3 (6.1)	<0.001
Abdominal pain†	12 (12.1)	11 (22)	1 (2.04)	0.002
Groin pain†	98 (98.9)	49 (98)	49 (100)	0.505
Scrotal Tenderness†	97 (97.9)	49 (98)	48 (97.9)	0.747
Scrotal redness†	57 (57.5)	23 (46)	34 (69.3)	0.015
Symptom duration, hour*	8 (6- 24)	6 (3-8)	24 (12-48)	<0.001

**: median (IQR) (Mann–Whitney U), †: n(%) (chi-square or Fisher's exact test)*

hours (IQR: 12–48)] (p<0.001). Of the 50 patients diagnosed with TT, seven had a symptom duration of 12 hours or longer, and necrotic areas were detected in four of these patients (57.1%) during surgery. In 43 TT patients (86%), the symptom duration was less than 12 hours, and necrotic areas were detected in three of them (6.9%). High-riding testis (p<0.001), absence of cremasteric reflex (p<0.001), and nausea or vomiting (p<0.001) were significantly more common in the TT group. Additionally, abdominal pain was also reported more frequently in the TT group (p=0.020). The edian TWIST Score was significantly higher in TT patients [(4.0 (IQR: 2.0–5.0)] compared to EO patients [2.0 (IQR: 2.0–3.25)] (p<0.001). The demographic and clinical characteristics of patients diagnosed with TT and EO are presented in Table I.

CDUS was performed on all patients. According to the results, TT diagnosis was initially made in 51 patients using CDUS, but EO diagnosis was confirmed in three of these patients (5.9%) as a result of surgical exploration. In contrast, normal perfusion was observed on CDUS in two patients (4.0%) who ultimately received a TT diagnosis.

When the laboratory data of patients at the time of presentation were evaluated, the median WBC (p<0.001), ANC (p<0.001), NLR (p<0.001), PLR (p=0.002), and SII (p<0.001) values were found to be significantly higher in TT patients. The laboratory data of the patients are presented in Table II.

Table II: Laboratory parameters and diagnostic performance of TWIST, inflammatory markers and combined model in diagnosing testicular torsion

Laboratory Parameter	TT Group*	EO Group*	p
WBC (×10³/µL)	12.3 (10.6–14.8)	9.2 (7.8–10.9)	<0.001
ANC (×10³/µL)	8.4 (6.7–10.2)	5.6 (4.2–7.0)	<0.001
NLR	4.2 (3.1–5.8)	2.1 (1.5–3.0)	<0.001
PLR	152 (132–179)	110 (91–127)	0.002
SII	1120 (905–1410)	650 (478–815)	<0.001

**: median (IQR) (Mann–Whitney U)*

ROC analysis demonstrated that NLR and SII have high diagnostic performance in identifying TT. The AUC for NLR was 0.871 (95% CI: 0.79–0.93), and the optimal cut off value was determined to be 3.16; at this value, sensitivity was 84.0% and specificity was 77.6%. The AUC for SII was 0.866 (95% CI: 0.79–0.92), with a cutoff value of 921; sensitivity was determined to be 78.0% and specificity 81.6%. PLR showed moderate performance (AUC: 0.726). In multivariable logistic regression analysis, TWIST ≥5 (OR =7.3, 95% CI: 3.1–17.4, p<0.001) and NLR >3.16 (OR=5.8, 95% CI: 1.9–11.6, p=0.002) were identified as independent predictors for TT (Table III). To avoid statistical collinearity while capturing both clinical and inflammatory risk factors, a combined diagnostic model integrating the TWIST score with NLR was evaluated. According to ROC analysis, the AUC value of the combined model (TWIST+NLR) was 0.915, demonstrating superior diagnostic performance compared to the original TWIST Score alone (AUC:0.795, sensitivity 76.0%, specificity 71.0%). Comparative ROC curves are presented in Figure 2, while detailed laboratory values and diagnostic measurements are presented in Table II-III.

Discussion

In this study, we evaluated pediatric patients presenting to the emergency department with acute scrotal pain to determine the diagnostic utility of combining clinical risk stratification with systemic inflammatory biomarkers. Differentiating testicular torsion from epididymo-orchitis remains a high-stakes clinical challenge where rapid diagnosis directly dictates organ salvage. Our findings indicate that integrating peripheral inflammatory markers—specifically the neutrophil-to-lymphocyte ratio—with the TWIST score substantially improves diagnostic performance.

Testicular torsion and EO are among the most common causes of acute scrotum, and confirming the diagnosis is important for rapid treatment planning (12). While the main treatment option for TT is surgical intervention, conservative treatments are preferred for EO (13). When torsion develops, testicular venous drainage is affected first, followed by edema, hemorrhage, and finally a decrease in arterial blood flow (14). If blood flow decreases, the testicle begins to be affected within 4–6 hours and necrosis occurs (15). The testis preservation rate is nearly 100% in cases operated on within the first 6 hours, while this rate drops to 20% in cases treated after 12 hours (16,17). In our study, consistent with

Table III: ROC analysis for diagnostic accuracy and multivariable logistic regression for independent predictors of testicular torsion

Variable	AUC	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds Ratio (95% CI)	p
TWIST Score	0.795	≥5	76.0	71.0	78.5	69.2	7.3 (3.1–17.4)	<0.001
NLR	0.871	>3.16	84.0	77.6	80.7	81.2	5.8 (1.9–11.6)	0.002

ROC: *Receiver Operating Characteristic,* ***AUC:*** *Area Under the Curve,* ***PPV:*** *Positive Predictive Value,* ***NPV:*** *Negative Predictive Value.*

the literature, necrotic areas were detected in four (57.1%) of seven TT patients with a symptom duration of 12 hours or longer. No necrosis was observed in three (6.9%) of the 43 TT patients with a symptom duration of less than 12 hours. Therefore, early diagnosis and prompt treatment in patients suspected of having TT are crucial in preventing the development of necrosis. Clinical findings are highly valuable in the diagnosis of TT in children presenting with scrotal pain. The TWIST score is the most commonly used scoring system for diagnosing TT (12,18). In a study evaluating 96 pediatric patients presenting with acute scrotal complaints, the mean TWIST score was 5.7±1.2 in the TT group and 1.46±0.67 in the non-torsion group (19). In our study, the median TWIST score was 4.0 (2.0–5.0) in TT patients and 2.0 (2.0–3.25) in EO patients. The absence of the cremasteric reflex, a component of the TWIST scoring system, is an important finding in favor of TT (20). In our study, 86% of TT patients had no cremasteric reflex, while this rate was 24.4% in EO patients. Other components of the TWIST scoring system, such as high-riding testis and nausea/vomiting, were also more common in TT patients. The TWIST score may be guiding in the differentiation between TT and EO in patients presenting with acute scrotal pain.

In the diagnosis of acute scrotum, CDUS can be used to evaluate testicular perfusion, testis size, and echogenicity. Absence of arterial perfusion may indicate TT or early-stage partial/intermittent torsion, but continued perfusion does not rule out TT. In the early stages of TT, CDUS may cause false negative results in intermittent or incomplete torsion (21). In this study, two patients with CDUS results favorable for EO were diagnosed with TT during surgery. Additionally, three patients suspected of having TT based on CDUS were diagnosed with EO after surgery. These findings highlight the drawbacks of relying solely on ultrasound findings, particularly in cases of intermittent or partial torsion or when the operator's experience is limited.

Systemic inflammation plays a prominent role in the ischemic cascade following spermatic cord torsion (22). Torsional ischemia triggers an acute systemic stress response characterized by rapid neutrophil activation and relative lymphopenia. In previous studies, when patients diagnosed with acute scrotum were compared with healthy control groups, WBC, ANC, AMC, PLR, and NLR levels were found to be higher in TT patients (23,24). It has been reported that NLR levels show a positive correlation with symptom duration and represent a critical factor affecting testicular salvage within the first 12 hours (25). Zhu et al. (26) mphasized that WBC, PLT, and NLR may be decisive in distinguishing TT from EO. It is well established that ischemia and reperfusion injury are the fundamental mechanisms in TT (27). During this process, ALC decreases while ANC increases in peripheral blood in response to systemic inflammation (28). In our study, WBC, ANC, NLR, PLR, and SII were likewise significantly elevated in TT patients. While hematologic parameters demonstrated diagnostic capacity in our cohort, incorporating the NLR alongside the TWIST score into a combined multivariable predictive model achieved superior diagnostic accuracy compared to the TWIST score alone. This combined approach may offer significant practical benefits in emergency settings. Integrating laboratory-derived inflammatory indicators with clinical examination scores may enable clinicians to make safer, faster surgical decisions, particularly in resource-limited or high-volume pediatric emergency departments.

Limitations

This study has limitations, including its retrospective single-center design and relatively small sample size. Additionally, systemic inflammatory markers can be influenced by concurrent systemic conditions or infections. Prospective, multicenter studies with larger pediatric cohorts are warranted to validate these clinical decision models.

Conclusion

In conclusion, combining the clinical TWIST score with the neutrophil-to-lymphocyte ratio may enhance diagnostic performance for distinguishing testicular torsion from epididymo-orchitis in pediatric emergency practice. This integrated strategy may provide a reliable, accessible decision-support mechanism when ultrasound is unavailable or equivocal.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital (21.09.2022, reference number: E-22/09-434).

Contribution of the authors

Study concept and design: BA, AG, İB, OA, NT. Analysis and interpretation of data: BA, OA, BÖ, RMY, Cİ. Drafting of the manuscript: BA, AG, HGÇ, İFÖ, MMG. Critical revision of the manuscript for important intellectual content: BA, AG, NT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Improving time to antibiotic administration in febrile neutropenia: A quality improvement initiative in a pediatric oncology inpatient unit

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ABSTRACT

Objective: Febrile neutropenia (FN) is a medical emergency requiring prompt initiation of empirical antibiotic therapy. We aimed to evaluate the impact of a structured, unit-based quality improvement intervention on time to antibiotic administration (TTA) in hospitalized pediatric oncology patients.

Materials and Methods: This single-center quality improvement study was conducted in a pediatric oncology inpatient unit. The intervention consisted of a structured educational program targeting healthcare professionals, including physicians and nurses. FN episodes were analyzed across pre-intervention, intervention, and post-intervention phases, and TTA was compared between these periods.

Results: A total of 73 FN episodes in 40 patients were included. Median TTA decreased from 38 minutes in the pre-intervention phase to 32 minutes during the intervention phase and to 18 minutes in the post-intervention phase ($p<0.001$). The proportion of patients receiving antibiotics within 60 minutes increased from 77% to 100% ($p=0.010$).

Conclusion: A structured, unit-based quality improvement intervention significantly reduced TTA in hospitalized pediatric oncology patients. These findings highlight the importance of system-level strategies in improving time-sensitive clinical processes in high-risk patient populations.

Keywords: Antibiotic, febrile neutropenia, quality improvement, oncology

Introduction

Febrile neutropenia (FN) is a life-threatening complication of cancer treatment requiring prompt medical intervention. It is defined as a single oral temperature ≥38.3°C or a sustained temperature ≥38.0°C for at least one hour in patients with an absolute neutrophil count (ANC) <500/mm³ or expected to decrease below this threshold within 48 hours (1).

FN remains a common clinical problem in pediatric oncology, occurring in up to 30–50% of patients undergoing chemotherapy, and is associated with significant morbidity and risk of bloodstream infections (2,3). Early initiation of empirical broad-spectrum antibiotics is the cornerstone of FN management. Current international guidelines strongly recommend administration of the first antibiotic dose within the first hour of fever detection (4-6). Despite these recommendations, delays in antibiotic delivery remain frequent in real-world clinical practice and are often related to workflow inefficiencies and communication gaps within healthcare teams.

The concept of quality improvement (QI) in oncology is based on identifying existing problems and implementing appropriate strategies to enhance patient outcomes and safety. The ASCO Quality Oncology Practice Initiative (QOPI) program aims to promote such QI efforts across outpatient oncology practices. The effectiveness of QI initiatives depends on addressing clinical, logistical, and administrative gaps. Ultimately, the goal of these interventions is to achieve sustainable improvement through collaboration, networking, and shared learning (7). Quality improvement interventions have emerged as effective strategies to optimize time-sensitive clinical processes in pediatric oncology settings. These interventions typically focus on system-level modifications, team training, and standardization of care

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pathways to improve adherence to evidence-based practices. Several studies conducted in emergency departments have demonstrated that structured QI initiatives can significantly reduce time to antibiotic administration (TTA) and improve compliance with the one-hour target (8,9). However, data regarding inpatient settings, where workflow dynamics and team structures differ, remain limited.

In this study, we implemented a structured, team-based educational intervention as part of a unit-based quality improvement initiative in a pediatric oncology inpatient unit. The primary aim was to evaluate its impact on time to antibiotic administration (TTA) in febrile neutropenia episodes and to increase the proportion of patients receiving antibiotics within one hour of fever detection.

Materials and Methods

Study design and setting

This study was designed as a single-center, unit-based quality improvement (QI) initiative conducted in the Pediatric Hematology and Oncology inpatient unit of Istanbul University, between January 2023 and September 2023. The study was structured in accordance with the Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines (10).

Participants and study population

The study included pediatric oncology patients hospitalized for chemotherapy during the study period. A total of 40 patients were included, and 73 FN episodes were evaluated.

Intervention process

The intervention consisted of a structured, team-based educational program targeting healthcare professionals working in the inpatient unit, including residents, fellows, and clinical nurses.

The study was conducted in three sequential phases

Pre-intervention phase (3 months): FN episodes were recorded retrospectively based on routine clinical practice without additional training. No aspect of standard care was altered during this phase. During this phase, standard clinical practice was followed without any intervention, encompassing fever detection, staff notification, clinical assessment, antibiotic selection and prescription, and subsequent administration. Communication among healthcare staff and all steps involved in antibiotic administration were observed.

Intervention phase (3 months): A structured FN education program was implemented. Training sessions were delivered by a pediatric hematology and oncology specialist using standardized presentations. Each session lasted approximately one hour and was conducted weekly to ensure coverage of staff working in different shifts. Participants attended these sessions multiple times during the intervention period.

The training content included:

- recognition of febrile neutropenia
- risk assessment
- key components of physical examination
- selection and ordering of empirical antibiotics
- logistics of antibiotic delivery from the hospital pharmacy
- obtaining blood and other cultures prior to antibiotic administration
- confirmation of antibiotic administration
- communication and handover between shifts

Post-intervention phase (3 months): FN episodes were prospectively recorded following completion of the educational intervention.

Due to shift-based working conditions, not all team members were exposed to the intervention simultaneously. Repeated sessions were used to maximize coverage across the entire inpatient team.

Data collection and definitions

For each FN episode, the following data were recorded:

- time of fever onset
- time of temperature measurement
- time of notification of healthcare staff
- time of clinical assessment
- time of antibiotic prescription
- time of antibiotic administration
- total time to antibiotic administration (TTA)

Febrile neutropenia was defined as a temperature ≥38.3°C once or ≥38.0°C sustained for at least one hour, in the presence of neutropenia (absolute neutrophil count <500/mm^3 or expected decline within 48 hours). According to institutional protocols, empirical antibiotic therapy was initiated in all patients meeting FN criteria without waiting for culture results. The primary outcome of the study was TTA measured at the level of FN episodes. This study aimed to evaluate a unit-level clinical process indicator rather than individual healthcare worker performance.

Team performance was indirectly assessed through improvements in process-of-care indicators, particularly time to antibiotic administration (TTA), rather than through individual-level performance metrics.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, as appropriate, while categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using Student's t-test or one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. A two-sided p value < 0.05 was considered statistically significant. Because some patients contributed multiple FN episodes, comparisons across study phases were additionally performed using a linear mixed-effects model with a patient-level random intercept to account for within-patient clustering.

Results

A total of 73 febrile neutropenia (FN) episodes in 40 patients were included in the analysis. Of the patients, 17 (42.5%) were female. The distribution of underlying diagnoses was as follows: leukemia (n=15), neuroblastoma (n=6), lymphoma (n=5), brain tumor (n=4), hepatoblastoma (n=3), Ewing sarcoma (n=3), and

Table I: Clinical characteristics of participants

Characteristics	Study group
Total number of patients	40
Gender*	
Male	23 (57.5)
Female	17 (42.5)
Age†	7.2±5.3/6.0
Disease duration†	1.4±1.0/1.3
Age at diagnosis†	6.4±5.2/5.1
Disease Group*	
Leukemia	15 (37.5)
Neuroblastoma	6 (15)
Lymphoma	5 (12.5)
Brain tumor	4 (10)
Hepatoblastoma	3 (7.5)
Ewing Sarcoma	3 (7.5)
Others	4 (10)
Education status of parents*	
Primary/Secondary School	23 (57.5)
High School	7 (17.5)
University	10 (25)

**: n(%), †: mean±SD year/median*

Table II: Comparison of Time to antibiotic (TTA) dependent on quality improvement intervention

Values	Pre-Intervention	Post-Intervention	p
Total number of episodes	31	21	-
Time to antibiotic administration, min			
mean±SD**	47.3 ± 25.3	21.7 ± 9.4	<0.001*
95% CI of the mean	38.1–56.6	17.4–26.0	
median (IQR)	38 (32–52)	18 (16–23)	<0.001†
range	30–135	14–55	
antibiotic administered within 1 h, n (%)	24 (77.4)	21 (100.0)	0.033‡

**: Welch t test, †: Mann–Whitney U test, ‡: Fisher exact test, CI: confidence interval*

Table III: Effect estimates for the difference between the pre-intervention and post-intervention phases

Measure	Estimate (95% CI)	Test statistic	p
mean difference, min	–25.7 (–35.7 to –15.6)	t = 5.15, df = 41.0	<0.001
median difference, min*	–19.0 (–25.0 to –15.0)	U = 611	<0.001
relative reduction, %	–53.0 (–61.8 to –42.2)	-	-
Cohen d	–1.25 (–1.86 to –0.65)	-	-
rank-biserial correlation	–0.88	-	-

: Hodges–Lehmann estimator. Negative differences indicate shorter time to antibiotic administration. **CI: confidence interval, **df:** degrees of freedom.*

other malignancies (n=4). The mean age was 7.2±5.3 years (median, 6 years). The mean disease duration was 1.4±1.0 years (median, 1.3 years), and the mean age at diagnosis was 6.4±5.2 years (median, 5.1 years) (Table I).

Time to antibiotic administration

The mean time to antibiotic administration (TTA) was 47.3±25.2 minutes (median, 38.0 minutes) in the pre-intervention phase, 32.8±2.5 minutes (median, 32.0 minutes) during the intervention phase, and 21.6±9.4 minutes (median, 18.0 minutes) in the post-intervention phase. TTA decreased significantly from the pre-intervention phase to the post-intervention phase. (p<0.001) (Table II-III).

Table IV: Comparison of Time to Antibiotic (TTA) dependent on tumor type among all event

Characteristics	Leukemia	Lymphoma	Other Solid Tumors	p
Total number of episodes	24	13	36	-
Time to Antibiotic (TTA) min*	27.9±10.4 (30)	35.9±12.9 (37)	40.9±25.3 (32)	0.048

**: mean±SD (median)(One-way ANOVA), post hoc Tukey test showed significance between leukemia and other solid tumors (p=0.030).*

Table V: Comparison of Time to Antibiotic (TTA) within each tumor type group based on intervention

Characteristics	Pre-Intervention	Post-Intervention	p
Leukemia*	34.0±6.9 (30)	23.2±11.1 (20)	0.070
Lymphoma*	42.1±9.0 (40)	18.0±5.2 (16)	0.010
Other Solid Tm*	51.8±30.9 (38)	19.0±2.0 (18)	<0.001

**: mean±SD (median)(Student T Test)*

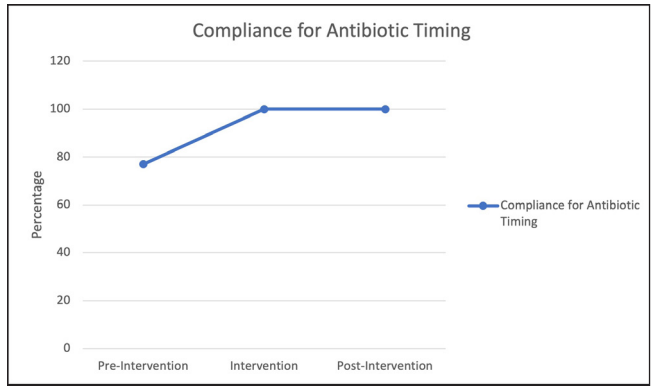


Figure 1: The change in the percentage of compliance for antibiotic timing (the percentage shows the rate of children receiving antibiotics in less than 60 minutes)

Percentage of patients receiving antibiotics within 60 minutes

The proportion of FN episodes in which antibiotics were administered within 60 minutes increased from 77% in the pre-intervention phase to 100% in post-intervention phase (p=0.010) (Figure 1).

Subgroup analysis by disease type

Across all FN episodes, the median TTA was 30 minutes among patients with leukemia, 32 minutes among patients with solid tumors, and 37 minutes among patients with lymphoma (Table IV). In disease-specific analyses, TTA decreased after the intervention across all diagnostic categories. This reduction did not reach statistical significance among patients with leukemia (p=0.070), but it

was significant among those with lymphoma (p=0.010) and solid tumors (p<0.001) (Table V).

Additional analyses

TTA did not differ significantly according to parental educational status (p=0.510). No FN-related mortality occurred during the study period. No patient contributed episodes to both the pre-intervention and the post-intervention phase, so the two groups are independent samples. Repeated episodes within each group nevertheless remain a source of clustering (52 episodes from 29 patients; intraclass correlation coefficient 0.77). A linear mixed model with a patient-level random intercept yielded a mean difference of –29.6 min (95% CI –45.8 to –13.5; p < 0.001), confirming the finding with a wider confidence interval.

Discussion

In this study, we demonstrated that a structured, unit-based educational intervention significantly reduced time to antibiotic administration (TTA) in hospitalized pediatric oncology patients with febrile neutropenia. The reduction in TTA was observed consistently across all study phases, with the most pronounced improvement in the post-intervention period.

Timely initiation of empirical antibiotic therapy remains a cornerstone of febrile neutropenia management. FN continues to be associated with substantial morbidity in pediatric oncology patients, with bloodstream infections representing the most common documented source of infection and reported mortality rates ranging from 0.4% to 3% (3,11,12). For this reason, international guidelines recommend administration of the first dose of antibiotics within one hour of fever detection (8).

Previous studies have shown that quality improvement interventions can effectively reduce TTA, particularly in emergency department settings. In one such study, implementation of a structured educational and process-based intervention reduced TTA from 64 minutes to 53 minutes and increased the percentage of patients receiving antibiotics within one hour from 59% to 84%, with further improvement after iterative cycles (13). Similarly, other studies have reported increased compliance with timely antibiotic administration following targeted interventions, with rates improving from 30% to 80% (14). In a comparable inpatient-focused intervention, the implementation of a structured protocol resulted in a reduction in mean TTA from 48 minutes to 39 minutes and achievement of full compliance within one hour (15).

Our findings are consistent with these studies and extend the existing literature by demonstrating that similar improvements can be achieved in inpatient settings. Unlike emergency departments, inpatient units involve different workflow dynamics, including shift-based care and multidisciplinary coordination. In this context, delays in antibiotic administration are often related to system-level factors such as communication gaps, unclear task allocation, and logistical barriers.

In the present study, the intervention primarily targeted these system-level processes. The observed improvement in TTA suggests that delays were largely attributable to workflow inefficiencies rather than clinical decision-making. Reinforcing team communication, clarifying responsibilities, and standardizing critical steps in patient management appeared to play a key role in improving timely antibiotic delivery.

Recent studies have questioned the strict association between TTA and clinical outcomes. Some investigations have reported no significant difference in mortality, intensive care unit admission, or length of hospital stay between patients receiving antibiotics within or beyond 60 minutes (16-18). These findings suggest that TTA alone may not be a direct surrogate for clinical outcomes. However, TTA remains an important quality-of-care indicator, reflecting the efficiency and responsiveness of healthcare systems in managing time-critical conditions. However, TTA remains an important quality-of-care indicator, reflecting the efficiency and responsiveness of healthcare systems in managing time-critical conditions (19-20).

Limitations

This study has several limitations. First, it was conducted in a single center with a relatively small sample size and short study duration. Microbiological data, including blood culture results, were not systematically analyzed in this study and therefore were not included. Second, although the intervention targeted healthcare professionals, outcomes were measured at the level of FN episodes, and individual healthcare worker performance was not assessed.

Despite these limitations, this study highlights the effectiveness of structured, team-based educational interventions as part of a quality improvement strategy in reducing delays in antibiotic administration in pediatric oncology inpatient settings.

Conclusion

This study demonstrates that a structured, unit-based educational intervention can significantly reduce time to antibiotic administration in hospitalized pediatric oncology patients with febrile neutropenia. The findings suggest that delays in antibiotic delivery are largely related to modifiable system-level factors and can be improved through targeted quality improvement strategies.

While the impact of TTA on clinical outcomes remains a subject of ongoing investigation, optimizing time-sensitive care processes represents an important component of high-quality clinical practice. Further studies are needed to evaluate the effect of such interventions on patient-centered outcomes, including morbidity and healthcare utilization.

Main points

- Febrile neutropenia is a time-critical clinical condition requiring prompt antibiotic administration in pediatric oncology patients
- Quality improvement strategies targeting system-level processes can effectively reduce delays in antibiotic delivery
- In this study, a structured educational intervention significantly decreased time to antibiotic administration (TTA)
- The percentage of patients receiving antibiotics within 60 minutes increased from 77% to 100% following the intervention

Ethics committee approval
This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Istanbul University (06.01.2023, reference number: 2023/28).

Contribution of the authors
Study conception and design: YY, HGT; data collection: YY, CCE, EMAP, SS, GE, OK, PT, VK, GG ; analysis and interpretation of results: YY, HGT, DT; draft manuscript preparation: YY, HGT. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Original Article

Family relationships in the digital age: The impact of problematic screen use on parent–adolescent relationships

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ABSTRACT

Objective: Problematic screen use (PSU) in adolescence has been linked to impaired well-being, but its associations with parent–adolescent relationship quality remain insufficiently characterized. This study examined whether PSU levels were associated with positive relationship, negative relationship, and openness dimensions in mother– and father–adolescent relationships.

Materials and Methods: This cross-sectional study included 196 adolescents aged 11–18 years who presented to a pediatric outpatient clinic. Data were collected using a Sociodemographic Information Form, the Child–Adolescent Digital Addiction Scale, and the Parent–Adolescent Relationship Quality Scale. Group differences were evaluated using appropriate non-parametric statistical methods.

Results: The mean age of the participants was 14.29±2.21 years, and 59.7% were female. Positive relationship with mother scores differed significantly across PSU groups (p=0.029), with post hoc analysis indicating a difference primarily between healthy users and adolescents in the digital addiction group. Negative relationship with mother scores also differed significantly (p<0.001), with healthy users scoring lower than those in the excessive use and digital addiction groups. Paternal openness (p=0.007), positive relationship with father (p = 0.038), and negative relationship with father (p=0.012) also varied significantly across groups, whereas maternal openness showed a borderline association (p=0.055).

Conclusion: Higher PSU was associated with poorer parent–adolescent relationship quality, particularly in the domains of conflict and positive relational functioning. These findings suggest that assessment of adolescent PSU should incorporate family relational processes, especially trust-based communication and parent–adolescent conflict.

Keywords: Adolescents, family conflict, technology addiction, parent-child relations

Introduction

The widespread integration of digital technologies into adolescents' daily lives has become increasingly prominent. However, problematic screen use (PSU) cannot be reduced simply to the amount of time spent in front of screens. Emerging evidence suggests that PSU, rather than self-reported screen time alone, may be more closely linked to adolescent well-being, particularly when it is accompanied by functional impairment (1). Accordingly, recent research has shifted its focus from screen time per se to the broader construct of PSU, which encompasses maladaptive, compulsive, and functionally impairing patterns of engagement with digital activities such as social media, smartphone use, and gaming (1). In this context, the defining feature is not merely duration of use, but rather diminished control over screen-related behaviors and disruption in daily functioning associated with such use (1). PSU has been described as involving compulsive and distress-related features, whereas prolonged screen exposure does not necessarily indicate problematic use (2). Moreover, in the original development study of the Digital Addiction Scale, the construct of digital addiction was shown to include compulsive use characteristics as well as tolerance and withdrawal-like symptoms (3). Throughout this manuscript, the term PSU is used as the overarching construct to refer to maladaptive, compulsive, and functionally impairing screen-related behaviors. The term digital addiction is retained only when referring to the name or original conceptual framework of the Child–Adolescent Digital Addiction Scale (CADAS). Systematic reviews further indicate that PSU is significantly associated with adolescent mental health difficulties, sleep disturbances, and poorer psychosocial adjustment (4,5).

The family context is considered one of the most important environmental domains in the development and maintenance

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of PSU (6). Positive parent-adolescent relationships (PAR), a supportive family climate, and warm and consistent parenting practices have been associated with lower levels of problematic social media and screen use (4,6). In contrast, a conflictual family environment, insufficient parental monitoring, and parents' own excessive screen use have been linked to greater risk (7,8). Large-sample studies have demonstrated that parental monitoring and appropriate limit-setting are associated with lower levels of PSU, whereas parental screen habits, screen exposure during mealtimes, and high family conflict may contribute to both increased screen use and more problematic usage patterns among adolescents (7,8). In addition, adolescents' involvement in establishing screen-related rules has been associated with better prosocial functioning (9). Taken together, these findings suggest that family processes should be viewed not only as risk or protective factors, but also as dynamic relational mechanisms that shape the broader context in which PSU emerges and persists.

PSU is not only influenced by family processes, but may also, in turn, affect the quality of family relationships (10,11). Longitudinal evidence suggests that problematic smartphone use may increase parent–adolescent conflict and weaken family communication (10). Similarly, parent–adolescent conflict has been shown to predict problematic internet use over time, with depressive symptoms acting as a mediator in this association (11). Parents' own problematic internet use and poor-quality communication with their adolescents regarding internet use have likewise been associated with higher levels of problematic use in adolescents (12). Furthermore, bidirectional associations have been reported between parental technoference and adolescents' problematic mobile phone use, indicating that digital habits within the family may operate in a mutually reinforcing manner (13).

Although the literature on PSU has grown substantially in recent years, existing research has focused predominantly on individual symptoms, mental health outcomes, and platform-specific usage patterns (1). In contrast, studies comprehensively examining the impact of PSU on PARs through the broader lenses of communication, conflict, relationship quality, and family functioning remain relatively limited (10,12,13). This gap highlights the need for a more detailed understanding of how PSU operates within the family system, both as an outcome of relational processes and as a factor that may further sustain relational difficulties (12,13). Therefore, the present study aimed to examine the associations between PSU and PARs, with particular emphasis on communication, conflict, relationship quality, and family functioning.

Materials and Methods

Study design and participants

This cross-sectional study was conducted during January and February 2026 among adolescents aged 11–18 years who presented to the general pediatric outpatient clinic of Kartal Dr. Lütfi Kırdar City Hospital for routine follow-up visits and were consecutively recruited.. Eligibility criteria included the ability to read and understand Turkish and voluntary agreement to participate in the study. Written informed consent was obtained from the parents, and assent was obtained from the adolescents before study participation. Exclusion criteria were the presence of a neurodevelopmental disorder, major neurological disease, psychotic disorder, cognitive impairment severe enough to interfere with the assessment process, and any acute clinical condition.

All procedures were carried out in accordance with the Declaration of Helsinki. Data were collected face to face during outpatient visits under appropriate conditions. Participants completed the study instruments under the supervision of the researcher. The administration process took approximately 5–10 minutes.

A priori power analysis was conducted using G*Power. For a four-group comparison, assuming a Type I error rate (α) of 0.05, a statistical power (1−β) of 0.80, and a medium effect size (f = 0.25), the minimum required sample size was estimated to be 180 participants. To account for potential exclusions or incomplete data, recruitment above the minimum sample size was planned. A total of 197 adolescents were recruited, and one participant was excluded, resulting in a final sample of 196 participants.

Data collection instruments

Data were collected using a Sociodemographic Information Form developed by the researcher, the CADAS to assess PSU, and the Parent-Adolescent Relationship Quality Scale (PARQS) to evaluate the quality of PAR.

Sociodemographic information form

This form was developed by the researcher and included questions on participants' sociodemographic characteristics, including age, gender, parental educational level, perceived socioeconomic status, family structure, and number of siblings.

Child-adolescent digital addiction scale

CADAS is a 10-item self-report instrument developed to assess addictive tendencies related to digital device use among individuals aged 11-19 years. In the original scale development study, k-means cluster analysis was used to examine external validity, and four user profiles with mean digital addiction scores clustering around approximately 20, 30, 40, and 50 were identified. These profiles were defined as healthy users, users at risk, excessive users, and digitally addicted users. This classification was based on the profile approach reported in the original development study and does not represent a clinical or diagnostic cut-off (3). The Turkish validity and reliability study of the scale was conducted by Türk et al. (14). Items are rated on a 7-point Likert scale ranging from 1 (never) to 7 (always). Total scores range from 10 to 70, with higher scores indicating higher levels of digital addiction. The Turkish adaptation study reported high internal consistency for CADAS (Cronbach's α = 0.875) (14).

Parent-adolescent relationship quality scale

PARQS is an 18-item, 5-point Likert-type instrument developed to assess the quality of the PAR (15). Each item is answered separately for the mother and the father, yielding

distinct scores for each parent. The scale comprises three subdimensions: positive PAR, negative PAR, and disclosure/openness (15). The Turkish adaptation of the PARQS was conducted among middle- and high-school students in Ankara and supported a three-factor structure broadly consistent with the original scale. The internal consistency coefficients were high, ranging from 0.89 to 0.93 in middle-school students and from 0.82 to 0.92 in high-school students (16).

Statistical analysis

Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR), according to distributional characteristics, while categorical variables were presented as frequencies and percentages. Normality was evaluated using the Shapiro–Wilk test together with visual inspection of histograms and Q–Q plots. Because PAR subscale scores were not normally distributed, comparisons across CADAS-defined PSU groups (healthy use, at-risk use, excessive use, and digital addiction) were conducted using the Kruskal–Wallis test. When the overall group comparison was significant, post hoc pairwise comparisons were performed using the Dwass–Steel–Critchlow–Fligner test. All statistical tests were two-sided, and $p<0.050$ was considered statistically significant. Pairwise comparisons with $p<0.050$ were considered statistically significant; comparisons with p values between 0.050 and 0.100 were reported as trend-level findings for descriptive completeness. Statistical analyses were performed using JAMOVI software, version 2.6.44.

Results

A total of 196 adolescents were included in the study, with a mean age of 14.29±2.21 years; 59.7% of the participants were female. According to the CADAS-defined categories, 74 adolescents were classified as healthy digital device users (37.8%), 56 as being at risk of digital addiction (28.6%), 33 as excessive digital device users (16.8%), and 33 as digitally addicted users (16.8%). In 84.2% of cases, the parents were reported to be living together. Perceived socioeconomic status was most reported as moderate (37.8%) or high (40.8%) (Table I).

Table I: Sociodemographic characteristics of the participants

Variable	Values
Age (years)*	14.29±2.21
Gender†	
Female	117 (59.7)
Male	79 (40.3)
Maternal education level†	
Illiterate	3 (1.5)
Primary school	35 (17.8)
Middle school	32 (16.3)
High school	73 (37.2)
University	44 (22.4)
Postgraduate	9 (4.6)
Perceived socioeconomic status†	
Low	42 (21.4)
Middle	74 (37.8)
High	80 (40.8)
Family structure†	
Parents living together	165 (84.2)
Parents separated	14 (7.1)
Single-parent family (parental death)	2 (1.0)
Other	15 (7.7)
Number of siblings,‡	2 (2–3)

**: mean ± SD, †: n(%), ‡: median (IQR)*

Table II: Descriptive statistics of the PARQS subdimensions

Subdimension	Values*
Maternal openness	22.48±5.84
Positive relationship with mother	22.84±6.14
Negative relationship with mother	13.72±6.77
Paternal openness	18.43±6.61
Positive relationship with father	18.61±6.48
Negative relationship with father	12.58 ± 6.07

**: mean±SD*

Descriptive statistics for the PARQS are presented in Table II. For mother-related subdimensions, the mean scores were 22.48±5.84 for maternal disclosure/openness, 22.84± 6.14 for positive relationship with mother, and 13.72±6.77 for negative relationship with mother. For father-related subdimensions, the mean scores were 18.43±6.61 for paternal disclosure/openness, 18.61±6.48 for positive relationship with father, and 12.58±6.07 for negative relationship with father (Table II).

Comparisons of PAR subscale scores across CADAS-defined PSU groups showed no statistically significant overall group difference in maternal openness, although the result approached significance ($p=0.055$). In contrast, positive relationship with mother scores differed significantly across the groups ($p=0.029$). Post hoc analyses indicated that this difference was mainly driven by the comparison between healthy users and adolescents in the digital addiction group ($p=0.044$). Negative relationship with mother scores also differed significantly among the groups ($p<0.001$), with healthy users showing lower scores than adolescents in both the excessive use and digital addiction groups ($p=0.039$ and $p<0.001$, respectively). For father-related dimensions, paternal disclosure/openness scores differed significantly across the CADAS-defined groups ($p= 0.007$), and this difference was particularly evident between healthy users and adolescents in the at-risk group ($p=0.004$). Positive relationship with father scores also showed a statistically significant overall group difference ($p=0.038$), although pairwise comparisons suggested that these differences were limited. Similarly, negative relationship with father scores varied significantly across the groups ($p=0.012$), with the healthy user group showing lower negative relationship scores than the other groups ($p=0.073$, $p=0.054$, and $p= 0.063$, respectively) (Table III).

Discussion

The main finding of this study is that higher levels of PSU were associated with significant differences in PAR quality, particularly in the positive and negative relationship dimensions. The finding that adolescents with a healthy pattern of use reported higher positive relationship scores and lower negative relationship scores with both their mothers and fathers suggests that PSU should be considered not only as an individual media-related behavior, but also as a process closely linked to patterns of family relationships. This finding

Table III: Comparison of PARQS subscale scores according to CADAS total score groups

Subscale	Healthy users*	At-risk users*	Excessive users*	Digital addiction*	p
Total number of patients	74	56	33	33	-
Maternal openness	25.0 (20.0–28.5)	22.0 (17.8–25.0)	25.0 (17.0–28.0)	23.0 (16.0–25.0)	0.055
Positive relationship with mother	26.0 (21.5–29.0)[a]	22.0 (17.8–27.0)	25.0 (18.0–29.0)	20.0 (16.0–25.0)[a]	0.029
Negative relationship with mother	10.0 (7.0–13.5)[a,b]	11.5 (8.8–19.0)	13.0 (10.0–17.0)[a]	19.0 (10.0–23.0)[b]	<0.001
Paternal openness	21.0 (15.0–25.0)[a]	16.0 (12.8–19.3)[a]	16.0 (13.0–21.0)	17.0 (11.0–23.0)	0.007
Positive relationship with father	22.0 (16.0–25.0)	18.5 (14.0–22.0)	18.0 (14.0–21.0)	17.0 (12.0–23.0)	0.038
Negative relationship with father	9.0 (7.0–12.0)	12.0 (8.0–18.0)	12.0 (9.0–18.0)	13.0 (8.0–19.0)	0.012

**: median (IQR) (Kruskal–Wallis test), [a,b]: Matching superscript letters indicate significant pairwise differences between the corresponding groups (Dwass–Steel–Critchlow–Fligner test)*

is consistent with current approaches emphasizing that PSU should be understood not only in terms of screen time, but also in relation to impaired control, functional disruption, and interpersonal consequences (1).

The findings regarding the mother–adolescent relationship are particularly noteworthy. The significant difference in positive relationship with mother scores between healthy users and adolescents in the digital addiction group, together with the increase in negative relationship with mother scores as the level of problematic use increased, suggests that family climate may be associated with adolescents' digital use patterns. Recent systematic reviews have shown that a supportive family environment, warm parenting attitudes, and a positive parent–child relationship are associated with lower levels of problematic social media and screen use (4,6). In contrast, a conflictual family environment, low parental monitoring, and intensive parental media use have been reported to be associated with greater risk (7,8). Within this framework, the findings of the present study suggest that PSU may be associated with reduced emotional closeness, lower relationship satisfaction, and greater conflict in the mother–adolescent relationship.

The findings related to the openness subdimension are also important. In the PAR, openness reflects the adolescent's willingness to share experiences, emotions, and everyday events voluntarily with the parent, and is considered an important dimension of relationship quality (15,17). In our study, the borderline difference in maternal openness suggests that this dimension may show a weaker or less consistent association with PSU than the positive and negative relationship dimensions. In contrast, the significant difference observed in paternal openness scores may suggest a possible association between PSU and father–adolescent patterns of voluntary sharing; however, the direction of this association cannot be determined in this cross-sectional study. Indeed, previous studies showing that parental modelling, open communication, and media mediation strategies are associated with adolescents' digital use patterns support the relevance of the openness dimension in this context (7,18). The finding that low-quality parent–adolescent communication is associated with problematic internet use further strengthens this interpretation.

The findings related to father–adolescent relationship dimensions suggest that maternal and paternal relational patterns may not be entirely homogeneous; however, these associations should be interpreted cautiously given the cross-sectional design. The significant differences observed in paternal openness and negative relationship with father scores suggest that the father–adolescent relationship should be considered a distinct and clinically important dimension in the context of PSU (13,19). Recent longitudinal studies have shown that parental technoference and adolescents' problematic mobile phone use are bidirectionally related, and that attachment to both mother and father may mediate this relationship (13). In addition, meta-analytic findings demonstrating a positive association between parental technoference and problematic media use in children and adolescents support the influence of parents' own digital behaviours on the relational context within the family (20). Therefore, the father-related findings of our study may warrant further attention in clinical assessment, particularly with respect to trust-based sharing, communication, and conflict; however, longitudinal studies are needed before drawing stronger conclusions.

Another important finding of the present study was that CADAS-defined PSU groups showed more pronounced differences particularly in the negative relationship dimension. This suggests that PSU may be associated with greater tension, criticism, mutual dissatisfaction, and conflict within the family. Longitudinal studies have similarly shown that problematic smartphone use may increase parent–adolescent conflict and weaken family communication (10). Likewise, parent–adolescent conflict has been reported to predict problematic internet use over time, with depressive symptoms potentially mediating this association (11). Findings showing that family conflict and low parental monitoring are associated with higher levels of screen use further support this interpretation (7,8). In this context, although the cross-sectional design of the present study does not allow causal inferences, the co-occurrence of PSU and more negative PAR scores suggest the possibility of a mutually reinforcing relational pattern between these two domains.

Limitations

This study has several limitations that should be acknowledged. The cross-sectional design limits causal and directional interpretations of the association between PSU and PAR quality; therefore, the findings should be interpreted as associations rather than evidence of causal effects. In addition, the use of self-report measures may have introduced common method bias, and the single-centre clinical outpatient sample may restrict the generalisability of the findings. Adolescents presenting to a pediatric outpatient clinic may differ from community-based adolescent populations in terms of health-related concerns, family characteristics, psychological

distress, and patterns of healthcare-seeking behavior, which should be considered when interpreting the findings. Furthermore, the CADAS-defined groups reflect analytical rather than clinical diagnostic classifications and should therefore be interpreted as indicators of relational risk patterns. Nevertheless, the separate examination of mother- and father-related dimensions, together with the inclusion of the openness subdimension, represents a notable strength by providing a more nuanced understanding of the familial relational correlates of PSU.

Conclusion

In conclusion, the present study suggests that PSU in adolescents is associated with the quality of the PAR, particularly in the dimensions of positive relationship, negative relationship, and, to some extent, openness. The finding that adolescents with healthier digital use patterns reported more positive and less conflictual relationships with their parents suggests that relational vulnerabilities become more apparent as the level of PSU increases. Therefore, assessment of PSU in adolescents should consider the quality of family relationships, particularly indicators of trust-based communication.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kartal Dr. Lütfi Kırdar City Hospital (27.01.2026, reference number: 2026/010.99/24/22).

Contribution of the authors

Study conceptualization and design: BY, EK; data collection: BY, EK; analysis and interpretation of results: BY, EK; manuscript preparation: BY, EK. All authors reviewed the results and approved the final version of the manuscript.

Presented

This study was previously presented as an oral presentation at the ADSAD 3rd National Adolescent Health Congress.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Comparison of febrile neutropenia episodes and outcomes in Turkish versus refugee children with cancer: A single-center experience

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ABSTRACT

Objective: Febrile neutropenia (FN) is a frequent and potentially life-threatening complication of chemotherapy in pediatric oncology. Refugee and immigrant children are often considered to be at higher risk for adverse infectious outcomes due to socioeconomic disadvantage, substandard living conditions, and language barriers. This study aimed to compare FN episodes and short-term clinical outcomes between refugee/immigrant and Turkish pediatric oncology patients managed within a universal healthcare system.

Materials and Methods: This retrospective, single-center study analyzed 50 FN episodes, with one episode included per patient, occurring between May and July 2022 at a tertiary pediatric oncology center. Patients were stratified by residency status as Turkish citizens (n=31) or refugee/immigrant children (n=19), primarily Syrian refugees under temporary protection. Comparative analyses included demographic characteristics, clinical presentation, microbiological findings, treatment characteristics, length of hospital stay (LOS), and socioeconomic parameters. Group comparisons were performed using Chi-square and Mann–Whitney U tests.

Results: Refugee families demonstrated significantly greater socioeconomic disadvantage, with 94.7% having household incomes at or below the minimum wage compared with 38.7% of Turkish families ($p<0.001$). Blood culture positivity was higher among refugee patients (26.3% vs. 3.2%, $p=0.024$). Despite these differences, no significant between-group differences were observed in length of hospital stay (10.42 days for Turkish vs. 12.05 days for refugee patients, $p=0.335$), treatment intensity, or antifungal therapy requirements. Short-term FN-related clinical outcomes during hospitalization were comparable between groups.

Conclusion: Despite marked socioeconomic and housing disadvantages and higher rates of documented bacteremia, refugee and immigrant children experienced short-term FN outcomes comparable to those of Turkish patients when managed in a standardized inpatient setting. These findings suggest that system-level factors—such as universal healthcare access, centralized tertiary care, standardized FN protocols, and language support—may help mitigate the impact of socioeconomic disparities on acute infectious outcomes. However, these results are limited to hospitalized FN episodes and should not be extrapolated to long-term cancer outcomes or outpatient care settings.

Keywords: Febrile neutropenia, global health, health disparities, refugee children

Introduction

Global migration has emerged as a critical humanitarian challenge of the 21st century, placing unprecedented demands on healthcare systems worldwide. Children constitute a particularly vulnerable demographic within displaced populations, especially those diagnosed with life-threatening malignancies. Factors such as the disruption of healthcare continuity, diagnostic delays, malnutrition, substandard living conditions, and limited health literacy may synergistically impair treatment outcomes for pediatric oncology patients displaced by conflict or political instability (1,2).

Currently hosting the world's largest Syrian refugee population, Türkiye serves as a pivotal destination and transit hub for migrants, primarily from the Middle East and Africa. Since the 2011 Syrian conflict, approximately four million Syrians have resided in Türkiye under "temporary protection" status (3,4). National legislation and international agreements grant these individuals comprehensive access to healthcare, including tertiary pediatric oncology services. Furthermore, Türkiye's role is expanded by bilateral health agreements that facilitate the admission of pediatric patients from various African nations.

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Febrile neutropenia (FN) remains one of the most frequent and life-threatening complications of chemotherapy in pediatric oncology, serving as a primary driver of infection-related morbidity, prolonged hospitalization, and increased resource utilization (5-7). While early recognition and standardized management are key to favorable outcomes, refugee populations often face socioeconomic deprivation, language barriers, and suboptimal hygiene. These factors, coupled with limited caregiver education, may elevate both the incidence and clinical severity of infectious episodes (8,9) .Although existing literature suggests that refugee children often present with advanced-stage disease and higher rates of treatment-related complications, data specifically focused on FN episodes in this population remain scarce—particularly in countries like Türkiye, which offer structured healthcare integration (10-12). Comparative studies evaluating FN outcomes between native and refugee populations are notably limited.

This study aimed to compare the clinical characteristics, socioeconomic determinants, and febrile neutropenia outcomes between Turkish citizens and refugee/immigrant children treated at a tertiary pediatric oncology center. We specifically sought to evaluate whether disparities in living conditions and socioeconomic status translate into measurable differences in FN-related clinical outcomes.

Materials and Methods

Study design and population

This retrospective, single-center observational study was conducted at the pediatric oncology department of a tertiary referral hospital -Ankara Bilkent City Hospital- in Türkiye. Febrile neutropenia (FN) episodes occurring in children receiving chemotherapy between May 2022 and July 2022 were retrospectively reviewed.

To ensure statistical independence, only one FN episode per patient was included in the analysis, even if a patient experienced multiple FN episodes during the study period. When a patient had more than one episode, the first qualifying episode within the study period was selected. Accordingly, each FN episode represents a unique patient encounter. This approach was chosen to preserve the statistical independence of observations and to allow a focused evaluation of acute FN management, while avoiding the clustering effects and intra-patient correlation that would arise from including repeated episodes in the same individual.

Patients were categorized into two groups based on legal residency status: Turkish citizens and refugee/immigrant patients. Refugee/immigrant patients were defined as individuals under temporary protection status granted by the Turkish government (primarily Syrian refugees) or those admitted through bilateral international healthcare agreements. All patients, regardless of residency status, received care under Türkiye's universal healthcare system with equal access to diagnostic and therapeutic services.

Inclusion criteria were as follows:

- Age <18 years
- Confirmed diagnosis of malignancy (solid tumor or lymphoma)
- Active receipt of chemotherapy during the study period
- Occurrence of at least one FN episode during the specified timeframe

Exclusion criteria included FN episodes with incomplete medical records and episodes in which fever was clearly attributable to non-infectious causes in the absence of neutropenia.

Data collection and variables

Data were extracted from electronic medical records and archived physical files by trained research personnel. The following variables were systematically collected:

- Demographic characteristics: age, sex, and residency status (Turkish citizen vs. refugee/immigrant)
- Disease-related variables: type of malignancy (solid tumor or lymphoma) and disease status (remission vs. active disease) at the time of the FN episode
- Clinical presentation: presenting symptoms, physical examination findings, and the interval between the last chemotherapy administration and onset of fever

Baseline laboratory values at admission were compared between the two groups. The median white blood cell count was lower in refugee/immigrant patients (500 vs. 700 cells/mm^3, p=0.026), whereas the median C-reactive protein level was significantly higher (83 vs. 50 mg/L, p=0.029). No significant between-group differences were observed in absolute neutrophil count (50 vs. 120 cells/mm^3, p=0.133), hemoglobin (9.0 vs. 9.3 g/dL, p=0.303), platelet count (50 vs. 88 $\times 10^3$/mm^3, p=0.219), erythrocyte sedimentation rate (36 vs. 27 mm/h, p=0.294), interleukin-6 (35 vs. 20 pg/mL, p=0.107), or procalcitonin (2.0 vs. 0.7 ng/mL, p=0.667).

Microbiological evaluation consisted of blood cultures obtained prior to initiation of empirical antibiotic therapy, with identification of causative organisms and antimicrobial susceptibility testing when cultures were positive. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction testing and a comprehensive respiratory viral panel (including influenza A/B, respiratory syncytial virus, parainfluenza virus, adenovirus, and other respiratory pathogens) were performed when clinically indicated.

Clinical management and outcome variables included empirical antibiotic regimens, treatment modifications based on microbiological results or clinical response, use of antifungal agents, duration of antimicrobial therapy, fluid resuscitation or vasopressor support was required in only one Turkish patient (1/31, 3.2%) and in no refugee/immigrant patients (0/19), with no significant difference between groups (p=1.000).

Socioeconomic data—including monthly household income, parental education level, and housing conditions—were obtained from standardized social work assessments routinely performed during hospitalization. Household income was categorized relative to the Turkish minimum wage at the time of data collection (5.004 TL/month in 2022, approximately $300 USD). Housing conditions were assessed based on the number of rooms, the number of individuals living in the household, adequacy of heating

systems, and overall housing quality, as documented in the medical record. Household crowding was estimated as the number of persons per room.

Clinical definitions

Febrile neutropenia was defined according to international guidelines as a single oral temperature ≥38.3°C or a sustained temperature ≥38.0°C for at least one hour in the presence of an absolute neutrophil count (ANC) <500 cells/mm³, or an ANC expected to decrease to <500 cells/mm³ within 48 hours.

Remission status was determined based on disease-specific response criteria (e.g., RECIST criteria for solid tumors and Lugano criteria for lymphomas) as documented at the time of the FN episode. Length of hospital stay was defined as the number of days from admission for FN to hospital discharge. Treatment intensity was defined as the number of different antimicrobial agents administered during the FN episode and the overall duration of antimicrobial therapy.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are reported as medians with ranges for continuous variables and frequencies with percentages for categorical data. Between-group comparisons (Turkish citizens vs. refugees/immigrants) were performed using the Chi-square test or Fisher's exact test (when expected cell counts were <5) for categorical variables. The Mann-Whitney U test was employed for continuous variables due to non-normal distribution. A two-tailed p-value <0.050 was considered statistically significant.

Results

Patient demographics and baseline characteristics

A total of 50 febrile neutropenia (FN) episodes were analyzed: 31 (62%) occurring in Turkish patients and 19 (38%) in refugee/immigrant patients. The median age was similar between groups (p=0.060). Male patients comprised 72% (n=36) of the cohort, with no significant sex distribution differences between Turkish and refugee groups (p=1.000). Detailed demographic characteristics are presented in Table I.

Regarding underlying malignancies, solid tumors predominated in both groups: 22/31 (71.0%) in Turkish patients versus 18/19 (94.7%) in refugee patients, while lymphomas accounted for 9/31 (29.0%) versus 1/19 (5.3%), respectively (p=0.067). At the time of FN episodes, 25/31 (80.6%) Turkish patients were in remission compared to 19/19 (100%) of refugee patients; this difference was not statistically significant (p=0.071).

Clinical presentation and physical findings

The most common presenting symptoms were fever (96%, n=48), fatigue (22%, n=11), and sore throat (10%, n=5). Physical examination revealed mucositis in 62% (n=31) of patients and oropharyngeal hyperemia in 30% (n=15) of patients. The distribution of presenting symptoms and physical findings was comparable between Turkish and refugee groups (p>1.000 for all comparisons). Detailed clinical presentation and physical findings are presented in Table II.

Table I: Patient characteristics

Variable	Turkish Patients	Refugee/ Immigrant Patients	p
Total number of patients	31	19	
Demographics			
Male sex*	22 (71.0)	14 (73.7)	1.000
Disease characteristics*			
Type of malignancy			
Lymphoma	9 (29.0)	1 (5.3)	0.067
Solid tumor	22 (71.0)	18 (94.7)	
Remission status at FN			
In remission	25 (80.6)	19 (100)	0.071
Non-remission	6 (19.4)	0 (0)	
Socioeconomic characteristics*			
Monthly household income ≤1× minimum wage	12 (38.7)	18 (94.7)	<0.001
Parental education			
Pre-primary/primary	10 (32.3)	14 (73.7)	0.008
Secondary or higher	21 (67.7)	5 (26.3)	
Living conditions			
Number of rooms			
2 rooms*	6 (19.4)	0 (0)	0.041
3 rooms*	25 (80.6)	19 (100)	
Mean (range)	2.8 (2-3)	3.0 (3-3)	
Heating system*			
Central heating	18 (58.1)	14 (73.7)	0.366
Other heating systems	13 (41.9)	5 (26.3)	
Household members†	4 (2-7)	4 (2-6)	0.638
Persons per room†	1.33 (0.5-3.0)	1.33 (0.75-3.0)	0.507

**: n(%) (Fisher's exact test), †: median(range) (Mann–Whitney U), At the time of data collection (2022), the Turkish minimum wage was 5004 TL/month (approximately $300 USD). Income at or below this threshold represents extreme poverty in the Turkish socioeconomic context.*

The median time interval between the last chemotherapy administration and the onset of fever was 5.0 days for both Turkish (IQR: 3.5-6.0, range: 1-10 days) and refugee children (IQR: 4.5-6.5, range: 2-12 days), with no significant difference between groups (p=0.473).

Microbiological evaluation

Blood cultures were obtained from all patients prior to antibiotic initiation. Culture positivity was observed in 6 of 50 (12.0%) patients, with a significantly higher rate among refugee patients (5/19 [26.3%] vs. 1/31 [3.2%], p=0.024) (13,14). The identified organisms were *Escherichia coli* (n=2), *Klebsiella pneumoniae* (n=1), *Staphylococcus epidermidis* (n=2), and *Staphylococcus aureus* (n=1). All three Gram-negative *Enterobacterales* isolates (two *E. coli* and one *K. pneumoniae*) were identified in the refugee/immigrant group, and both *E. coli* isolates were extended-spectrum β-lactamase (ESBL)-producing; these two patients were escalated to meropenem in accordance with antimicrobial susceptibility results. As all patients had indwelling port catheters, the *S. epidermidis* isolates (one in each group) were regarded as clinically significant catheter-associated organisms rather than contaminants. All patients tested negative for SARS-CoV-2, and respiratory viral panel testing identified one positive case of influenza (2.0%).

Socioeconomic characteristics

Significant socioeconomic disparities were identified between groups (Table I). Household income at or below

Table II: Clinical features and outcomes of febrile neutropenia episodes

Variable	Turkish patients	Refugee/ Immigrant patients	p
Total number of patients	31	19	-
Presenting symptoms*			
Fever at presentation	30 (96.8)	18 (94.7)	1.000
Fatigue	7 (22.6)	4 (21.1)	1.000
Sore throat	3 (9.7)	2 (10.5)	1.000
Physical examination findings*			
Mucositis on examination	19 (61.3)	12 (63.2)	1.000
Oropharyngeal hyperemia	9 (29.0)	6 (31.6)	1.000
Treatment and outcomes† Length of hospital stay, days	10.42 (5-30)	12.05 (6-30)	0.335

**: n(%) (Fisher's exact test), †: median (range) (Mann–Whitney U)*

Table III: Treatment characteristics and clinical outcomes

Variable	Turkish citizens	Refugees	p
Total number of patients	31	19	-
Empirical antibiotic regimen*			
Single-agent	16 (51.6)	8 (42.1)	0.718
Combination therapy	15 (48.4)	11 (57.9)	
Antifungal therapy*	8 (25.8)	5 (26.3)	1.000
Length of hospital stay, days †			
Median (IQR)	10.4±5.6 8.0 (7.0-14.0)	12.1±5.9 11.0 (8.0-14.0)	0.335
Treatment intensity†	1.74±0.82	1.84±0.76	0.668

**: n(%) (Fisher's exact test), †: mean±SD (Independent Samples T Test)*

the minimum wage (≤1× minimum wage; 5004 TL/month in 2022, approximately $300 USD) was documented for 18/19 (94.7%) of refugee families compared to 12/31 (38.7%) of Turkish families (p<0.001). This marked income disparity reflects profound differences in economic status between the two populations.

Parental education levels also differed significantly. Among refugee families, 14/19 (73.7%) of parents had primary education only, compared to 10/31 (32.3%) of Turkish families (p<0.008). Secondary or higher education was attained by 21/31 (67.7%) of Turkish parents versus 5 /19 (26.3%) of refugee parents.

Housing conditions and household composition revealed additional differences (Table I). The number of individuals living in the same household was comparable between the two groups (median 4 persons in both groups; p=0.638), as was the degree of household crowding expressed as the number of persons per room (median 1.33 in both groups; p=0.507). Assessment of other housing parameters, including the number of rooms and heating systems, showed some differences, with detailed comparisons presented in Table I.

Treatment and clinical outcomes

The mean length of hospital stay was 10.42 days (range, 5-30) for Turkish patients and 12.05 days (range, 6-30) for refugee/immigrant patients (Table III). Despite the slightly longer hospital stay observed in the refugee group, this difference did not reach statistical significance (p=1.000). This comparable length of stay occurred despite the marked socioeconomic disparities described above, suggesting that standardized inpatient care protocols effectively normalized acute FN management outcomes between the two groups.

Treatment characteristics and clinical outcomes are summarized in Table III. Empirical antibiotic regimens were comparable between Turkish and refugee patients, with single-agent therapy used in 51.6% versus 42.1% and combination therapy in 48.4% versus 57.9%, respectively (p=0.718). Antifungal therapy was required in similar proportions between groups (25.8% vs. 26.3%, p=1.000). Hospital length of stay was significantly longer in patients receiving antifungal therapy compared to those who did not (16.7±7.3 vs. 9.1±3.4 days, p<0.001), regardless of residency status. However, the mean length of hospital stay showed no significant difference between Turkish and refugee patients (10.4±5.6 vs. 12.1±5.9 days, p=0.335). Treatment intensity, defined as the mean number of antimicrobial agents used, was similar between groups (1.74±0.82 vs. 1.84±0.76, p=0.668). In summary, despite significant socioeconomic disadvantages affecting the refugee population—including markedly lower household income (94.7% vs. 38.7% at or below minimum wage, p<0.001) and lower parental education (73.7% vs. 32.3% primary or less, p=0.008)—clinical outcomes during FN episodes, including length of hospital stay and treatment intensity, were comparable between Turkish and refugee children.

Discussion

In this retrospective study, we compared febrile neutropenia (FN) episodes in Turkish and refugee/migrant children with cancer and evaluated the potential impact of socioeconomic and living conditions on FN-related outcomes. Our findings demonstrate marked socioeconomic and housing disparities between the two groups. The vast majority of refugee families (94.7%) had a household income at or below the minimum wage level, compared with 38.7% of Turkish families, and parental education levels were significantly lower among refugees, with 73.7% having only primary education or less. Despite these profound disadvantages, no statistically significant differences were observed in length of hospital stay or intensity of antimicrobial treatment during FN episodes.

Children from refugee populations are generally considered to be at increased risk for infectious complications due to poor hygiene, overcrowded living environments, nutritional deficiencies, limited access to preventive health services, and language barriers that may delay medical care. Based on these factors, worse FN-related outcomes might be anticipated in refugee children. However, our results do not support this assumption for short-term inpatient FN outcomes.

One explanation for these findings is that all FN episodes were managed in the same standardized inpatient setting. Regardless of home living conditions or socioeconomic status, both refugee and Turkish patients were hospitalized and treated under identical infection control measures, including strict hospital hygiene protocols, standardized FN management algorithms, and neutropenic diets prepared according to food safety regulations. These institutional practices likely minimized exposure to environmental risk factors present in the home setting and contributed to comparable short-term outcomes during hospitalization.

Importantly, although overall clinical outcomes were similar, blood culture positivity was significantly higher among refugee

patients. This finding may reflect delayed presentation to healthcare facilities, higher baseline microbial colonization, and suboptimal living and sanitation conditions (13,14). Nevertheless, this increased rate of documented bacteremia did not translate into longer hospitalization or greater treatment intensity. Early initiation of empirical broad-spectrum antibiotics, adherence to standardized FN treatment protocols, and close inpatient monitoring likely mitigated the clinical impact of microbiologically documented infections, resulting in similar short-term outcomes between groups.

All three Gram-negative Enterobacterales isolates—one Klebsiella pneumoniae and two *Escherichia coli*—were identified in the refugee/immigrant group, and both *E. coli* isolates were ESBL-producing. The remaining isolates comprised one *Staphylococcus aureus* in the refugee/immigrant group and one *S. epidermidis* in each group; given that all patients had indwelling port catheters, these latter isolates were regarded as clinically significant catheter-associated organisms rather than contaminants. This predominance of Gram-negative and multidrug-resistant organisms among refugee children is consistent with prior reports documenting high rates of ESBL-producing Enterobacterales and other multidrug-resistant infections, including carbapenem-resistant bloodstream infections, in vulnerable pediatric oncology populations (15). Several mechanisms may contribute, including prior antibiotic exposure, disrupted healthcare continuity, crowded living conditions during displacement, and differences in baseline gastrointestinal colonization. Importantly, both patients with ESBL-producing *E. coli* were promptly escalated to meropenem in accordance with culture results, and their clinical course was comparable to that of the overall cohort. This observation reinforces the central finding of our study: when a standardized inpatient protocol with timely, culture-guided antimicrobial escalation is applied, the higher burden of resistant pathogens among refugee children does not necessarily translate into worse short-term outcomes. Nonetheless, this pattern underscores the importance of incorporating local and population-specific resistance epidemiology into empiric antimicrobial decision-making and supports the potential value of targeted admission screening for multidrug-resistant organisms to guide both empiric therapy and infection-control practices in this population.

Beyond hospitalization-related factors, the structure of the Turkish healthcare system may have contributed substantially to these findings. Refugees under temporary protection status are granted free and unrestricted access to pediatric oncology services, eliminating financial barriers that might otherwise delay care. This is particularly relevant given that nearly all refugee families in our cohort lived in extreme poverty. In addition, referral of pediatric oncology patients to tertiary centers ensures access to experienced multidisciplinary teams and standardized care pathways, which may further reduce outcome disparities.

Effective communication also plays a critical role in FN management. Prompt recognition of fever, early hospital referral, and accurate reporting of symptoms are essential for optimal outcomes. These processes can be challenging for families with low educational attainment and language barriers. At our center, the availability of professional interpreters and telephone-based translation services supported by the national health system likely facilitated timely communication, improved caregiver understanding of warning signs, and enhanced adherence to medical recommendations.

It is important to emphasize that our findings should not be extrapolated to long-term cancer outcomes. Febrile neutropenia represents an acute complication managed intensively in a controlled hospital environment. In contrast, overall survival and treatment success depend on multiple factors beyond inpatient FN management, including adherence to outpatient therapy, nutritional status, continuity of care, and living conditions between chemotherapy cycles. Previous studies have shown poorer long-term outcomes among refugee children with cancer despite access to healthcare, suggesting that socioeconomic disadvantages continue to influence survival outside the hospital setting (16-20).

From a health policy perspective, our results highlight the potential of structured healthcare integration to reduce short-term outcome disparities in vulnerable populations. While studies from Europe have reported persistent inequalities in cancer outcomes among migrant populations, often related to delayed diagnosis and inadequate supportive care, our findings suggest that universal health coverage, centralized tertiary care, standardized treatment protocols, and comprehensive language support may help equalize outcomes for acute complications such as FN (21,22).

Nevertheless, significant challenges remain. Extreme poverty, inadequate housing and sanitation, food insecurity, and limited social support continue to affect refugee families and may increase the risk of infection during outpatient treatment periods. The lack of adequate sanitation infrastructure, in particular, represents an ongoing risk factor for recurrent FN episodes, even if individual episodes are effectively managed during hospitalization (23). Addressing these broader social determinants of health will require sustained policy efforts, intersectoral collaboration, and international support aimed at improving living conditions and environmental health (24,25).

Limitations

This study has several limitations. Its retrospective, single-center design and modest sample size limit generalizability. The analysis focused on short-term inpatient outcomes, and no multivariable analyses were performed; therefore, the findings reflect associations rather than causal relationships. To ensure statistical independence, only a single FN episode per patient was included in the analysis; while this approach avoided clustering effects arising from repeated episodes within the same individual, it does not capture the full burden of recurrent FN, which may disproportionately affect socioeconomically disadvantaged children, and this should be taken into account when interpreting our findings. In addition, the small number of positive blood cultures limits the conclusions that can be drawn regarding pathogen distribution and antimicrobial resistance patterns. Finally, psychosocial factors, nutritional status, and vaccination history were not systematically assessed. Future prospective, multicenter studies incorporating both short- and long-term outcomes are needed to better understand FN risk and cancer care trajectories in refugee populations.

Conclusion

In conclusion, despite profound socioeconomic disadvantages, refugee children with cancer experienced short-term FN outcomes comparable to those of Turkish patients when managed in a standardized inpatient setting. These findings suggest that system-level interventions—such as universal access to healthcare, centralized specialized care, evidence-based protocols, and language support—may help mitigate the impact of socioeconomic inequalities on acute treatment-related complications.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (04.02.2026, reference number: TABED 2-26-1944).

Contribution of the authors

Study conception and design: FBK,SÇ,İİE; data collection: FBK, AYE; analysis and interpretation of results: FBK,DÖ,AY,SÇ ; draft manuscript preparation: FBK,AÖP,NS. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Case Report

Surgical management of ductal origin of the right pulmonary artery in an infant

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ABSTRACT

This clinical case report describes a 1.5-month-old infant with ductal origin of the right pulmonary artery. The surgical management included reconstruction of the right ventricular outflow tract and reimplantation of the right pulmonary artery using a 6-mm ringed expanded polytetrafluoroethylene (ePTFE) graft.

Keywords: Congenital heart defect, ductal origin of the pulmonary artery, pulmonary hypertension

Introduction

We present the case of an infant initially diagnosed on transthoracic echocardiography as having an absent right pulmonary artery, which was subsequently confirmed to represent ductal origin of the right pulmonary artery. This rare congenital anomaly is associated with a high risk of pulmonary hypertension and right ventricular overload if left untreated. Early recognition and timely revascularization of the affected pulmonary artery branch are crucial to prevent irreversible pulmonary vascular changes and adverse clinical outcomes.

Case Reports

The patient was a 1.5-month-old female weighing 5.6 kg who presented with dyspnea. Transthoracic echocardiography (TTE) performed one month prior had demonstrated absence of the right pulmonary artery (RPA). On admission, the patient was in good general condition. Physical examination revealed no cardiac murmurs. Vital signs were as follows: blood pressure 100/65 mmHg, heart rate 138 bpm, and respiratory rate 35 breaths per minute. Oxygen saturation (SpO_2) was 94% on room air.

TTE demonstrated absence of antegrade flow into the RPA. The pulmonary trunk measured 12.3 mm (z-score +1.71), and the left pulmonary artery (LPA) measured 7.5 mm (z-score +2.28). Estimated right ventricular systolic pressure (RVSP) was 100 mmHg. No right pulmonary venous return was observed. Additional findings included right ventricular outflow tract (RVOT) muscular hypertrophy and a 6-mm atrial septal defect (ASD) with right-to-left shunting (Figure 1A).

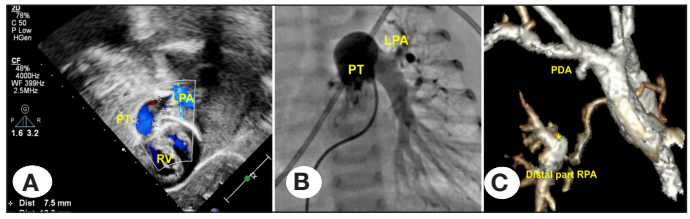


Figure 1: A) TTE showing absence of the right pulmonary artery. B) Cardiac catheterization demonstrating the PT with the left pulmonary artery. C) MSCT with 3D-reconstruction. LPA indicates left pulmonary artery; PDA, patent ductus arteriosus; PT, pulmonary trunk; RPA, right pulmonary artery; RV, right ventricle.

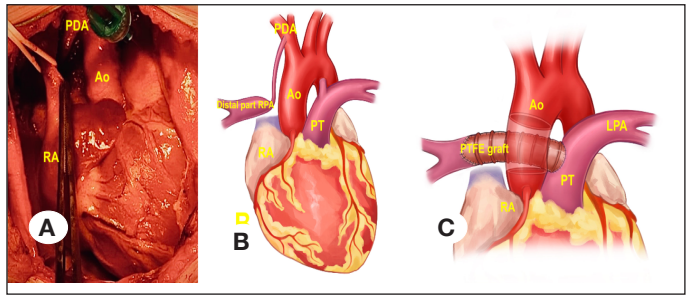


Figure 2: The operating view (A, B) and scheme of surgery (C). Ao indicates ascendens aorta; LPA indicates left pulmonary artery; PDA, patent ductus arteriosus; PT, pulmonary trunk; PTFE graft, polytetrafluoroethylene; RA, right atrium; RPA, right pulmonary artery

Cardiac catheterization revealed identical pressures in the pulmonary trunk and the LPA: 124/84 mmHg (mean 98 mmHg). The right ventricular pressure was 120/0 mmHg. Retrograde contrast injection visualized the distal RPA via collateral filling from the right pulmonary veins (Figure 1B).

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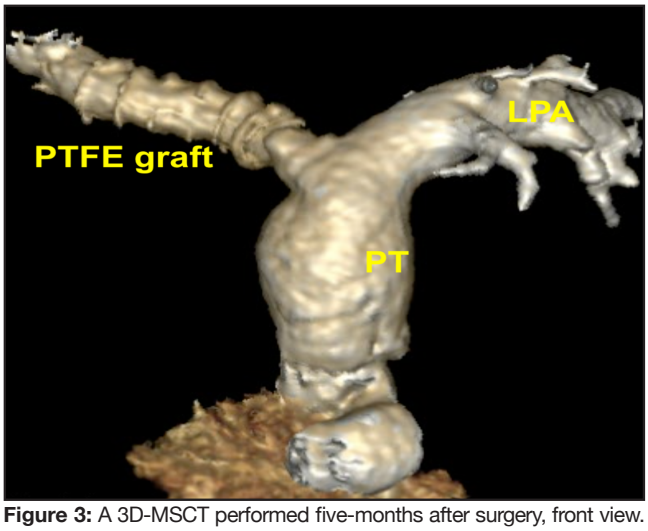


Figure 3: A 3D-MSCT performed five-months after surgery, front view. LPA indicates left pulmonary artery; PT, pulmonary trunk; PTFE graft, polytetrafluoroethylene.

Multislice spiral computed tomography (MSCT) with three-dimensional reconstruction showed the pulmonary trunk continuing solely as the LPA. A small segment of a right-sided patent ductus arteriosus (PDA) was identified near the proximal brachiocephalic trunk, and the distal RPA was also visualized (Figure 1C).

Given the imaging findings and the significant risk of pulmonary hypertension developing in the single functional lung, endovascular revascularization was attempted but was unsuccessful. Consequently, the patient was referred for surgical repair of the RPA

Via a median sternotomy, bicaval and ascending aortic cannulations were performed, cardiopulmonary bypass (CPB) was initiated, and a left ventricular vent was placed.

The ligamentum arteriosum, extending between the brachiocephalic trunk and the confluence of the distal RPA, was dissected and resected (Figure 2). To reconstruct the RPA, a 6-mm ringed polytetrafluoroethylene (PTFE) graft was anastomosed between the pulmonary trunk and the distal RPA and positioned in an anatomical course beneath the aortic arch.

Subsequently, cardioplegic arrest was induced. The RVOT was incised, and the hypertrophic muscle bundles were resected. The RVOT was reconstructed using an autologous pericardial patch. The right atrium was opened, and the ASD was closed with a Dacron patch incorporating a 3-mm fenestration.

After successful weaning from CPB, the sternum was closed, and the patient was transferred to the intensive care unit.

Early postoperative TTE demonstrated a significant reduction in right ventricular systolic pressure (RVSP) to 40–45 mmHg, along with a decrease in left ventricular end-diastolic volume. The shunt across the interatrial fenestration had converted to a left-to-right direction.

The postoperative course was complicated by bilateral pneumonia, which progressed to septic shock and necessitated a 21-day stay in the intensive care unit. The patient was discharged on postoperative day 43 in satisfactory condition on a moderate-dose sildenafil regimen.

At the 5-month follow-up, the patient was in good clinical condition on an unchanged medication regimen. Follow-up TTE revealed a persistent RVSP of 42 mmHg with a subnormal right ventricular volume. Hypertrophy of the interventricular septum and right ventricular walls persisted. A left-to-right shunt through the interatrial fenestration remained present. Subsequent CT angiography confirmed the graft patency and satisfactory function (Figure 3).

Discussion

Ductal origin of a pulmonary artery is a rare anomaly, with a reported incidence of approximately 0.1% (1). There are the following types: 1) PA origin from the ascendingaorta; 2) PA origin from the aortic arch; 3) PA origin from PDA; 4) PA origin from the descending aorta (2).

There is no universally accepted management strategy for patients with this anomaly. Approximately 100–120 pediatric cases detailing management approaches have been published. The two primary strategies are endovascular revascularization of the ductus arteriosus or surgical repair (3).

Endovascular intervention, while less invasive, carries a high risk of inducing unilateral pulmonary hypertension and is associated with a substantial re-intervention rate, reported to be as high as 68%.

When endovascular treatment is not feasible, surgical options include direct anastomosis, a systemic-to-pulmonary shunt, or prosthetic branch pulmonary artery grafting. A systemic-to-pulmonary shunt is associated with risks of unilateral pulmonary hypertension, shunt thrombosis, and coronary steal syndrome. Direct anastomosis between the distal pulmonary artery and the pulmonary trunk is often preferred but may be precluded by a significant distance between these structures (4). In such cases, interposition grafting remains the only viable option, although its major drawback is the need for reoperation due to patient growth (5). Alternatives to synthetic grafts include techniques utilizing autologous pericardium, xenomaterials, or homografts, and the optimal graft positioning (anatomical vs non-anatomical) remains a matter of debate.

In the present case, initial endovascular revascularization of the PDA was unsuccessful. A systemic-to-pulmonary shunt was contraindicated due to pre-existing supra-systemic pressures in the right heart chambers, which posed a significant risk of further exacerbating pulmonary hypertension in the contralateral lung. Consequently, we performed surgical reconstruction with a ringed PTFE graft, placed in an anatomical position beneath the aortic arch to minimize the risk of graft compression and kinking.

The main limitation of this approach is the anticipated need for reoperation due to somatic growth. At the six-month follow-up, the patient remained in good clinical condition on sildenafil therapy, with an RVSP of approximately 45 mmHg. Nevertheless, long-term surveillance with periodic

echocardiography and CT angiography is essential to monitor graft function and hemodynamics as the patient grows into adolescence and adulthood.

Conclusion

The optimal treatment strategy for ductal origin of a pulmonary artery remains a subject of debate. Available clinical reports describe a spectrum of approaches, ranging from conservative management with targeted pulmonary hypertension therapy to early surgical revascularization. The timing of intervention is of paramount importance, as delays of even several weeks after birth may allow the development of advanced pulmonary hypertension and heart failure, significantly complicating subsequent management.

This case underscores the importance of actively considering ductal origin of a pulmonary artery in infants with an "absent" pulmonary artery branch on echocardiography and severe pulmonary hypertension. Accumulation and careful analysis of such clinical cases will improve our understanding of this rare anomaly and help refine surgical techniques and postoperative management strategies for patients with ductal origin of the pulmonary artery.

Contribution of the authors

Study conception and design: OE, RK, FC; data collection: PE, ZSH; analysis and interpretation of results: PE, ZSH; draft manuscript preparation: ZSH, OE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Case Report

Robotic-assisted Kasai portoenterostomy in biliary atresia: A case report and technical considerations

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ABSTRACT

Biliary atresia is a rare and fatal cholestatic disorder characterized by progressive obliteration of the extrahepatic and intrahepatic bile ducts, typically presenting during the neonatal period. Ethology remains uncertain, although immune-mediated injury, viral triggers, and developmental anomalies have been implicated.

Kasai portoenterostomy is the primary treatment for biliary atresia, with optimal outcomes achieved when performed within the first 60 days of life. Despite early intervention, many patients experience progressive cirrhosis and portal hypertension. Liver transplantation remains the definitive therapeutic option.

The timing of liver transplantation in early infancy remains controversial. A primary concern is increased mortality associated with the inability to administer live childhood vaccines to infants transplanted before six months of age, thereby elevating the risk of subsequent life-threatening infections.

A 6-kg infant was diagnosed with biliary atresia and underwent surgery 84 days of age. Robotic-assisted Kasai portoenterostomy was performed to maintain bile flow until transplantation and to minimize adhesion formation, both of which are beneficial for subsequent transplantation. This report presents the technical aspects of the procedure.

Keywords: Biliary atresia, child, jaundice, portoenterostomy, robotic-assisted surgery, Kasai procedure

Introduction

Biliary atresia is a congenital cholangiopathy characterized by the progressive obliteration of both extrahepatic and intrahepatic bile ducts (1,2). Although there are various forms of disease, their etiopathogenesis is heterogeneous. While the exact mechanisms are not known, it is hypothesized that immune-mediated damage, perinatal viral infections, and developmental abnormalities each contribute to the development of these diseases (2,3). Clinically, this condition presents in the neonatal period with persistent jaundice, acholic stools, and hepatomegaly. In the absence of treatment, cholestatic injury initiated during the first months of life progresses rapidly to fibrosis, resulting in cirrhosis and ultimately end-stage liver failure (1). Untreated patients typically experience mortality within one year.

Kasai portoenterostomy (KPE) is the standard treatment for biliary atresia. This procedure excises the fibrous remnant of the bile ducts at the porta hepatis and facilitates drainage of the microscopic bile ducts through a jejunal portoenterostomy (4). The success of the procedure is closely linked to early surgical intervention, as delays increase the risk of complications. Furthermore, the precision of porta hepatis dissection is critical, since meticulous technique reduces the likelihood of injury to vital structures and improves patient outcomes (1). Nevertheless, a significant proportion of patients experience progressive liver failure, ultimately necessitating liver transplantation (5). The primary factors determining the success of Kasai portoenterostomy, ranked by significance, are age at initial surgery, restoration of postoperative bile flow, presence of microscopic ductal structures in the hepatic portal, degree of hepatic parenchymal disease at diagnosis, and the specific techniques employed in portoenterostomy anastomosis. Among these, age at operation is most frequently identified as the key prognostic variable. Surgical intervention before 60 days of age is associated with a favorable outcome, whereas delayed surgery typically results in the development of cirrhosis within three to four months.

Robotic surgery provides enhanced control in confined and deep anatomical regions through the use of three-dimensional imaging, tremor suppression, and articulated instruments (6,7). Recent studies indicate that robot-assisted Kasai portoenterostomy is associated with reduced blood loss, decreased transfusion requirements, improved jaundice resolution in select cases, and fewer adhesions during subsequent liver transplantation compared to open or laparoscopic approaches (8,9).

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This case report describes the short- and medium-term outcomes of robot-assisted laparoscopic Kasai portoenterostomy, performed for the first time in Türkiye in a pediatric patient, and includes a review of the relevant literature.

Case Reports

A male infant was initially evaluated at an external facility on day 45 for persistent jaundice, pale stools, and dark urine. He was subsequently admitted to our hospital on day 84 with a preliminary diagnosis of biliary atresia. On physical examination, hepatomegaly was observed. Laboratory evaluation demonstrated direct hyperbilirubinemia, with total bilirubin 8.8 mg/dL and direct bilirubin 8.1 mg/dL.

Liver function tests showed elevated transaminases (AST: 369 U/L; ALT: 550 U/L) and increased gamma-glutamyl transferase (GGT: 767 U/L). The coagulation profile revealed an international normalized ratio (INR) of 1, and serum albumin was 4.1 g/dL. Abdominal ultrasound showed an atrophic gallbladder, visualized as a thin line without a discernible lumen. No evidence of ascites was present, and neither clinical nor radiological findings suggested portal hypertension at the initial evaluation. Nutritional assessment showed the patient's weight was at the sixth percentile for age. Upon referral to our center at 84 days of age, the infant weighed 6 kg and had a preliminary diagnosis of biliary atresia. After multidisciplinary evaluation, surgical intervention was recommended. In the absence of clinical or radiological evidence of portal hypertension or ascites, and with no overt liver failure observed at the time of consultation, Kasai portoenterostomy was deemed an appropriate initial intervention, despite the patient's relatively advanced age.

Furthermore, limited access to immediate liver transplantation and challenges with donor availability necessitated a bridging strategy to maintain clinical stability. A robot-assisted laparoscopic approach was selected to enhance surgical precision and potentially reduce intra-abdominal adhesions, thereby facilitating a future liver transplant.

A 12 mm incision was created 2 cm below the umbilicus using a 12 mm camera trocar. The patient, aged 85 days, underwent the procedure. Under direct visualization, two 8 mm robotic arms were inserted at the level of the navel through the lateral rectus muscles, and a 10 mm auxiliary port was placed at the anterior axillary line in the upper left quadrant (Figure 1). Prior to robotic docking, the liver was suspended from the abdominal wall with 0 silk suture, guided by the camera, beginning at the falciform ligament. The liver appeared brownish-green, oedematous, and slightly nodular. The atrophic gallbladder remnant was fibrotic and notably small. It was grasped with a dissector, and intraoperative cholangiography was performed under fluoroscopy following insertion of a 22-G needle through the abdominal wall. Intraoperative cholangiography demonstrated no opacification of the intrahepatic ducts and no passage of contrast to the duodenum, consistent with biliary atresia with obliteration at the porta hepatis (Kasai type III). After completion of the diagnostic phase, the robotic system was docked (Figure 2). The procedure was performed using the

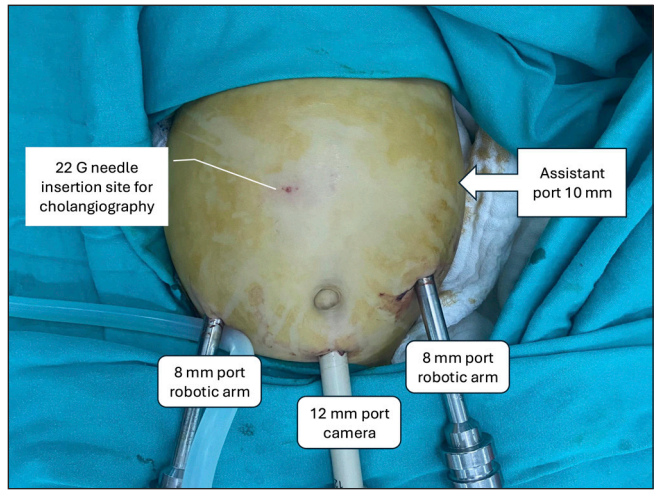


Figure 1: The patient was positioned in the reverse Trendelenburg position, and the robot approached from the cranial side. A 12-mm camera trocar was inserted below the umbilicus prior to the robot's approach. Under camera visualization, a 22G needle was inserted and placed into the gallbladder, and a cholangiogram was performed after administering a contrast agent. An 8 mm working trocar was inserted through both lateral rectus muscles, and a 10 mm assistant trocar was inserted through the left upper quadrant.

da Vinci Si robotic system (Intuitive Surgical, Sunnyvale, CA, USA). The patient was placed in the supine position, and a pneumoperitoneum was created at 10 mmHg. Adhesions were removed, and to enhance visualization, the gallbladder was fixed to the abdominal wall with 0 silk suture at its most fibrous point. The gallbladder was separated from the hepatic beds using both sharp and blunt dissection. The Lund's lymph node was excised. The common bile duct (choledochus) was exposed and ligated to the duodenum with 4/0 Vicryl. Fibrous structures corresponding to the gallbladder, choledochus, and common duct toward the portal region of the liver were cleared using sharp and blunt dissection (Figure 3). These structures were traced and excised up to the portal region, just above the portal vein and hepatic artery. No bile flow was observed. The portal plate (hepatic hilum) was exposed, and fibrotic tissue was carefully cleared. Under magnification, fine, diffuse canalicular structures were identified above the hepatic artery. The hepatic hilum was fully exposed. The extrahepatic bile ducts were dissected while preserving the hepatic artery and portal vein. Atretic bile ducts were excised after tracing their course proximally to the hepatic hilum. No significant bile flow was observed. The residual biliary ducts and adjacent liver tissue were excised, revealing minimal bile flow. The jejunum was transected 20 cm distal to the ligament of Treitz using a blue stapler. A window was created in the mesocolon, and with the distal end positioned laterally, a single-layer anastomosis was performed between the seromuscular edge of the Roux limb and the portal plate using 6/0 and 5/0 Vicryl sutures. The anastomosis was completed as a single layer at the lower edge, due to proximity to the hepatic artery, and as a double layer at the upper wall. A Jackson-Pratt drain was placed. Wedge and core liver biopsies were obtained; the wedge biopsy was performed with scissors, and the core biopsy was obtained via an abdominal wall incision. The jejunojejunostomy was

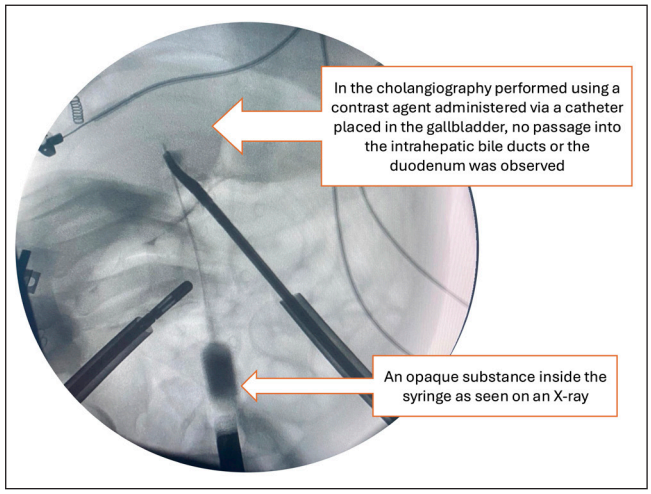


Figure 2: A 22G needle was inserted into the gallbladder, and a contrast agent was injected. No passage of the contrast agent into the intrahepatic bile ducts or the duodenum was observed. The gallbladder, held in place with a laparoscopic dissector to prevent leakage of the contrast agent, is visible under fluoroscopy.

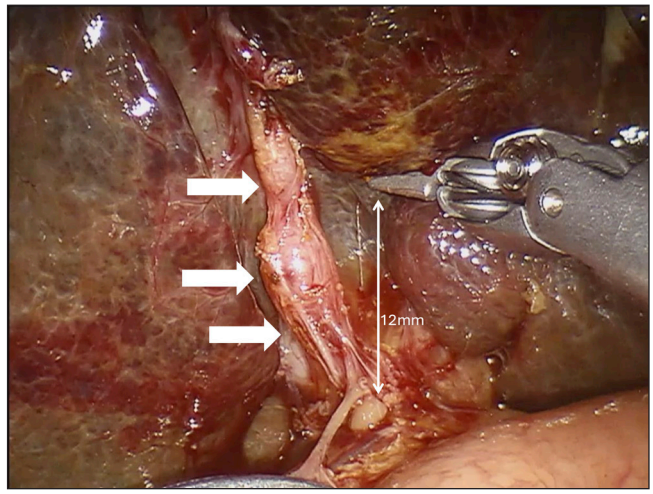


Figure 3: A nodular and cirrhotic-appearing liver is observed. The gallbladder is fibrotic and notably small, measuring approximately 15 mm in length.

exteriorized through the camera trocar and sutured end-to-end in two layers using Connell and Lambert sutures with 5/0 Vicryl. The abdominal cavity was inspected. The fascia was closed in layers with 2/0 Vicryl, and the skin with 5/0 Rapid Vicryl. No bleeding or complications were observed. The total duration of the procedure was 480 minutes, with 257 minutes allocated to console operation (except during laparoscopic cholangiography). Estimated blood loss was minimal, and no intraoperative transfusion was necessary.

Early oral feeding was initiated during the postoperative period. In the initial follow-up, jaundice levels decreased and no complications were observed. Total bilirubin levels decreased by 6.75 mg/dL three weeks after the operation. Histopathological analysis of wedge and core liver biopsies revealed bile duct proliferation, portal fibrosis, and cholestasis, which are consistent with a diagnosis of biliary atresia. The patient was enrolled in a follow-up program to provide bridging treatment until liver transplantation. Twenty days postoperatively, a port-side hernia developed at the trocar insertion sites due to ascites. In the absence of obstruction and given the risk of surgical adhesions, continued monitoring was chosen In the second postoperative month, the patient was hospitalized for cholangitis treatment. In the third postoperative month (day 77), excessive ascites necessitated placement of an intra-abdominal drain and initiation of intermittent drainage. At the six-month follow-up, live vaccines were administered. Currently, in the sixth postoperative month (ninth postnatal month), the patient experienced another episode of cholangitis. The patient remains on the waiting list for liver transplantation.

Discussion

Kasai portoenterostomy is the primary surgical intervention for biliary atresia, including in infants with advanced-stage disease, as it aims to preserve native liver function prior to liver transplantation. The success of this procedure depends largely on the preservation of microscopic bile ducts at the porta hepatis, which contributes to the significant technical complexity of the surgery (4).

Robotic surgery may provide more controlled and stable dissection in anatomically challenging areas. Experimental studies also indicate that robotic systems support complex hepatobiliary anastomoses using minimally invasive techniques (6). Clinical trials indicate that robotic Kasai portoenterostomy reduces blood loss and accelerates post-operative recovery compared to open surgery (8). Furthermore, the robotic approach delivers better technical outcomes than laparoscopic surgery and results in higher rates of early-stage jaundice resolution (9). Studies indicate that robotic surgery requires more time than laparoscopic or open procedures (8). The results obtained in this study were consistent with those reported in the literature.

Liver transplantation is generally considered inevitable in cases of biliary atresia; however, determining the optimal timing, particularly for patients younger than six months, remains challenging due to the inability to administer live vaccines and the increased risk of infection (3,5). A successful Kasai portoenterostomy is essential to maintain patient health until transplantation becomes feasible. In this case, a robot-assisted laparoscopic Kasai portoenterostomy was performed to provide sufficient time for live vaccine administration and to facilitate subsequent liver transplantation by minimizing adhesion formation.

In biliary atresia, the initial treatment is typically Kasai portoenterostomy (open, laparoscopic, or robotic). However, its ability to cure is limited; many will ultimately require a liver transplant. Thus, Kasai serves mainly as a temporary, first-line intervention rather than a definitive cure (10,11). Recent studies provide information on surgical and short- to medium-term outcomes for robotic Kasai surgery, but there is limited data on transplant outcomes. Although robot-assisted Kasai portoenterostomy may provide benefits such as improved visualization and reduced adhesions, these advantages are largely unproven and based on a single case.

In 2007, Dutta and colleagues reported three successful robotic portoenterostomies. Meehan and colleagues demonstrated feasibility in two additional cases. Between 2002 and 2005, Dutta's group performed 10 minimally invasive Kasai procedures, using robotic techniques in three cases and standard laparoscopy in seven.

This is the first reported robot-assisted laparoscopic Kasai portoenterostomy from Türkiye. Minimally invasive approaches may reduce intra-abdominal adhesions, but we could not evaluate this benefit as this initial report lacks long-term follow-up (12,13).

Conclusion

This study is limited to a single case, and long-term outcomes have not been reported. Robot-assisted Kasai surgery, when performed prior to liver transplantation, appears to be safe and feasible. In comparison to open and laparoscopic techniques, the robotic approach may reduce intraoperative blood loss and facilitate faster bowel recovery. Although some studies report improved jaundice resolution with the robotic method, these results remain inconsistent. There is currently no demonstrated benefit in long-term liver survival. Most available evidence is derived from small, retrospective studies. The literature suggests that the robotic approach may be a viable option in experienced centers, although surgeon expertise, technical resources, and associated costs require careful consideration.

Contribution of the authors
Concept or design: SEUB GBB; Acquisition of data: OMÇ FBŞ; Analysis or interpretation of data: BG MBÇ ; Drafting of the article: SEUB GBB; Critical revision for important intellectual content: SD

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The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on: Bone mineral density in pediatric celiac disease: Clinical, biochemical, and serologic profiles—a retrospective cohort study

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Introduction

Teke and Basaran published an exciting study in the latest issue of the journal. On utlizing dual-energy X-ray absorptiometry (DEXA) and referral to the Turkish pediatric bone mineral density reference curves (BMDRCs) (2), they found substantial BMD impairments (37.4%) among pediatric patients with celiac disease (CD) (1). The most prominent improvement was noted during follow-up among patients adherent to the gluten-free diet (GFD). Moreover, shorter GFD period and lower body mass index z-scores were noticed among the study CD patients with low BMD, which might help display risk stratification (1). We acknowledge two pertinent points.

First, it is to be noted that densitometry, measured by DEXA, is effective in early identifying individuals at risk for bone frailty, defining the grade of defective bone mass among those with confirmed bone fragility, and guide the necessary therapy. It is necessary to refer to the appropriate BMDRCs, which should enlist an adequately substantial size of healthy individuals of the general population to hold variations in bone measurements while simultaneously accounting for age, gender, and ethnicity. An accurate evaluation of bone health integrity in a given pediatric population relies upon formulation of robust BMDRCs to define if a particular child's BMD is comparable with same-age and gender-peers (3,4). As a result, BMDRCs have been developed for numerous pediatric populations. Updating the established BMDRCs is essential to amend the BMD baseline for the growing population while accounting for demographic and regional differences, prevent under/over-diagnosis of defective bone mineralization, and monitor treatment lines. Indeed, updating the existed BMDRCs for certain population were done and revealed relevant differences in BMD values between the established BMDRCs and updated ones triggering a substantial potential for osteoporosis/osteopenia misdiagnosis (5-7). The validity of the current Turkish pediatric BMDRCs is ruined by several limitations, involving the fact that it was released two decades ago, that it was inspired from a small sample size (n=345), and that participants were recruited from a single region (Izmir) (2). Thus, it is not representative of the whole pediatric population in Türkiye. We hope that the study by Teke and Basaran would provoke the necessity for updating the available BMDRCs , which in our opinion, tremendously help pediatricians in Türkiye sincerely investigate, monitor, and treat childre (1,2).

Second, although DEXA analysis is considered the clinical reference standard for evaluating BMD, it suffers from numerous drawbacks, namely operator dependency, limited sensitivity to early changes in the bone microarchitecture, restricted availability in primary healthcare setups, and an inadequate capability to predict fracture risk, if employed alone. Artificial intelligence (AI), incorporating deep learning and machine learning, provides a transformative potential in improving DEXA-based bone health evaluation (8). The AI algorithms' integration into DEXA image interpretation yields improvements in diagnostic precision and low BMD risk stratification as well as it reduces interpretation times beyond the traditional methods. It allows extraction of complex characteristics of DEXA images and increases the sensitivity to detect early microstructural deterioration, which is typically not identified by the standard DEXA. The combination of comprehensive demographic and clinical data and quantitative image characteristics could improve the early identification of disturbed skeletal BMD and enable personalized therapeutic strategies (8). Interestingly, a chest xray-based AI model has been developed and proved effective in accurately predicting pediatric BMD z scores and detecting low BMD (9). In this regard, we suggest future research on implementing AI-based technology within the pediatric clinical workflows in Türkiye and exploring its integration with other diagnostic tools for a comprehensive BMD assessment among those suspected to have compromised skeletal mineralization, including CD patients.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Response to comment "Bone mineral density in pediatric celiac disease: Clinical, biochemical, and serologic profiles—a retrospective cohort study"

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Introduction

We thank the authors for their interest in our study and for their constructive comments. We appreciate their emphasis on the need to update pediatric bone mineral density (BMD) reference data in Türkiye and on the potential future role of artificial intelligence (AI)-assisted approaches in pediatric bone health assessment.

In our study, lumbar BMD was assessed at the L2–L4 vertebrae, and age-adjusted BMD z-scores (BMD-AAz) and height-adjusted BMD z-scores (BMD-HAz) were calculated using reference curves derived from healthy Turkish children (1,2). Although evaluating whether these reference curves require updating was beyond the scope of our study, we consider the authors' emphasis on the need for updated and more representative national reference data important. We agree that pediatric reference data derived from larger, multicenter, and contemporary populations could contribute to the interpretation of dual-energy X-ray absorptiometry (DEXA) findings and improve comparability across future studies in Türkiye.

We also appreciate the authors' comments regarding our findings in the gluten-free diet (GFD)-adherent follow-up group (FU-Adh group). Although higher BMD values were observed in this group, our study compared patients assessed at diagnosis with those assessed during follow-up rather than evaluating serial DEXA measurements in the same individuals. Therefore, prospective studies incorporating repeated DEXA measurements may further clarify changes in bone mineralization during follow-up on a GFD.

Finally, we agree that AI-assisted methods represent a promising area in pediatric bone health assessment. Their ability to integrate imaging, clinical, and demographic data may improve risk stratification; however, prospective validation in pediatric populations will be important before their broader clinical implementation.

We thank the authors once again for their valuable comments and for highlighting important directions for future research.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on: "Transcatheter atrial septal defect closure in children weighing ≤15 kg: Is body weight still the appropriate threshold?"

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Introduction

We read with great interest the article by Pamuk et al. (1) entitled "Transcatheter atrial septal defect closure in children weighing ≤15 kg: A single-center experience". The authors should be congratulated for addressing an important and still controversial issue in pediatric interventional cardiology. Transcatheter closure of secundum atrial septal defects (ASDs) in small children has traditionally been approached with caution because of concerns regarding vascular access, device-to-body size relationships, cardiac chamber dimensions, and the potential for procedural complications.

The most important finding of this study is the 100% procedural success rate and the very low incidence of complications. Among 34 children weighing ≤15 kg, only one patient experienced a brief, self-limited episode of supraventricular tachycardia, while no device embolization or other major complications were observed (1). These findings are encouraging and support the concept that body weight alone should not necessarily constitute an absolute contraindication to transcatheter ASD closure in appropriately selected patients.

The findings are consistent with previous studies. Bartakian et al. reported that device closure of secundum ASD in children weighing <15 kg can be performed successfully, although complication rates and the indications for referral require careful consideration (2). Similarly, Joseph et al. demonstrated the feasibility of transcatheter device closure in symptomatic children weighing <15 kg, providing further evidence that selected patients below the conventional weight threshold may undergo successful transcatheter treatment (3).

However, an important point should be emphasized when interpreting the current study. Although the authors studied children weighing ≤15 kg, the median body weight was 14.25 kg and the lowest weight was 12 kg. Therefore, the findings predominantly represent children close to the conventional 15-kg threshold rather than very small infants. This distinction is clinically important because children weighing 12–15 kg may differ substantially from those weighing <10 kg in terms of vascular access, cardiac dimensions, device-to-body size relationships, and procedural complexity.

Indeed, previous studies have demonstrated that transcatheter ASD closure can also be performed in children weighing <10 kg. Puthiyedath et al. (4) recently reported successful device closure in 95 of 96 symptomatic children weighing <10 kg, while Knop et al. (5) demonstrated successful Amplatzer device implantation in 26 of 28 children weighing ≤10 kg. These studies suggest that the lower limit for transcatheter intervention may be substantially below 15 kg in selected patients. Nevertheless, the favorable outcomes observed in a cohort with a minimum body weight of 12 kg cannot necessarily be extrapolated to children weighing <10 kg, who may have substantially different anatomical and procedural characteristics.

Another strength of the study is its emphasis on careful patient selection and device sizing. The mean device-to-weight ratio was 1.05±0.27, and the authors reported no excessive defect-to-weight ratio in their cohort. The high procedural success may therefore partly reflect appropriate anatomical selection, meticulous echocardiographic assessment, balloon sizing, and operator experience. Notably, this ratio was considerably lower than the median device-to-body-weight ratio of 1.93 reported by Puthiyedath et al. (4) in children weighing <10 kg. In our opinion, these factors may be more clinically relevant than body weight alone when determining the feasibility of transcatheter ASD closure.

The rapid right ventricular remodeling observed in the study is also noteworthy. Right ventricular dimensions normalized in most patients within the first few days, with a median normalization time of one day. This finding supports the physiological benefit of eliminating significant left-to-right shunting in appropriately selected symptomatic children. Nevertheless, because the study was retrospective, single-center, and lacked a control group, it remains difficult to determine whether early remodeling translates into superior long-term clinical outcomes compared with surgical closure or delayed intervention.

The clinical indications reported by the authors also deserve attention. Failure to thrive and recurrent respiratory infections were important reasons for early intervention, while right ventricular enlargement was used as an indication primarily in children older than four years and close to 15 kg. These findings further emphasize that the decision for early closure

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should integrate clinical symptoms, shunt magnitude, right ventricular volume overload, ASD morphology, rim adequacy, and patient size rather than relying on body weight alone.

Taken together, the available evidence suggests that the conventional 15-kg threshold may increasingly be regarded as a pragmatic reference point rather than a strict biological or anatomical boundary. Nevertheless, moving below this threshold should not imply that weight is irrelevant. Instead, transcatheter closure should probably be considered within a multidimensional assessment incorporating patient weight, age, ASD size, defect-to-body-weight relationship, device-to-body-weight relationship, rim anatomy, cardiac chamber dimensions, pulmonary hemodynamics, and operator experience. In this context, body weight may be more appropriately viewed as a continuous risk modifier rather than a binary eligibility criterion.

We therefore believe that the study by Pamuk et al. (1) makes an important contribution to the growing literature on transcatheter ASD closure in small children. Future multicenter studies including substantially smaller children—particularly those weighing <10 kg—with longer follow-up and standardized anatomical and procedural criteria would be valuable in defining the true lower limits of safe transcatheter ASD closure.

In conclusion, the present study provides reassuring evidence that transcatheter ASD closure can be performed safely and effectively in carefully selected children weighing ≤15 kg. However, because the study population ranged from 12 to 15 kg, its findings should not be directly extrapolated to substantially smaller children, particularly those weighing <10 kg. Rather than using body weight as an isolated exclusion criterion, an individualized approach based on anatomy, hemodynamics, device-to-body size relationship, clinical status, and operator experience may provide a more appropriate framework for decision-making.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Rethinking growth faltering in children: From anthropometrics to a biopsychosocial approach"

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Introduction

The recently published 2026 American Academy of Pediatrics (AAP) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) clinical practice guideline on faltering weight represents an important advance in the terminology, diagnostic criteria, and clinical evaluation of growth faltering in children (1). Beyond these diagnostic refinements, the guideline also provides an opportunity to reconsider growth faltering within a broader biopsychosocial and family-centered framework. Growth faltering is a multidimensional clinical entity that requires the concurrent evaluation of medical, nutritional, developmental-behavioral, and social factors. In this letter, we discuss these dimensions in the context of current evidence and highlight the importance of integrating standardized growth assessment with individualized, family-centered clinical care.

This evolution is more than semantic. The 2017 National Institute for Health and Care Excellence (NICE) guidance reframed recognition of faltering growth around defined thresholds on WHO growth charts and favored graded clinical concern over any single cut-off (2). More recently, the 2026 AAP/NASPGHAN guideline formally replaced "failure to thrive" with "faltering weight" and anchored the diagnosis in z-score–based criteria rather than percentile—defining faltering weight as a weight-for-length or body mass index (BMI)-for-age below –1.65 z-score, a weight-gain velocity below –2 z-score in children younger than two years, or a decline of at least 1 z-score in weight, weight-for-length, or BMI (1). Consistent with this, current reference sources recommend assessing growth with WHO charts under two years of age and CDC charts thereafter, and using anthropometric z-scores in preference to the older, less precise percentile-based criteria (3,4). Importantly, these guidelines converge on a single clinical message that echoes the biopsychosocial perspective advanced here: diagnostic testing should be reserved for children with specific clinical concerns or persistent faltering, explicitly to curb the overuse of laboratory and imaging investigations (1,2).

Moving beyond the traditional approach to growth faltering, Tang et al. emphasized that the evaluation process must encompass a detailed medical and nutritional history, developmental assessment, parent-child interactions, and the psychosocial characteristics of the family (5). This perspective underscores that growth faltering cannot be evaluated based solely on anthropometric measurements, and that the child's medical, nutritional, developmental-behavioral, and social characteristics must be considered collectively. Accordingly, integrating a biopsychosocial approach into clinical practice can support comprehensive clinical evaluation, thereby contributing to the reduction of unnecessary investigations and the enhancement of individualized care.

Supporting this view, Franceschi et al.(6) proposed a stepwise evaluation algorithm applicable to infants and toddlers. In this approach, the initial step comprises a detailed history, physical examination, and the assessment of serial growth charts, while laboratory investigations, imaging modalities, and specialist consultations are recommended for cases exhibiting red flag findings in the clinical history or physical examination. The presented flowchart offers a practical model that can aid in minimizing unnecessary laboratory testing and specialist consultations, particularly in cases of non-organic growth faltering. This staged logic is now mirrored at the guideline level: the 2026 AAP/NASPGHAN guidance similarly reserves laboratory testing, imaging, and endoscopy for children with focal clinical concerns or persistent faltering weight (1). Nevertheless, because the algorithm is derived from a single-center study and was evaluated exclusively in children aged two years and younger, it necessitates support from external validation studies conducted across diverse healthcare systems, in primary and tertiary care settings, and among broader age groups.

The social determinants of growth faltering also hold significant importance in the current clinical approach. Rabinowitz highlighted that food insecurity, in particular, is a critical factor to consider during the evaluation of growth faltering, noting that the term "failure" may induce feelings of guilt or inadequacy in families (7). Therefore, the evaluation should not be restricted solely to the child's nutritional history; the family's economic circumstances, access to adequate and safe food, and health literacy must also be systematically assessed, and families identified with food insecurity should be directed to appropriate social support and nutritional services as an integral component of a family-centered, holistic approach. Importantly, addressing these social needs is distinct from using socioeconomic status

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as a diagnostic label: the 2026 AAP/NASPGHAN guideline explicitly advises against treating socioeconomic status as an assigned risk factor when diagnosing faltering weight (1), a distinction that helps direct support to families without stigmatizing them.

Alongside clinical research, Brady's personal narrative—authored from the dual perspective of a physician and a mother—draws attention to the psychosocial impacts of growth faltering on the family (8). Brady expressed that the persistent focus on her child's slow but consistent weight gain resulted in repetitive feeding interventions, specialist evaluations, and intense pressure regarding breastfeeding, while the child's developmental progress, overall health status, and the mother's psychological well-being were inadequately considered. Although this article does not present research data, it serves as a powerful reminder that parental experience and family-centered communication must not be overlooked in the assessment of growth faltering. Evaluating anthropometric targets in conjunction with the child's overall health, developmental trajectory, feeding function, and the psychosocial burden on the family—coupled with healthcare professionals tailoring their recommendations to individual family circumstances and avoiding accusatory communication—aligns with the contemporary understanding of family-centered care. This perspective suggests that while patient and family experiences do not replace an evidence-based medical approach, they should be regarded as an important and complementary component.

It also remains essential not to overlook organic causes. Hill emphasized that growth faltering is a significant clinical finding in infants and children with congenital heart disease (9). In this population, increased energy requirements, feeding difficulties, and inadequate energy intake can play a major role in the development of growth faltering. Consequently, the regular monitoring of weight, length/height, and growth velocity, along with a thorough assessment of nutritional status in children identified with growth faltering, is crucial.

Furthermore, data regarding the use of laboratory biomarkers advocate for a cautious approach. Ranasinghe et al. reported that while prealbumin can serve as an adjunctive biomarker in evaluating nutritional status, it can be significantly influenced by inflammation, infection, starvation, liver diseases, and other systemic conditions (10). Therefore, biomarkers such as prealbumin should not be utilized in isolation for diagnosing nutritional deficiency or for clinical decision-making; they must be interpreted in conjunction with the medical and nutritional history, anthropometric measurements, growth charts, and physical examination findings.

When these studies and guidelines are considered collectively, it becomes evident that the current literature prioritizes detailed clinical evaluation, serial growth monitoring, targeted diagnostic investigations in selected cases, and the assessment of social factors in the management of growth faltering. Instead of implementing routine, broad-spectrum laboratory screenings for every child, this approach advocates for the individualization of investigations based on clinical history, growth patterns, and physical examination findings. Moreover, rather than focusing exclusively on numerical weight targets, the child's developmental status, feeding function, family circumstances, and the psychosocial needs of the parents must be taken into account.

In conclusion, current evidence—and now converging international guidance—demonstrates that evaluating growth faltering merely on the basis of deviations in growth charts or inadequate weight gain is insufficient. The stakes extend beyond the immediate weight trajectory: population-based cohort data link weight faltering in infancy to a higher risk of later childhood neurodevelopmental difficulties, underscoring the importance of early, holistic recognition (11). Adopting a biopsychosocial approach in clinical decision-making, applying standardized (z-score–based) diagnostic criteria alongside targeted diagnostic investigations, and strengthening family-centered care will contribute to both reducing unnecessary testing and improving long-term growth and neurodevelopmental outcomes in children. Additionally, this approach can foster the more efficient utilization of healthcare resources by mitigating unwarranted laboratory investigations and inappropriate referrals. It is imperative that future prospective and multicenter studies elucidate the impact of this holistic approach on clinical outcomes, quality of life, and the psychosocial well-being of families.

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