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Turkish Journal of Pediatric Disease
Volume 20 Number 5 September 2026

TJPD Turkish Journal of Pediatric Disease

Turkish Journal of Pediatric Disease

Türkiye Çocuk Hastalıkları Dergisi

Turk J Pediatr Dis

Volume 20 • Number 5 • September 2026

https://turkjpediatrdis.org

ISSN 1307-4490
E-ISSN 2148-3566

ISSN: 1307-4490
E-ISSN 2148-3566

Vol.20, No.5, September 2026

Turkish Journal of Pediatric Disease

Official Journal of Ankara Bilkent City Hospital, Children's Hospital

Vol.20, No.5, September 2026

Turkish Journal of Pediatric Disease

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Tel: +90 (312) 397 38 78 - Fax: +90 (312) 397 56 31

Publication Type

Common periodical

Published six issues per year

January, March, May, July, September, November

Printing Date : 16.09.2026

Publication Languag : English

Publishing Frequency : Bimonthly

Turkish Journal of Pediatric Disease has been a member of the DOI® system since March 2013.

Turkish Journal of Pediatric Disease is indexed in Turkish Medical Index of TUBITAK/ULAKBIM, EBSCOhost Research Databases, CINAHL and Türkiye Citation Index.

The paper used to print this journal conforms to ISO 9706: 1994 standard (Requirements for Permanence).
The National Library of Medicine suggests that biomedical publications be printed on acid-free paper (alkaline paper).

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Original Articles

Case Report

Letters to the Editor

Turkish Journal of Pediatric Disease

Original Article

Investigation of the relationship between motor performance and sensory processing skills and quality of life in preschool children with type 1 diabetes

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Received : 10.01.2026, Accepted : 16.04.2026 DOI: 10.12956/TJPD.2026.1299

ABSTRACT

Objective: The aim of this study was to examine the relationship between motor performance and sensory processing skills and quality of life in preschool children with type 1 diabetes (T1DM).

Materials and Methods: The study included children with T1DM aged between 60 and 78 months. Sociodemographic information of the children was recorded. Motor performance were assessed using the "Bruininks-Oseretsky Motor Competency Test 2 (BOT 2)," sensory processing skills using the "Sensory Processing Scale (SPM) House Form," and quality of life using the "Children's Quality of Life Scale (CQL).

Results: A total of 20 children with T1DM were included in the study. In the relationship between BOT 2 and CQL, the following BOT 2 parameters were found to be associated with CQL; fine motor sensitivity [physical functioning (r=-0.510, p=0.020), school functioning (r=-0.580, p=0.010), and total CQL score (r=-0.550, p=0.010)], fine motor integration [emotional functioning (r=-0.450, p=0.040), psychosocial health (r=-0.570, p=0.010), and total CQL score (r=-0.520, p=0.010)], hand dexterity [school functioning (r=-0.480, p=0.020)], and bidirectional coordination [physical functioning (r=-0.450, p=0.040)]. A moderately positive correlation was found between physical functionality and the SPM parameters body awareness (r=0.049, p=0.020), planning and ideation (r=0.047, p=0.030), and total SPM score (r=0.450, p=0.040). A moderately positive correlation was found between planning and ideation and the total CQL score (r=0.440, p=0.040).

Conclusion: In preschool children with T1DM, impairments in motor skills and sensory processing abilities are associated with quality of life. It is recommended to assess motor performance and sensory processing skills in early childhood.

Keywords: Diabetes mellitus type 1, motor skills, sensation disorders

Introduction

Diabetes mellitus is a metabolic disorder characterized by impaired insulin secretion and high blood sugar levels, leading to significant long-term complications (1). According to etiological classification, there are four distinct types. One of these, Type 1 Diabetes Mellitus (T1DM), is a disease frequently seen in children and adolescents, caused by the destruction of β cells in the islets of Langerhans of the pancreas, and manifesting itself as a lack of or insufficient insulin production in the body (2).

Children with T1DM may experience skeletal muscle disorders and myopathies. Skeletal muscle disorders are characterized by decreased muscle mass in the lower extremities, general weakness, loss of functional skills, and reduced physical capacity. Muscle weakness increases the risk of diabetes-related physical disability in children (3, 4). Studies have shown that fine motor skills are particularly affected, and this impact is more pronounced in early-onset T1DM (5). Interactive coordination of fine motor and visual perceptual skills constitutes visual-motor integration (6). Children with T1DM are also at risk of developing neurocognitive dysfunction in the area of visual-motor integration (7, 8).

Skill development and the application of skills in children depend on the processing of information from primary sensory systems. It is stated that impairments in processing sensory stimuli can affect children's learning capacity and social relationships (9). Goldberg et al. (10) reported that sensory processing impairments are more common in individuals with T1DM compared to other individuals.

Impairments in motor and sensory functions can negatively affect the quality of life in children. It has been noted that factors such as limitations in daily activities, weakness, disease symptoms, repeated hospitalizations/frequent check-ups, dependence on a medical device, daily insulin injections, and blood sugar monitoring in children with T1DM can lead to deterioration in their physical well-being and a decrease in their quality of life (11-13).

Since factors such as writing and physical education classes can cause changes in motor and sensory skills in children starting primary school, this study will evaluate preschool children. Furthermore, no studies were found that examined motor performance, sensory processing skills, and quality of life in preschool children with T1DM. The aim of this study was to examine the relationship between motor performance and sensory processing skills and quality of life in preschool children with T1DM.

Material and Methods

Children aged 60-78 months who presented to the Pediatric Endocrinology Outpatient Clinic of Ankara Bilkent City Hospital between September 2024 and April 2025 and who had been diagnosed with T1DM at least 6 months prior were included in the study. Those with diabetes, any neurodevelopmental disorder, and those starting first grade were excluded from the study.

The study included 20 children with T1DM, and their sociodemographic information was recorded. Motor performance was assessed using the "Bruininks-Oseretsky Motor Proficiency Test 2 (BOT 2)", sensory processing skills using the "Sensory Processing Scale (SPM) House Form", and quality of life using the "Children's Quality of Life Scale (CQL)".

The Bruininks-Oseretsky Motor Skills Test 2 (BOT 2) is a scale developed to assess motor skills in children aged 4-21 years. The test consists of 8 subtests and 53 items and takes approximately 40-60 minutes to complete. The maximum possible score on the test is 243 points. Higher scores indicate better motor skills. The subtests are: fine motor sensitivity (7 items), fine motor skill integration (8 items), dexterity (5 items), bilateral coordination (7 items), balance (9 items), speed and agility of movement (5 items), upper extremity coordination (7 items), and strength (5 items). The total engine composite score is obtained by summing all subcategories (14). A validity and reliability study was conducted in Turkish (15).

The Sensory Processing Scale (SPM) House Form is a 75-item scale developed to assess sensory processing skills in children aged 5-12 years. Social Participation is assessed using eight subscales: Vision, Hearing, Touch, Body Awareness, Balance and Movement, Planning and Ideas, and Total Sensory Systems. Total Sensory Systems refers to the sum of scores obtained from the subscales of Vision, Hearing, Touch, Body Awareness, Balance and Movement, as well as Taste and Smell, which are not subscales in themselves. Each item is scored according to its frequency of occurrence: Never (1 point), Sometimes (2 points), Frequently (3 points), and Always (4 points). Completing the scale takes approximately 15-20 minutes. High scores indicate poorer sensory processing skills. Turkish adaptation has been made (16, 17).

The Children's Quality of Life Scale (CQL) was developed to measure the health-related quality of life of children and adolescents aged 2-18 years. The 23-item scale assesses physical health, emotional functioning, and social functioning characteristics of well-being as defined by the World Health Organization. School functioning is also evaluated. The scoring is done in three areas: total score (TS), total physical health score (PHS), and total psychosocial health score (PSHS), which consists of calculating item scores that assess emotional, social, and school functioning. As the score increases, the quality of life decreases (18). A validity and reliability study has been conducted in Turkish (19).

Statistical analysis:

Statistical analyses were performed using IBM SPSS Statistics 26.0 (SPSS Inc, Chicago, IL, USA) software package. Descriptive statistics were presented as frequency and percentage values for nominal and ordinal variables, and as mean, standard deviation or median, minimum-maximum values for numerical variables. The normality of the distribution of numerical variables was examined using visual (histograms and probability plots) and analytical methods (Shapiro–Wilk test, skewness and kurtosis values, coefficient of variation). The relationships between the parameters were examined using Spearman correlation analysis (20, 21). For all analyses, cases where the type 1 error level was below 5% were considered statistically significant. Correlation coefficients were interpreted as follows: 0.9-1 indicates very high correlation, 0.70-0.89 indicates high correlation, 0.40-0.69 indicates moderate correlation, and 0.20-0.39 indicates low correlation (22).

Results

The study, conducted with children aged 60-78 months with T1DM, was completed with 20 children. Demographic characteristics including age, Body Mass Index (BMI), gender, duration of diabetes, and educational status of the children are presented in Table I.

In preschool children with T1DM, a moderately negative correlation was found between fine motor sensitivity and physical functioning (r=-0.510, p=0.020), school functioning (r=-0.580, p=0.010), and the total CQL (r=-0.550, p=0.010)

Table I: Demographic characteristics of the patients

Number of patients	20
Age (months)*	71 (60-78)
Body Mass Index (kg/m^2)*	16.41 (11.53-18.75)
Gender†	
Female	5 (25)
Male	15 (75)
Duration of diabetes (months)*	11 (6-57)
Educational background†	
Absent	2 (10)
Kindergarten	2 (10)
Preschool	16 (80)

**: median (min-max), †: n(%)*

Table II: Correlation between motor performance and quality of life

	Values	Quality of Life Scale for Children					
		Physical Functioning	Emotional Functioning	Social Functioning	School Functionality	Psychosocial Health	Total score
Bruininks-Oseretsky Motor Proficiency Test 2							
Fine Motor Sensitivity*	19.2±8.54	-0.51 / 0.02	-0.15 / 0.52	-0.09 / 0.69	-0.58 / 0.01	-0.41 / 0.06	-0.55 / 0.01
Fine Motor Consolidation*	13.5±8.34	-0.33 / 0.15	-0.45 / 0.04	-0.21 / 0.36	-0.39 / 0.08	-0.57 / 0.01	-0.52 / 0.01
Manual Dexterity*	15.9±6.73	-0.32 / 0.15	-0.25 / 0.28	-0.05 / 0.81	-0.48 / 0.02	-0.36 / 0.11	-0.41 / 0.07
Bilateral coordination †	17.5 (0-24)	-0.45 / 0.04	-0.09 / 0.69	-0.07 / 0.76	-0.36 / 0.11	-0.21 / 0.37	-0.38 / 0.09
Balance*	23.25±5.91	-0.23 / 0.32	-0.14 / 0.53	0.05 / 0.83	-0.16 / 0.47	-0.05 / 0.82	-0.16 / 0.49
Speed of movement and agility*	20.85±7.03	-0.27 / 0.23	-0.37 / 0.10	-0.04 / 0.84	-0.18 / 0.44	-0.40 / 0.07	-0.35 / 0.12
Upper extremity coordination*	13.95±8.72	-0.35 / 0.13	-0.34 / 0.14	-0.03 / 0.87	-0.23 / 0.33	-0.33 / 0.15	-0.35 / 0.12
Strength †	22.5 (9-38)	-0.30 / 0.18	-0.02 / 0.93	0.02 / 0.90	-0.19 / 0.40	-0.07 / 0.73	-0.19 / 0.40
Total score*	145.9±51.16	-0.37 / 0.10	-0.29 / 0.20	-0.12 / 0.61	-0.38 / 0.09	-0.41 / 0.07	-0.43 / 0.05

***:** *mean±SD; rho/p* **†:** *median (min-max); rho/p*

Table III: Correlation between sensory processing and quality of life

	Values	Quality of Life Scale for Children					
		Physical Functioning	Emotional Functioning	Social Functioning	School Functionality	Psychosocial Health	Total score
Sensory Processing Scale Home Form*							
Social Participation†	34.1±4.35	-0.24/0.29	-0.02/0.90	-0.30/0.18	-0.34/0.14	-0.28/0.22	-0.33/0.14
Visual†	14 (11/25)	0.42/0.06	-0.22/0.33	0.10/0.67	0.37/0.10	0.07/0.75	0.27/0.25
Auditory†	10 (8/20)	0.13/0.57	-0.01/0.99	0.04/0.83	0.44/0.05	0.17/0.47	0.16/0.49
Tactile†	15 (11/27)	0.26/0.26	-0.15/0.51	-0.07/0.75	0.28/0.21	-0.04/0.84	0.13/0.58
Taste and smell†	5.5 (5/10)	0.07/0.76	0.03/0.87	-0.16/0.49	-0.12/0.61	-0.15/0.51	-0.07/0.75
Body awareness†	13 (10/20)	0.49/0.02	0.19/0.41	0.13/0.57	0.21/0.36	0.20/0.38	0.36/0.10
Balance and movement*	16 (13/21)	-0.06/0.78	-0.30/0.18	-0.09/0.70	0.05/0.80	-0.26/0.26	-0.19/0.41
Planning and thought*	13±3.08	0.47/0.03	0.13/0.58	0.32/0.16	0.29/0.20	0.25/0.28	0.44/0.04
Sensory systems*	75.5±12.03	0.42/0.06	-0.14/0.53	0.16/0.49	0.32/0.16	0.07/0.76	0.27/0.24
Total*	122.6±11.59	0.45/0.04	-0.11/0.63	0.14/0.53	0.23/0.31	0.04/0.84	0.26/0.25

***:** *mean±SD; rho/p* **†:** *median (min-max); rho/p*

score. A moderately negative correlation was found between fine motor integration and emotional functioning (r=-0.450, p=0.040), psychosocial health (r=-0.570, p=0.010), and total CQL (r=-0.520, p=0.010). A moderate negative correlation was found between manuel dexterity and school functioning (r=-0.480, p=0.020), and between bilateral coordination and physical functioning (r=-0.450, p=0.040). No correlation was found between other BOT 2 parameters and the CQL parameters (Table II). When the relationship between sensory processing and quality of life was examined in children with T1DM, no relationship was found between social participation, visual, auditory, tactile, taste and smell, balance and movement, sensory systems and quality of life. A moderately positive correlation was found between body awareness (r=0.049, p=0.020), planning and ideation (r=0.047, p=0.030), and the total SPM score (r=0.450, p=0.040) and physical functioning. A moderately positive correlation was also found between planning and ideas and the total score of the CQL (r=0.440, p=0.040) (Table III).

Discussion

This study, which examined the relationship between motor performance, sensory processing skills, and quality of life in preschool children with type 1 diabetes, concluded that motor performance and sensory processing skills are associated with quality of life. In preschool children with type 1 diabetes, impairments in sub-parameters of motor performance, such as fine motor sensitivity, fine motor integration, dexterity, and bilateral coordination, have been observed to be associated with the children's quality of life.When examining the effects of sensory processing on quality of life in children with type 1 diabetes, the relationship between sensory processing impairments, particularly in the areas of body awareness, planning, and idea generation, and quality of life stands out.It is known that the metabolic changes occurring in individuals with T1DM lead to a number of different problems. One of these is that hyperglycemia seen in T1DM causes damage, particularly to peripheral motor neurons, resulting in a loss of motor performance (23). Children with T1DM may experience musculoskeletal disorders and myopathies (3). It has been reported that there are particular effects on fine motor skills (4). Problems with motor skills can also affect individuals' quality of life. A systematic review published in 2023 reported that motor impairments in children negatively affect their quality of life (24). We concluded fine motor sensitivity, fine motor integration, dexterity, and bilateral coordination were associated with quality of life parameters. Fine motor sensitivity was found to be associated with physical functioning, and fine motor sensitivity and dexterity were found to be associated with school functioning. Since a large proportion of the children attended daycare and preschool, the impairments in fine motor sensitivity and hand dexterity may have led to their inability to perform necessary functions at school and to physical deficiencies.

Fine motor coordination skills were found to be associated with emotional functioning, psychosocial health, and overall quality of life scores. Children with inadequate fine motor skills may feel inadequate compared to their peers, potentially lowering their psychosocial quality of life. In children with T1DM, impairments in fine motor skills have been shown to negatively affect their quality of life. Rehabilitation programs that focus on fine motor skills, especially in the preschool years, can improve children's quality of life. Bilateral coordination skills were found to be associated with physical functionality. A review of the literature indicates that studies in different patient groups have shown that as children's bilateral coordination skills improve, their quality of life also improves (25). Based on this, rehabilitation programs aimed at improving bilateral coordination skills can be used to enhance the quality of life for children with T1DM. In children with T1DM, other motor parameters such as strength, speed and agility, and balance may also be affected, but the impact may not be severe enough to affect quality of life and therefore may not be reflected in the results. Further studies comparing motor skills in healthy children and children with T1DM may be important. The results of this study are consistent with the literature, showing that fine motor skills are affected and that this impact negatively affects the quality of life of children.

In individuals with T1DM, the insulin-producing beta cells of the pancreas are destroyed autoimmuneally. Insulin deficiency in the body leads to uncontrolled blood sugar levels. Therefore, there is a need to take insulin from an external source (26). Studies on the effects of insulin on the brain suggest that insulin has a regulatory effect on sensory processing. Kern et al. (27) suggest that insulin has a direct effect on the modulation of brain functions. Goldberg et al. (10), in their study examining sensory processing in individuals with T1DM, concluded that these individuals have sensory processing disorders. Sensory processing has been defined as the ability to analyze, modulate, and organize incoming sensory information in order to respond to environmental stimuli (28). Therefore, low or high sensitivity in sensory processing can make it difficult to cope with environmental factors, affecting individuals' quality of life. (29,30). In this study, which examined the relationship between sensory processing and quality of life in children with T1DM, we concluded that sensory processing disorders affect quality of life. In children with T1DM, effects on body awareness and planning and thought skills were found to be related to the physical functioning parameter of quality of life. Pfeiffer et al. (31) also reported in their studies that sensory modulation problems affect the physical aspect of quality of life. They noted that hypersensitive individuals, in particular, may experience physical fatigue and a decrease in their physical quality of life as a result of high arousal levels.

Healthy body awareness is crucial for coordinating movements, maintaining posture and balance, and performing holistic physical functions (32). Studies examining the relationship between body awareness and quality of life have shown that individuals with higher body awareness have a higher quality of life (33). Our study also shows that impaired body awareness in individuals with T1DM is associated with their quality of life. In particular, impairments in physical function may result in children with type 1 diabetes having reduced body awareness, which can lead to difficulties in demonstrating physical skills and consequently a decreased quality of life.Motor planning and conception is the process of preparing and organizing motor behaviors to perform specific, goal-oriented actions. It involves integrating intrinsic motor knowledge with sensory information to design, plan, and execute movements. Deficiencies in motor planning can affect a child's independence and social participation because they can impact daily living activities such as dressing and writing (34). Although no studies examining planning and ideation skills in children with T1DM were found, our study concluded that impairments in these skills negatively affect physical functionality and overall quality of life. This may be because children with T1DM have difficulties performing physical skills due to deficits in motor planning Further studies examining the motor planning and decision-making skills of children with T1DM and healthy control groups may be important.

Limitations

Limitations of the study include the lack of a healthy control group and the failure to assess the children's physical activity levels. Further studies comparing motor performance, sensory processing, and quality of life in healthy children and children with T1DM will contribute to the literature. Furthermore, the inclusion and exclusion criteria limited the sample size of the study. The small number of participants is among the limitations. This study included children diagnosed with T1DM for at least 6 months due to the limited age range. Further studies with children diagnosed with T1DM for longer periods may benefit the literature. Another limitation of the study is that metabolic control parameters (HbA1c, etc.) were not included in the analyses. The relationship between these variables and functional outcomes should be investigated in future studies.

Conclusion

In conclusion, motor performance and sensory processing skills are associated with quality of life in children with T1DM. Rehabilitation approaches that improve motor skills and sensory processing abilities in children with T1DM can be important in improving their quality of life.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (05.06.2024, reference numbe:1-24-295).

Contribution of the authors

Idea/Concept: AAB, BE; Design: AAB, BE; Supervision: FG, MB, BE; Funding and Resource Provision: AAB; Materials: AAB, FG, MB, BE; Data Collection and/or Processing: AAB, FG, MB; Analysis/ Interpretation: AAB, BE; Literature Review: AAB, FG, MB, BE; Article Writing: AAB, BE; Critical Review: AAB, FG, MB, BE.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Factors affecting mortality in patients during postoperative follow-up after cardiac surgery in a pediatric intensive care unit

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Received : 06.01.2026, Accepted : 21.04.2026 DOI: 10.12956/TJPD.2026.1295

ABSTRACT

Objective: Congenital heart diseases (CHD) frequently necessitate cardiovascular surgery (CVS) in pediatric patients. This study aimed to evaluate postoperative complications following CVS and to investigate their association with mortality.

Materials and Methods: In this retrospective study, the medical records of 124 patients who underwent CVS and were subsequently monitored in the pediatric intensive care unit were reviewed.

Results: Among the 124 patients who underwent cardiovascular surgery, 52.4% (n=65) were male. The median age was 7 months (range, 2–71). Ventricular septal defect closure (n=49) and complete atrioventricular septal defect repair (n=15) were the most frequently performed procedures. Twenty-seven patients had chromosomal anomalies, most commonly Down syndrome. No postoperative complications were observed in 95 patients. The most common complications were atelectasis, arrhythmia, and subcutaneous emphysema. Extracorporeal therapy was administered to 12 patients. Overall mortality was 8.8% (n=11). Preoperative pulmonary hypertension (PHT) was the most common cause of death. Among the deceased patients, additional factors associated with mortality include infection and lower albumin levels, while nitric oxide therapy and intraoperative cardiopulmonary bypass use were also more common, possibly reflecting greater clinical severity.

Conclusion: As the use of cardiovascular surgery for CHD continues to increase in pediatric patients, optimizing intraoperative management and promptly identifying postoperative complications are crucial for improving survival outcomes.

Keywords: Congenital heart diseases, cardiac surgical procedures, pulmonary hypertension, postoperative complications

Introduction

Congenital heart diseases (CHD) are the most common type of congenital anomaly, which may or may not have a genetic origin. Approximately 40–50% of cases are diagnosed within the first week of life, and 50–60% within the first month (1,2). CHD affects approximately 9 per 1000 live births. Annually, nearly 40000 infants in the United States and 15000 in Türkiye are born with CHD. Almost half of these patients require intervention within the first year of life, and many subsequently require cardiac intensive care support (3,4). It accounts for 3% of neonatal death and 46% of death from all congenital malformations and is the leading cause of neonatal mortality (5-7). CHD is typically classified according to hemodynamic characteristics. It is categorized into four groups based on hemodynamic effects: defects associated with increased pulmonary blood flow (i.e., left-to-right shunts), defects associated with decreased pulmonary blood flow (i.e., right-to-left shunts), obstructive lesions, and defects with mixed circulation (1). Recent data indicate that 61.9% of patients with CHD admitted to the neonatal intensive care unit had cyanotic heart disease, and 87.5% of these cases were classified as complex cardiac defects (8).

Investigations such as echocardiography (ECHO) and electrocardiography (ECG) play a key role in the diagnosis and follow-up of CHD. In complex cases, additional diagnostic modalities, including computed tomography (CT), magnetic resonance imaging (MRI), cardiac catheterization, and angiography, may be required (9).

Patients with CHD may require corrective and/or palliative surgical interventions based on the specific cardiac lesion and hemodynamic condition. Surgical outcomes are

influenced by multiple factors, including genetic syndromes, low birth weight, and preoperative clinical severity (10).

After cardiovascular surgery, patients with CHD are generally monitored in the intensive care unit under endotracheal intubation for approximately 5–8 hours. They continue to receive care in the pediatric intensive care unit (PICU) or pediatric cardiac intensive care unit (PCICU) until hemodynamic stability is established (11). In recent years, postoperative care for pediatric patients undergoing cardiac surgery has been provided in neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs) worldwide, including in Türkiye. However, despite the high volume of cardiac surgeries, the number of pediatric cardiac intensive care units (PCICUs) remains insufficient (4).

This study investigated the clinical course and postoperative complications of patients undergoing cardiovascular surgery (CVS) and examined their association with mortality in a tertiary pediatric intensive care unit (PICU).

Materials and Methods

The medical data of 124 pediatric patients who underwent cardiovascular surgery and were monitored in the postoperative period in the Pediatric Intensive Care Unit of Diyarbakır Gazi Yaşargil Training and Research Hospital between July 1, 2021, and December 1, 2022 were retrospectively reviewed and recorded. Data were collected from archived files, patient follow-up forms, physician and nursing notes, operative reports, anesthesia records, and discharge summaries stored in the hospital electronic database. The following variables were recorded: demographic characteristics (age and gender), echocardiographic diagnosis, associated syndromes, duration of PICU stay, time to initiation of postoperative feeding, echocardiographic ejection fraction (EF), mortality, and discharge outcomes.

In addition, PRISM scores at PICU admission; vital signs (blood pressure, pulse rate, oxygen saturation, respiratory rate, and level of consciousness); postoperative complications (including pleural effusion, subcutaneous emphysema, atelectasis, pneumothorax, chylothorax, arrhythmias, convulsions, pediatric acute respiratory distress syndrome [PARDS], and hemophagocytic syndrome); type of surgical procedure; extracorporeal therapies administered (peritoneal dialysis [PD], hemodiafiltration [HDF], and extracorporeal membrane oxygenation [ECMO]); laboratory parameters; neutrophil-to-lymphocyte ratio (NLR); and lactate clearance were documented.

For the deceased patients, the following data were additionally recorded: duration of surgery (hours); duration of ICU stay (days); duration of mechanical ventilation (hours); time to initiation of postoperative feeding; postoperative ejection fraction (EF); first-day fluid balance; aortic cross-clamp time (CCT); cardiopulmonary bypass (CPB) time; neutrophil-to-lymphocyte ratio (NLR); postoperative day one albumin level; lactate level at admission; lactate clearance; C-reactive protein-to-albumin (CRP/albumin) ratio; and lactate-to-albumin ratio. Surgical risk stratification was performed using the RACHS-1 (Risk Adjustment for Congenital Heart Surgery) classification system. Each patient was assigned a RACHS-1 category based on the primary surgical procedure. RACHS-1 has been previously validated as a reliable method for risk adjustment in congenital cardiac surgery and shown to be associated with postoperative mortality (12). Due to the limited number of mortality events in our cohort, RACHS-1 categories were dichotomized into low surgical risk (categories 1–2) and high surgical risk (≥3) groups for statistical analysis to avoid sparse data bias and improve model stability.

Pulmonary hypertension was defined based on echocardiographic findings documented by a pediatric cardiologist. Peritoneal dialysis was initiated in patients with fluid overload unresponsive to medical treatment or acute kidney injury. ECMO was initiated in patients with refractory cardiogenic shock or PARDS despite maximal medical therapy. Pediatric acute respiratory distress syndrome (PARDS) was defined according to the Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria (13).

All echocardiographic evaluations were performed by experienced pediatric cardiologists using standardized institutional protocols. Inhaled nitric oxide (iNO) therapy was initiated at an initial dose of 10-20 ppm and adjusted based on arterial oxygenation, pulmonary artery pressure, and overall hemodynamic status. The dose was individualized according to clinical response and gradually weaned once oxygenation improved. The type and dosage of inotropic agents were recorded. For statistical analysis, the maximum VIS value within the first 24 hours after PICU admission was used. The daily vasoactive-inotropic score (VIS) was calculated using the following formula: VIS=dopamine dose (mcg/kg/min)+dobutamine dose (mcg/kg/min)+100×epinephrine dose (mcg/kg/min)+10 × milrinone dose (mcg/kg/min)+10.000 × vasopressin dose (U/kg/min) + 100×norepinephrine dose (mcg/kg/min) (14).

Statistical analysis

Statistical analyzes were performed using SPSS for Windows, Version 26.0 (Chicago, IL, USA). Descriptive statistics were presented as mean and standard deviation or median (minimum–maximum) for continuous variables and as percentages for categorical variables. Normality of distribution was assessed using the Kolmogorov–Smirnov test. Depending on data distribution, comparisons between groups were performed using the Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A two-tailed p-value < 0.050 was considered statistically significant. Univariate logistic regression analysis was performed to evaluate the association between high-risk RACHS category (≥3) and mortality. The strength of association was expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminative performance of RACHS category for predicting mortality, and the area under the curve (AUC) was calculated. Due to the limited number of mortality events (n=11), multivariate logistic regression analysis was not performed to avoid model overfitting.

Results

Of the 124 pediatric patients who underwent cardiovascular surgery (CVS) and were admitted to the pediatric intensive

care unit over a one-year period, 65 (52.4%) were male and 59 (47.6%) were female. The median age was 7 months (range: 2–71 months). The demographic characteristics of the patients are presented in Table I.

Table I: Demographic data of patients

Variables	Values
Gender*	
Male	65 (52.4)
Female	59 (47.6)
Age, months†	7 (2-71)
Body weight, kg†	5.8 (2.50-53)
Patients with genetic syndromes*	27 (21.8)
Exitus*	11 (8.8)

***:** n(%), **†:** median(min-max)*

Table II: Cardiac diagnoses and corresponding surgical interventions in the study population

Diagnosis/ operation	Primary	Secondary
Ventricular septal defect	51 (41.1)	16 (12.9)
Common atrioventricular canal defect	18 (14.5)	-
Tetralogy of Fallot	13 (10.5)	-
Coarctation of Aortic	7 (5.6)	6 (4.8)
Transposition of great arteries	7 (5.6)	-
Single ventricle	6 (4.8)	-
Total anomalous pulmonary venous drainage	5 (4.0)	-
Hypoplastic left heart syndrome	4 (3.2)	-
Tricuspid atresia	3 (2.4)	-
Double outlet right ventricle	3 (2.4)	-
Patent Ductus Arteriosus	2 (1.6)	32 (25.8)
Atrial septal defect	1 (0.8)	10 (8.1)
Aortopulmonary window	1 (0.8)	-
Hypoplastic right ventricle	1 (0.8)	-
Truncus arteriosus	1 (0.8)	-
Mitral atresia	1 (0.8)	-
Cardiac tumour	-	1 (0.81)
VSD closure	49 (39.5)	3
CAVCD repair	15 (12.1)	1
Pulmonary banding	11 (8.9)	-
Complete repair of tetralogy of Fallot	11 (8.9)	-
Bidirectional cavopulmonary anastomosis	10 (8.1)	-
Aortic Coarctation Repair	8 (6.5)	-
TAPVD repair	5 (4.0)	-
PDA ligation	4 (3.2)	42
Norwood stage 2	3 (2.4)	-
Aortopulmonary Window Closure	2 (1.6)	-
PDA closure	1 (0.8)	7
ASD repair	1 (0.8)	19
Hypoplastic Aortic Arcus Reconstruction	1 (0.8)	-
Blalock-Taussig Shunt	1 (0.8)	1
Kawashima procedure	1 (0.8)	-
Intracardiac tumour repair	1 (0.8)	-
Atrial septectomy	-	3
Pulmonary banding	-	4
Valvuloplasty/annuloplasty, tricuspid valve repair	-	8

***:** n(%), **ASD:** Atrial septal defect, **CAVCD:** Common atrioventricular canal defect, **PDA:** Patent ductus arteriosus, **TAPVD:** Total anomalous pulmonary venous drainage, **VSD:** Ventricular septal defect*

Table III: Complications

Complications	Values
No complication	95 (76.6)
Atelectasis	10(8)
Subcutaneous emphysema	9 (7.2)
Arrhythmia	9 (7.2)
JET	4 (3.2)
SVT	2(1.6)
VT	2(1.6)
AT	1(0.8)
Hypertension	4(3.2)
Chylothorax	3(2.4)
Pleural effusion	3(2.4)
Pneumothorax	3(2.4)
Pulmonary oedema	2(1.6)
Convulsion	2(1.6)
PARDS	2(1.6)
Diaphragmatic paralysis	1(0.8)
Cardiac tamponade	1(0.8)
Haemophagocytic syndrome	1(0.8)

***PARDS:** Pediatric acute respiratory distress syndrome, **AT:** Atrial tachycardia, **JET:** Junctional ectopic tachycardia, **SVT:** Supraventricular tachycardia, **VT:** Ventricular tachycardia*

The most common diagnoses were ventricular septal defect (VSD), common atrioventricular canal defect (CAVCD), tetralogy of Fallot (TOF), coarctation of the aorta (CoA), transposition of the great arteries (TGA), and other disorders, in descending order of frequency. The most frequently performed procedures were VSD closure (n=49) and CAVCD repair (n=15). In addition, 42 patients underwent concomitant patent ductus arteriosus (PDA) ligation. The primary and secondary procedures are presented in Table II. Twenty-seven patients had genetic syndromes, including 26 with Down syndrome and one with Trisomy 18 (Table I). The patient with trisomy 18 underwent VSD closure and PDA ligation. Among patients with Down syndrome, VSD closure was the most frequently performed procedure (n=12).

Ninety-five patients (76.6%) developed no postoperative complications. Twenty-nine patients experienced complications, most commonly atelectasis, followed by arrhythmia and subcutaneous emphysema. The least frequent complication was diaphragmatic paralysis (0.8%). Multiple complications occurred in 17 patients (13.7%) (Table III).

Extracorporeal therapy was administered to 12 patients: peritoneal dialysis (n=7), hemodiafiltration (n=2), extracorporeal membrane oxygenation (ECMO) (n=2), and plasmapheresis (n=1).

A total of 113 patients were discharged from the PICU to the cardiovascular surgery ward, whereas 11 patients (8.8%) died. Among the deceased patients, three had undergone bidirectional cavopulmonary anastomosis, two pulmonary banding, two VSD closure, two CAVCD repair, and two complete repair of TOF. One patient with Down syndrome who underwent CAVCD repair died. Three of the seven patients who received peritoneal dialysis died, whereas the remaining nine patients who received extracorporeal therapy were discharged from the PICU.

Table IV: Evaluation of data of patients with and without exitus

Variables	Discharged	Exitus	p
Total number of patients	113	11	-
Duration of surgery (hours)*	3.5 (1-6)	4.25 (3-6)	0.306
PICU hospitalisation duration (days)*	5.5 (2-113)	17 (3-6)	0.103
Duration of mechanical ventilator stay (hours)	4.5 (1-36)	9.5 (1-23)	0.710
Post-op feeding initiation time (hours)*	11 (4-51)	10 (4-51)	0.549
VIS score*	12 (5-27)	19.5 (5-31)	0.076
Post-op ejection fraction*	65 (50-75)	65 (50-75)	0.407
Total fluid given on the first day (ml/kg/day)*	100 (60–160)	95 (70–120)	0.241
Cross clamp time (minutes)*	73 (10–186)	95 (18–198)	0.225
Cardiopulmonary bypass time (minutes)*	117 (38-227)	141.5 (60-190)	0.649
Neutrophil/lymphocyte ratio*	3.44 (0.88-17.13)	2.68 (1.12–7.81)	0.452
Albumin post-op 1st day*	33 (16–48)	26 (2.9–47)	0.049
Initial lactate level at admission*	2.8 (0.8-12.69)	3 (1.4–10.09)	0.161
Lactate clearance*	30 (-180–100)	-17.41 (-85.71–32.30)	0.157
C reactive protein/albumin*	0.19 (0.01–7.56)	1.1 (0.34–8.52)	0.001
Lactate/albumin ratio*	0.08 (0.02–0.43)	0.10 (0.03–2.01)	0.075
Patients with genetic syndromes†	25 (22.1)	2 (18.2)	0.763
Complications†	35 (31)	6 (54.5)	0.114
Chylothorax†	7 (6.2)	1 (9.1)	0.133
Additional surgery†	37 (32.7)	2 (18.2)	0.348
Heart failure†	46 (40.7)	4 (36.4)	0.142
Pulmonary hypertension†	28 (24.8)	6 (54.5)	0.035
Nitric oxide†	20 (17.7)	4 (36.4)	0.002
Development of infection†	42 (37.2)	3 (27.3)	0.023
Sepsis†	10 (8.8)	6 (54.5)	0.002
Ventilator-associated pneumonia†	2 (1.8)	1 (9.1)	0.131
Cardiopulmonary bypass†	39 (34.5)	3 (27.3)	0.013

:** *Median (min–max) (Mann–Whitney U test),* **†:** *n (%) (Fisher's exact test),* ***PICU: *Pediatric intensive care unit,* ***VIS:*** *Vasoactive inotrope score*

Table V: ROC analysis of mortality predictors

Variable	AUC	95% CI	Cutoff	Sensitivity (%)	Specificity (%)
Albumin	0.748	0.155–0.349	≤42.5 g/L	100	48.7
CRP/Albumin	0.843	0.770–0.916	≥0.465	90.9	75.2
RACHS (1–4)	0.626	0.462–0.790	≥3	63.6	63.7

Comparison of survivors and non-survivors revealed significant associations between mortality and the presence of preoperative pulmonary hypertension (PHT), lower postoperative albumin levels, higher C-reactive protein-to-albumin (CRP/albumin) ratios, nitric oxide administration, infection, and use of cardiopulmonary bypass (Tables IV).

Univariate logistic regression analysis was performed to evaluate the association between high-risk RACHS category (≥3) and mortality. Although patients in the high-risk RACHS group had a higher odds of mortality (OR: 3.07, 95% CI: 0.85–11.13), this association did not reach statistical significance (p=0.087).

Receiver operating characteristic (ROC) curve analysis demonstrated limited discriminative ability of RACHS category for predicting mortality, with an area under the curve (AUC) of 0.626, indicating poor-to-fair performance. There were 11 deaths (8.9%) among 124 patients. ROC analysis demonstrated that the CRP/albumin ratio predicted mortality with an AUC of 0.843, indicating good discriminative ability. The optimal cutoff value was ≥0.465, yielding a sensitivity of 90.9% and a specificity of 75.2%. ROC analysis demonstrated that postoperative albumin predicted mortality with an AUC of 0.748. The optimal cutoff value was ≤42.5 g/L, yielding a sensitivity of 100% and a specificity of 48.7% (Table V).

With respect to surgical type, mortality was highest among patients who underwent CAVCD repair (3/11). These patients developed complications including arrhythmia, PHT, pneumothorax, and pleural effusion. Two of them required intraoperative cardiopulmonary bypass. No significant difference in age was observed between deceased and surviving patients.

Two patients died within the first 48 hours postoperatively. One had undergone complete TOF repair with prolonged aortic cross-clamp time (198 minutes) and signs of sepsis. The other patient, who underwent VSD closure, had preoperative PHT and developed postoperative atelectasis.

The median maximum VIS within the first 24 hours after PICU admission was higher in non-survivors compared to survivors (22 vs. 12). However, this difference did not reach statistical significance (p=0.076).

Discussion

In our study, preoperative pulmonary hypertension was the most frequently observed clinical characteristic among non-survivors. Analysis of the 11 deceased patients further showed that infection and lower albumin levels were more common in this group. Nitric oxide therapy and intraoperative cardiopulmonary bypass use were also more frequently observed among non-survivors; however, these interventions were initiated in response to clinical deterioration and may therefore reflect postoperative instability rather than independent predictors of mortality. ROC analysis demonstrated that lower postoperative albumin levels had moderate discriminative ability for predicting mortality. In contrast, the CRP/albumin ratio showed good predictive performance. Nevertheless, due to the limited number of mortality events, these findings should be interpreted with caution and require validation in larger, prospective cohorts. Previous studies have demonstrated that survival rates after pediatric cardiac surgery have increased in recent years, whereas the rate of early mortality is reported to be approximately 3–4% (14-18).

Although nitric oxide administration and ECMO support were statistically associated with mortality, these findings should be interpreted as indicators of disease severity rather than independent causal factors. The requirement for advanced cardiopulmonary support generally reflects a more critical clinical status, which itself contributes to increased mortality risk.

In a cohort of 174 patients, Gaies et al. (14). reported a mortality rate of 12% following pediatric cardiovascular surgery. Comparatively, the mortality rate in our study was 8.8%. Early mortality (within the first 48 hours) occurred in two patients, representing 1.6% of the entire cohort and 18.2% of total deaths (14).

Twenty-nine patients (23.4%) developed postoperative complications. Arrhythmia and atelectasis were the most common complications. In a study conducted in adult patients, Khajali et al. (19) reported a respiratory complication rate of 14.9%. In a cohort of 326 adult patients, pleural effusion occurred in 5% of cases, while 3.75% developed other pulmonary complications (20). Studies involving pediatric patients undergoing CVS have generally not provided detailed information regarding postoperative complications. However, arrhythmias are consistently reported as the most common complication in the postoperative period.

In our cohort, arrhythmia was among the most frequent complications and occurred in 9 patients (7.2%). These included four cases of junctional ectopic tachycardia (JET), two supraventricular tachycardia (SVT), two cases of ventricular tachycardia, and one atrial tachycardia. One patient with JET died postoperatively. Consistent with our findings, Khan et al. (21) reported an arrhythmia rate of 10%, while Ergün et al. (22) reported a rate of 9.2%.

In a study including patients older than 15 years who underwent total correction of tetralogy of Fallot (TCTF), Khajali et al. (19) reported multiorgan failure in 5 of 94 patients, all of whom died. Among these five patients, two developed sepsis, two experienced acute kidney injury, and three required extracorporeal membrane oxygenation (ECMO).

In our study, one patient who died after complete repair of tetralogy of Fallot underwent cardiopulmonary bypass and had a prolonged aortic cross-clamp time (198 minutes), along with clinical signs of sepsis.

Similarly, Öztürk et al. (10) reported ECMO use in 26 patients (2.9%) with transposition of the great arteries (TGA) as the primary diagnosis. ECMO was initiated mainly due to hypoxemia secondary to PARDS, while other indications were cardiac causes. Two patients in our study required extracorporeal membrane oxygenation (ECMO) due to PARDS. Their primary diagnoses were left ventricular hypoplasia and tetralogy of Fallot (TOF). Both patients survived and were discharged.

None of the patients who underwent surgery for transposition of the great arteries (TGA) required ECMO support. Nine patients required extracorporeal therapies other than ECMO, including peritoneal dialysis (PD) and hemodiafiltration (HDF), due to fluid overload and/or renal failure. One patient underwent plasmapheresis for hemophagocytic lymphohistiocytosis.

Öztürk et al. (10) reported that 12% (107/895) of patients undergoing CVS had associated genetic syndromes, including Down syndrome and DiGeorge syndrome. In our study, 27 patients (21.7%) had genetic syndromes, consisting of Down syndrome and trisomy 18. The higher prevalence observed in our cohort may be related to advanced maternal age in the region where the study was conducted.

Although the high-risk RACHS category (≥3) was associated with an approximately three-fold increase in mortality, this association did not reach statistical significance. The limited number of mortality events in our cohort may have reduced the statistical power to detect a significant difference. Furthermore, ROC curve analysis demonstrated limited discriminative ability of RACHS for predicting mortality (AUC=0.626), indicating poor-to-fair performance. This modest predictive value may be explained by the small number of deaths and the heterogeneity of surgical procedures included in the study population.

In our study, non-survivors demonstrated higher VIS values within the first 24 hours, this difference did not reach statistical significance. The maximum VIS in the first 24 hours is one of the most commonly used and validated parameters in the pediatric cardiac surgery literature, as it effectively reflects early postoperative hemodynamic support requirements and has been shown to correlate with important clinical outcomes including morbidity and mortality.While serial or trend-based VIS assessments at multiple postoperative time points may provide additional insight into the dynamic clinical course, as emphasized by Davidson et al. (23), we selected the maximum value in the first 24 hours because this approach is practical, widely accepted in retrospective studies, and strongly supported by previous validation studies (24,25).

Limitations

This study has several limitations. First, it was conducted at a single center with a relatively small sample size, which

may limit the generalizability of the findings. Second, the number of mortality events was low (n=11), which restricted the statistical power of the analyses and precluded multivariate logistic regression modeling. Third, due to the observational design of the study, causal relationships between identified risk factors and mortality cannot be established. In addition, the heterogeneity of surgical procedures included in the cohort may have influenced the overall predictive performance of the RACHS classification. Larger, multicenter studies with a greater number of events are needed to validate these findings.

Conclusion

In conclusion, CVS procedures for congenital heart disease (CHD) have steadily increased in the pediatric population. Awareness of intraoperative factors and early recognition of postoperative complications may improve survival outcomes in these patients.

Presented

This study was accepted for oral presentation and presented at the 69th Turkish National Pediatrics Congress, held on October 15–19, 2025, at Elexus Hotel, Turkish Republic of Northern Cyprus (TRNC).

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Diyarbakır Gazi Yaşargil Training and Research Hospital (09.07.2021, reference number: 830).

Contribution of the authors

Study conception and design: MNT, EET; Data collection: ÖO, FK, MNT; Analysis and interpretation of results: AA, FK; Draft manuscript preparation: MNÖ, BA, A A; All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

The role of essential fatty acid deficiencies in cognitive function among patients with organic acidemias

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Received : 28.01.2026, Accepted : 05.05.2026 DOI: 10.12956/TJPD.2026.1300

ABSTRACT

Objective: Organic acidemias (OAs) are metabolic disorders characterized by enzyme deficiencies that impair amino acid catabolism, leading to metabolic imbalances. Essential fatty acids (EFAs), particularly Omega-3 and Omega-6, are vital for cellular and neurological functions but are often affected by protein-restricted diets used in OA management. The aim of this study was to evaluate the plasma EFA levels in OA patients and explores their clinical relevance.

Materials and Methods: A prospective, case-control design was adopted, including 26 OA patients (methylmalonic acidemia, propionic acidemia, isovaleric acidemia, maple syrup urine disease) and 22 healthy age- and gender-matched controls. Plasma EFA levels were quantified via gas chromatography-mass spectrometry. Cognitive and psychiatric evaluations were performed using standardized tests, including DSM-V-TR criteria, Wechsler Intelligence Scale for Children, and other psychometric tools. Statistical analyses assessed the relationships between EFA levels and clinical findings.

Results: Organic acidemias patients exhibited significantly lower levels of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) + DHA, and Omega-3 compared to controls, with higher Omega-6/Omega-3 ratios. Despite these findings, no significant correlations emerged between EFA levels and cognitive or psychiatric outcomes.

Conclusion: EFA deficiencies are prevalent among OA patients on protein-restricted diets, underscoring the potential need for targeted nutritional interventions. However, the absence of a direct association with clinical findings suggests multifactorial influences on disease outcomes. Future research should explore the longitudinal effects of EFA supplementation and its role in mitigating neurodevelopmental impairments in OA.

Keywords: Docosahexaenoic acid, essential fatty acids, metabolic disease, omega-3

Introduction

Organic acids are compounds with weak acidic properties that contain carbon skeletons. In patients diagnosed with organic acidemia, there is a deficiency in the enzymes responsible for amino acid catabolism. As a result, organic acids, which emerge as intermediate metabolites during physiological processes, accumulate and disrupt acid-base balance and intracellular biochemical and metabolic pathways. To date, many types of organic acidemia have been identified. The most common group involves disorders of branched-chain amino acid metabolism, including maple syrup urine disease (MSUD), methylmalonic acidemia (MMA), propionic acidemia (PA), and isovaleric acidemia (IVA). Other frequently seen types are biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, and ketothiolase deficiency (1).

The analysis of organic acids in urine is crucial for diagnosing organic acidemia. The diagnosis is confirmed through high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), or tandem mass spectrometry, followed by enzyme and DNA analyses (2). A key principle of treatment is the rapid removal of toxic substrates and the early implementation of dietary therapy by restricting specific nutrients. This approach increases long-term survival and reduces complications. Patients

with organic acidemia must avoid not only animal-based foods but also some plant-based foods with high protein content. Severe protein restriction can be compensated by consuming specialized amino acid mixtures that lack critical amino acids. However, dietary protein restrictions may lead to reduced intake of amino acids, vitamins, trace elements, and polyunsaturated fatty acids (3).

Fatty acids are named according to the position of their first double bond from the terminal omega carbon, resulting in classifications such as Omega-3, Omega-6, Omega-7, and Omega-9. Essential fatty acids, which the body cannot synthesize and must be obtained from the diet, cause characteristic symptoms when deficient. While humans can produce saturated and monounsaturated fatty acids, they cannot generate the double bonds present in Omega-3 and Omega-6 fatty acids, making these two critical members of the essential fatty acid group (4).

This study aimed to determine the levels of essential fatty acids in patients with organic acidemia on protein-restricted diets and to evaluate the clinical significance of essential fatty acid deficiencies.

Materials and Methods

This study was designed as a prospective, cross-sectional case-control study. It included 26 patients diagnosed with organic acidemia (MMA, PA, IVA, MSUD) who had been followed for at least six months at the Metabolism and Nutrition Outpatient Clinic of the Ankara Pediatric Hematology Oncology Training and Research Hospital. All patients over six months old who applied between January 2018 and October 2018 were included in the study. Patients with cobalamin-related hyperhomocysteinemia were excluded. Informed consent was obtained from all participants.

During routine follow-up visits, patients were informed about the study, and their physical examinations were conducted by a metabolic specialist. Measurements, including head circumference, body weight, and height, were recorded and evaluated against standard growth curves. The findings from physical examinations were documented. On the same day, blood samples were taken for routine tests and serum lipid profiling. Blood samples for essential fatty acid analysis were collected in heparin tubes after at least three hours of fasting. A minimum of 3 cc of blood was collected, centrifuged, and stored at -80°C until analysis. For comparison, the control group included 23 healthy children of similar age and gender who were followed at the general outpatient clinic.

The specific amino acid mixtures provided to the patients were as follows:

- MMA and PA patients: OS-1® or OS-2®, containing restricted valine, isoleucine, methionine, and threonine.
- IVA patients: Leu-1® or Leu-2®, containing restricted leucine.
- MSUD patients: MSUD-1® or MSUD-2®, containing restricted valine, leucine, and isoleucine.

All samples from the patients and controls were analyzed together in a single batch. Essential fatty acid levels were measured using gas chromatography-mass spectrometry (GC-MS) following the SIM analysis method. Plasma samples underwent methylation and hydrolysis before being injected into the Shimadzu GCMS QP 2010SE device. The column oven temperature was gradually increased from 100°C to 220°C, with the helium gas flow set at 1 mL/min. Results were expressed as percentages.

On the same day as their physical examinations, the patients were evaluated by a child psychiatrist. If a same-day psychiatric evaluation was not feasible, it was conducted within 1–3 months during subsequent follow-up visits. Psychiatric evaluations were carried out in accordance with DSM-V-TR criteria (Diagnostic and Statistical Manual of Mental Disorders). Depending on the patients' age, screening tools or cognitive tests were administered. Cognitive assessments included: Ankara Developmental Screening Inventory (AGTE), Stanford-Binet Intelligence Test, and Wechsler Intelligence Scale for Children – Revised Version (WISC-IV) (5-7). For patients whose developmental and cognitive levels permitted, additional psychometric tests, such as the Stroop Test and Cancellation Test, were used to assess attention. IQ levels were classified as follows: Bright intelligence (IQ>120), Normal cognitive function (IQ 90–120), Borderline intelligence (IQ 80–90), Mild cognitive delay (IQ 70–80), Moderate cognitive delay (IQ 50–70), and Severe cognitive delay (IQ<50).

Statistical analysis:

All data were analyzed using IBM Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The Mann-Whitney U test and Independent samples T test were used for comparing two independent groups by distribution type. For comparisons involving more than two groups, the Kruskal-Wallis one-way analysis of variance was used. Categorical data were analyzed using the Chi-square test. Relationships between quantitative variables were assessed using Spearman's rank correlation analysis. Descriptive statistics were expressed as mean and standard deviation (SD) for normally distributed variables and as median (minimum–maximum) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. Statistical significance was set at $p<0.050$.

Results

This study included 26 patients diagnosed with branched-chain amino acid metabolism disorders (MSUD, MMA, PA, IVA). Of these patients, nine (35%) had MSUD, seven (27%) had MMA, five (19%) had PA, and five (19%) had IVA. The ages of the patients ranged from four months to 24 years, with a mean age of 6.31±5.45 years (median; 5.34 years). Of the total patients, 17 (65.4%) were male, and nine (34.6%) were female. The age at diagnosis ranged from the neonatal period to eight years, with a median age of one month and a mean age of 1.01±2.18 years. The average total protein intake was 2.06±0.48 g/kg/day, while the natural protein intake averaged 0.87±0.17 g/kg/day.

Psychiatric assessments were not performed on five of the patients. Among the remaining 21 patients, 14.3% (n=3)

Table I: Cognitive and psychiatric assessments of the patient group

	Values*
Cognitive Evaluation	
Normal intelligence	3 (14.3)
Borderline intelligence	3 (14.3)
Mild cognitive delay	8 (38.1)
Moderate cognitive delay	4 (19.0)
Severe cognitive delay	3 (14.3)
Psychiatric Diagnosis	
No diagnosis	5 (23.8)
Attention-Deficit/Hyperactivity Disorder (ADHD)	1 (4.8)
Specific learning disorder	1 (4.8)
Autism	1 (4.8)
Autism + Cognitive Delay	3 (14.3)
Cognitive Delay only	10 (47.6)

: *n (%)

Table II: Serum lipid profiles of the patient group

Lipid Parameter	Values*
Total cholesterol (mg/dL)	143.04±39.34
Triglycerides (TG) (mg/dL)	107.92±52.08
HDL (mg/dL)	48.89±13.84
LDL (mg/dL)	71.88±32.21
VLDL (mg/dL)	21.49±10.87

: *mean±SD

had normal cognitive function, while the majority (52.4%, n=11) were classified with borderline intelligence or mild cognitive delay. In 33% (n=7) of the patients, moderate to severe cognitive delay was observed. Table I summarizes the cognitive and psychiatric assessments of the patients.

Table II summarizes the serum lipid profiles of the patient group. The mean total cholesterol level was 143.04±39.34 mg/dL, indicating overall cholesterol values within a generally acceptable range. Triglyceride levels averaged 107.92± 52.08 mg/dL, showing moderate variability among patients. The mean HDL cholesterol level was 48.89±13.84 mg/dL, reflecting relatively favorable protective lipid levels, while LDL cholesterol averaged 71.88±32.21 mg/dL. Additionally, the mean VLDL level was 21.49±10.87 mg/dL. Overall, the lipid profile suggests a balanced lipid status in the patient group, with considerable interindividual variation.

No statistically significant differences were observed between groups for ALA and EPA levels (p=0.103 and p=0.062, respectively). However, DHA levels were markedly lower in the patient group compared with controls (p=0.001). While linoleic acid (LA), DGLA, and arachidonic acid (AA) levels were similar between groups, combined EPA+DHA and total omega-3 fatty acid levels were significantly reduced in patients (p=0.001). In contrast, omega-6 levels were significantly lower in the patient group (p=0.004), yet the omega-6/omega-3 ratio was dramatically higher among patients, indicating a pronounced imbalance favoring omega-6 fatty acids (p=0.004). Additionally, the AA/DHA ratio was significantly elevated in the patient group (p=0.005), whereas the AA/EPA ratio did not differ significantly between groups. Overall, DHA, EPA+DHA, Omega-3 and Omega-6 levels were significantly lower in the patient group compared

Table III: Comparison of essential fatty acid levels between patient and control groups

Fatty Acid	Control	Patient	p
Number of patients	22	26	-
ALA (%)*	0.10 (0.1-0.1)	0.10 (0-0.10)	0.103
EPA (%)*	0.10 (0.10-2.8)	0.10 (0-3.91)	0.062
DHA (%)*	2.36 (0.1-5.76)	0.10 (0-12.52)	0.001
LA (%) †	69.47±28.36	71.22±29.19	0.591
DGLA (%) †	2.44±0.98	2.68±3.00	0.373
AA (%) †	13.09±4.41	13.10±10.80	0.396
EPA+DHA (%) †	2.89±1.84	1.58±3.42	0.001
Omega-3 (% †)	2.98±1.83	1.67±3.42	0.001
Omega-6 (%) †	92.51±20.67	86.79±32.14	0.004
Omega 6/ Omega- 3 †	39.45±22.69	195.37±152.59	0.004
AA/EPA †	106.53±62.75	118.95±103.29	0.772
AA/DHA †	6.19±3.67	62.20±89.63	0.005

: *median (min-max) (Mann Whitney U test),* †: *mean±SD (Independent samples T test)***

to the control group. Conversely, Omega-6/Omega-3, and AA/DHA ratios were significantly higher in the patient group (Table III).

Table IV shows the relationship between cognitive levels and essential fatty acid profiles. Although mean EPA+DHA and total omega-3 levels were higher in the normal/borderline cognitive group compared with the mild and moderate–severe delay groups, these differences were not statistically significant (p=0.659). In contrast, omega-6 levels and the omega-6/omega-3 ratio tended to increase with lower cognitive impairment, but no significant associations were observed (p=0.659). The AA/EPA and AA/DHA ratios also showed a progressive increase from normal/borderline cognition to moderate–severe delay, suggesting a trend toward a more pro-inflammatory fatty acid profile with worsening cognitive status; however, these trends did not reach statistical significance (p=0.564 and p=0.343, respecively). Overall, while variations in fatty acid composition across cognitive levels were apparent, no significant relationships were identified in this analysis.

Discussion

There are only a limited number of studies in the literature comparing Omega-3 and Omega-6 levels in patients diagnosed with organic acidemia. In this study, we compared the ratios of Omega-3 and Omega-6 fatty acids between the patient and control groups. Our findings are consistent with the few similar studies in the literature. This study also included a larger number of patients compared to previous research. Cognitive function and neurodevelopment in individuals with organic acidemia may be affected not only by the primary disease but also by Omega-3 deficiency. For this reason, we evaluated both cognitive status and Omega-3/Omega-6 levels, but no significant correlation was found.

Sanjurjo et al. (8) compared five patients with MMA and eight with urea cycle defects—both on protein-restricted

Table IV: Relationship between cognitive levels and essential fatty acid levels

Fatty Acid	Normal / Borderline*	Mild Delay*	Moderate / Severe Delay*	p†
EPA+DHA (%)	4.61±6.42	0.80±0.89	0.85±1.14	0.659
Omega-3 (%)	4.69±6.40	0.90±0.89	0.95±1.14	0.659
Omega-6 (%)	95.31±6.40	99.10±0.89	99.05±1.14	0.659
Omega-6/Omega-3	180.13±168.30	219.64±142.11	248.54±143.12	0.659
AA/EPA	99.28±96.92	129.39±88.61	161.88±130.50	0.564
AA/DHA	36.44±37.29	51.74±63.71	103.58±138.00	0.343

**: mean±SD, †: Kruskal-Wallis*

diets—with a control group of 50 healthy individuals. In their study, the free plasma levels of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were found to be lower in the patient group. The only discrepancy with our study lies in the EPA levels, which were also low in our control group, possibly explaining this difference.

Vilaseca et al. (9) divided patients with metabolic disorders into two groups: those on protein-restricted diets and those not on such diets. The study included 63 patients (four with PA, five with MSUD, and nine with cobalamin deficiency) on restricted diets and 69 patients on unrestricted diets. Higher erythrocyte and plasma DHA levels were found in the group without dietary restrictions. Similarly, in our study, DHA levels were significantly lower in the patient group following a protein-restricted diet compared to the control group.

Mazer et al. (10) evaluated six female MSUD patients aged 12–30 years and compared their essential fatty acid levels with those of 12 healthy controls. They found lower DHA levels and higher alpha-linolenic acid (ALA) levels in the MSUD group, which is consistent with our findings. Vlaardingerbroek et al. (11) studied 33 patients with metabolic disorders, including 10 with branched-chain amino acid metabolism disorders, and compared them with 38 controls. In their study, DHA levels were lower in the patient group, which aligns with the results of our study.

Drecksen et al. (12) compared the essential fatty acid levels of 10 IVA patients with those of 53 healthy controls. They reported a decrease in all Omega-3 fatty acid levels and an increase in the Omega-6/Omega-3 ratio in the patient group. As emphasized by Simopoulos et al. (13), maintaining a proper balance between essential fatty acids is crucial for normal growth and development. Consistent with both Drecksen's and our study, the Omega-6/Omega-3 ratio was found to be elevated in the patient group.

Aldámiz-Echevarría et al. (14) conducted a study in which 4 patients with MMA received DHA supplementation. They compared the total cholesterol, HDL, triglyceride (TG), and essential fatty acid levels of these patients with those of control and placebo groups. At the start of the study, the mean levels of total cholesterol, HDL, and TG were 114.7 mg/dL, 48.5 mg/dL, and 144 mg/dL, respectively. No significant difference in essential fatty acid levels was observed between the groups at baseline. However, after DHA supplementation, DHA and Omega-3 levels increased significantly, while TG levels decreased. In our study, DHA and Omega-3 levels were significantly lower in the patient group compared to the control group. The average levels of total cholesterol, HDL, and TG in our study were 143 mg/dL, 48.9 mg/dL, and 108.89 mg/dL, respectively. Differences in essential fatty acid levels between studies may be due to variations in sample size and patient age. Additionally, the higher total cholesterol and lower TG levels in our study are noteworthy.

Barschak et al. (15) evaluated the biochemical parameters of seven MSUD patients and compared them with healthy controls. They found that total cholesterol levels were significantly higher in the control group, but no significant differences were observed in HDL, LDL, or TG levels. In our study, HDL, LDL, and TG levels were within normal reference ranges and were not compared with those of the control group.

No studies in the literature have directly explored the effects of essential fatty acid levels on cognitive development in individuals with organic acidemia. However, El-Ansary et al. (16) conducted an animal study in which rats were given propionic acid to induce neurotoxicity. They found that Omega-3 fatty acids increased the levels of GABA, serotonin, and dopamine in the brain, as well as the formation of phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine. Omega-3 fatty acids also protected the rats from propionic acid-induced neurotoxicity.

In phenylketonuria (PKU), another metabolic disorder requiring a protein-restricted diet, several studies have examined the effects of essential fatty acid supplementation on cognitive and neurological function. Koletzko et al. (17) administered DHA supplements to 36 children with PKU for three months and reported improvements in visual function, motor skills, and coordination, accompanied by increased plasma DHA and EPA levels and decreased arachidonic acid (AA) levels. Children underwent visual evoked potentials (VEP) testing before and after supplementation, and a subgroup was additionally assessed using the Rostock–Oseretzky Scale (ROS), with untreated age-matched controls showing no comparable improvements. Similarly, Agostoni et al. (18) conducted a double-blind study in 20 patients with hyperphenylalaninemia who received DHA and EPA supplementation for 12 months and observed improvements in visual function alongside increased DHA levels. In contrast, more recent randomized controlled trials in PKU have shown that although DHA supplementation dose-dependently increases plasma DHA levels, it does not consistently result in measurable improvements in cognitive

or neurological outcomes within the tested dose ranges (19). In line with these observations, our study conducted in children with organic acidemias found that mean EPA+DHA and total omega-3 levels tended to be higher in the normal/borderline cognitive group compared with the mild and moderate–severe delay groups; however, these differences did not reach statistical significance, limiting conclusions regarding a direct association. In comparison, randomized controlled trials in healthy school-aged children have indicated that regular consumption of oily fish, rather than isolated supplementation, may be associated with modest improvements in cognitive and socioemotional functioning, particularly in attention and cognitive flexibility, as well as reductions in parent-reported internalizing and overall difficulties (20). The presence of dose–response relationships with EPA+DHA status and the use of whole fish underscore the potential importance of combined nutritional effects during ongoing brain development, while also highlighting the need for further adequately powered studies across different metabolic conditions.

Limitations

Several limitations of this study should be acknowledged. First, only free plasma essential fatty acid levels were measured; fatty acid composition in erythrocyte membranes or phospholipid fractions, which may better reflect long-term fatty acid status, was not assessed. Second, the cross-sectional design limits causal inference between fatty acid levels and cognitive outcomes. Third, although this study includes one of the largest cohorts of patients with organic acidemias evaluated for essential fatty acid status to date, the sample size may still be insufficient to detect subtle associations with neurodevelopmental measures. Finally, the absence of reference data on essential fatty acid levels in healthy Turkish children limits population-specific comparisons. Despite these limitations, this study provides valuable insight into essential fatty acid profiles in organic acidemias and highlights important directions for future research.

Conclusion

The findings of this study are consistent with the limited existing literature on essential fatty acid profiles in patients with organic acidemias. Our results confirm that children with organic acidemias, particularly those on protein-restricted diets, exhibit lower omega-3 fatty acid levels and higher omega-6/omega-3 ratios compared with healthy controls. Although omega-3 fatty acids are known to play an important role in neurodevelopment, no significant association was identified between omega-3 or omega-6 levels and cognitive outcomes in the present cohort. This lack of association may reflect the multifactorial nature of neurodevelopment in organic acidemias, in which metabolic control, disease severity, dietary management, and genetic factors interact alongside fatty acid status. Future longitudinal and interventional studies with larger sample sizes are needed to better define the clinical relevance of essential fatty acid supplementation and to clarify its potential role in improving neurodevelopmental outcomes in this patient population.

Ethics committee approval
This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Pediatric Hematology Oncology Training and Research Hospital (25.12.2017 , reference number: 2017-137).

Contribution of the authors
Study conception and design: EKK, ÖÜU; data collection: KÇ, AS, ÇU,MY; analysis and interpretation of results: MY, FK, ÖÜU, EKK, AKY, MG; draft manuscript preparation: EKK, KÇ,MY,FK. All authors reviewed the results and approved the final version of the article.

Source of funding
The authors declare the study received no funding.

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

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Turkish Journal of Pediatric Disease

Original Article

Clinical characteristics of juvenile systemic lupus erythematosus: Prepubertal and pubertal onset

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Received : 28.01.2026, Accepted : 05.05.2026 DOI: 10.12956/TJPD.2026.1304

ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems and is characterized by periods of flare-ups and remission. In approximately 15-20% of SLE patients, clinical symptoms onset during childhood or adolescence and are defined as juvenile SLE (jSLE). Age at disease onset has been suggested to influence the clinical phenotype, severity of inflammatory activity, and overall disease course in jSLE. The aim of this study was to compare clinical features and disease course between prepubertal (<10 years) and pubertal (≥10 years) jSLE patients.

Materials and Methods: This retrospective, single-center, cross-sectional study was conducted on patients diagnosed with jSLE who were followed up at the pediatric rheumatology clinic between January 2015 and September 2025. Patients included in the study had been diagnosed with jSLE according to the 2012 Systemic Lupus International Collaborating Clinics classification criteria.

Results: A total of 54 patients with juvenile-onset SLE were included, of whom 88.9% were female. Patients were grouped according to age at diagnosis: prepubertal-onset jSLE (<10 years) included 9 patients (16.7%), and pubertal-onset jSLE (≥10 years) included 45 patients (83.3%). Fever and elevated C-reactive protein levels were significantly more common in jSLE with pre-pubertal onset, whereas mucocutaneous involvement was more prevalent in jSLE with pubertal onset. Renal, hematological, and neurological involvement, autoantibody profiles, and disease activity and damage index at diagnosis were similar across groups. At the last visit, disease activity was significantly lower in jSLE with pre-pubertal onset. No differences in treatment were observed between age groups.

Conclusion: In this cohort, prepubertal-onset jSLE tended to present with more prominent inflammatory features, whereas pubertal-onset jSLE more often showed mucocutaneous involvement. Despite these observed phenotypic differences, cumulative organ damage appeared similar between groups.

Keywords: Age of onset, puberty, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems and is characterized by periods of flare-ups and remission. In approximately 15-20% of SLE patients, clinical symptoms onset during childhood or adolescence and are defined as juvenile SLE (jSLE) (1). The prevalence of jSLE is 1.1–25.7 per 100000 children (2). The median age at diagnosis for jSLE has been reported to range from 11.67 to 13.9 years (3-5).

Juvenile SLE is generally characterized by a more severe disease course and higher disease activity compared with adult-onset SLE (6,7). Beyond the differences between adult and juvenile SLE, current data suggest that jSLE exhibits distinct clinical differences among pediatric age groups. In particular, the age of disease onset has been reported to impact clinical phenotype, severity of inflammatory activity, and disease course (1).

Pre-school children with SLE (<6 years) show an equal gender distribution female-to-male ratio, 1:1. In school-age children and adolescents, the female-to-male ratio is approximately 4-5:1,whereas after adolescence it shifts to a female predominance (9-10:1) characteristic of adult-onset SLE (8). This age-related change in gender distribution, together with increased hormonal activity during adolescence, suggests that sex hormones may play an important role in the pathogenesis of

SLE, in addition to genetic, environmental and infectious factors. Sex hormones are known to affect the regulation of the immune system and the shaping of autoimmune processes (9).

The aim of this study was to compare the clinical characteristics of patients diagnosed with jSLE during the prepubertal (<10 years) and pubertal (≥10 years) periods and to identify age-related differences in clinical features and disease course.

Materials and Methods

This retrospective, single-center, cross-sectional study was conducted on patients diagnosed with jSLE who were followed up at the Department of Pediatric Rheumatology of Ankara Bilkent City Hospital between January 2015 and September 2025. Patients with a follow-up period of less than 6 months, those with missing data, and those with monogenic lupus confirmed by genetic mutation were excluded.

Patients included in the study were diagnosed with jSLE according to the 2012 Systemic Lupus International Collaborating Clinics classification criteria (10). All patients' data were obtained retrospectively from the hospital's electronic medical record system. Patients' demographic characteristics (gender, age at diagnosis, follow-up duration), laboratory parameters [erythrocyte sedimentation rate, C-reactive protein (CRP), antinuclear antibody (ANA), anti-dsDNA, anti-smith antibody, ribonucleoprotein antibody, ribosomal P and low complement, antiphospholipid (aPL) antibodies] clinical findings and organ involvements, and treatments were recorded. If a renal biopsy was performed, the renal biopsy findings were documented according to the 2003 Lupus Nephritis Classification of the International Society of Nephrology/Renal Pathology Society (11). The activity of the disease at the time of diagnosis and during follow-up was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) (12). The damage related to the disease itself and medications was asssessed at last outpatient clinic examination based on the pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (PedSDI) (13).

Patients were divided into prepubertal (<10 years) and pubertal (≥10 years) groups based on the age at diagnosis, according to the World Health Organisation's definition of adolescence (10–19 years) (14).

Statistical analysis

IBM Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). In the descriptive statistics section, categorical variables were presented in tables with counts and percentages, while continuous variables that did not follow a normal distribution were presented with median (interquartile range) values. The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Mann–Whitney U test was used in comparisons of continuous variables that did not conform to normal distribution between two groups. The chi-square test was used in comparisons of categorical variables. Statistical significance level was accepted as $p \leq 0.050$

Results

During the study period, 65 jSLE patients were followed up in the pediatric rheumatology department. Two patients with a follow-up period of less than 6 months, four patients with missing data, and five patients with monogenic lupus confirmed by genetic mutation were excluded from the study. The remaining 54 jSLE patients were included in the study. Of these patients, 48 (88.9%) were female. The median follow-up duration was 31.5 (12-54) months, and the median age at symptom onset was 12.7 (10.5-14.9) years.

Constitutional symptoms were observed in 42 patients (77.8%), followed by renal involvement in 31 (57.4%), cutaneous involvement in 30 (55.6%), hematological involvement in 29 (53.7%), arthritis in 24 (44.4%) and neurological involvement in 20 (37.0%) (Table I). Among patients with renal involvement (n=31), lupus nephritis was classified as Class I in 3 patients (9.7%), Class II in 11 (35.5%), Class IV in 11 (35.5%), and Class V in one patient (3.2%) based on renal pathology.

Among the immunological parameters, hypocomplementemia was observed in 40 patients (74.1%), ANA positivity in 52 patients (96.3%), anti-dsDNA positivity in 44 patients (81.5%), and antiphospholipid antibody positivity in 12 patients (22.2%). The median SLEDAI score was 14.5 (8–20.3) at diagnosis and 2 (0–4) at the last visit. The baseline demographic and clinical characteristics of all patients are shown in Table I.

Comparison of clinical characteristics in prepubertal- and pubertal-onset juvenile systemic lupus erythematosus

Patients were grouped according to age at diagnosis: prepubertal-onset jSLE (<10 years) included 9 patients (16.7%), and pubertal-onset jSLE (≥10 years) included 45 patients (83.3%).

Seven patients (77.8%) with prepubertal-onset jSLE and 41 patients (91.1%) with pubertal-onset jSLE were female. There was no statistically significant difference between the groups in terms of gender (p=0.259). The female-to-male ratio was 3.5:1 in the <10 age group and 10.2:1 in the pubertal group. The follow-up period was 35.5 months (31.5–72) in the prepubertal-onset jSLE and 25 months (12–47.5) in the pubertal group, although it was longer in the prepubertal group (p=0.051). The median age at symptom onset was 8.4 (7.2–8.9) years in the prepubertal-onset jSLE and 12.9 (11.8–15.1) years in the pubertal-onset jSLE (p<0.001).

Fever was more common in prepubertal-onset jSLE, occurring in 7 patients (77.8%), whereas it was observed in 17 patients (37.8%) in the pubertal-onset jSLE group (p=0.027). Lymphadenopathy was present in 4 patients (9.1%), alopecia in 6 patients (13.3%), and oral ulceration in 7 patients (15.6%), and was only observed in the pubertal-onset jSLE. Cutaneous involvement was present in 2 patients (22.2%) in the prepubertal onset jSLE and in 28 patients (62.2%) in the pubertal group, and was significantly more prevalent in the pubertal onset jSLE (p=0.027).

There was no significant difference between the prepubertal and pubertal onset jSLE patients regarding renal involvement (66.7% vs 55.5%, p=0.680), haematological involvement (77.8% vs 48.9% p=0.153) or neurological involvement (22.2% vs 40.0%, p=0.458).

Table I: Clinical characteristics of prepubertal- and pubertal-onset jSLE

	Total	Prepubertal-onset jSLE	Pubertal-onset jSLE	p
Number of patients	54	9	45	-
Gender, female*	48 (88.9)	7 (77.8)	41 (91.1)	0.259‡
Age at symptom onset, years†	12.7 (10.5-14.9)	8.4 (7.2-8.9)	12.9 (11.8-15.1)	<0.001§
Time elapsed until diagnosis, months†	2 (1-6)	2 (1.5-4)	2.5 (1-6)	0.720§
Follow-up duration, months†	31.5 (12.0-54.0)	35 (31.5-72.0)	25 (12.0-47.5)	0.051§
Clinical manifestation*				
Constitutional symptom	42 (77.8)	8 (88.9)	34 (75.6)	0.665‡
Fever	24 (44.4)	7 (77.8)	17 (37.8)	0.027‡
Weakness	37 (69.8)	7 (77.8)	30 (68.2)	0.706‡
Weight loss	14 (26.4)	1 (11.1)	13 (29.5)	0.416‡
Lymphadenopathy	4 (7.5)	0 (0.0)	4 (9.1)	N/A
Arthritis	24 (44.4)	2 (22.2)	22 (48.9)	0.270‡
Serositis	19 (35.2)	5 (55.6)	14 (31.1)	0.251‡
Cutaneous involvement	30 (55.6)	2 (22.2)	28 (62.2)	0.027‡
Oral ulcers	7 (13,0)	0 (0.0)	7 (15.6)	N/A
Alopecia	6 (11.1)	0 (0.0)	6 (13.3)	N/A
Renal involvement	31 (57.4)	6 (66.7)	25 (55.5)	0.717‡
Neurological involvement	20 (37.0)	2 (22.2)	18 (40.0)	0.458‡
Hematological involvement	29(53.7)	7 (77.8)	22 (48.9)	0.153‡
Anemia	19 (35.2)	5 (55.6)	14 (31.1)	0.251‡
Thrombocytopenia	15 (27.8)	4 (44.4)	11 (24.4)	0.244‡
Lymphopenia	17 (31.5)	3 (33.3)	14 (31.1)	>0.999‡
Laboratory findings*				
Elevated erythrocyte sedimentation rate	30 (55.6)	5 (55.6)	25 (55.6)	>0.999‡
Elevated CRP	19 (35.8)	7 (77.8)	12 (27.3)	0.007‡
ANA positivity	52 (96.3)	8 (88.9)	44 (97.8)	0.308‡
Anti-dsDNA positivity	44 (81.5)	9 (100.0)	35 (77.8)	N/A
Hypocomplementemia	40 (74.1)	8 (88.9)	32 (71.1)	0.418‡
Direct coombs positivity	34 (69.4)	8 (88.9)	26 (65.0)	0.242‡
Anti-Sm	11 (35.5)	3 (50.0)	8 (32.0)	0.638‡
Anti-ribosomal P	10 (33.3)	2 (33.3)	8 (33.3)	>0.999‡
Anti-RNP	7 (29.2)	3 (50.0)	4 (22.2)	0.307‡
aPL positivity	12 (23.1)	2 (22.2)	10 (23.3)	>0.999‡
SLEDAI-2K score at SLE diagnosis†	14.5 (8.0-20.3)	16 (6.0-19.0)	13 (8.5-22.5)	0.609§
SLEDAI-2K score at last visit†	2 (0.0-4.0)	0 (0.0-0.5)	2 (0.0-4.0)	0.015§
PedSDI score†	0 (0-1)	1 (0-1)	0 (0-1)	0.103§
Remission status*	33 (67.3)	6 (66.7)	27 (67.5)	>0.999‡
Treatmen*				
Methylprednisolone	51 (94.4)	9 (100.0)	42 (93.3)	N/A
Hydroxychloroquine	49 (90.7)	9 (100.0)	40 (88.9)	N/A
Mycophenolate mofetil	22 (40.7)	5 (55.6)	17 (37.8)	0.461‡
Azathioprine	3 (5.6)	1 (11.1)	2 (4.4)	0.428‡
Methotrexate	5 (9.3)	1 (11.1)	4 (8.9)	>0.999‡
Cyclophosphamide	24 (44.4)	6 (66.7)	18 (40.0)	0.165‡
IVIG	14 (25.9)	2 (22.2)	12 (26.7)	>0.999‡
Rituximab	8 (14.8)	1 (11.1)	7 (15.6)	>0.999‡

:** *n (%),* **†:** *median (IQR),* **‡:** *Chi-square test,* **§:** *Mann-Whitney U test,* ***N/A: *Not Applicable,* ***CRP:*** *C-reactive protein,* ***ANA:*** *Antinuclear antibody,* ***anti-dsDNA****: Anti–double-stranded DNA antibody,* ***anti-Sm:*** *Anti-Smith antibody,* ***aPL:*** *Antiphospholipid antibodies,* ***anti-RNP:*** *Anti–ribonucleoprotein antibody,* ***SLEDAI-2K:*** *Systemic Lupus Erythematosus Disease Activity Index 2000,* ***IVIG:*** *Intravenous Immunoglobulin,* ***PedSDI:*** *Pediatric SLICC/ACR Damage Index*

Elevated CRP levels were more frequently observed in the pre-pubertal onset jSLE (7 patients, 77.8%) compared to the pubertal-onset jSLE (12 patients, 27.3%) (p=0.007). Autoantibody profiles, including ANA, anti-dsDNA, and aPL positivity, were similar in both groups. At diagnosis, the SLEDAI score was 16 (6–19) in the <10 age group and 13 (8.5–22.5) in the ≥10 age group, with no significant difference between the two groups (p=0.609). At the last visit, the SLEDAI score was 0 (0–0.5) in the prepubertal onset jSLE and 2 (0–4) in the pubertal onset jSLE. It was significantly higher in the pubertal onset jSLE (p=0.015). Regarding treatment and pedSDI no difference was observed between the two age groups. Comparisons of clinical characteristics between prepubertal- and pubertal-onset jSLE patients are presented in Table I.

Discussion

Juvenile SLE is a multisystem inflammatory disease characterised by a highly variable presentation and clinical course compared to SLE seen in adults (3). Given the impact of major organ involvement on morbidity and mortality, early diagnosis and age-specific clinical awareness are of crucial importance in pediatric patients. In this retrospective study, the clinical characteristics of jSLE patients were evaluated according to their age at diagnosis. Fever and elevated CRP were observed more frequently in patients diagnosed prepuberally, while cutaneous involvement was more common in patients diagnosed during puberty. Furthermore, lymphadenopathy, oral ulcers, and alopecia were only detected in patients diagnosed during puberty.

Age at diagnosis in the SLE UK cohort was reported to be 12.8 years on average, while a Turkish series reported this age to be 13 years (15,16). In our study, the median age at diagnosis of jSLE was 12.7 years, and 88.9% of patients were female. Murine lupus models have demonstrated that oestrogen accelerates disease development, supporting a key role for sex hormones in lupus pathogenesis (17,18). In our study, the female-to-male ratio was 3.5:1 in pre-pubertal onset jSLE and 10.2:1 in pubertal onset SLE, clearly indicating a predominance in females. This age-related change in gender distribution appears consistent with previous data suggesting a potential role for sex hormones in lupus pathogenesis.

Fever has been reported in 20.4–68.4% of jSLE patients and in 15.4–64.9% of adult-onset SLE patients (19). In a large jSLE cohort, fever was reported as the most common initial symptom of the disease (57.6%) (20). A multicentre study conducted in Brazil demonstrated that fever was significantly more frequent in jSLE patients under 6 years of age compared to older age groups (21). Our data support the observation that younger patients are more prone to febrile episodes, similar to reports of jSLE patients under age six. Interestingly, this age-related trend extended to CRP levels in our study. In jSLE, it is known that elevated CRP levels may reflect accompanying inflammatory conditions such as infection rather than disease activity (22). Approximately 41.9% of newly diagnosed SLE patients were reported to have an infection, and CRP levels were shown to be higher in these cases compared to patients without infection (23). This suggests that elevated CRP levels in the pre-adolescent group may be related to accompanying inflammatory processes, primarily infections, rather than disease activity.

According to data from the UK jSLE study group, more active mucocutaneous, musculoskeletal, renal, and cardiorespiratory involvement, as well as higher overall disease activity, were observed at diagnosis in patients diagnosed during puberty (24). Li et al. (20) have shown that alopecia is more common in adolescents than in other age groups. In contrast, another study found that the frequency of cutaneous findings was more common in those under 10 years of age and that disease activity was higher in the pubertal group (25). In our study, cutaneous involvement was more common in pubertal-onset SLE than in pre-pubertal-onset jSLE, but major organ involvement was similar in both age groups. Furthermore, oral ulcers and alopecia were observed only in the pubertal age group. Disease activity was also similar in both age groups. All these findings indicate that jSLE has a heterogeneous clinical course and severity depending on age, but also suggest that pubertal-onset jSLE presents a more 'classic' phenotype with more pronounced mucocutaneous findings, similar to adult SLE. Furthermore, the observation that some clinical findings were limited to the adolescent group may be related to differences in group size between the two groups. These findings should be confirmed in further studies with larger cohorts.

Although the literature reports a wide range of disease activity scores at diagnosis in patients with SLE, our study found that SLEDAI-2K scores at diagnosis were similar between pubertal and prepubertal groups (24,25). However, higher SLEDAI-2K scores at the last visit among patients in the pubertal period suggest that disease control is more difficult to achieve in this age group. The management of juvenile SLE may be further complicated by the physiological and psychosocial changes of adolescence, as shown in a study (26). These factors may limit optimal disease control during adolescence and may be associated with ongoing disease activity.

In the present study, no significant difference was found between the prepubertal and pubertal groups in terms of cumulative organ damage assessed by pedSDI. This result is consistent with previous jSLE studies reporting similar damage accumulation between groups based on disease onset age (27, 28). All these data suggest that age at disease onset alone may not be a sufficient predictor of cumulative organ damage.

Limitations

There are some limitations to our study; due to its retrospective design and single-centre setting, the number of patients is limited. In addition, the relatively small size of the prepubertal-onset group may have limited the detection of age-related differences between groups.The inability to evaluate patients under six years of age as a separate group has restricted a more detailed analysis of the clinical phenotype specific to early childhood.

Conclusion

In conclusion, our results demonstrate that prepubertal-onset jSLE is characterized by a more prominent inflammatory presentation, including higher frequencies of fever and elevated CRP, whereas pubertal-onset jSLE more often presents with mucocutaneous manifestations. Despite these age-related differences in clinical phenotype, cumulative organ damage assessed by pedSDI was similar across groups. Further large-scale studies are needed to comprehensively define age-specific clinical characteristics in patients with jSLE.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (10.12.2025, reference number: TABED 2-25-1715).).

Contribution of the authors

Conceptualization: EÖ, BÇA; Methodology: EÖ, BÇA, EÇ, ZET, CK, EET, ŞE, Formal analysis and investigation: EÖ, MIE, SNY, DÖ, YUE, ŞET, USB, BPZ, ÖAB; Writing - original draft preparation: EÖ, ZET;

Writing - review and editing: EÖ, BÇA ; Funding acquisition: None ; Resources: None; Supervision: BÇA

Source of funding
The authors declare the study received no funding.

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

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Turkish Journal of Pediatric Disease

Original Article

Diagnostic accuracy of ultrasonography versus Tc-99m DMSA for detecting renal parenchymal damage in children with recurrent urinary tract infections and vesicoureteral reflux: Patient-level and regression-based analyses

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Received : 19.02.2026, Accepted : 22.05.2026 DOI: 10.12956/TJPD.2026.1315

ABSTRACT

Objective: We aimed to assess the diagnostic performance of renal ultrasonography (USG) compared with technetium-99m dimercaptosuccinic acid renal cortical scintigraphy (DMSA scintigraphy) in detecting renal parenchymal damage in paediatric patients with vesicoureteral reflux (VUR) and/or recurrent urinary tract infection (rUTI).

Materials and Methods: We retrospectively analysed 181 paediatric patients who underwent both renal USG and DMSA scintigraphy. Kidneys coded as absent were excluded. Diagnostic accuracy indices (sensitivity, specificity, PPV, NPV, accuracy, and AUC with 95% confidence intervals) were calculated at kidney and patient levels. Logistic regression was performed to evaluate the impact of age, gender, and renal uptake.

Results: In comparison to DMSA scintigraphy as the reference standard, USG identified parenchymal damage with a sensitivity of 50.9% for the left kidney and 44.7% for the right kidney, while demonstrating exceptional specificity (>99%). At the patient level (n=162), USG achieved a sensitivity of 49.4%, specificity of 100%, accuracy of 76%, and AUC of 0.75. DMSA scintigraphy identified significantly more kidneys with parenchymal injury than USG in all age cohorts. Logistic regression further indicated that advancing age and diminished renal uptake on DMSA scintigraphy were independent predictors of parenchymal damage, while sex was not significant.

Conclusion: Ultrasonography demonstrated excellent specificity but limited sensitivity compared with DMSA scintigraphy. These findings indicate that USG alone is inadequate for the early detection of renal parenchymal damage in children with VUR and/or rUTI. DMSA scintigraphy remains essential in this high-risk population.

Keywords: Pyelonephritis, Tc-99m DMSA, urinary tract infections, ultrasonography, vesicoureteral reflux

Introduction

Urinary tract infection (UTI) is among the most common bacterial infections of childhood, while VUR predisposes to recurrent UTIs and renal damage (1,2). Both conditions can lead to long-term complications such as hypertension, renal scarring, and chronic kidney disease (3–7). The prompt identification and prevention of recurrent infections are crucial.

The incidence of UTIs varies by sex, age, and circumcision status, and is higher in females than in males (8,9). VUR has been reported in 16–23% of pediatric populations and is more prevalent in females (10). The risk of renal impairment increases with reflux grade and may approach 50% in children with grade IV–V VUR (10,11). Recurrent urinary tract infections (rUTIs) occur in 10–30% of children after an initial febrile episode, particularly in those with VUR or bladder-bowel dysfunction (12).

Imaging modalities are crucial for the evaluation and surveillance of children with rUTI and VUR. Ultrasonography is radiation-free, widely available, and recommended as an initial modality for assessing renal morphology and urinary tract obstruction (13). However, previous studies have shown that its sensitivity for renal scars and subtle parenchymal changes is limited (14,15). DMSA scintigraphy is a reference method for evaluating cortical integrity and differential renal function and can identify both acute pyelonephritis and chronic scarring (13,16).

Prior research has shown that USG may miss a substantial proportion of parenchymal lesions compared with DMSA scintigraphy (14,15). Similar findings have been reported in children with febrile UTI despite normal renal USG results (17). Missed early lesions may progress to scarring (4,7), increasing the risk of hypertension and renal insufficiency in later life (3,5,6,16). Accordingly, guidelines emphasise complementary use of USG and DMSA scintigraphy, particularly in children with VUR and rUTI (2,12,13).

Therefore, the primary aim of this study was to compare the diagnostic performance of USG against Tc-99m DMSA scintigraphy for detecting renal parenchymal damage in children with VUR and/or recurrent UTI at both kidney and patient levels. The secondary aim was to evaluate whether age, sex, and differential renal uptake were independently associated with DMSA-defined parenchymal damage. We hypothesized that USG would show high specificity but limited sensitivity relative to DMSA scintigraphy, and that older age and lower renal uptake would be associated with parenchymal damage.

Materials and Methods

Study population

We retrospectively reviewed the records of 400 pediatricpatients who underwent DMSA scintigraphy at Goztepe Prof. Dr. Suleyman Yalcin City Hospital between May 2020 and January 2022. Patients under the age of 18 years with a diagnosis of VUR and/or rUTI who had both renal USG and DMSA scintigraphy performed within a 90-day interval were eligible. Patients who underwent DMSA scintigraphy for other indications were omitted. A total of 181 patients (117 girls, 64 boys; 174 left kidneys and 169 right kidneys) met the inclusion criteria and were analysed. Kidneys classified as “absent” (code=2) were excluded from the comparative analyses. The interval between USG and DMSA scintigraphy was up to 90 days, which may have allowed progression from acute pyelonephritis to chronic scarring. Thus, our analyses reflect overall parenchymal damage rather than acute versus chronic differentiation.

USG evaluation

USG examinations were performed and reported by pediatricradiologists according to institutional protocols. For the purposes of this study, USG reports were retrospectively categorised as either normal (code=0) or abnormal (code =1) based on predefined parenchymal features: loss of corticomedullary differentiation, diffuse increased parenchymal echogenicity, cortical thinning or irregularity, renal asymmetry in size, and compensatory hypertrophy of the contralateral kidney. Simple, uncomplicated cysts were not considered abnormal findings.

DMSA scintigraphy protocol

Tc-99m DMSA scintigraphy was performed in accordance with the European Association of Nuclear Medicine (EANM) guidelines (13). Administered activity was weight-adjusted (15–185 MBq). Planar anterior, posterior, and oblique views were obtained 2–3 hours post-injection using a Mediso Anyscan gamma camera (128×128 matrix, 500K counts). Single-photon emission computed tomography (SPECT) acquisition was performed after planar imaging. Patients were hydrated prior to imaging, and no sedation was required.

Image interpretation

The DMSA scintigraphy results were independently evaluated by two experienced nuclear medicine physicians. The geometric mean of anterior and posterior counts was used to calculate differential renal function. Hypoactive cortical areas, contour irregularities, and focal defects were defined as parenchymal damage/scarring. For statistical comparisons, DMSA scintigraphy was used as the reference standard.

Statistical analysis

All statistical analyses were performed using STATA version 18.0 (StataCorp LLC, College Station, TX, USA), IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA), and Python version 3.10. Diagnostic accuracy indices (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the ROC curve (AUC) with 95% confidence intervals) were calculated separately for left and right kidneys and also at the patient level (defined as abnormal if either kidney was abnormal). For AUC analyses, p-values were computed assuming a null AUC of 0.5 (reflecting no discrimination). Logistic regression analysis was used to evaluate independent predictors of parenchymal damage on DMSA scintigraphy, including age, gender, and renal uptake. Odds ratios (OR) with 95% confidence intervals were reported. A two-sided $p < 0.05$ was considered statistically significant. Model assumptions were assessed with standard tests (Breusch–Pagan, White). A formal a priori power analysis was not performed due to the retrospective design. However, logistic regression models had adequate events per variable (EPV ≈ 26 at the patient level), exceeding the commonly recommended threshold of 10 for stable estimates. In addition to regression outputs (ESM1; Tables S1–S3), raw contingency tables are provided for kidney- and patient-level diagnostic accuracy (ESM1; Tables S4–S6).

Results

Study population

A total of 181 pediatricpatients (117 girls, 64 boys) with VUR and/or rUTI were included. After excluding kidneys coded as absent, 174 left kidneys and 169 right kidneys were analysed. At the patient level, paired USG and DMSA scintigraphy data were available for 162 children. Baseline demographics and functional characteristics are summarised in Table I.

Diagnostic performance of USG (kidney-based analysis)

For the left kidney, USG identified parenchymal damage with a sensitivity of 50.9%, a specificity of 100%, accuracy of 85%, and an AUC of 0.76 (95% CI: 0.69–0.83; p<0.001). For the right kidney, sensitivity was 44.7%, specificity 99.2%, accuracy 84%, and AUC 0.72 (95% CI: 0.64–0.80; p<0.001). The reported p-values for ROC analyses reflect testing against a null hypothesis of AUC=0.5.

Table I: Demographic and functional characteristics of the study population

Characteristic	Value
Total patients	181
Girls*	117 (64.6)
Boys*	64 (35.4)
Left kidneys analysed	174
Right kidneys analysed	169
Patient-level analyses	162
Age (years)	8.8 (5.2–13.2)† 9.1±5.0‡
Differential renal uptake (%)	
Left†	51.0 (45.0–59.0)
Right†	49.0 (41.0–55.0)

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

Table II: Diagnostic performance of USG compared with DMSA scintigraphy

Metric	Left kidney- Value	Right kidney - Value
Sensitivity*	50.9	44.7
Specificity*	100.0	99.2
Accuracy*	85.0	84.0
PPV*	100.0	95.5
NPV*	82.3	82.3
AUC	0.76	0.72
95% CI	0.69–0.83	0.64–0.80

: %, **PPV: Positive predictive value, **NPV:** Negative predictive value, **AUC:** Area under the ROC curve*

Table III: Diagnostic performance of USG compared with DMSA scintigraphy at the patient level

Metric	Value
Sensitivity*	49.4
Specificity*	100
Accuracy*	76
PPV*	100.0
NPV*	68.6
AUC	0.75
95% CI	0.67–0.82

: %, **PPV: Positive predictive value, **NPV:** Negative predictive value, **AUC:** Area under the ROC curve*

These kidney-based results are presented in Table II, with ROC curves illustrated in Figure 1.

Representative cases

Figure S1-3 in ESM 1 provide representative DMSA scintigraphy from three patients in whom USG failed to detect parenchymal defects that were clearly visible on scintigraphy, which emphasises the clinical value of DMSA scintigraphy in this population.

Diagnostic performance at the patient level

When parenchymal damage was defined as abnormality in either kidney on DMSA scintigraphy, USG showed a sensitivity of 49.4%, a specificity of 100%, an accuracy of 76%, and an AUC of 0.75 (95% CI: 0.67–0.82; p<0.001) (Table III).

Age-related distribution

The age distribution of normal and abnormal kidneys differed between modalities. Compared with USG, DMSA scintigraphy identified more kidneys with parenchymal damage across nearly all age groups, as illustrated in Figure S4 and Figure S5.

Table IV: Logistic regression analysis for predictors of parenchymal damage

Variable	Left kidney			Right kidney		
	OR	95% CI	p	OR	95% CI	p
Age (per year)	1.12	1.03–1.22	0.005	1.10	1.01–1.21	0.020
Gender	1.50	0.66–3.39	0.330	1.10	0.49–2.44	0.820
Renal uptake (%)	0.93	0.89–0.96	<0.001	0.94	0.90–0.97	<0.001

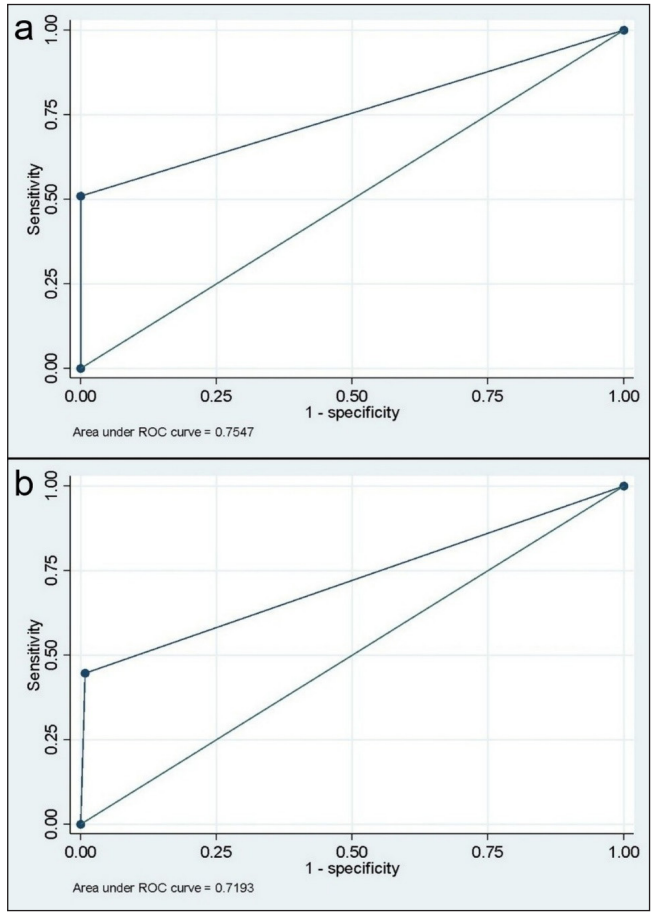

Figure 1: Receiver operating characteristic (ROC) curve of ultrasonography for detecting parenchymal damage in the (a) left and (b) right kidneys

Predictors of parenchymal damage (logistic regression)

Multivariable logistic regression identified increasing age (OR 1.12 per year, 95% CI 1.05–1.23; p=0.005 for the left kidney; OR 1.10, 95% CI 1.04–1.20; p=0.02 for the right kidney) and decreasing renal uptake (OR 0.93 per 1% decrease, 95% CI 0.90–0.97; p<0.001 for the left kidney; OR 0.94, 95% CI 0.90–0.97; p<0.001 for the right kidney) as independent predictors of parenchymal damage on DMSA scintigraphy. Gender was not associated with damage (female vs male: OR 1.50, 95% CI 0.66–3.39; p=0.33 for the left kidney; OR 1.10, 95% CI 0.49–2.44; p=0.82 for the right kidney) (Table IV, Table S1 and Table S2). Re-estimation with heteroskedasticity-robust (HC3) standard errors did not materially change the effect estimates or statistical significance (Figure 2, Table S3, Figure S6).

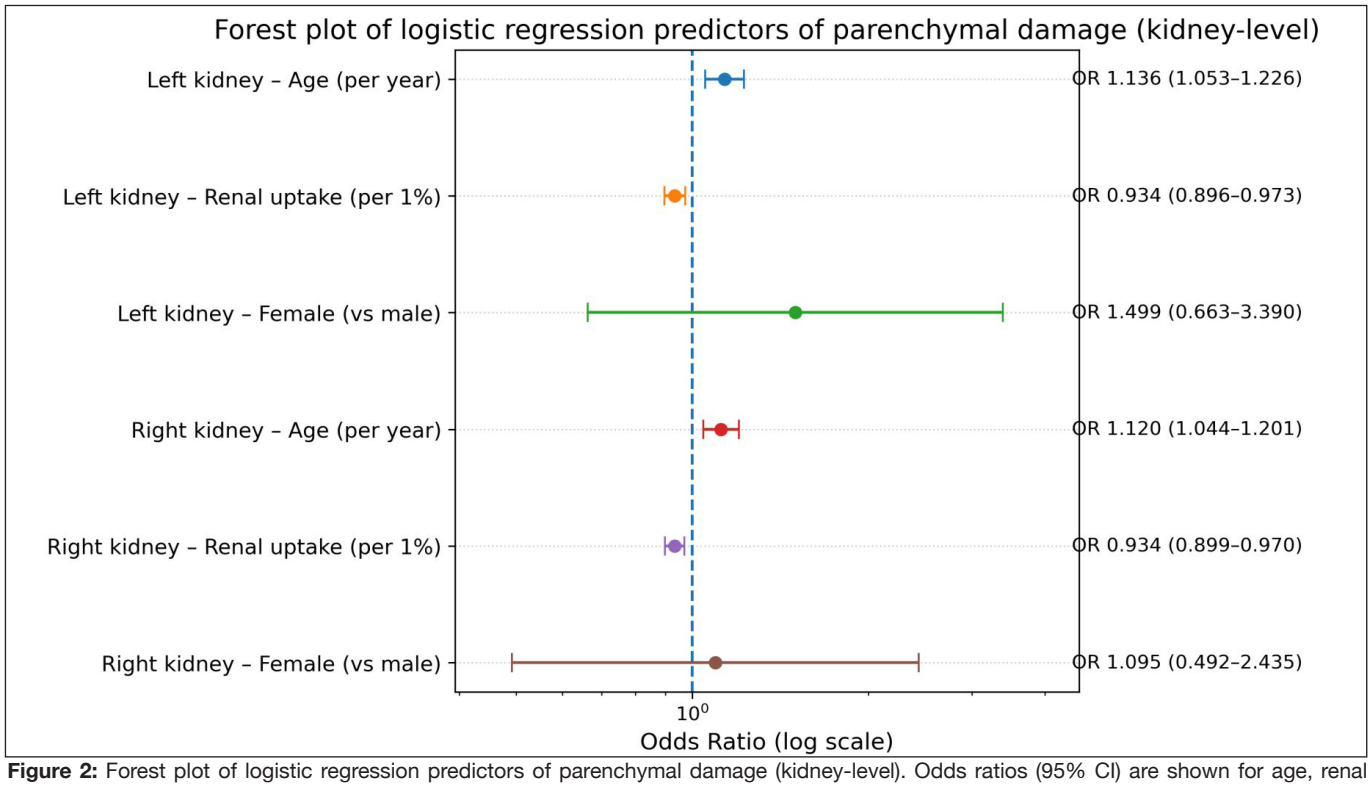

Figure 2: Forest plot of logistic regression predictors of parenchymal damage (kidney-level). Odds ratios (95% CI) are shown for age, renal uptake, and gender (female vs male). The dashed line represents the null value (OR = 1.0).

When stratified by age categories, DMSA scintigraphy positivity increased from 28.6% (<5 years) to 40.9% (5–10 years) and 57.5% (>10 years). The trend was statistically significant ($\chi^2 = 9.67$, p=0.008).

Discussion

The present study reaffirms that renal USG, despite its excellent specificity (>99%), has limited sensitivity (≈45–51% at the kidney level and 49% at the patient level) compared with DMSA scintigraphy. Our incremental contribution is twofold: first, we quantify these performance gaps at the patient level, which better reflects clinical decision-making; and second, we identify age and lower differential renal uptake as independent predictors of parenchymal damage in multivariable models. Together, these findings provide confirmatory yet clinically useful evidence to guide imaging pathways in high-risk rUTI/VUR cohorts.

While DMSA should remain the reference test for confirming cortical damage in high-risk children, magnetic resonance imaging (MRI) can be considered in selected circumstances such as contraindications to radiopharmaceuticals, the need for multiparametric assessment, or equivocal DMSA scintigraphy. In clinical practice, a stepwise strategy can be applied: ultrasound serves as the initial screening tool, while DMSA scintigraphy or MRI can be performed when necessary for patients at high clinical risk or to confirm the renal scar, guiding treatment and follow-up decisions.

Cost and availability vary widely across settings; DMSA scintigraphy is generally accessible and relatively low-dose. Yet parental concerns about radiation are legitimate and should be addressed through shared decision-making and clear communication of benefits and risks. Our patient-level results caution against USG-only strategies in high-risk children, given the substantial false-negative rate.

Our logistic regression model confirmed that increasing age and decreasing renal uptake were independent predictors of parenchymal damage consistent with the progressive nature of scarring in children with VUR and rUTI.

Re-estimation with heteroskedasticity-robust standard errors did not materially change effect estimates or statistical significance.

The age effect was also supported by categorical analyses showing progressively increasing rates of DMSA scintigraphy positivity from early childhood to adolescence. The trend across age groups (<5, 5–10, >10 years) was statistically significant, strengthening the interpretation that parenchymal damage increases with age.

Our findings are consistent with previous literature. Hoberman et al. (14) reported that USG frequently misses acute pyelonephritis and renal scars, but DMSA scintigraphy clearly identifies them. Lavocat et al. (15) similarly showed the limited sensitivity of USG in early parenchymal damage (17). Research indicates that around 20% of children with febrile UTI exhibit kidney damage identified by DMSA scintigraphy, despite normal USG results. These data underscore the risk of relying on USG alone in high-risk children.

Unnoticed parenchymal defects can progress to scarring, and are associated with long-term outcomes such as hypertension and reduced kidney function (3-7,16). Guidelines recommend combining USG and DMSA scintigraphy for comprehensive evaluation (2,12,13).

While USG is useful for assessing renal size, asymmetry, hydronephrosis, and bladder abnormalities, it lacks sufficient sensitivity for the reliable detection of cortical scars (14,15,17); DMSA scintigraphy, particularly with SPECT acquisition, remains the gold standard (13,18–20).

Although treated as the reference standard here, DMSA scintigraphy is not infallible; timing relative to acute infection and inter-observer variability may affect interpretation. These caveats underscore the value of standardized acquisition/reading and, where feasible, correlation with clinical course.

This single-centre, retrospective study relied on existing USG reports, introducing potential operator variability and selection bias (21, 22). The USG–DMSA scintigraphy interval (≤90 days) may have allowed lesion evolution, and the lack of standardized timing for infections and imaging limited the ability to distinguish acute pyelonephritis from chronic scarring. Blinded re-review of USG images and a narrower imaging window were not feasible retrospectively. We also did not perform separate analyses of SPECT versus planar acquisitions or lesion counts (18–20). A priori power analysis was not conducted; however, the number of events per variable at the patient level (~26) exceeded conventional thresholds, supporting model stability. Finally, although radiation exposure remains a concern, the effective dose of DMSA scintigraphy is relatively low (~1 mSv), and recent studies suggest transient DNA effects without long-term oxidative stress (23,24). Generalisability to other settings warrants prospective validation.

Limitations

Despite these limitations, our research confirms and expands upon previous findings. Using a large single-center cohort and rigorous statistical analyses, we present compelling evidence that, despite being highly specific, USG guidance fails to detect nearly half of children with kidney parenchymal damage. This highlights that DMSA scintigraphy serves an essential role in the evaluation and follow-up of pediatricpatients with VUR and recurrent urinary tract infections.

Our inclusion of patient-level diagnostic accuracy is clinically meaningful since management decisions are made for patients rather than individual kidneys. This analysis shows the practical limitations of USG as an independent test.

In conclusion, USG alone is insufficient for detecting renal parenchymal damage in pediatricpatients with VUR and/or rUTIs. DMSA scintigraphy is essential for accurate diagnosis, risk evaluation, and management guidance in this high-risk group of patients.

Conclusion

In children with rUTI and/or VUR, renal USG demonstrated excellent specificity but insufficient sensitivity, with nearly half of affected patients missed if used as the sole imaging modality. Increasing age and low renal uptake emerged as independent predictors of parenchymal damage. DMSA scintigraphy is essential for definitive diagnosis, risk assessment, and long-term follow-up in children at risk of renal scarring.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Medeniyet University Göztepe Training and Research Hospital (24/11/2021, reference number: 0597).

Contribution of the authors

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgements

We would like to express our deepest gratitude to Prof. Dr. Ferda Yerdelen Tatoğlu for her invaluable guidance and support throughout the statistical analysis of this study. Her expertise and insightful feedback significantly contributed to the quality and rigour of this research. We are truly grateful for her patience, encouragement, and dedication, which have been instrumental in completing this work.

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Turkish Journal of Pediatric Disease

Original Article

Tracheostomy in pediatric intensive care: A comprehensive overview of indications, clinical outcomes, and the role of palliative care

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Received : 17.02.2026, Accepted : 01.06.2026
DOI: 10.12956/TJPD.2026.1313

ABSTRACT

Objective: Tracheostomy is frequently required in pediatric intensive care units (PICUs), particularly for children with complex neurological or respiratory conditions. This study aimed to evaluate the indications, outcomes, and the role of pediatric palliative care (PPC) services in the post-tracheostomy management of pediatric patients.

Materials and Methods: This retrospective, single-center study included 42 pediatric patients (0–18 years) who underwent their first tracheostomy in the PICU between January 2020 and November 2024. Demographics, clinical indications, complication rates, palliative care utilization, and discharge outcomes were analyzed descriptively.

Results: The median age was 2 (0–11.25) years, with 66.7% male patients. Prolonged intubation was the most common indication (66.7%), followed by subglottic stenosis and neuromuscular causes. Tracheostomy-related complications occurred in 40.4% of patients. Remarkably, 95.2% were transferred to the PPC unit, where they stayed for a median of 21 days. Discharge to home was achieved in 88.1% of patients, and overall mortality was 11.9%, with no deaths directly attributable to tracheostomy. Among discharged patients, 60.5% required home mechanical ventilation.

Conclusion: This study highlights the critical role of PPC services in facilitating safe discharge and optimizing outcomes for children undergoing tracheostomy. The high home discharge rate and low mortality underscore the benefits of a structured, multidisciplinary care model. Integration of PPC services should be considered standard in the post-tracheostomy management of children with complex comorbidities.

Keywords: Artificial, intensive care units, pediatric, palliative care, respiration, tracheostomy

Introduction

Tracheostomy is a surgical procedure increasingly utilized in pediatric intensive care units (PICUs), particularly in patients requiring prolonged mechanical ventilation, with upper airway obstruction, or with neuromuscular disorders (1). The frequency of tracheostomy in pediatric populations has increased significantly in recent years, parallel to advances in medical care that have extended the survival of children with chronic conditions (2). Tracheostomy improves airway management in ventilated patients, facilitates secretion clearance, and reduces airway-related complications. Furthermore, it enables earlier weaning from mechanical ventilation and discharge, improving the quality of life for both patients and families (3).

Due to advancements in technology and the expansion of neonatal and pediatric intensive care services, the indications for tracheostomy have evolved considerably. Although indications and durations for prolonged ventilation are better defined in adult populations, such data in children remain limited (4,5). There are also regional and ethnic differences in both the indications for tracheostomy and management approaches, underscoring the need for population-specific protocols (6). The decision to perform a tracheostomy in children is complex, requiring multidisciplinary evaluation, and marks the beginning of a long-term care process rather than merely a surgical intervention (7).

Post-tracheostomy care necessitates specialized approaches due to the risk of complications, increased caregiving demands, and the social impact on families (8).

Pediatric palliative care services offer critical support, not only during end-of-life care but throughout the management of life-limiting conditions that lead to significant functional impairments (9). These services provide multidisciplinary, patient-centered care, assisting in clinical management, caregiver education, and discharge planning for tracheostomized children (10.)

In this study, we retrospectively evaluated the clinical and demographic characteristics of pediatric patients who underwent tracheostomy for the first time in a tertiary care PICU. In addition, the impact of pediatric palliative care services on mortality and discharge home rates were analyzed in the light of the existing literature. This topic was selected due to the growing prevalence of pediatric tracheostomy procedures and the critical need for comprehensive understanding of outcomes and optimal care strategies, particularly regarding the knowledge gap in pediatric tracheostomy management and palliative care integration.

Materials and Methods

This retrospective, cross-sectional study was conducted at the Pediatric Intensive Care Unit (PICU) of Kayseri City Hospital between January 2020 and November 2024. The study population consisted of pediatric patients aged 0-18 years who underwent their first tracheostomy procedure during hospitalization in the PICU. All patients who met the inclusion criteria during the study period were enrolled.

Inclusion criteria were pediatric patients aged 0-18 years, first-time tracheostomy performed during PICU hospitalization, and complete medical records available. Exclusion criteria included patients who underwent tracheostomy at another facility, patients admitted only for routine tracheostomy tube changes, and patients with incomplete medical data.

Patient data were retrospectively collected from electronic medical records. The following variables were recorded: age, sex, nationality, primary admission diagnosis, tracheostomy indication, duration of intubation prior to tracheostomy, requirement for home mechanical ventilation (HMV), length of stay in the pediatric palliative care unit, discharge status, mortality outcomes, and cause of death when applicable.

Statistical analysis

Data analysis was performed using TURCOSA Analytics software (Turcosa Analytics Ltd. Co., Kayseri, Türkiye; accessed in 2025). Descriptive statistics were expressed as frequencies and percentages, means and standard deviation, and medians (minimum and maximum). Quantitative data were summarized based on their distribution. The study was designed for descriptive purposes only; therefore, no inferential statistical tests were applied.

Results

A total of 42 pediatric patients were included. The mean age was 5.05 ± 5.87 years (range: 0–16 years), and the median age was 2 years. Males constituted 66.7% (n=28) of the cohort, while 33.3% (n=14) were female. Nationality distribution included 69.0% Turkish (n=29); 28.6% Syrian (n=12) and 2.4% Afghan (n=1). At discharge, 88.1% (n=37) of patients were successfully sent home, while mortality was recorded in 11.9% (n=5). Tracheostomy-related complications occurred in 40.4% (n=17), the most common being cannula occlusion (9.5%, n=4); cuff rupture (7.1%, n=3); cannula fracture (2.4%, n=1); and pneumothorax (9.5%, n=4). Additional complications included skin infections (7.1%, n=3), subcutaneous emphysema (2.4%, n=1); and tracheal fistula (2.4%, n=1). No complications occurred in 59.6% (n=25) of patients. Causes of death included respiratory arrest secondary to acute respiratory failure (60%, n=3) and septic shock (40%, n=2) (Table I).

Table I: Demographic characteristics of patients and study data

Variable	n (%)
Male	
Female	14 (33.3)
Male	28 (66.7)
Nationality	
Republic of Türkiye	29 (69.0)
Syria	12 (28.6)
Afghanistan	1 (2.4)
Discharge status	
Discharged	37 (88.1)
Deceased	5 (11.9)
Post-procedure complications	
Complications observed	17 (40.4)
No complications	25 (59.6)
Observed complications	
Cannula-related problems	8 (19.0)
Pneumothorax	4 (9.52)
Cannula site skin infection	3 (7.14)
Subcutaneous emphysema	1 (2.38)
Tracheal fistula	1 (2.38)
Cause of death	
Acute respiratory failure*	3 (7.14)
Septic shock	2 (4.76)

***:** *Respiratory arrest was considered secondary to acute respiratory failure according to the clinical findings.*

Table II: Data on length of stay and patient age

Variable (n=42)	Median (IQR)
Age (years)	2 (0–11.25)
Pre-procedure MV duration (days)	25 (17–36)
Palliative care duration (days)	21 (15–34)

***MV:** mechanical ventilator, Data are presented as median (25th–75th percentile)*

The median duration of intubation prior to tracheostomy was 25 days (IQR: 17–36). Of the cohort, 95.23% (n=40) were transferred to the pediatric palliative care unit, where they stayed for a median duration of 21 days (IQR: 15–34) (Table II).

Only 7.1% (n=3) of the patients had no comorbidities. The most prevalent comorbidities were cerebral palsy (35.7%, n=15); epilepsy (33.3%, n=14); metabolic disorders (14.3%, n=6); and laryngomalacia (11.9%, n=5). Other significant conditions included SMA, Down syndrome, diffuse axonal injury, chronic lung disease, hypothyroidism, immunodeficiencies, genetic muscle and mitochondrial diseases, scoliosis, congenital heart disease, and global developmental delay (Table III).

Table III: Comorbidity profile of the patient group

Variable	n (%)
Group	
With comorbidities	39 (92.9)
Without comorbidities	3 (7.1)
Comorbidity Details	
Cerebral palsy	15 (35.7)
Epilepsy	14 (33.3)
Non-mitochondrial metabolic disease	6 (14.4)
Laryngomalacia	5 (11.9)
Diffuse axonal injury (post trauma)	4 (9.5)
Hypothyroidism	4 (9.5)
HIE sequelae	3(7.1)
Hypotonia*	3 (7.1)
SMA	3 (7.1)
Immunodeficiency	2 (4.8)
Scoliosis	2 (4.8)
Earthquake victim (Crush syndrome)	2 (4.8)
Down syndrome	2 (4.8)
Growth retardation / malnutrition	2 (4.8)
Chronic renal failure	2 (4.8)
Chronic lung disease	2 (4.8)
Hydrocephalus	1 (2.4)
Lissencephaly	1 (2.4)
Syringomyelia	1 (2.4)
Neurological sequelae (caused by kernicterus)	1 (2.4)
Intellectual disability	1 (2.4)
Achondroplasia	1 (2.4)
Alexander disease	1 (2.4)
Hypertrophic cardiomyopathy	1 (2.4)
Presence of patent ductus arteriosus	1 (2.4)
Known history of supraventricular tachycardia	1 (2.4)
Duchenne muscular dystrophy	1 (2.4)
Genetic disease (with muscle weakness)	1 (2.4)
Mitochondrial disease	1 (2.4)
Congenital cataract	1 (2.4)
Vocal cord paralysis	1 (2.4)

Patients may have more than one comorbidity. ***HIE:*** *hypoxic ischemic encephalopathy,* ***SMA:*** *spinal muscular atrophy *Hypotonia was considered a clinical manifestation associated with underlying neurological or neuromuscular disorders rather than an independent diagnosis.*

Table IV: Hospitalization and tracheostomy indications and discharge clinic

	n (%)
Diagnosis of hospitalization	
Pneumonia	17 (40.47)
Respiratory distress	5 (11.90)
Status epilepticus	5 (11.90)
Acute bronchiolitis	3 (7.14)
Post-cardiac arrest	4 (9.52)
Traffic accident	3 (7.14)
Earthquake - trauma	3 (7.14)
Meningitis	1 (2.38)
Acute gastroenteritis	1 (2.38)
Indications for tracheostomy	
Prolonged intubation	28 (66.66)
Subglottic stenosis	5 (11.90)
Diffuse axonal injury	3 (7.14)
Respiratory muscle weakness	3 (7.14)
Laryngomalacia	2 (4.76)
Vocal cord paralysis	1 (2.38)
Need for home MV at discharge	
Required	23 (62.16)
Not required	14 (37.83)

Primary PICU admission diagnoses were pneumonia/bronchopneumonia (40.5%), respiratory distress (11.9%), and status epilepticus (11.9%). The leading indication for tracheostomy was prolonged intubation (66.7%, n=28); followed by subglottic stenosis (11.9%, n=5); diffuse axonal injury (7.14%, n=3); respiratory muscle weakness (7.14%, n=3); laryngomalacia (4.76%, n=2); and vocal cord paralysis (2.4%, n=1). While 62.16% (n=23) of the patients needed HMV at discharge, 37.83% (n=14) were discharged without the need for HMV (Table IV).

Discussion

In this study, the demographic characteristics, clinical indications, home mechanical ventilation (MV) requirements at discharge, palliative care processes, and discharge outcomes of 42 patients who underwent tracheostomy in our pediatric intensive care unit were evaluated. The majority of patients (95.23%, n=40) who were anticipated to be discharged after tracheostomy were transferred to the pediatric palliative care service; individualized care plans were created, family education was provided, and home care support was organized. Our findings are noteworthy for a low mortality rate (11.9%) and a high home discharge rate (88.1%). In our study, the most common indication for tracheostomy was prolonged intubation (66.7%). Among these patients, 24% and 60% of those with subglottic stenosis were discharged without the need for home MV. These findings suggest that tracheostomy performed in a timely manner and with appropriate indications in the suitable patient group increases the rate of discharge from intensive care to home, and that management of the post-tracheostomy process with a multidisciplinary approach and palliative care services positively influences patient outcomes.

To the best of our knowledge, this represents one of the few studies specifically examining the role of pediatric palliative care services in tracheostomy outcomes among children with complex neurological and respiratory conditions. The strength of this study lies in its comprehensive evaluation of patients with diverse underlying conditions including cerebral palsy, epilepsy, spinal muscular atrophy, metabolic disorders, and diffuse axonal injury, reflecting the real-world complexity of pediatric intensive care populations. The systematic approach to palliative care integration, with a median 21 days in the palliative care unit, allowed for thorough preparation of both patients and families for home discharge. Pediatric palliative care is a multidisciplinary approach aimed at providing symptom control, improving quality of life, and supporting families of children with life-threatening or life-limiting conditions (9). In our center, patients who underwent tracheostomy were transferred to the pediatric palliative care unit following the intensive care period as part of a standardized care model. During the palliative care process, families received education on tracheostomy and ventilator management, including cannula care and secretion management; respiratory physiotherapy was provided, and enteral nutrition planning and preparation for home care were organized. This process was carried out by a multidisciplinary team consisting of pediatric intensive care specialists, pediatric neurologists, respiratory therapists, nutrition support teams, and psychosocial support units. This

study addresses a significant gap in the literature regarding the clinical benefits of palliative care services beyond end-of-life care, demonstrating their crucial role in improving discharge readiness and long-term outcomes.

In the literature, prolonged intubation has been reported as an indication for tracheostomy at rates ranging from 50–90% (6,11–14.) The rate in our study (66.7%) is consistent with these data. Additionally, indications such as diffuse axonal injury, subglottic stenosis, laryngomalacia, and neuromuscular insufficiency support findings from other studies in which neurological causes were prominent (14–16). The median MV duration before tracheostomy in our study was 25 days, which is longer than the 7–21 days reported in the literature (17–18). This difference may be attributed to several factors (12). First, a substantial proportion of our patients had complex neurological or neuromuscular conditions, which often require prolonged attempts at weaning and repeated extubation trials before a decision for tracheostomy is made. Second, socioeconomic and cultural characteristics of families may influence the timing of tracheostomy, as caregivers often require additional time to understand the long-term implications of tracheostomy and home ventilator care. Finally, variability in the informed consent process and the need for detailed family counseling may prolong the decision-making period. These factors together may explain the relatively longer duration of mechanical ventilation prior to tracheostomy observed in our cohort. Our findings underscore that pediatric intensive care units serve a wide spectrum of patients with neurologic and respiratory failure, and tracheostomy remains a frequent necessity for this patient population.

The need for MV after tracheostomy varies from 41–89% in the literature and is generally related to the indication for the procedure (14,16,17,19). Similarly, decannulation rates have been reported to be 74% in patients with airway obstruction and 52% in those with prolonged intubation (20). However, studies assessing indication-specific MV dependence are limited. In our study, 60.52% of patients discharged home required home MV support. Twenty-four percent of patients who underwent tracheostomy due to prolonged intubation, 60% of those with subglottic stenosis, and all patients with respiratory muscle weakness were discharged without the need for home MV. These findings show that, in our clinic, post-tracheostomy planning includes effective use of home ventilation to shorten the intensive care period on a patient-specific basis. However, the low weaning rate from MV among patients receiving long-term ventilatory support highlights ongoing challenges in managing this patient group.

Early discharge from the intensive care unit is important for preventing nosocomial infections and MV-related complications, as well as reducing healthcare costs (3,10). Although the literature has not yet reached a consensus on the effects of early versus late tracheostomy on mortality and morbidity, the high MV requirement following prolonged intubation suggests the need for further studies focusing on the timing of tracheostomy, particularly with consideration of comorbidities (14,21–23).

In our study, a substantial number of patients had severe neurologic or neuromuscular comorbidities, including cerebral palsy, epilepsy, spinal muscular atrophy (SMA), mitochondrial diseases, and metabolic disorders. Literature suggests that most pediatric patients undergoing tracheostomy have such comorbid neurodevelopmental or chronic systemic diseases, which increases both the need for tracheostomy and the complexity of post-discharge care (14–16).

During the post-tracheostomy period, a multidisciplinary approach and palliative care services are essential to facilitate safe discharge by managing infection risk, secretion control, and home care processes (6,10). At least one parent must be adequately trained in post-tracheostomy care and emergency procedures (24). Pediatric palliative care services offer significant advantages by reducing infection risk, educating families, and ensuring individualized care planning (25,26). In our study, 95.23% (n = 40) of the patients expected to be discharged were transferred to the pediatric palliative care service, where they were followed for a median of 2 days. During this period, comprehensive care plans were implemented, families were trained, and home care support was arranged. Given that discharge rates from intensive care units in the literature range between 32–77%, our study's high home discharge rate (88.1%) and low mortality rate (11.9%) are remarkable (3,14,16).

All observed deaths were associated with critical conditions such as respiratory arrest secondary to acute respiratory failure and septic shock; no mortality directly attributable to tracheostomy was reported. Our mortality rate was lower than the 14–40% reported in the literature and consistent with findings that associate mortality primarily with sepsis and underlying disease rather than the tracheostomy procedure itself (11,14,20,27). These favorable outcomes may reflect the active involvement of the palliative care team, structured planning of respiratory support, and the inclusion of families in care processes.

Tracheostomy carries certain risks of complications. In our study, the tracheostomy-related complication rate was 40.4%, which aligns with reported rates in the literature (approximately 25–42%) (6,11,15). Differences between centers may be explained by variations in how complications are defined and recorded. In our study, not only major surgical complications but also minor and manageable events occurring during the follow-up period—such as cannula occlusion, cannula cuff rupture, and local skin infection at the cannula site—were systematically documented. In contrast, some studies report only major or early postoperative complications, which may result in lower reported complication rates. In addition, no complications resulting in permanent sequelae or intraoperative adverse events were observed in our cohort. Pneumothorax (9.52%) was among the common complications noted, consistent with literature in patients managed with MV (28). Problems such as cannula occlusion, cannula cuff rupture and skin infection at the cannula site are preventable conditions seen in patients preparing for discharge after the procedure and once again reveal the importance of family education and palliative care support.

Limitations

Several limitations should be acknowledged in this study. The retrospective design limits the ability to establish

causal relationships between palliative care intervention and improved outcomes. The relatively small sample size and single-center design may limit the generalizability of findings to other pediatric intensive care settings. Additionally, long-term follow-up data regarding home care outcomes, quality of life measures, and re-hospitalization rates were not available for analysis

Conclusion

This study demonstrates that pediatric palliative care services play a crucial role in optimizing outcomes for children undergoing tracheostomy, extending well beyond traditional end-of-life care paradigms. The integration of palliative care services resulted in exceptional home discharge rates and low mortality, particularly in patients with complex neurological conditions such as cerebral palsy, epilepsy, and neuromuscular disorders. The indication-specific variations in home mechanical ventilation requirements provide valuable prognostic information for clinical decision-making and family counseling. Future research should focus on prospective multicenter studies examining long-term outcomes, quality of life measures, and cost-effectiveness of palliative care integration in pediatric tracheostomy management. These findings support the routine involvement of pediatric palliative care teams in the management of children requiring tracheostomy, particularly those with complex underlying conditions.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kayseri City Training and Research Hospital (24.12.2024, reference number: 277).

Contribution of the authors

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

Presented

This study was previously presented as a poster presentation at the Turkish Pediatric Association Pediatric Schools Spring Symposium 2025.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Hematological markers of systemic inflammation potentially associated with migraine in pediatric patients

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Received : 18.02.2026, Accepted : 01.06.2026
DOI: 10.12956/TJPD.2026.1314

ABSTRACT

Objective: The aim of this study was to evaluate potential neuroinflammatory processes in pediatric migraine using hematological inflammatory indices and to examine their associations with age and gender.

Materials and Methods: This retrospective cross-sectional study included 90 children diagnosed with migraine and healthy control group, conducted between August 1, 2019, and August 1, 2025. Complete blood count parameters were analyzed for all participants. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and other hematological inflammatory markers were calculated. Comparisons were made between the migraine and control groups. Additionally, the migraine group was subdivided according to age, gender, and treatment status, and subgroup analyses were performed.

Results: Platelet-to-lymphocyte ratio values were significantly higher in the migraine group than in the control group. In gender-based comparisons, a statistically significant difference was observed only in red blood cell (RBC) counts, whereas no gender-related differences were detected in other inflammatory parameters. Within the migraine group, lymphocyte counts decreased in the older age subgroup, while platelet counts and NLR values showed a significant increase. Among patients receiving flunarizine treatment, no significant differences were observed in inflammatory markers, except for mean corpuscular volume (MCV).

Conclusion: Platelet-to-lymphocyte ratio may serve as a marker of increased inflammatory burden in pediatric patients with migraine. The age-related increase in inflammatory indices may reflect neuroinflammatory processes involved in migraine pathophysiology. These findings highlight the importance of considering age in the clinical evaluation of pediatric migraine patients.

Keywords: Child, flunarizine, migraine, neuroinflammation, platelet

Introduction

Migraine is a primary headache disorder characterized by pulsatile or throbbing headache accompanied by photophobia, phonophobia, nausea, and vomiting, and it is commonly observed in childhood (1). The World Health Organization has identified migraine as one of the top ten causes of disability worldwide (2). The prevalence of migraine in children is approximately 10%, and it has a substantial negative impact on school performance and quality of life (3). Although no significant gender differences are observed in migraine prevalence during the prepubertal period, migraine occurs more frequently in girls during adolescence (4).

The diagnosis of migraine in children differs in certain aspects from that in adults. Headache attacks in children are typically shorter in duration. The pain may be unilateral or bilateral. However, similar to adults, childhood migraine is expected to exhibit at least two core features, including a pulsatile quality, moderate to severe intensity, and worsening with routine physical activity. In addition, at least one associated symptom, such as nausea, vomiting, photophobia, or phonophobia, is required for diagnosis. However, children may have difficulty expressing symptoms such as photophobia and phonophobia; instead, they may demonstrate behaviorals, such as seeking a dark and quiet environment (5).

Neurogenic inflammation plays a key role in the pathophysiology of migraine. Migraine-related headache is thought to result from activation of the trigeminovascular system, which consists of peripheral trigeminal nerve fibers that innervate the vascular structures of the dura mater (6). Various cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), and adiponectin, are involved in regulating inflammatory processes, altering pain thresholds, increasing trigeminal nerve sensitization, and the development of migraine attacks (7). Experimental studies have demonstrated significantly increased TNF-α expression and macrophage presence in the trigeminal ganglia during inflammatory processes (8). In addition, increased serum concentrations of IL-1β, IL-6, IL-8, and TNF-α have been reported during migraine attacks (9). A meta-analysis has shown that serum CRP, IL-1β, IL-6, and TNF-α levels are higher in patients with migraine than in healthy controls. These findings support the role of inflammation in the pathophysiology of migraine (10).

The NLR and MLR are practical hematological parameters used to assess the presence and severity of systemic inflammation. These indices are calculated by dividing peripheral neutrophil and monocyte counts by lymphocyte counts (11). Previous pediatric studies have reported significant associations between NLR, MLR, and PLR values and various diseases, suggesting that these parameters may serve as useful diagnostic and therapeutic biomarkers (12,13). Recent studies indicate that inflammation may play a role in the pathophysiology of childhood migraine and highlight inflammatory response markers as potential biomarkers. Therefore, this study aimed to investigate whether NLR, MLR, and PLR are potential markers associated with inflammatory processes in childhood migraine.

Materials and Methods

This single-center, retrospective cross-sectional study was conducted at Balıkesir University Health Practice and Research Hospital between August 1, 2019, and August 1, 2025. A total of 90 pediatric patients diagnosed with migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3), were included. During the same period, children who presented to the pediatric and Pediatric Neurology-1 outpatient clinics for routine follow-up and had no history of headache (n=100) were included as the control group.

Patients with signs of acute infection, chronic inflammatory diseases, hematological disorders, a history of autoimmune disease, those receiving systemic corticosteroids or immunomodulatory therapy, and those with incomplete medical records were excluded from the study.

Data Collection

Demographic data were retrospectively obtained from medical records. Laboratory data were collected from complete blood count (CBC) results obtained from peripheral venous blood samples drawn at the time of admission. CBC parameters included white blood cell count (WBC), RBC, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count (PLT), platelet distribution width (PDW), and neutrophil, lymphocyte, monocyte, and eosinophil counts.

Calculation of inflammatory hematological indices

The following inflammatory ratios were calculated from the complete blood count data:

- NLR: calculated by dividing the neutrophil count by the lymphocyte count
- PLR: calculated by dividing the platelet count by the lymphocyte count
- MLR: calculated by dividing the monocyte count by the lymphocyte count

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Data were presented as number (n), minimum–maximum values, and mean and standard deviation. Group comparisons were performed using the independent samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. A p value of <0.050 was considered statistically significant.

Results

A total of 190 participants were included in the study. The ages of the participants ranged from 5 to 18 years, with a mean age of 12.0±3.6 years. When stratified by age groups, the majority of participants were in the 5–13-year age range (Table I).

The clinical characteristics of the participants are summarized in Table II. Regarding attack frequency, the most common

Table I: Demographic characteristics of the migraine and control groups

Variables	Migraine group*	Control group*
Age group		
5-12 years	39 (43.3)	74 (74)
12-18 years	51 (56.7)	26 (26)
Gender		
Female	52 (57.8)	45 (45)
Male	38 (42.2)	55 (55)
Treatment		
Yes	10 (11)	-
No	80 (89)	-

**: n(%)*

Table II: Clinical characteristics of participants with migraine

Variables	n (%)
Attack Frequency	
Every day	24 (26.6)
2–6 times per week	35 (38.8)
Once per week	10 (11.1)
1–3 times per month	21 (23.3)
Attack Duration	
<1 hour	18 (20)
1–3 hours	46 (51.1)
3–6 hours	16 (17.7)
More than 6 hours	10 (11.1)
Migraine Type	
Without aura	83 (92.2)
With aura	7 (7.8)
Family History	
Present	56 (62.2)
Absent	34 (37.8)

Table III: Comparison of age and hematological parameters between the migraine and control groups

Variables	Migraine group*	Control group*	p
Total number of patients	90	100	
Age (years)	12.18±3.63	9.84±2.99	<0.010‡
WBC (×10³/μL)	7.44±2.21	7.59±2.06	0.636‡
RBC (×10⁶/μL)	4.91±0.39	4.94±0.36	0.460†
Hb (g/dL)	13.29±1.25	13.07±0.93	0.160‡
Hct (%)	39.46±3.19	38.63±2.62	0.520†
MCV (fL)	80.59±5.67	78.36±4.85	0.040‡
MCHC (g/dL)	33.52±1.45	33.85±0.71	0.470‡
RDW (%)	13.78±1.10	14.14±1.02	0.190‡
Neutrophils (×10³/μL)	4.20±1.87	3.94±1.70	0.301‡
Lymphocytes (×10³/μL)	2.44±0.73	2.73±0.84	0.011‡
Monocytes (×10³/μL)	0.57±0.18	0.59±0.20	0.622‡
Eosinophils (×10³/μL)	0.18±0.17	0.26±0.23	0.090‡
Platelets (×10³/μL)	312.41±82.00	327.57±86.37	0.166†
NLR	1.87±1.10	1.59±0.99	0.710‡
MLR	0.25±0.11	0.23±0.09	0.103‡
PLR	134.27±37.80	130.92±66.70	0.046†

**: mean±SD †: Mann–Whitney U test, ‡: Independent samples t-test*

pattern was 2–6 attacks per week (38.8%), followed by daily attacks (26.6%), 1–3 attacks per month (23.3%), and once-weekly attacks (11.1%). In terms of attack duration, most participants reported attacks lasting 1–3 hours (51.1%), whereas 20% had attacks lasting less than 1 hour, 17.7% reported durations of 3–6 hours, and 11.1% experienced attacks lasting more than 6 hours. The majority of patients were diagnosed with migraine without aura (92.2%), whereas migraine with aura was less frequent (7.8%). A positive family history of migraine was present in 62.2% of the participants.

Evaluation of complete blood count parameters revealed that WBC values ranged from 3.4 to 17.7×10³/μL, RBC values from 4.08 to 6.09×10⁶/μL, hemoglobin levels from 10.1 to 17.4 g/dL, and hematocrit values from 30.5% to 49.6%. MCV ranged from 58.1 to 92.4 fL, MCHC from 25.3 to 37.0 g/dL, and RDW from 12.1% to 17.7%.

Regarding platelet parameters, platelet counts ranged from 140 to 637×10³/μL, plateletcrit (PCT) from 0.14% to 0.45%, and PDW from 15.7 to 18.2 fL. Neutrophil counts ranged from 1.0 to 11.4×10³/μL, lymphocyte counts from 0.5 to 6.0×10³/μL, monocyte counts from 0.0 to 1.1×10³/μL, and eosinophil counts from 0.0 to 1.3×10³/μL.

When inflammatory hematological indices were evaluated, the NLR ranged from 0.43 to 8.60, the PLR ranged from 65.46 to 638.00, and the MLR ranged from 0.00 to 1.00.

As shown in Table III, statistically significant differences were observed between the migraine and control groups with respect to age (p<0.010), lymphocyte count (p=0.011), MCV (p=0.040), and PLR (p=0.046). Compared with the control group, patients with migraine were older and had lower lymphocyte counts as well as higher MCV and PLR values. No statistically significant differences were detected between the groups for the remaining parameters.

As shown in Table IV, male patients exhibited significantly higher RBC counts than female patients (p<0.001), whereas

Table IV: Comparison of hematological parameters by gender in the migraine group

Variables	Female group*	Male group*	p
Total number of patients	52	38	
WBC (×10³/μL)	7.43±1.98	7.47±2.50	0.935‡
RBC (×10⁶/μL)	4.79±0.38	5.09±0.34	<0.001†
Hb (g/dL)	13.10±1.10	13.56±1.39	0.085‡
Hct (%)	39.46±3.19	38.63±2.62	0.183†
MCV (fL)	81.63±6.03	79.16±4.87	0.041‡
MCHC (g/dL)	33.37±1.43	33.73±1.48	0.240‡
RDW (%)	13.73±1.15	13.83±1.03	0.667‡
Neutrophils (×10³/μL)	4.26±1.65	4.13±2.15	0.737‡
Lymphocytes (×10³/μL)	2.40±0.73	2.50±0.72	0.516‡
Monocytes (×10³/μL)	0.55±0.17	0.60±0.20	0.191‡
Eosinophils (×10³/μL)	0.18±0.20	0.20±0.13	0.544‡
Platelets (×10³/μL)	306.75±74.60	320.16±91.62	0.644†
NLR	1.91±0.87	1.82±1.38	0.710‡
MLR	0.24±0.08	0.26±0.15	0.364‡
PLR	134.37±36.01	134.13±40.61	0.455†

**: mean±SD, †: Mann–Whitney U test, ‡: Independent samples t-test*

Table V: Comparison of hematological parameters according to age categories in the migraine group

Variables	Migraine age group 1 (5–12 years)*	Migraine age group 2 (12–18 years)*	p
WBC (×10³/μL)	7.53±2.68	7.38±1.78	0.752‡
RBC (×10⁶/μL)	4.93±0.28	4.91±0.46	0.468†
Hb (g/dL	13.09±0.76	13.44±1.51	0.193‡
Hct (%)	38.89±2.16	39.89±3.76	0.202†
MCV (fL)	79.10±2.78	81.72±6.95	0.029‡
MCHC (g/dL)	33.72±1.35	33.37±1.53	0.261‡
RDW (%)	13.64±0.84	13.88±1.26	0.293‡
Neutrophils (×10³/μL)	3.92±2.07	4.42±1.69	0.205‡
Lymphocytes (×10³/μL)	2.74±0.85	2.21±0.51	<0.001‡
Monocytes (×10³/μL)	0.59±0.19	0.56±0.17	0.388‡
Eosinophils (×10³/μL)	0.2 ±0.14	0.16±0.19	0.081‡
Platelets (×10³/μL)	343.36±88.80	288.75±68.24	0.020†
NLR	1.48±0.71	2.17±1.26	0.030‡
MLR	0.23±0.09	0.27±0.13	0.140‡
PLR	131.13±34.75	136.67±40.15	0.550†

**: mean±SD, †: Mann–Whitney U test, ‡: Independent samples t-test*

female patients had significantly higher MCV values (p=0.041). No significant gender-related differences were detected for the other hematological parameters (all p>0.050)

When migraine patients were divided into two age-based categories as Group 1 (5–12 years) and Group 2 (12–18 years), statistically significant differences were observed in MCV (p=0.029), lymphocyte count (p<0.001), platelet count (p=0.029), and NLR (p=0.030).

A statistically significant difference was observed only in MCV, which was significantly lower in patients receiving treatment compared to those not receiving treatment (p<0.010). No statistically significant differences were found between the treated and untreated groups in terms of age, white blood cell count, RBC count, hemoglobin, hematocrit, platelet count, leukocyte subtypes, or inflammatory ratios including NLR, MLR and PLR.

Table VI: Comparison of hemogram parameters in migraine patients receiving and not receiving treatment

Migraine group	Treated*	Untreated*	p
Age (years)	13.60±3.34	12.00±3.65	0.580‡
WBC (×10³/μL)	7.19±1.31	7.48±2.30	0.700‡
RBC (×10³/μL)	5.14±0.57	4.89±0.36	0.163†
Hb (g/dL)	12.63±1.39	13.37±1.21	0.750‡
Hct (%)	37.86±3.70	39.66±3.09	0.125†
MCV (fL)	74.59±10.36	81.34±4.35	<0.010‡
MCHC (g/dL)	33.32±1.33	33.55±1.48	0.640‡
RDW(%)	14.30±1.38	13.71±1.05	0.109‡
Neutrophils (×10³/μL)	3.97±1.05	4.23±1.95	0.676‡
Lymphocytes (×10³/μL)	2.25±0.43	2.46±0.75	0.385‡
Monocytes (×10³/μL)	0.64±0.11	0.57±0.19	0.219‡
Eosinophils (×10³/μL)	0.29±0.37	0.17±0.13	0.380‡
Platelets (×10³/μL)	324.80±81.82	310.86±82.40	0.599†
NLR	1.81±0.55	1.88±1.16	0.842‡
MLR	0.29±0.08	0.25±0.12	0.206‡
PLR	148.74±42.56	132.46±37.06	0.215†

**: mean±SD, †: Mann–Whitney U test, ‡: Independent samples t-test*

Discussion

Migraine is one of the most common primary headache disorders in childhood and primarily affects the central nervous system. However, accumulating evidence suggests that migraine is not only a neurovascular disorder but also a condition with a significant inflammatory component (14). In our study, the migraine group demonstrated lower lymphocyte counts, higher MCV levels, and increased PLR values compared with the control group. These findings suggest that such hematological alterations may represent indirect reflections of the neuroinflammatory processes involved in migraine pathophysiology. Accordingly, readily available complete blood count parameters, particularly lymphocyte count, MCV, and PLR, may serve as practical, inexpensive, and clinically applicable indicators of neuroinflammatory activity in childhood migraine.

Previous studies have likewise emphasized the role of immune-mediated inflammation in pediatric migraine. Elevated levels of proinflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), as well as pentraxin-3 (PTX-3), a marker involved in both acute and chronic inflammation, have been reported in children with migraine (10,15). Increased levels of these biomarkers indicate immune activation both within the central nervous system and in the peripheral circulation. Monocytes and lymphocytes are key cellular components of the innate and adaptive immune response. Proinflammatory mediators released during migraine attacks may enhance monocyte activation and promote their differentiation into macrophages. Alterations in lymphocyte counts may likewise be associated with immune regulation and systemic inflammatory processes. Although some studies have not demonstrated a significant association between lymphocyte subgroups and pediatric migraine, a mild reduction in lymphocyte counts during the attack period has been reported (16). Since our findings were obtained during the interictal period, the observed hematological changes may reflect chronic low-grade systemic inflammation accompanying migraine rather than transient inflammatory responses occurring during acute attacks.

In our study, MCV values were significantly higher in pediatric migraine patients compared with controls. Although MCV is primarily used in the differential diagnosis of anemia, increasing evidence suggests that erythrocyte indices may also be influenced by systemic inflammation, oxidative stress, and vascular alterations. However, no previous study has clearly demonstrated elevated MCV levels in patients with migraine. On the contrary, available data indicate either no significant difference or lower MCV values in migraine patients compared with controls. For instance, Şahin et al. (17) reported that MCV levels in pediatric migraine patients were comparable to those of the control group, with no statistically significant difference. In adult patients, Ertekin found that individuals with chronic migraine had significantly lower MCV levels compared with those suffering from tension-type headache (18). In our study, the observed increase in MCV may reflect subtle inflammatory, metabolic, or oxidative changes associated with the pathophysiology of pediatric migraine rather than a simple hematological variation. Given that current evidence remains limited and inconsistent, further prospective multicenter studies are warranted to clarify the clinical significance of this finding.

In our study, no significant differences were found in NLR and MLR between migraine patients and controls, suggesting that changes in neutrophil and monocyte counts may have occurred proportionally to lymphocyte changes. Because migraine-related inflammation is typically chronic rather than acute, neutrophil counts may remain relatively stable. If lymphocyte counts decrease while neutrophil counts remain stable or decrease proportionally, NLR may not show a significant increase. Similarly, parallel changes in monocyte and lymphocyte counts may result in stable MLR values. For example, one clinical study reported decreased monocyte counts and increased MLR in migraine patients (19). In our study, the absence of significant differences in MLR may be explained by similar directional changes in monocyte and lymphocyte counts. Furthermore, ratios such as NLR and MLR are often considered markers of infectious or acute inflammatory processes; therefore, their sensitivity may be limited in sterile inflammatory conditions such as migraine.

PLR, defined as the ratio of peripheral platelet count to lymphocyte count, is a readily accessible marker reflecting systemic inflammation. In our study, PLR was found to be increased in pediatric migraine patients. An elevated PLR may theoretically result from an increase in platelet count, a decrease in lymphocyte count, or a combination of both. In the present study, lower lymphocyte counts may have contributed to the higher PLR values observed in the migraine group. In a pediatric migraine study, platelet counts in the migraine group were found to be significantly lower than those in the tension-type headache group (20). However, other studies have suggested that platelet activation, rather than absolute platelet count alone, may play a more important role in migraine pathophysiology. Activated platelets can release proinflammatory mediators, serotonin, and vasoactive substances that may contribute to neurovascular dysfunction and trigeminovascular activation during migraine attacks (21). Therefore, an increased PLR in our study may reflect the combined effect of relative lymphocyte reduction and heightened platelet-related inflammatory activity, supporting

a possible association between migraine and low-grade inflammatory processes.Therefore, the observed increase in PLR should be interpreted with caution, and further well-designed studies are warranted to clarify the underlying biological mechanisms and its potential relationship with neuroinflammatory processes in pediatric migraine.

The prevalence and clinical characteristics of migraine change with age. In our study, no significant differences were observed according to gender, whereas significant differences were identified between age groups. Migraine attacks in preschool-aged children are often shorter in duration and atypical, whereas school-aged children and adolescents tend to exhibit more classical features, with increasing prevalence (1). For example, it has been reported that the frequency of chronic migraine doubles around the age of 12 and that overall migraine prevalence exceeds 18% during adolescence (22). Early-onset migraine may be associated with genetic predisposition or developmental stages of the immune system. Because the immune system is not fully mature during early childhood, migraine attacks at younger ages may manifest through different inflammatory responses, such as cyclic vomiting syndrome or abdominal pain (23). Hormonal and neuroendocrine changes also influence migraine frequency until adolescence. While migraine prevalence is similar between boys and girls before puberty, it tends to be 2–3 times higher in girls after puberty (24). Consistent with these findings, our study demonstrated significant age-related differences but no significant gender-related differences between groups.

Within the migraine group, a significant difference between genders was observed only in erythrocyte count, whereas no differences were found in lymphocyte, monocyte, platelet counts, or inflammatory parameters such as NLR. This finding may be explained by the fact that RBC count in pediatric populations is more strongly influenced by physiological and biological factors than by inflammation. Erythrocyte count is a gender-sensitive parameter in childhood, particularly near puberty, as androgens stimulate erythropoiesis, resulting in higher RBC levels in boys (25). In contrast, lymphocyte and platelet counts, as well as NLR, are more closely related to immune activation and systemic inflammation and are therefore expected to be independent of gender in pediatric migraine (26).

Significant differences in lymphocyte count, platelet count, and NLR values were observed between age groups in our study. This may reflect age-related changes in immune system maturation and hematological responses. Although migraine prevalence increases toward school age and adolescence, studies have shown that prevalence is approximately 5% in children aged 5–10 years and rises to around 15–18% during adolescence, particularly between 12 and 15 years of age (27). Large pediatric reference studies of hemogram-based inflammatory markers have demonstrated that parameters such as NLR, PLR, and LMR vary with age, showing distinct distributions from infancy to adolescence (28). This phenomenon may be explained by immune system maturation, with lymphocyte predominance in early childhood and increasing neutrophil responses with advancing age. Additionally, platelets are known to play roles not only in hemostasis but also in inflammation and immune modulation, which may lead to age-related variations in platelet counts and platelet-based indices. Accordingly, age-dependent variability in NLR and other inflammatory indices has been reported in neuroinflammatory conditions such as pediatric migraine, supporting the age-related differences observed in our study (29).

No significant differences in hematological parameters were observed between migraine patients receiving flunarizine treatment and those not receiving treatment. However, this finding should be interpreted with caution, as the retrospective design, lack of standardized treatment duration, and relatively small sample size limit the ability to draw definitive conclusions regarding treatment effects.

Flunarizine primarily acts on central calcium channels, with unclear effects on systemic inflammation (30). Previous studies have suggested that combination therapies may influence inflammatory markers; however, such findings cannot be directly extrapolated to flunarizine monotherapy (31). Therefore, our results do not provide sufficient evidence to determine whether flunarizine has a measurable effect on peripheral inflammatory parameters, and further prospective studies are needed to clarify this relationship.

Conclusion

In this study, PLR values were significantly higher in pediatric migraine patients than controls. This finding suggests that migraine in childhood may be associated with inflammatory processes. The inflammatory response in pediatric migraine appears to be independent of gender. Age-based analysis demonstrated significantly higher inflammatory markers in the 12–18 age group compared with the 5–12 age group, age-related increases in inflammatory markers may reflect immune system maturation. These findings indicate that pediatric migraine may be associated with age-sensitive inflammatory mechanisms and suggest that PLR may serve as a readily accessible inflammatory marker in clinical practice. Flunarizine treatment showed no effect on inflammatory parameters.

Limitations

This study has several limitations. Only interictal migraine patients were evaluated, and inflammatory marker changes during migraine attacks were not assessed. The cross-sectional and single-center design limits causal inference and generalizability. Furthermore, the inability to perform subgroup analyses based on flunarizine dose, treatment duration, and pediatric age groups partially restricts interpretation of treatment-related inflammatory changes. Therefore, detailed subgroup analyses of hematological parameters according to specific pediatric age groups could not be performed. Although it is well established that hematological parameters show the most pronounced physiological variations during the neonatal and infancy periods, and tend to be relatively stable in later childhood, certain parameters such as hemoglobin (Hb), MCV, and MCHC may still vary according to age and gender during adolescence. In addition, existing literature demonstrates heterogeneity in age-related reference ranges of

hematological parameters across different populations, which may be influenced by ethnic background, nutritional status, and environmental factors. Accordingly, the inability to perform age-stratified analyses represents an important limitation of this study. Future studies with larger sample sizes and stratification according to age and pubertal stage are needed to provide a more detailed evaluation of hematological parameters in pediatric populations.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Balıkesir University (06.01.2026, reference number: 2025/365).

Contribution of the authors

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Platelet indices as predictors of late-onset sepsis and mortality in thrombocytopenic neonates: A retrospective cohort study

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Received : 27.02.2026, Accepted : 08.06.2026
DOI:10.12956/TJPD.2026.1319

ABSTRACT

Objective: Late-onset neonatal sepsis (LOS) is frequently complicated with thrombocytopenia. The aim of this study was determine the prevalence of LOS, and whether platelet indices affect LOS and mortality in neonates with thrombocytopenia in the neonatal intensive care unit (NICU) population.

Materials and Methods: This retrospective observational cohort study included neonates admitted to a level 4 NICU between 2018 and 2022 who developed thrombocytopenia (platelet count <150×10^9/L). Platelet indices were recorded during thrombocytopenic episodes preceding or coinciding with late-onset sepsis (LOS). Multivariable logistic regression and Cox proportional hazards models were used.

Results: A total of 223 (13.3%) thrombocytopenic neonates were included in the study. According to multivariable logistic regression analysis, multiparity (OR: 3.32 95% CI 1.40-7.89, p=0.006), caesarean section (OR: 5.81, 95% CI 1.99-16.89, p<0.001), invasive ventilation (OR: 8.43 95% CI 3.60-19.75, p<0.001, high MPV levels (OR: 1.62 95% CI 1.24-2.12, p<0.001) and duration of thrombocytopenia (OR: 1.13 95% CI 1.06-1.20, p=0.001), duration of hospitalization (OR: 1.03 95% CI 1.01-1.05, p=0.004) were independently associated with the development of LOS. Multivariable Cox hazard modelling demonstrated that invasive ventilation (HR: 9.459, 95% CI 3.38-26.45, p<0.001), platelet transfusion (HR: 2.833 95% CI 1.54-5.20, p=0.001), lymphopenia (HR: 0.766, 95% CI 0.64-0.92, p=0.003), grade 2≥ of NEC (HR: 7.274, 95% CI 1.68-31.52, p=0.008), any type of haemorrhage (HR: 2.728, 95% CI 1.69-9.10, p=0.001), platelet nadir (HR: 0.972, 95% CI 0.96-0.98, p<0.001), MPV (HR: 0.805, 95% CI 0.66-0.98, p=0.032), and lymphopenia (HR: 0.745, 95% CI 0.63-0.89, p=0.001) independently predicted overall mortality.

Conclusion: Key findings indicate that larger platelet sizes, prolonged thrombocytopenia, and extended hospitalization are linked to late neonatal sepsis. Furthermore, lower platelet levels characterized by smaller platelet sizes and the necessity for platelet transfusions may also contribute to these adverse outcomes.

Keywords: Mean platelet volume, newborn, late neonatal sepsis, thrombocytopenia

Introduction

Platelets are central players in hemostasis and thrombosis. Thrombocytopenia is a common hematological issue in neonates, with varying incidence across different populations. Thrombocytopenia affects an estimated 22-35% of neonates in the NICU, particularly in younger and more vulnerable infants (1,2).

Platelets play a vital role in innate immunity by directly binding to pathogens, aiding in their neutralization and destruction. They are crucial for containing infections, eliminating pathogens, and facilitating immune responses (3-4). Current clinical research on platelet function now emphasizes its role beyond hemostasis.

Neonatal sepsis is categorized as early or late onset, with late-onset sepsis (LOS) occurring after 72 hours postnatally. It is often associated with nosocomial or community settings and significantly impacts morbidity and mortality in the NICU (5). Early identification, thorough evaluation, and prompt treatment are crucial to prevent serious complications. Late neonatal sepsis is often associated with thrombocytopenia (6). Research has mostly focused on the link between platelet indices and transfusion practices concerning intraventricular hemorrhage (IVH) and mortality. Growing interest in platelets

as mediators of inflammation enhances our understanding of neonatal and pediatric sepsis (7-9). To understand the role of platelets in infections in newborns, we need to study conditions with low platelet counts. Our focus should be on two main areas: how platelets affect the prevalence of infections and how they influence clinical outcomes once an infection is established.

Despite increasing interest in platelet indices as biomarkers in neonatal sepsis, evidence specifically addressing thrombocytopenic neonates remains limited. In this population, platelet dynamics may differ significantly due to both consumption and production abnormalities. Furthermore, the temporal relationship between thrombocytopenia and LOS remains unclear, making causal interpretation challenging. The study aimed to assess the prevalence of LOS among thrombocytopenic neonates and evaluate the impact of platelet indices on LOS and mortality in this NICU population. We hypothesized that platelet indices measured during thrombocytopenic episodes are independently associated with the development of LOS and mortality in NICU patients.

Materials and Methods

This study was performed between January 2018 and December 2022 at Gülhane Training and Research Hospital. A total of 372 neonates who developed at least one episode of thrombocytopenia (platelet count <150×10^9/L) were identified. Neonates with only a single transient thrombocytopenic episode without adequate follow-up (n=129), lack of informed consent (n=11), missing hematological data (n=6), and those transferred within 24 hours (n=3) were excluded. The final cohort consisted of 223 neonates. Due to the retrospective design, a formal sample size calculation was not performed; however, all eligible neonates within the study period were included to maximize statistical power (Figure 1).

The main objective was to assess the prevalence of LOS in thrombocytopenic neonates. Secondary outcomes included the relationship between platelet count, plateletcrit, mean platelet volume (MPV), LOS, and mortality. Sepsis was identified by positive blood cultures in infants with clinical signs, with LOS occurring after 48 hours of life, typically acquired from the environment (10-11). To reduce confounding factors, the study focused solely on hematologic parameters associated with the thrombocytopenic episode linked to LOS, excluding earlier sepsis instances that might have affected platelet levels.

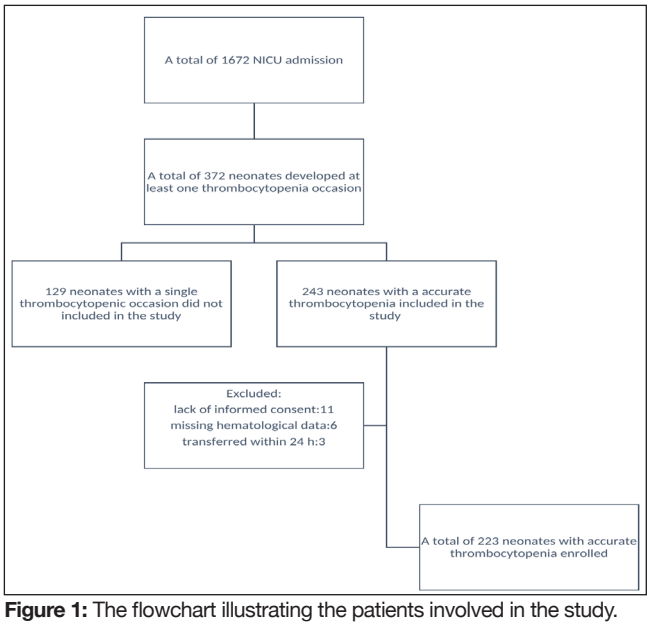

Figure 1: The flowchart illustrating the patients involved in the study.

Data were extracted from the hospital's patient database, which includes medical histories, diagnoses, treatment plans, and lab results.

The recorded maternal data included pregnancy-induced hypertension, preeclampsia, eclampsia, diabetes, intrauterine growth failure, premature rupture of membranes, placental abruption, TORCHes infection, chorioamnionitis, opioid abuse, and mode of delivery. The neonatal data included gestational age, birth weight, small for gestational age (SGA), day of NICU admission, asphyxia, early and late-onset sepsis, duration of thrombocytopenia, hemorrhage occurrences, platelet transfusions, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), neonatal alloimmune thrombocytopenia (NAIT), hemolytic disease of the newborn (HDN), length of hospital stay, and in-hospital mortality.

Thrombocytopenia is categorized into four groups based on platelet levels: mild (101-149x10^9/L), moderate (51-100x10^9/L), severe (21-50x10^9/L), and very severe (≤20x10^9/L). The onset is noted on the day of initial presentation, while duration refers to the time from diagnosis until platelet counts exceed 150x10^9/L, confirmed by two measurements 24 hours apart. Hematologic parameters for each neonate include initial platelet count, nadir count, mean platelet volume (MPV), and plateletcrit. For cases associated with late-onset sepsis (LOS), these parameters were closely monitored. This study focused on a specific instance of thrombocytopenia, analyzing selected platelet parameters related to the lowest recorded count.

Platelet transfusions followed department protocols. The observed bleeding disorders included intraventricular hemorrhage (IVH), pulmonary hemorrhage, gastrointestinal bleeding, hematuria, and cutaneous bleeding such as petechiae, ecchymoses, and hematomas. IVH was classified per Papile et al. (12), and necrotizing enterocolitis was determined to be stage 2A or greater per modified Bell criteria. Patent ductus arteriosus (PDA) was identified as an open ductus requiring intervention.

Statistical analysis

Descriptive statistics were reported as mean and standard deviation for normally distributed variables, median with interquartile range (IQR) for non-normally distributed variables, and as counts and percentages for nominal and ordinal data. Bivariate associations between the primary outcome and independent variables were analyzed using Student's t-test, Mann-Whitney U test, Pearson's chi-square test, or Fisher's exact tests. Multivariable logistic regression controlled for associations among independent variables based on theoretical rationale, timing of occurrences, and minimizing reverse causation. The analysis included the most clinically significant correlated risk factor to avoid multicollinearity. Final models featured main effects significant at p<0.050 and

interactions significant at p<0.200, employing the backward method. Adjusted odds ratios (OR) and 95% confidence intervals were calculated. Univariable and multivariable Cox regression identified independent predictors of exitus development, with adjusted hazard ratios (HR) calculated as well. Gestational age and birth weight were evaluated as potential confounders. These variables were initially included in multivariable models; however, due to collinearity with clinical severity indicators, the most clinically relevant variables were retained in the final models. Overall survival was measured from hospital admission to death and analyzed via the Kaplan-Meier method and Log-rank test. A p-value <0.050 indicated statistical significance, with analyses conducted using IBM Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Armonk, NY, IBM Corp., USA).

Results

Among the enrolled neonates, there were 263 instances of thrombocytopenia, with 26 cases (11.7%) being recurrent. The distribution of platelet counts showed: 44 neonates

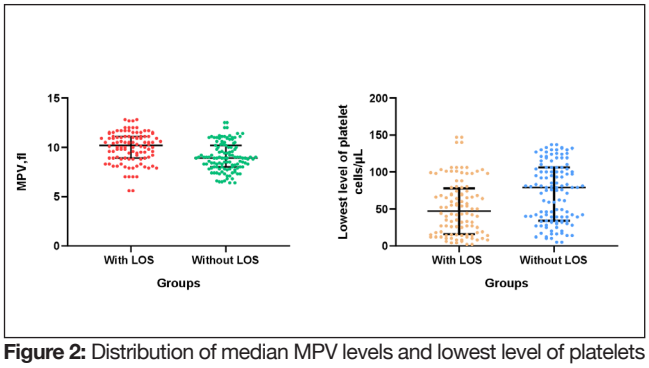

Figure 2: Distribution of median MPV levels and lowest level of platelets between subgroups.

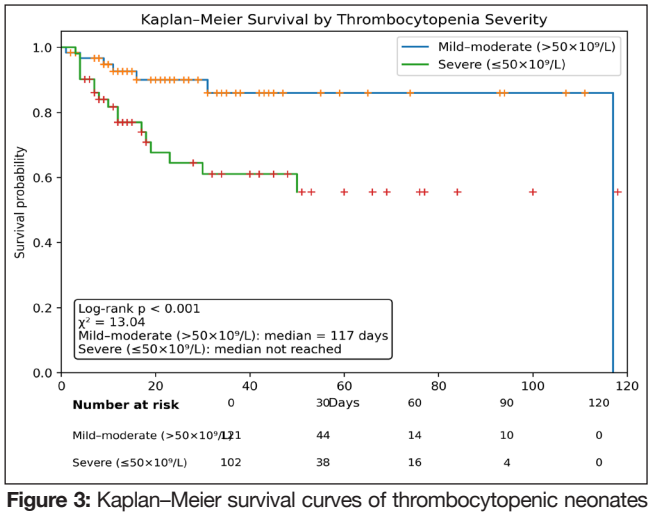

Figure 3: Kaplan–Meier survival curves of thrombocytopenic neonates stratified by severity of thrombocytopenia. Survival probability was significantly lower in neonates with severe thrombocytopenia (platelet count ≤50×10^9/L) compared to those with higher platelet counts (>50×10^9/L). Survival distributions were compared using the log-rank test. Hazard ratios were estimated using Cox proportional hazards models adjusted for clinically relevant covariates. Kaplan–Meier survival analysis demonstrated significantly lower survival in neonates with severe thrombocytopenia (log-rank p<0.001).

Table I: Neonatal thrombocytopenia related maternal and infantile conditions in the study

Identifiable cause	No (%)
Late onset neonatal sepsis	99 (44.4)
Intrauterine growth failure	36 (16.1)
Maternal preeclampsia	24 (10.8)
Early onset neonatal sepsis	20 (8.9)
Hypoxic ischemic encepahalopathy	14 (6.3)
Placental abruption	10 (4.5)
TORCHes infection	6 (2.7)
Maternal pregnancy-induced hypertension	4 (1.8)
Thrombosis	4 (1.8)
Neonatal alloimmune thrombocytopenia	3 (1.3)
Hemolytic disease of the newborn	2 (0.9)

(19.7%) with very severe thrombocytopenia, 58 (26%) with severe, 75 (33.6%) with moderate, and 46 (20.6%) with mild. Overall, 70 neonates (31.4%) received at least one platelet transfusion, 44 (19.7%) had hemorrhages, and 48 (21.5%) experienced neonatal mortality. Maternal and neonatal factors linked to thrombocytopenia are detailed in Table I.

Late-onset sepsis was identified in 99 of 223 neonates with thrombocytopenia, a 44.4% incidence. Among these, gram-positive pathogens dominated with 70 cases (70.7%), while gram-negative pathogens accounted for 34 cases (34.3%). The most common organism was coagulase-negative *Staphylococcus* in 57 cultures, followed by *Klebsiella pneumoniae* in 28, *Staphylococcus aureus* in 7, vancomycin-resistant *Enterococcus* in 6, and *Enterobacter* in 4. No fungal growth was seen. Infants who developed LOS exhibited significantly lower gestational ages and birth weights than those without LOS (p<0.001). Infants diagnosed with thrombocytopenia who subsequently developed LOS exhibited a higher incidence of multiparity, twin gestations, and cesarean section deliveries. Detailed baseline characteristics of the cohort are outlined in Table II.

The clinical and hematologic parameters distinguishing infants with LOS from those without are detailed in Table III. The median day of presentation for thrombocytopenia was 9 (IQR 11) in the LOS group, compared to 1 (IQR 1) in the non-LOS group (p<0.001). Initial platelet count before decline was 100x10^9/L (IQR 56) in LOS versus 116 x10^9/L (IQR 57) in non-LOS (p=0.352). Platelet counts were significantly lower in LOS: median 44x10^9/µL (IQR 59) vs. 77.5x10^9/L (IQR 72) (p<0.001). Median plateletcrit was 74.75 (IQR 79.90) in LOS and 120 in non-LOS (p=0.006). No link between gestational age or birth weight and lowest platelet levels (p=0.149 and p=0.738). Platelet sizes were larger in LOS, with MPV of 10.4 fl vs. 8.9 fl in non-LOS (p<0.001). Figure 2 illustrates the distribution of median MPV levels alongside the minimum platelet counts across the different study groups. The duration of thrombocytopenia was significantly longer in the LOS group, with a median of 9 days (IQR 10) versus 6 days (IQR 6) in the non-LOS group (p<0.001). A higher proportion of neonates with LOS received platelet transfusions, at 48.5% (48 out of 99), versus 17.7% (22 out of 124) for those without LOS (p<0.001). Among transfusion recipients, the median number of transfusions was similar: 1.5 (IQR 3) for the LOS group and 2 (IQR 2) for the non-LOS group (p=0.914), as shown in Table III. In neonates with late-onset sepsis, the median platelet

Table II: Demographic variables of thrombocytopenic neonates, divided into subgroups by late onset septicemia (LOS)

	Overall	With	Without	p
Total number of patients	223	99	124	-
Maternal age, y	29 (25-34)* 29.34±6.10†	29 (25-34)* 29.62±5.96†	29 (25-34.5)* 29.09±6.24†	0.530 0.523
Primiparous‡	87 (39)	25 (25.3)	62 (50)	0.001
IVF‡	6 (2.6)	2 (2.02)	4 (3.25)	0.428
Infant gender‡ female male	 84 (37.7) 139 (62.3)	 38 (38.4) 61 (61.6)	 46 (37.1) 78 (62.9)	0.844
Vaginal delivery‡	67 (30)	16 (16.2)	51 (41.1)	<0.001
Birth place‡ outborn inborn	 98 (43.9) 125 (56.1)	 45 (45.5) 55 (55.5)	 53 (42.7) 70 (56.5)	0.775
Gestational age, w*	34 (7)	32 (7)	35 (6)	<0.001
Birth weight, g*	2010 (1590)	1460 (1508)	2200 (1135)	<0.001
Twin pregnancy	28 (12.6)	20 (20.2)	8 (6.5)	0.002
Proportion‡ SGA AGA LGA	 54 (24.2) 155 (69.5) 14 (6.3)	 15 (15.2) 74 (74.7) 10 (10.1)	 39 (31.5) 81 (65.5) 4 (3.2)	0.004
PROM‡	8 (3.6)	4 (4)	4 (3.2)	0.745
Chorioamnionitis‡	6 (2.7)	2 (2)	4 (3.2)	0.566
Maternal UTI‡	4 (1.8)	2 (2)	2 (1.6)	0.820
Preeclampsia‡	24 (10.8)	11 (11.1)	13 (10.5)	0.881
IUGR‡	36 (16.1)	10 (10.11)	26 (21)	0.028
Gestational diabetes‡	6 (2.7)	0 (0)	6 (4.8)	0.035
Congenital disorder	35 (15.7)	14 (14.1)	21 (16.9)	0.569
HIE‡	14 (6.3)	2 (2)	12 (9.7)	0.019
Invasive ventilation‡	100 (44.8)	67 (67.7)	33 (26.6)	<0.001
Surfactant administration‡	66 (29.6)	43 (43.4)	23 (18.5)	<0.001
PDA‡	18 (8.1)	14 (14.1)	4 (3.2)	0.005
NEC‡	22 (9.9)	20 (21)	2 (0.8)	<0.001
Severe thrombocytopenia‡	102 (45.7)	51 (51.5)	51 (41.1)	0.003
Length of hospital stay, days˙	18 (32)	35.5 (49)	12 (15)	<0.001
Mortality‡	48 (21.5)	27 (27.3)	21 (16.9)	0.062

:** *median (IQR) (Mann-Whitney U Test),* **†:** *mean±SD (Independent Samples t Test),* **‡:** *n (%)(Pearson Chi-Square Test) (Fisher's Exact Test).* ***SGA: *Small for gestational age (birthweight <10th percentile for gestational age),* ***AGA:*** *Appropriate for gestational age (birth weight between 10–89th percentile for gestational age),* ***LGA:*** *Large for gestational age (birthweight >90 th percentile for gestational age),* ***PROM:*** *Premature rupture of membranes,* ***UTI:*** *Urinary Tract Infection,* ***IUGR:*** *Intrauterine Growth Retardation,* ***HIE:*** *Hypoxic Ischemic Encephalopaty (Grade ≥2),* ***PDA :*** *Patent ductus arteriosus,* ***NEC:*** *Necrotising Enterocolitis (Grade ≥2)*

transfusions were 1 (IQR 1-2.25) for the gram-positive subgroup and 1.5 (IQR 1-5.5) for the gram-negative subgroup (p=0.424). A higher percentage of neonates with gram-negative sepsis received platelet transfusions (70.6%, 24 out of 34) compared to those with gram-positive sepsis (37.1% - 26 of 70) (p=0.001).

In the multivariable logistic regression analysis, factors including multiparity (OR: 3.32, 95% CI 1.40-7.89, p=0.006), cesarean delivery (OR: 5.81, 95% CI 1.99-16.89, p<0.001), invasive mechanical ventilation (OR: 8.43, 95% CI 3.60-19.75, p<0.001), elevated MPV levels (OR: 1.62, 95% CI 1.24-2.12, p<0.001), prolonged thrombocytopenia (OR: 1.13, 95% CI 1.06-1.20, p=0.001), and extended hospital stay (OR: 1.03, 95% CI 1.01-1.05, p=0.004) were found to be independently linked to the occurrence of LOS in neonates with thrombocytopenia during their NICU stay. Table IV illustrates the various risk factors that are associated with LOS, providing a comprehensive overview of the elements that may influence this metric.

The overall mortality rate in our group was 21.5% (48 out of 223) and was greater among neonates with platelet counts of ≤ $50x10^9$/L (33.3%, 34 out of 102) when compared to those with platelet counts > $50x10^9$/L (11.6%, 14 out of 121) (p<0.001). The mortality rates were comparable in neonates with late-onset sepsis (27.3%, 27 out of 99) when compared to those without late-onset sepsis (16.9%, 21 out of 124) (p=0.062). In the Cox proportional multivariable analysis, model b showed that invasive ventilation (HR: 9.459, 95% CI 3.38-26.45, p<0.001), platelet transfusion (HR: 2.833, 95% CI 1.54-5.20, p=0.001), and lymphopenia (HR: 0.766, 95% CI 0.64-0.92, p=0.003) were significantly associated with mortality. In model c, invasive ventilation (HR: 12.593, 95% CI 4.48-35.41, p<0.001), grade 2 or higher of NEC (HR: 7.274, 95% CI 1.68-31.52, p=0.008), any hemorrhage (HR: 2.728, 95% CI 1.69-9.10, p=0.001), platelet nadir (HR: 0.972, 95% CI 0.96-0.98, p<0.001), MPV (HR: 0.805, 95% CI 0.66-0.98, p=0.032), and lymphopenia (HR: 0.745, 95% CI 0.63-0.89, p=0.001) were independently linked to increased mortality in neonates experiencing thrombocytopenic events during their NICU stay (Table V). The Kaplan-Meier analysis of survival outcomes for patients with thrombocytopenia is presented in Figure 3. The findings indicate that survival rates are significantly lower in cases of severe thrombocytopenia.

Discussion

This retrospective observational cohort study aimed to assess the prevalence of LOS in thrombocytopenic neonates at a single center. Our findings revealed that approximately half of the thrombocytopenia cases within our cohort were linked to LOS. Over a five-year period, the overall prevalence of thrombocytopenia among neonates admitted to the NICU was recorded at 13.3%. Notably, the proportions of neonates with severe and very severe thrombocytopenia were higher than those reported in prior studies (13,14). Von Lindern et al. (15) indicated that the rate of mild to moderate thrombocytopenia was 68%, while Resch et al. (16) reported a slightly higher rate of 71%. Our study observed that the proportion of mild and moderate cases was 54.2%, highlighting some variability in findings across different studies.

Gestational age is a well-established determinant of thrombocytopenia, sepsis, and mortality. Previous studies, including those by Christensen et al.(17), have shown that both the incidence and severity of thrombocytopenia are strongly influenced by prematurity. In our study, although gestational age differed between LOS and non-LOS groups, it did not remain an independent predictor after adjustment, possibly due to its interaction with clinical severity factors. The main factors increasing the risk of LOS in neonates are decreased gestational age and low birth weight, with our study showing

Table III: Clinical characteristics and complete blood count parameters (CBC) of thrombocytopenic neonates, divided into subgroups by late onset septicemia (LOS)

	Overall	With	Without	p
Total number of patients	223	99	124	-
Presentation day of thrombocytopenia, d*	2 (8)	9 (11)	1(1)	<0.001
Initial platelet count just before declining, cells/µL*	103 (61)	100 (56)	116 (57)	0.186
Lowest level of platelet, cells/µL*	59 (71)	44 (59)	77.5 (72)	<0.001
Duration of thrombocytopenia, d*	6 (9)	9 (10)	6 (6)	<0.001
PDW,%*	15.35 (4.03)	15.3 (2.88)	17.5 (4.90)	0.512
MPV, fl*	9.4 (2.60)	10.4 (2.10)	8.9 (2.25)	<0.001
Plateletcrit*	79.62 (84.75)	74.75 (79.90)	120 (101.66)	0.006
WBC cells/mm^{3*}	8.30 (6.60)	8.30 (8.1)	8.25 (5)	0.537
Neutrophil cells/mm^{3*}	3.60 (4.73)	3.70 (6.50)	3.50 (3.65)	0.689
Neutrophil/Lymphocyte*	1.24 (1.80)	1.50 (2.08)	1.10 (1.60)	0.257
Lymphocyte cells/mm^{3*}	3.00 (2.10)	2.60 (2.70)	3.1 (2)	0.112
Platelet transfusion†	70 (31.4)	48 (48.5)	22 (17.7)	<0.001
Platelet transfusion counts, n*	2 (2)	1.5 (3)	2 (2)	0.914
Any type of hemorrhage†	44 (11.7)	22 (22.2)	22 (17.7)	0.404
Pulmonary hemorrhage†	10 (4.5%)	8 (8.1)	4 (3.2)	0.110
Gastrointestinal hemorrhage†	12 (5.4)	6 (6)	6 (4.9)	0.712
Skin hemorrhage†	2 (0.9)	2 (2)	0 (0)	0.196
IVH†	22 (10.7)	10 (11.9)	12 (9.9)	0.651
Severe IVH†	2 (1)	0(0)	2 (1.7)	0.514

:** *median (IQR) (Mann-Whitney U Test),* **†:** *n(%) (Pearson Chi-Square/ Fisher's Exact Test).* ***MPV: *Mean platelet volume,* ***WBC:*** *White blood cell,* ***IVH:*** *Intraventricular hemorrhage*

Table IV: Risk factors for late onset septicemia: Univariable and multivariable Logistic Regression results

	Univariable*			Multivariable (Adjusted Model)†		
	OR	95% CI	p	OR	95% CI	p
Multiparity	3.05	1.72-5.41	<0.001	3.32	1.40-7.89	0.006
Twin-pregnancy	3.59	1.51-8.56	0.004	-	-	-
Cesarean delivery	3.34	1.78-6.30	<0.001	5.81	1.99-16.89	0.001
Gestational age	0.85	0.79-0.91	<0.001	-	-	-
Strata <34 GA	5.147	2.90-9.11	<0.001	-	-	-
Birth weight	1.00	0.99-1.00	0.002	-	-	-
Invasive ventilation	6.04	3.38-10.82	<0.001	8.43	3.60-19.75	<0.001
Surfactant administration	3.61	1.97-6.62	<0.001	-	-	-
Platelet transfusion	4.583	2.47-8.48	<0.001	-	-	-
Lowest level of platelet	0.985	0.98-0.99	<0.001	-	-	-
MPV	1.69	1.38-2.06	<0.001	1.62	1.24-2.12	<0.001
Plateletcrit	0.989	0.982-0.997	0.004	-	-	-
Platelet transfusion counts	1.52	1.19-1.95	0.001	-	-	-
Duration of thrombocytopenia	1.18	1.1-1.26	<0.001	1.13	1.06-1.20	0.001
Length of hospital stay	1.05	1.03-1.06	<0.001	1.03	1.01-1.05	0.004

GA: *Gestational age,* ***PDA:*** *Patent ductus arteriosus requiring treatment,* ***MPV:*** *Mean platelet volume.* ****:*** *Variables were separately included in the model if they if they were considered potential factors in preliminary analyses.* ***†:*** *In adjusted model, platelet nadir and MPV were simultaneously included as variables. Additionally, parity, twin pregnancy, mode of delivery, gestational age, invasive ventilation, surfactant administration, platelet transfusion and counts, duration of thrombocytopenia, length of hospital stay were included, which a backward elimination method was utilized for logistic regression*

that 70% of cases were born before 37 weeks (18). However, we found no significant link between prematurity or low birth weight and the lowest observed platelet levels, consistent with a recent study by Ree et al.(19) We noted significant differences in factors like twin births, cesarean deliveries, invasive ventilation needs, surfactant administration, and PDA of grade 2 or higher among infants with and without LOS. The rise in cesarean deliveries may be connected to a higher prevalence of twin births and maternal preeclampsia, which can increase the likelihood of surgery. Higher rates of invasive procedures and conditions like NEC were observed in infants with LOS and thrombocytopenia, likely due to younger gestational ages, making them not significant risk factors in our logistic regression analysis. Our research also indicates that elevated MPV levels are independently linked to a higher incidence of LOS in thrombocytopenic neonates, with each increase in MPV correlating to a 62% increased risk of this condition. In sepsis, the clotting cascade is disrupted, leading to the release of pro-inflammatory and anti-inflammatory cytokines. This results in thrombi formation, depletion of fibrinolytic

Table V: Univariable and multivariable Cox proportional hazards regression analyses of factors associated with mortality

	Univariable*			Multivariable (Adjusted Model)†			Multivariable (Adjusted Model)‡		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Gestational age	0.935	0.87-1.00	0.062	-	-	-	-	-	-
Congenital disorder	1.845	0.96-3.56	0.068	-	-	-	-	-	-
Invasive ventilation	10.562	3.77-29.57	<0.001	9.459	3.38-26.45	<0.001	12.593	4.48-35.41	<0.001
Surfactant administration	2.606	1.45-4.70	0.001	-	-	-	-	-	-
PDA requiring treatment	3.569	1.98-6.45	<0.001	-	-	-	-	-	-
NEC	3.840	1.06-6.98	0.038	-	-	-	7.274	1.68-31.52	0.008
Any type of hemorrhage	2.192	1.12-4.28	0.022	-	-	-	2.728	1.69-9.10	0.001
Pulmonary hemorrhage	2.318	0.93-5.81	0.073	-	-	-	-	-	-
Platelet transfusion	2.892	1.60-5.24	<0.001	2.833	1.54-5.20	0.001	-	-	-
Platelet nadir	0.983	0.97-0.99	<0.001	-	-	-	0.972	0.96-0.98	<0.001
Plateletcrit	0.983	0.97-0.99	<0.001	-	-	-	-	-	-
MPV	0.983	0.82-1.18	0.853	-	-	-	0.805	0.66-0.98	0.032
Hemoglobin	0.898	0.83-0.97	0.009	-	-	-	-	-	-
Hematocrit	0.972	0.95-1.00	0.033	-	-	-	-	-	-
Lymphocyte	0.812	0.68-0.96	0.018	0.766	0.64-0.92	0.003	0.745	0.63-0.89	0.001

HR: *Hazard Ratio,* ***PDA:*** *Patent ductus arteriosus requiring treatment,* ***NEC:*** *Necrotising Enterocolitis (Grade ≥2),* ***MPV:*** *Mean platelet volume,* ****:*** *Variables were separately included in the model if they if they were considered potential factors in preliminary analyses.* ***†:*** *In adjusted model, MPV was simultaneously included as variable. Additionally, gestational age in weeks, congenital disorder, invasive ventilation, surfactant administration, any type of haemorrhage, pulmonary haemorrhage, platelet transfusion, platelet transfusion counts, Hb and lymphocyte levels were included, which a backward elimination method was utilized for cox regression.* ***‡:*** *In adjusted model, platelet nadir and MPV were simultaneously included as variables. Additionally, gestational age in weeks, congenital disorder, invasive ventilation, surfactant administration, PDA requiring treatment, Grade ≥2 of NEC, any type of haemorrhage, pulmonary haemorrhage, platelet transfusion, platelet transfusion counts, Hb and lymphocyte levels were included, which a backward elimination method was utilized for cox regression.*

substances, and potential disseminated intravascular coagulation (DIC). Sepsis can also cause thrombocytopenia due to non-immune peripheral destruction, histiocytosis, and bone marrow suppression, stimulating the production of larger, more active young platelets that enhance overall platelet function (9,20-22). Research indicates that MPV may be a predictive marker for neonatal sepsis. A recent meta-analysis by Wang et al. (23) found elevated MPV levels in neonatal sepsis cases, suggesting it could aid in the timely diagnosis of late-onset sepsis. Since the nonspecific symptoms of sepsis complicate prompt diagnosis, it's vital to avoid unnecessary antibiotic treatment for non-septic infants and to start antibiotics quickly when needed. Thus, accessible and affordable laboratory tests like MPV are essential. Omran et al. (24) found serum MPV had 100% sensitivity and 94.4% specificity (cutoff ≥ 9.2 fL) for LOS in full-term neonates. Milas et al. (25) indicated MPV shows good diagnostic accuracy for sepsis, which our study supports for thrombocytopenic infants with LOS. Our findings suggest that longer thrombocytopenia duration and extended hospital stays are independently associated with length of stay, consistent with previous research (11,18-19).

The overall mortality rate was 21.5%, with the LOS group at 27.3%, higher than previous studies (14-15). In thrombocytopenic neonates, mortality correlated significantly with invasive ventilation, NEC, platelet nadir severity, and any hemorrhage. Platelet transfusion was associated with increased mortality, consistent with previous research although the number of transfusions did not show a similar link (26,27). We assessed platelet nadir and mean platelet volume (MPV) as covariates, independent mortality risk factors. Each decrease in platelet count increased mortality by 2.8%, while decreased MPV raised it by nearly 20%. Without considering platelet nadir, transfusion raised mortality risk by 2.8 times.

The study primarily focused on objectives other than bleeding outcomes in thrombocytopenic infants. It found that infants with LOS showed no preference for specific types of hemorrhage, but any bleeding event was identified as an independent risk factor for death. Major bleeding occurs in 5% to 15% of neonates with severe thrombocytopenia, with intraventricular hemorrhage (IVH) being the most severe type (27). This prevalence of severe IVH is lower than reported by Ree et al.(19) Severe bleeding often happens early in a newborn's life during the peak of neonatal thrombocytopenia, but this correlation does not imply a direct cause-and-effect relationship, as factors like cardiovascular stability and capillary fragility also contribute. Other clinically important bleeding, such as pulmonary hemorrhage, complicates the care of critically ill neonates (28). A study by Stanworth et al. (20) found that 9% of 169 patients with severe thrombocytopenia experienced significant hemorrhagic events, excluding IVH, such as pulmonary hemorrhage, gastrointestinal bleeding, and hematuria. Our analysis indicated a higher incidence of gastrointestinal and pulmonary hemorrhages in neonates compared to this study.

The most important finding of this study is the divergent association of MPV with outcomes. While elevated MPV was independently associated with LOS, lower MPV was associated with increased mortality. This may reflect different stages of disease progression. Increased MPV likely represents heightened platelet activation during early inflammatory responses, whereas decreased MPV in critically ill patients may indicate bone marrow suppression and exhaustion in advanced disease.

Limitations

This study has limitations due to retrospective observational cohort data collection, which restricts detailed information on nutrition and antibiotic exposure. Additionally, residual confounding by prematurity and illness severity cannot be completely excluded. Although retrospective, the cohort design of this study allows temporal assessment of outcomes such as LOS and mortality, strengthening causal inference compared to purely cross-sectional analyses. Furthermore, prior research has already demonstrated correlations among gestational age, line utilization, and duration of hospitalization. Our findings highlight factors associated with late neonatal sepsis in thrombocytopenic NICU patients, such as multiparity, cesarean sections, and invasive ventilation. Mortality risk factors include invasive ventilation, NEC, hemorrhage, and lymphopenia. These insights underscore the importance of platelet indices for enhancing NICU care. This study has several strengths. First, it focuses on a specific high-risk population of thrombocytopenic neonates. Second, it integrates both logistic and survival analyses, providing comprehensive outcome assessment. Third, it evaluates widely available platelet indices, enhancing clinical applicability. We propose an intervention to help integrate these indices into clinical protocols, improving care quality for neonates.

Conclusion

Platelet indices, particularly MPV and thrombocytopenia duration, are independently associated with late-onset sepsis in thrombocytopenic neonates. Their relationship with mortality suggests a potential role in risk stratification; however, prospective studies are required to confirm these findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Gülhane Training and Research Hospital (01.04.2024, reference number: 2024-197).

Contribution of the authors

DY and BSK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. **DY and MM** designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All the tables and figures were prepared by **ED. DY, MM** and **BSK** coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Diagnostic discrimination of C-reactive protein and blood count-derived indices for concurrent urinary tract infection in pediatric urolithiasis

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Received : 29.03.2026, Accepted : 06.07.2026
DOI: 10.12956/TJPD.2026.1339

ABSTRACT

Objective: The aim of this study was to evaluate the diagnostic discrimination of CRP and CBC-derived inflammatory indices for identifying concurrent culture-confirmed UTI in children with urolithiasis during early clinical assessment.

Materials and Methods: This single-center retrospective observational study included 77 children with imaging-confirmed urolithiasis and 45 healthy controls. Concurrent UTI was defined by compatible symptoms together with urine culture growth of ≥10^5 colony-forming units/mL. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-platelet ratio (MPR), mean platelet volume (MPV), white blood cell count, and CRP were compared across study groups. Receiver operating characteristic analyses were used to assess diagnostic discrimination for culture-confirmed UTI.

Results: Among 77 children with urolithiasis, 46 (59.7%) had concurrent culture-confirmed UTI. Compared with both healthy controls and stone/UTI-negative patients, those with concurrent UTI had significantly higher NLR, MLR, MPR, white blood cell count, and CRP levels, whereas MPV showed poor discriminatory performance. CRP demonstrated the highest diagnostic discrimination for concurrent UTI (AUC 0.996), with a cutoff of ≥5 mg/L yielding 98.0% sensitivity and 100% specificity. Among the complete blood count–derived indices, NLR performed best (AUC 0.838), followed by MLR (AUC 0.827) and MPR (AUC 0.779). Secondary exploratory analyses suggested declining inflammatory markers after infection control and stone clearance in the surgical cohort, whereas a very small subgroup with culture-negative postoperative fever showed descriptive marker re-elevation in exploratory analyses.

Conclusion: In pediatric urolithiasis, CRP demonstrated the strongest diagnostic discrimination for concurrent culture-confirmed UTI, whereas NLR was the most informative supportive complete blood count–derived index. Secondary exploratory observations should be interpreted cautiously and require confirmation in larger cohorts. Overall, the present findings remain preliminary and require prospective validation before any routine clinical application.

Keywords: Biomarkers, child, C-Reactive Protein, inflammation, urolithiasis, urinary tract infections

Introduction

Pediatric urolithiasis has become an increasingly important clinical problem because of its rising incidence, high recurrence rates, and potential for long-term renal sequelae (1,2). Its prevalence varies according to geography, climate, genetic predisposition, hydration status, and dietary habits, and has increased in many regions in parallel with modern lifestyle changes (3). Beyond mechanical obstruction and urinary stasis, urinary stones may also provoke local and systemic inflammation through mucosal irritation and disruption of the epithelial barrier (4,5). When urinary tract infection (UTI) accompanies stone disease, clinical severity often increases, with higher rates of fever, hospitalization, and the need for invasive intervention (6).

Inflammation in urolithiasis is bidirectional: crystal deposition may initiate acute inflammatory responses, whereas persistent stone-related irritation may sustain chronic low-grade inflammation (5). Infection-related stones and recurrent UTIs further underscore the clinical relevance of inflammatory activity in stone disease (7,8). In routine practice, however, the more immediate challenge is to determine whether a child presenting with urolithiasis has concurrent bacterial infection

or sterile stone-related inflammation. This distinction is often difficult at initial presentation, when urine culture results are still pending but decisions regarding antibiotic therapy, hospitalization, and further intervention may already be required (6).

Accordingly, there is growing interest in routinely available inflammatory markers that may assist early assessment without additional cost or delay. Complete blood count (CBC)–derived indices have attracted attention as accessible markers of systemic inflammation. NLR and MLR have been evaluated across a range of infectious and inflammatory conditions, whereas evidence for MPR in pediatric urolithiasis remains limited (10-13). Mean platelet volume (MPV), although biologically linked to platelet activation and inflammation, has yielded inconsistent findings in pediatric stone disease (14,15). CRP is also widely used in the evaluation of bacterial infection, yet comparative data examining CRP together with multiple CBC-derived indices in children with urolithiasis remain limited.

The inflammatory profile of pediatric stone disease may also vary according to clinical context. Stone location may plausibly influence obstruction, urinary stasis, symptom burden, and the magnitude of the accompanying inflammatory response (9). In addition, postoperative febrile episodes with negative urine cultures may raise the possibility of sterile inflammatory activation rather than overt infection. These issues are clinically relevant, but they remain secondary to the central diagnostic question of whether routinely available inflammatory markers can help distinguish concurrent culture-confirmed UTI from noninfectious stone-related inflammation.

Comparative data evaluating CRP alongside multiple CBC-derived inflammatory indices in children with urolithiasis remain limited. Therefore, we aimed to assess the diagnostic discrimination of CBC-derived inflammatory indices and CRP for identifying concurrent culture-confirmed UTI in children with urolithiasis. Secondary exploratory analyses examined location-related variation in selected markers and described inflammatory marker trajectories in a small subgroup with culture-negative postoperative fever.

Materials and Methods

This single-center retrospective observational study was conducted at Gaziantep City Hospital after approval by the institutional ethics committee.'

Participants and eligibility criteria

Consecutive pediatric patients (0–18 years) evaluated for urolithiasis between October 2023 and January 2025 were screened. Urolithiasis was defined as the presence of a stone confirmed by imaging (ultrasonography, plain abdominal radiography, and/or non-contrast computed tomography). Patients were excluded if essential clinical or laboratory data were missing; if they had an acute infection unrelated to urolithiasis; chronic inflammatory/autoimmune disease; hematologic malignancy; immunosuppressive or systemic corticosteroid therapy; major surgery or trauma within the preceding three months; or a known metabolic stone disorder with distinct inflammatory profiles (e.g., primary hyperoxaluria or cystinuria). Individuals aged ≥18 years at the time of evaluation were not eligible.

A control group was retrospectively selected from healthy children without known urolithiasis and with no history of infection or surgical intervention within the preceding three months. Controls were recruited from routine outpatient assessments and were included only if they had no clinical evidence of acute illness at the time of blood sampling.

Clinical data and stone-related variables

Demographic variables (age and gender), prior UTI history, management strategy (surgical vs conservative), and laboratory values were abstracted from electronic medical records using a standardized data-extraction form.

Stone presence and location were initially assessed by ultrasonography (US) and, when feasible, corroborated by plain kidney–ureter–bladder radiography (KUB). Stone size was recorded as the largest diameter measured on imaging. To minimize modality-related measurement variability, a predefined hierarchy was applied for stone size: when non-contrast CT was available, the CT measurement was used; otherwise, the US measurement was used (KUB was employed for confirmation of stone presence rather than as the primary size measurement). According to institutional clinical practice, non-contrast CT was obtained for surgical planning when US demonstrated a stone diameter ≥15 mm. In addition, in patients with no visible stone on US but with hydronephrosis and costovertebral angle tenderness—particularly when ureteral stone was suspected—non-contrast CT was performed to confirm ureteral calculi. This approach was intended to address the limitations of US in detecting ureteral stones.

Because some stone-location subcategories had small sample sizes, stone location was collapsed into three clinical groups for analytic purposes: upper urinary tract (renal pelvis + lower pole), ureter, and lower urinary tract (bladder + urethra). The single case recorded as "ureter + renal pelvis" (n=1) was included in the ureter group. This approach was used to reduce the risk of spurious findings arising from small cell counts. For surgically treated patients, the index procedure was recorded (retrograde intrarenal surgery, percutaneous nephrolithotomy, extracorporeal shock wave lithotripsy, laser lithotripsy, or open surgery) in accordance with institutional practice.

Definition of UTI and related terms

Concurrent UTI was defined as compatible clinical findings (fever ≥38°C, dysuria, or pollakiuria) together with microbiological evidence of infection, specifically growth of $\geq 10^5$ colony-forming units/mL on urine culture obtained from a midstream clean-catch urine sample. Pyuria (e.g., ≥5 leukocytes/HPF or per institutional threshold) was recorded as a supportive finding but was not included in the primary UTI definition, because both irritative urinary symptoms and sterile pyuria may occur in children with urolithiasis in the absence of true bacterial infection. A culture-based definition was therefore preferred to improve diagnostic specificity for the primary analysis. Recurrent UTI was defined as ≥2 febrile episodes or ≥3 afebrile episodes documented in the medical record.

Laboratory measurements and inflammatory indices

Complete blood count (CBC) parameters and C-reactive protein (CRP) were obtained as part of routine care at presentation and, when applicable, during perioperative/postoperative follow-up. CBC measurements were performed using the same automated hematology analyzer throughout the study period, and CRP was processed in accredited laboratories according to institutional standards. To minimize analytical variability—particularly for platelet indices—samples were handled according to routine pre-analytical protocols and analyzed within the standard time window after venipuncture.

CBC-derived indices were calculated as follows:

- NLR = neutrophil count / lymphocyte count
- MLR = monocyte count / lymphocyte count
- MPR = monocyte count / platelet count

Mean platelet volume (MPV, fL) was recorded as reported by the laboratory. White blood cell count (WBC) and CRP (mg/L) were analyzed as reference inflammatory markers.

Timing of sampling and definition of time points

To preserve interpretability, analyses were restricted to clinically defined time points. The UTI-positive time point was defined as the laboratory measurement obtained within 24 hours of symptom onset during an episode fulfilling the study definition of UTI. In the surgical cohort, longitudinal comparisons were based on repeated measurements from the same patients at predefined time points. The preoperative time point was defined as the laboratory measurement obtained within 24 hours before surgery, whereas the postoperative stone-free/UTI-free time point was defined as the measurement obtained 4 weeks after surgery in the same patient, after confirmation of stone-free status and absence of UTI by clinical assessment, with urine culture considered when available. When multiple eligible measurements were available within the relevant time window, the value closest to the corresponding clinical event was selected to avoid duplication and standardize measurement selection. Paired analyses in the surgical cohort were restricted to patients with matched measurements available at the relevant predefined time points.

Culture-negative postoperative fever subgroup

A predefined subgroup analysis was performed in children who developed postoperative fever despite (i) radiologic confirmation of stone-free status and (ii) negative urine cultures. For this subgroup, hematologic and biochemical markers were compared across three clinically defined time points:

- preoperative UTI period (culture-confirmed UTI);
- intra-/perioperative period (stone present, urine culture negative); and
- postoperative febrile period (stone-free on imaging, urine culture negative, fever present).

This analysis was designed to descriptively characterize inflammatory trajectories in episodes suggestive of sterile postoperative inflammation.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics v25.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as numbers and percentages, while continuous variables are presented as mean and standard deviation or median with interquartile range (IQR), as appropriate. The normality of distribution was assessed using the Shapiro–Wilk test. Two-group comparisons were performed using Student's t-test or the Mann–Whitney U test, whereas comparisons across more than two groups were conducted using the Kruskal–Wallis test. When the overall comparison was significant, pairwise post hoc analyses were performed using Dunn's test (Bonferroni-adjusted). Paired comparisons were analyzed using the Wilcoxon signed-rank test, and categorical variables were compared using the chi-square or Fisher's exact test.

Diagnostic discrimination of NLR, MLR, MPR, MPV, and CRP for concurrent UTI was evaluated by receiver operating characteristic (ROC) analysis with calculation of the area under the curve (AUC) and 95% confidence intervals; optimal cutoffs were determined using the Youden index. ROC AUC comparisons were restricted to the prespecified comparison between the combined CRP+NLR logistic regression model and CRP alone, using the DeLong test. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Given the retrospective design and modest sample size, ROC-based estimates were interpreted as exploratory measures of discrimination rather than definitive indicators of clinical diagnostic accuracy. To further examine whether inflammatory markers were independently associated with concurrent culture-confirmed UTI within the stone cohort, exploratory multivariable logistic regression analyses were performed using clinically relevant covariates available in the dataset, including age, sex, stone size, stone location, management strategy, and hydronephrosis. Because several inflammatory markers showed right-skewed distributions, ratio-based markers were log-transformed before modeling when appropriate. Analyses of stone location and culture-negative postoperative fever trajectories were predefined as secondary exploratory analyses and were interpreted cautiously.

Results

Study population and baseline characteristics

A total of 122 children were included in the analysis: 77 patients with imaging-confirmed urolithiasis and 45 healthy controls. Among stone-bearing patients, 62 (80.5%) underwent surgical intervention and 15 (19.5%) were managed conservatively. The control and urolithiasis groups differed significantly in age (5.6± 2.8 vs 7.6±4.6 years; $p=0.038$) and sex distribution (male/female 40/5 vs 44/33; $p=0.001$).

Median stone size was significantly larger in surgically managed patients than in those followed conservatively (10.0 mm (IQR 8.0-13.0) vs 5.0 mm (IQR 4.5-7.0), $p<0.001$). The stone–UTI-positive group consisted of clinically compatible cases with culture-confirmed UTI ($\geq 10^5$ CFU/mL on urine culture); pyuria was not used as an inclusion criterion. Concurrent UTI was

Table I: Stone location, intervention type, and stone composition according to management strategy

Management strategy/ Stone location	n	Intervention(s) performed	Stone composition
Surgical (n=62)			
Renal pelvis	21	3 PCNL (staghorn), 18 RIRS	3 struvite (staghorn), 18 calcium oxalate (whewellite/weddellite)
Lower pole	20	RIRS	Calcium oxalate
Ureter	23	RIRS	Calcium oxalate
Ureter + renal pelvis	1	RIRS	Calcium oxalate
Bladder	4	2 open surgery, 2 laser lithotripsy	2 cystine, 2 calcium oxalate
Urethra	1	Laser lithotripsy	-
Non-surgical (n=15)			
Renal pelvis	2	1 ESWL, 1 medical therapy	-
Lower pole	10	7 ESWL, 1 spontaneous passage, 2 medical therapy	-
Ureter	3	3 spontaneous passage	-

***PCNL:** percutaneous nephrolithotomy, **RIRS:** retrograde intrarenal surgery, **ESWL:** extracorporeal shock wave lithotripsy. Dash indicates unavailable data.*

Table II: Hematological and biochemical parameters

Parameter	Control*	Stone-UTI negative*	Stone-UTI positive*	p†	p‡	p§	p‖
Total number of patients	45	31	46	-	-	-	-
NLR	0.9 (0.7-1.3)	1.3 (0.9-2.4)	2.7 (1.5-5.4)	<0.001	1.000	<0.001	<0.001
MLR	0.20 (0.16-0.26)	0.22 (0.17-0.28)	0.43 (0.28-0.67)	<0.001	1.000	<0.001	<0.001
MPR	0.0020 (0.0017-0.0024)	0.0016 (0.0013-0.0020)	0.0028 (0.0021-0.0035)	<0.001	0.058	0.002	<0.001
MPV, (fL)	9.7 (9.1–10.0)	8.1 (7.1–8.2)	8.2 (7.6–9.0)	<0.001	<0.001	<0.001	0.379
WBC, (10^3/µL)	7.2 (6.3–8.4)	7.5 (7.2–8.2)	12.6 (10.9–18.0)	<0.001	1.000	<0.001	<0.001
CRP, (mg/L)	1.7 (1.3–1.9)	1.7 (1.0–2.8)	12 (5–35)	<0.001	1.000	<0.001	<0.001

***: median (IQR), †: Kruskal–Wallis test, ‡: Control vs Stone-UTI negative, §: Control vs Stone-UTI positive, ‖: Stone-UTI negative vs positive (all post hoc tests Dunn's (Bonferroni-adjusted), **NLR:** neutrophil-to-lymphocyte ratio, **MLR:** monocyte-to-lymphocyte ratio, **MPR:** monocyte-to-platelet ratio, **MPV:** mean platelet volume, **WBC:** white blood cell count, **CRP:** C-reactive protein.*

Table III: Results of ROC analysis for distinguishing the presence of UTI in the stone cohort

Parameter	AUC (95% CI)	p	Optimal cutoff	Sensitivity (%)	Specificity (%)
CRP	0.996 (0.727-1.000)	<0.001	≥5 mg/L	98.0	100
NLR	0.838 (0.535-1.000)	<0.001	≥2	74.5	92.6
MLR	0.827 (0.526-1.000)	<0.001	≥0.333	61.7	100
MPR	0.779 (0.482-1.000)	<0.001	≥0.00237	66.7	92.6
MPV	0.642 (0.512–0.773)	0.043	≥8.7 fL	42.9	92.3
CRP + NLR	0.973 (0.693-1.000)	<0.001	Probability ≥0.555	95.7	100

***AUC:** area under the curve, **CI:** confidence interval, **CRP:** C-reactive protein, **NLR:** neutrophil-to-lymphocyte ratio, **MLR**: monocyte-to-lymphocyte ratio, **MPR:** monocyte-to-platelet ratio, **MPV:** mean platelet volume, **UTI:** urinary tract infection, *: For MPV, higher values were considered indicative of UTI; AUC and the optimal cutoff were derived accordingly. For the combined CRP+NLR model, the cutoff corresponds to the predicted-probability threshold from logistic regression. p values: DeLong test, AUC vs 0.50.'*

identified in 46 of 77 stone-bearing patients (59.7%) and was more frequent in the surgical group than in the conservative group (74.2% vs 13.3%, p<0.001); management-related stone characteristics are shown in Table I.

Between-group differences in inflammatory markers

Hematological and biochemical parameters differed across the study groups. For the primary clinically relevant comparison within the stone cohort, children with concurrent UTI had higher median NLR, MLR, and MPR values and higher WBC and CRP levels than stone/UTI-negative patients (all p<0.001). Comparisons with healthy controls were retained as secondary analyses to provide biological context. In post hoc pairwise analyses, adjusted using Bonferroni or Dunn correction according to data distribution, the overall between-group differences were attributable mainly to the contrast between stone/UTI-positive and stone/UTI-negative patients (MPR, control vs. stone/UTI-positive, p=0.002, all other p<0.001). By contrast, MPV was the only parameter that differed significantly between stone/UTI-negative patients and healthy controls (Table II). MPV values were lower in the stone cohort than in controls and showed poor discriminatory performance in ROC analysis (Table III).

Diagnostic discrimination for concurrent UTI

ROC analysis used culture-confirmed UTI as the reference standard. CRP showed the highest discrimination (AUC 0.996; 95% CI 0.727–1.000); confidence intervals were wide, likely reflecting sample size and case mix. A cutoff of ≥5 mg/L yielded 98.0% sensitivity and 100% specificity (Table III). Among CBC-derived indices, NLR performed best (AUC 0.838; cutoff ≥2.0), followed by MLR (AUC 0.827; cutoff ≥0.333) and MPR (AUC 0.779; cutoff ≥0.00237). MPV showed poor discrimination (AUC 0.642; 95% CI 0.512–0.773; cutoff ≥8.7 fL) (Table III). A CRP+NLR logistic model did not improve discrimination versus CRP alone (AUC 0.973 vs 0.996; DeLong p=0.628). Stone size was not correlated with inflammatory indices (NLR: r=0.198, p=0.215).

Table IV: Inflammatory markers by collapsed stone location during culture-confirmed UTI episodes

Parameter	Upper urinary tract (renal pelvis + lower pole)*	Ureter*	Lower urinary tract (bladder + urethra) *
Total number of patients	22	23	4
WBC (×10^3/μL)	12.0 (10.9-14.1)	15.0 (9.9-18.6)	22.1 (17.8-24.2)
CRP (mg/L)	10.3 (7.9-17.5)	13.0 (10.0-82.5)	27.5 (21.8-34.8)
NLR	2.07 (0.91-3.00)	2.91 (2.31-4.56)	4.31 (3.19-4.86)
MLR	0.26 (0.15-0.33)	0.48 (0.43-0.61)	0.49 (0.49-0.50)
MPR	0.00222 (0.00137-0.00281)	0.00463 (0.00276-0.00648)	0.01017 (0.00822-0.01169)
MPV (fL)	7.95 (7.60-8.65)	8.20 (7.55-9.00)	9.10 (9.00-9.20)

**: median (IQR)*

Table V: Longitudinal inflammatory marker changes in the surgical cohort and the culture-negative postoperative fever subgroup

Parameter	Preoperative	Perioperative/Intraoperative	Postoperative	p*
Panel A. Changes across predefined time points in the surgical cohort				
WBC (×10^3/μL)*	12.1 (n=48)	7.9 (n=55)	7.2 (n=62)	<0.001
NLR*	2.67 (n=45)	1.21 (n=58)	1.40 (n=62)	<0.001
MLR*	0.43 (n=47)	0.20 (n=59)	0.22 (n=62)	<0.001
MPR*	0.00282 (n=46)	0.00175 (n=59)	0.00159 (n=62)	<0.001
MPV (fL)*	8.20 (n=47)	7.95 (n=58)	7.60 (n=62)	0.042
CRP (mg/L)*	12.0 (n=47)	1.8 (n=58)	1.7 (n=61)	<0.001
Panel B. Inflammatory marker trajectories in the culture-negative postoperative fever subgroup				
WBC (×10^3/μL)†	17.8 (13.8-18.4) (n=8)	9.9 (8.2-11.2) (n=7)	14.5 (12.0-15.1) (n=8)	-
CRP (mg/L)†	21.0 (14.5-34.5) (n=7)	1.8 (1.2-3.0) (n=7)	17.5 (11.8-24.2) (n=8)	-
NLR†	3.23 (2.36-9.5) (n=7)	1.30 (0.73-2.9) (n=7)	3.46 (3.25-5.47) (n=8)	-
MLR†	0.33 (0.30-0.46) (n=7)	0.19 (0.15-0.26) (n=7)	0.40 (0.36-0.48) (n=8)	-
MPR†	0.0028 (0.002-0.007) (n=7)	0.0017 (0.0016-0.0023) (n=7)	0.0034 (0.0022-0.0046) (n=8)	-

****: median (Wilcoxon signed-rank test), †: median (Q1-Q3)***

Adjusted analyses within the stone cohort

In exploratory multivariable logistic regression analyses adjusted for age, gender, stone size, stone location, management strategy, and hydronephrosis, log-transformed NLR remained independently associated with concurrent UTI (OR 72.14, 95% CI 3.40–1530.34; p=0.006). However, the wide confidence interval suggests substantial imprecision and possible model instability. Hydronephrosis was also independently associated with concurrent UTI (OR 3.61, 95% CI 1.38–9.40; p=0.009). By contrast, a conventional adjusted logistic model including CRP was unstable because of quasi-complete separation, precluding reliable estimation of an adjusted effect size. These findings suggest that NLR may retain an independent signal, whereas the apparent strength of CRP should be interpreted cautiously despite its high discriminatory performance in ROC analysis.

Stone location–related differences

During UTI episodes, monocyte-based indices were evaluated according to stone location (Table IV). Because some location subcategories had small sample sizes, stones were collapsed into three clinical groups for analysis: upper urinary tract (renal pelvis + lower pole), ureter (ureter + renal pelvis), and lower urinary tract (bladder + urethra). In this classification, MLR and MPR values tended to be higher in ureteral and lower urinary tract stones than in upper urinary tract stones. Only limited differences were observed across groups for MPV, and no clear location-related differences were detected for CRP or NLR. Given the small size of the lower urinary tract group, these findings were interpreted as exploratory and inferential conclusions were avoided.

Temporal changes in the surgical cohort

In the surgical cohort, temporal comparisons were based on matched repeated measurements obtained from the same patients at predefined time points. Inflammatory markers declined consistently over time (Table V, Panel A). From the preoperative UTI period, defined as within 24 hours before surgery, to the perioperative period, significant reductions were observed in WBC, NLR, MLR, MPR, and CRP (all p<0.001), whereas the change in MPV did not reach significance (p=0.065). From the perioperative period to the postoperative stone-free/UTI-free assessment performed 4 weeks after surgery, WBC showed a further significant decline, whereas the other parameters remained stable. Comparisons between preoperative UTI values and postoperative stone-free/UTI-free values also demonstrated significant decreases across all markers.

Culture-negative postoperative febrile episodes

Eight patients developed postoperative fever despite radiologic confirmation of stone-free status and negative urine cultures. In this subgroup, inflammatory markers declined from the preoperative UTI period to the intraoperative period but increased again during the postoperative febrile episode (Table V, Panel B). This pattern was consistent across WBC, CRP, and CBC-derived indices.

Discussion

Primary diagnostic message: Early identification of concurrent UTI

In this retrospective cohort of children with urolithiasis, our primary objective was to determine whether routinely available inflammatory markers could support the early identification of concurrent urinary tract infection. The main finding was that CRP showed the strongest discrimination for concurrent culture-confirmed UTI, while NLR was the most informative adjunctive complete blood count–derived index. Within the stone cohort, children with concurrent UTI exhibited a distinct systemic inflammatory profile characterized by higher WBC, CRP, and leukocyte-derived ratios than stone/UTI-negative patients, whereas MPV showed limited discriminatory utility. Importantly, adding NLR to CRP did not improve diagnostic performance beyond CRP alone. Overall, these findings support the use of CRP, with NLR as a supportive adjunct, in the early clinical assessment of suspected infection in pediatric urolithiasis.

Inflammatory profile of infection in pediatric stone disease

Pediatric urolithiasis is increasingly encountered in clinical practice and is associated with substantial recurrence risk and potential long-term morbidity (1,2). Stones may induce inflammation through urothelial irritation and epithelial barrier disruption, while superimposed infection may further amplify this response (4,5). In our cohort, children with urolithiasis and concurrent UTI had higher NLR, MLR, MPR, WBC, and CRP levels than both stone/UTI-negative patients and healthy controls, supporting the presence of a systemic inflammatory response beyond stone-related local irritation alone. This finding is consistent with the broader clinical observation that UTI accompanying stone disease is associated with greater illness severity and increased healthcare utilization (6). Comparisons with healthy controls were retained to provide biological context, but the clinically relevant contrast in this study was the distinction between stone/UTI-positive and stone/UTI-negative patients.

Discriminatory performance of CRP and CBC-derived indices

CRP provided the strongest discrimination for concurrent UTI (AUC 0.996; cutoff ≥5 mg/L), consistent with its established role as an acute-phase reactant in bacterial infection. Nevertheless, this near-perfect performance should be interpreted with caution. In a retrospective single-center cohort of modest size, ROC-based estimates may be overly optimistic because of spectrum effects, case selection, timing of sampling, and the absence of internal validation. Accordingly, CRP should be regarded as an adjunctive marker rather than a stand-alone diagnostic test, and the observed cutoff and performance estimates require prospective confirmation in broader clinical settings.

Among the CBC-derived indices, NLR showed the most useful supportive performance (AUC 0.838; cutoff ≥2.0). NLR has been widely studied as a rapid marker of systemic inflammation and physiologic stress and has also been evaluated in pediatric urolithiasis with UTI (10-12,16). Our findings suggest that NLR may provide supportive information when interpreted together with clinical and microbiological data. MLR and MPR also demonstrated moderate discriminatory performance. These monocyte-based indices may reflect monocyte activation and broader inflammatory signaling, while MPR may additionally capture aspects of platelet–immune interaction, although evidence in pediatric urolithiasis remains limited (13,17). In practical terms, these indices may provide supportive information but are unlikely to outperform CRP in routine clinical presentations.

The combined CRP+NLR model did not improve discrimination beyond CRP alone, which is clinically plausible given that both markers likely reflect overlapping aspects of infection-driven systemic inflammation rather than independent diagnostic dimensions. By contrast, MPV showed poor discriminatory performance and was not considered clinically informative in this cohort, particularly in light of its recognized pre-analytical sensitivity and inconsistent findings in the literature (14,15,18,19).

Because several clinical variables differed across the cohort, we additionally performed exploratory multivariable analyses within the stone cohort. After adjustment for age, sex, stone size, stone location, management strategy, and hydronephrosis, NLR remained independently associated with concurrent UTI, whereas hydronephrosis also remained independently associated. In contrast, CRP could not be modeled reliably in a conventional multivariable logistic framework because of quasi-complete separation, underscoring both its strong apparent signal in this dataset and the need for caution when interpreting near-perfect discrimination in a modest retrospective cohort.

The width of several confidence intervals around ROC estimates further indicates limited precision and underscores the constraints imposed by sample size.

Secondary exploratory observations: Stone size and stone location

Beyond the primary diagnostic question, we explored whether inflammatory indices varied according to stone burden and anatomical location. We did not identify a significant correlation between stone size and inflammatory markers, suggesting that the systemic inflammatory signal at presentation was driven more by infection status than by stone burden in this cohort. We also observed an exploratory tendency toward higher monocyte-based indices in ureteral and lower urinary tract stones than in upper urinary tract stones. Anatomical location may plausibly influence obstruction dynamics, mucosal irritation, and urinary stasis, thereby modulating inflammatory responses; it is also clinically relevant to symptom profile and spontaneous passage potential (9). However, because some location-specific subgroups were small, particularly the lower urinary tract group, these observations should be interpreted cautiously and regarded as hypothesis-generating rather than definitive.

Exploratory postoperative fever subgroup

We additionally described inflammatory marker trajectories in a small subgroup of children who developed postoperative fever despite radiologic stone-free status and negative urine cultures. In the broader surgical cohort, inflammatory markers declined from the preoperative UTI period to

the perioperative and postoperative stone-free/UTI-free periods, consistent with reduced inflammatory burden after infection control and stone clearance; similar peri-procedural declines in leukocyte-derived parameters have been reported in related contexts (20). In the subgroup with culture-negative postoperative fever, marker levels again increased during the febrile episode after an initial perioperative decline. Nevertheless, this subgroup was very small, and alternative explanations—including antibiotic exposure, timing of sampling, low-level infection, or other postoperative inflammatory processes—could not be excluded. Accordingly, these findings should be interpreted strictly as descriptive and hypothesis-generating. Although postoperative fever after endourological procedures has been recognized previously, the present subgroup does not support clinical inference and requires confirmation in larger, prospectively characterized cohorts (21).

Clinical implications

From a clinical perspective, one of the main challenges in children presenting with urolithiasis is deciding whether empiric antibiotic therapy is warranted while urine culture results are pending. In this cohort, CRP and, to a lesser extent, NLR were associated with concurrent culture-confirmed UTI and may offer supportive information during early assessment. However, these markers should not replace urine culture or comprehensive clinical evaluation, and the very high discriminatory estimates observed here should be interpreted cautiously given the retrospective design, limited sample size, and lack of internal validation.

Limitations

This study has several strengths, including the concurrent evaluation of multiple complete blood count–derived indices together with CRP and its focus on a clinically relevant diagnostic question within the stone cohort. Several limitations should also be acknowledged. The retrospective single-center design limits generalizability and introduces the potential for selection bias and unmeasured confounding. The control and stone groups also differed in age and gender; although the multivariable model was adjusted for these covariates, residual confounding cannot be excluded. Although key sampling windows were predefined, the study remained based on routine-care retrospective data. Although the UTI definition was intentionally culture-based to improve diagnostic specificity in a setting where stone-related irritation may mimic infection, some misclassification remains possible; however, the use of midstream urine specimens and the absence of pyuria in culture-negative cases reduce the likelihood of substantial classification error. The culture-negative postoperative fever subgroup was very small and exploratory, precluding exclusion of alternative explanations for marker re-elevation. Moreover, given the number of comparisons performed across biomarkers, groups, and exploratory subanalyses, findings beyond the primary diagnostic question should be interpreted cautiously. Finally, the very high AUC observed for CRP may reflect spectrum effects, and without internal validation the reported discriminatory estimates may be optimistic; the wide confidence intervals around several ROC estimates further indicate limited precision. Prospective multicenter studies are needed before these findings can be confirmed..

Conclusion

In pediatric urolithiasis, CRP demonstrated the strongest diagnostic discrimination for concurrent culture-confirmed UTI, whereas NLR was the most informative supportive complete blood count–derived index. Secondary exploratory observations, including those related to stone location and culture-negative postoperative fever, should be interpreted cautiously and confirmed in larger cohorts. Overall, the present findings are preliminary and require prospective validation before informing routine clinical application.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Gaziantep City Hospital (March 19, 2025, reference number: 145/2025).

Contribution of the authors

DY: Study conception and design, data collection, data analysis and interpretation, literature review, manuscript drafting. HTT: Supervision, critical revision of the manuscript. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Bone health assessment in children with osteogenesis imperfecta from a pediatric endocrinology perspective

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Received : 20.04.2026, Accepted : 05.08.2026 DOI: 10.12956/TJPD.2026.1336

ABSTRACT

Objective: Osteogenesis imperfecta (OI) is an uncommon hereditary disorder of connective tissue that results in fragile bones due to abnormalities in collagen structure. This study aimed to evaluate bone health in children with OI who were hospitalized for fracture treatment.

Materials and Methods: This retrospective observational study reviewed the records of children aged 3–18 years and diagnosed with OI and hospitalized in the pediatric orthopedics ward for fractures between May 1, 2023, and January 31, 2026. The patients' demographic characteristics, biochemical parameters, bone mineral density (BMD) Z-scores, vertebral radiographs, vitamin D levels, sun exposure, and treatment status were evaluated.

Results: A total of 37 patients participated in the study. The average age of the patients was 10.35±3.82 years, and 78.4% were male. Mean BMD Z-score was -1.44±1.61. Vertebral fractures were present in 27% of the patients. Significant differences were observed between groups stratified by vitamin D levels for age ($p = 0.020$), serum calcium ($p = 0.003$), phosphorus ($p = 0.005$), alkaline phosphatase ($p = 0.027$), parathyroid hormone ($p = 0.018$), and BMD Z-score ($p = 0.023$). Patients with vitamin D deficiency showed lower serum calcium levels and BMD Z-scores. Additionally, a statistically significant positive correlation was identified between BMD Z-score and serum calcium levels ($r=0.343$; $p=0.038$).

Conclusion: Evaluation of skeletal health in children with OI should not rely solely on BMD measurements; vertebral fractures, biochemical markers, growth, and environmental factors should also be considered. Collaboration between pediatric orthopedics and pediatric endocrinology is vital for better long-term outcomes.

Keywords: Bone mineral density, child, osteogenesis imperfecta, spinal fractures, vitamin D

Introduction

Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder primarily associated with abnormalities in type I collagen. It is characterized by compromised bone integrity and heightened skeletal fragility (1). The clinical spectrum can vary widely, including low bone mineral density, recurrent long-bone fractures, vertebral deformities, short stature, skeletal anomalies, and hearing loss (2). Pathogenic variants identified in more than 20 genes today explain the genetic and clinical heterogeneity of OI and account for the significant variations in disease severity among individuals (2,3).

Recurrent fractures in children with OI may lead not only to physical morbidity but also to psychosocial difficulties due to repeated hospitalizations, immobilization, and surgical procedures (4,5). Especially in children who have orthopedic surgery because of fractures, issues like delayed mobilization, social withdrawal from peers, and missing school greatly reduce quality of life. Therefore, the main goal in managing OI is to reduce fracture frequency, alleviate bone pain, maintain bone health, and enable children to move safely and participate in daily activities (6). Current management strategies do not provide a definitive cure but include multidisciplinary approaches, such as antiresorptive therapies (e.g., bisphosphonates, especially intravenous (IV) pamidronate) to decrease fracture frequency and bone pain, along with physical therapy, rehabilitation, and orthopedic surgery when needed (7). However, in clinical practice, delaying or irregularly administering antiresorptive therapies after a fracture can result in insufficient gains in bone mineral density and a heightened risk of new fractures. This situation calls for increased awareness of bone health monitoring among both families and physicians practicing in pediatric orthopedics and pediatrics (8).

Although gene therapy and stem cell-based approaches have shown promise as long-term treatment options in

recent years, current clinical practice for maintaining bone health in children with OI still depends on regular monitoring, suitable antiresorptive therapy, sufficient calcium (Ca) and vitamin D supplementation, sunlight exposure, physical therapy, rehabilitation, orthopedic surgery, multidisciplinary follow-up, and early mobilization strategies (8). In this context, systematically evaluating bone metabolism in children with OI who have had surgery due to fractures is crucial for ensuring continued treatment and identifying risk factors (9). This study aimed to retrospectively evaluate children with OI hospitalized for fractures in the pediatric orthopedics clinic from a pediatric endocrinology perspective. By analyzing patients' bone mineral density, vertebral radiographs, antiresorptive treatment status, biochemical markers of bone metabolism, serum vitamin D levels, sun exposure, and the number of fractures, the study aimed to raise clinical awareness of the need for bone health monitoring after fractures. Another objective of the study was to contribute to follow-up approaches that support early and safe mobilization of children with OI, helping them adapt to social life and their peer environment.

Materials and Methods

This study was conducted as a retrospective observational study. The hospital records of 48 pediatric patients aged 3–18 years with a diagnosis of OI who were hospitalized and treated at the Ankara Bilkent City Hospital pediatric orthopedics clinic for fractures between May 1, 2023, and January 31, 2026, were reviewed. Consecutive patients meeting the study criteria during the study period were included in the analysis. The legal guardians of the patients were fully informed about the study, and their consent was obtained. After collecting demographic data on the patients, concurrent clinical and laboratory data were examined thoroughly. The laboratory tests evaluated included: serum Ca, corrected Ca, phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP), vitamin D, parathyroid hormone (PTH), albumin, urea, and creatinine. The patients' biochemical parameters were obtained from measurements taken within the three months prior to their hospitalization for the fracture. All biochemical and densitometric measurements were obtained during the post-fracture follow-up period and not during the acute trauma evaluation. The corrected Ca (mg/dL) value was calculated using the following formula: Corrected Ca = total Ca + 0.8 × (4 – albumin) (10). Bone mineral density (BMD) values collected within the last six months were analyzed. Lumbar spine bone mineral density (L1–L4) was assessed by dual-energy X-ray absorptiometry (DXA), and Z-scores were calculated based on the patients' gender and age. Additionally, vertebral radiographs taken within the past six months were reviewed by an experienced pediatric orthopedist for vertebral compression fractures. Genetic test results indicating the patients' OI subtype were obtained from hospital records. Records were also used to assess whether patients received regular IV pamidronate therapy, Ca and vitamin D supplements, and their sun exposure history. Regular IV pamidronate therapy was defined, according to medical records, as receiving scheduled antiresorptive treatment without interruption during the planned follow-up period. Treatment adherence was evaluated using outpatient follow-up notes and categorized as regular or irregular based on physician documentation. Sun exposure history was assessed from patient records and classified based on the presence of regular daytime outdoor exposure reported by caregivers. Anthropometric measurements were conducted by the same trained nurse using the same equipment to ensure consistency across all patients. Body weight was measured with a digital scale while patients were lightly clothed and barefoot. For children able to stand, height was measured with a stadiometer while standing. For patients unable to stand or with limited mobility, height was measured as the distance from the top of the head to the heels using the same measuring tape, with the patient in a supine position and muscles kept taut. The standard deviation score (SDS) values and BMD Z-scores for anthropometric measurements were calculated using ChildMetrics (11). Additionally, patients were assessed for vitamin D levels as deficient, insufficient, or normal (12). Patients with missing data in hospital records, those admitted for reasons other than fracture and followed up, and participants who did not give consent were excluded from the study.

Statistical analysis

Statistical analyses were performed utilizing SPSS software (Version 26.0, IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated through the Shapiro–Wilk test. For variables not normally distributed, the Kruskal–Wallis test was used to compare the three groups. When significant differences were found, pairwise comparisons were performed using the Dunn–Bonferroni post hoc test, and a Bonferroni correction was applied to address multiple comparisons. The Mann–Whitney U test was used to compare two groups. Categorical variables were analyzed using the chi-square or Fisher's exact test. Relationships between variables were assessed with Spearman's correlation analysis. Multivariable linear regression analysis was performed to identify variables independently associated with BMD Z-scores. Serum total calcium, PTH, and 25(OH)D levels were included in the multivariable model a priori because of their established clinical relevance to bone metabolism. Regression assumptions, including linearity, normality of residuals, and multicollinearity, were evaluated before model construction. A p-value of <0.050 was deemed statistically significant.

Results

Thirty-seven patients who met the study criteria were included in the analysis. According to the Tanner stage, 45.9% of patients were prepubertal, and 54.1% were pubertal. The mean age of the patients was 10.35±3.82 years, with an age range of 3.8 to 17.1 years. A total of 78.4% (n=29) of the patients were male, and 21.6% (n=8) were female. The mean height SDS was -2.02 ± 0.96, the weight SDS was -2.00±1.02, and the body mass index (BMI) SDS was -1.23±1.12. In biochemical evaluation, the mean serum total Ca was 9.46±0.47 mg/dL, corrected Ca was 9.42±0.39 mg/dL, P was 4.64±0.59 mg/dL, Mg was 1.85±0.16 mg/dL, ALP was 194.95±74.89 U/L, PTH was 45.24±15.41 pg/mL, and 25(OH) vitamin D level was 45.92±17.22 nmol/L. The mean BMD Z-score was –1.44±1.61 (Table I).

When patients were analyzed by genetic subtype, type 1 OI associated with a heterozygous COL1A1 mutation was identified in 15 patients (40.5%). The distribution of other genetic subtypes is shown in Figure 1.

Table I: Demographic characteristics and laboratory data for patients (n=37)

Variables	Values*	Reference Values
Age (years)	10.35 ± 3.82 (3.80-17.10)	-
Height SDS	–2.02 ± 0.96 (–4.70-–0.50)	-2< N <2
Weight SDS	–2.00 ± 1.02 (–4.80-–0.10)	-2< N <2
BMI SDS	–1.23 ± 1.12 (–4.00-0.90)	-2< N <2
Ca (mg/dL)	9.46 ± 0.47 (8.80-10.30)	8.5-10.5
Corrected Ca (mg/dL)	9.42 ± 0.39 (8.90-10.10)	8.5-10.5
Phosphorus (mg/dL)	4.64 ± 0.59 (2.90-5.40)	4-6.8
Magnesium (mg/dL)	1.85 ± 0.16 (1.50-2.10)	1.7-2.2
ALP (IU/L)	194.95 ± 74.89 (104.00-354.00)	150-400
PTH (pg/mL)	45.24 ± 15.41 (19.00-79.00)	15-65
Vitamin D (nmol/L)	45.92 ± 17.22 (15.00-90.00)	50-100
BMD Z-score	–1.44 ± 1.61 (–3.90-1.80)	>-2

***:** *mean±SD(min-max),* ***SDS:** standard deviation score,* ***BMI:** body mass index,* ***Ca:** calcium,* ***ALP:** alkaline phosphatase,* ***PTH:** parathyroid hormone,* ***BMD:** bone mineral density.*

Table II: Comparison of patients based on their vitamin D levels

Variable	Deficiency (<30 nmol/L)*	Insufficiency (30–50 nmol/L)*	Normal (>50 nmol/L)*	p†
Total number of patients	7	16	14	-
Age (years)	8.24±3.65	12.21±3.39	9.28±3.64	0.020
Height SDS	–1.67±0.46	–1.69±0.71	–2.58±1.16	0.086
Weight SDS	–1.89±0.36	–1.66±0.90	–2.45±1.23	0.072
BMI SDS	–1.51±0.86	–1.04±1.20	–1.31±1.18	0.575
Ca (mg/dL)	8.94±0.34	9.46±0.27	9.73±0.50	0.003
Corrected Ca (mg/dL)	9.16±0.29	9.34±0.25	9.63±0.46	0.029
Phosphorus (mg/dL)	4.00±0.80	4.64±0.42	4.96±0.35	0.005
Magnesium (mg/dL)	1.84±0.21	1.83±0.12	1.89±0.17	0.367
ALP (IU/L)	257.6±75.4	194.6±69.6	164.0±64.6	0.027
PTH (pg/mL)	59.1±11.5	42.4±13.7	41.6±15.9	0.018
BMD Z-score	–2.74±0.33	–1.22±1.59	–1.04±1.74	0.023

***:** *mean±SD,* **†:** *Kruskal Wallis test,* ***SDS:** standard deviation score,* ***BMI:** body mass index,* ***Ca:** calcium,* ***ALP:** alkaline phosphatase,* ***PTH:** parathyroid hormone,* ***BMD:** bone mineral density*

Regarding vitamin D levels, 18.9% of patients had deficiency (<30 nmol/L), 43.2% had insufficiency (30–50 nmol/L), and 37.8% had normal levels (>50 nmol/L). Significant differences were observed in age (p=0.020), serum Ca (p=0.003), corrected Ca (p=0.029), P (p=0.005), ALP (p=0.027), PTH (p=0.018), and BMD Z-score (p=0.023). No statistically significant differences were detected for height SDS (p = 0.086), weight SDS (p = 0.072), BMI SDS (p = 0.575), or Mg levels (p = 0.367) (Table II).

In post-hoc Dunn–Bonferroni analyses, patients with vitamin D deficiency had significantly lower serum Ca and BMD Z-scores, and higher PTH levels, compared with patients with vitamin D insufficiency and normal vitamin D levels. In addition, phosphorus and ALP differed significantly only between the vitamin D deficiency and normal vitamin D groups. No Bonferroni-corrected significant differences were observed between the insufficiency and normal vitamin D groups (Table III).

Table III: Results of the post-hoc Dunn-Bonferroni analysis based on patients' vitamin D levels.

Variable	Corrected p
Age	
<30 vs 30–50 nmol/L	0.027
<30 vs >50 nmol/L	0.488
30–50 vs >50 nmol/L	0.019
Ca	
<30 vs 30–50 nmol/L	0.005
<30 vs >50 nmol/L	0.001
30–50 vs >50 nmol/L	0.166
Corrected Ca	
<30 vs 30–50 nmol/L	0.027
<30 vs >50 nmol/L	0.038
30–50 vs >50 nmol/L	0.142
Phosphorus	
<30 vs 30–50 nmol/L	0.039
<30 vs >50 nmol/L	0.002
30–50 vs >50 nmol/L	0.052
ALP	
<30 vs 30–50 nmol/L	0.065
<30 vs >50 nmol/L	0.007
30–50 vs >50 nmol/L	0.240
PTH	
<30 vs 30–50 nmol/L	0.006
<30 vs >50 nmol/L	0.012
30–50 vs >50 nmol/L	0.697
BMD Z-score	
<30 vs 30–50 nmol/L	0.012
<30 vs >50 nmol/L	0.010
30–50 vs >50 nmol/L	0.790

***Ca:** calcium,* ***ALP:** alkaline phosphatase,* ***PTH:** parathyroid hormone,* ***BMD:** bone mineral density.* ***Bolded values:** Below the Bonferroni-corrected significance level (p < 0.0167)*

When the relationships between vitamin D groups and categorical variables were evaluated, significant differences were observed among the groups concerning vitamin D treatment status, with treatment rates of 57.1% (4/7), 87.5% (14/16), and 100% (14/14) in the deficiency, insufficiency, and normal groups, respectively (p=0.025), and treatment regimen, with regular treatment rates of 0% (0/7), 56.3% (9/16), and 78.6% (11/14), respectively (p=0.003). On the other hand, no significant association was observed between vitamin D groups and Ca treatment [14.3% (1/7), 50.0% (8/16), and 64.3% (9/14), respectively; p=0.114], sun exposure [42.9% (3/7), 68.8% (11/16), and 78.6% (11/14), respectively; p=0.273], the presence of vertebral fractures [28.6% (2/7), 31.3% (5/16), and 21.4% (3/14), respectively; p = 0.887], Tanner stage [pubertal: 28.6% (2/7), 75.0% (12/16), and 42.9% (6/14), respectively; p=0.086], or gender [male: 85.7% (6/7), 87.5% (14/16), and 64.3% (9/14), respectively; p=0.343]. When evaluating patients for vertebral fractures, 27.0% (n=10) of the cohort were found to have them. There were no statistically significant differences between patients with and without vertebral fractures in terms of age (p= 0.130), height SDS (p=0.229), weight SDS (p=0.389), BMI SDS (p=0.906), total Ca (p = 0.933), corrected Ca (p=0.602), P (p=0.933), Mg (p=0.674), ALP (p=0.933), PTH (p =0.511), or vitamin D levels (p=0.319). Although BMD Z-scores were lower in patients with vertebral fractures, the difference

Table IV: Comparison of patients based on the presence or absence of vertebral fractures

Variable	Vertebral fracture absent	Vertebral fracture present	p
Total number of patients	27	10	-
Age (years)*	9.79 ± 3.99	11.87 ± 3.00	0.130
Height SDS (-2< N<2)*	–2.17 ± 1.01	–1.63 ± 0.74	0.229
Weight SDS (-2< N<2)*	–2.08 ± 1.10	–1.79 ± 0.76	0.389
BMI SDS (-2< N<2)*	–1.24 ± 1.26	–1.20 ± 0.68	0.906
Ca (mg/dL) (N: 8.5-10.5)*	9.49 ± 0.53	9.39 ± 0.26	0.933
Corrected Ca (mg/dL) (N: 8.5-10.5)*	9.45 ± 0.43	9.32 ± 0.26	0.602
Phosphorus (mg/dL) (N: 4-6.8)*	4.61 ± 0.66	4.73 ± 0.32	0.933
Magnesium (mg/dL) (N: 1.7-2.2)*	1.85 ± 0.15	1.86 ± 0.19	0.674
ALP (IU/L) (N: 150-400)*	193.9 ± 74.7	197.8 ± 79.4	0.933
PTH (pg/mL) (N: 15-65)*	46.4 ± 15.2	42.1 ± 16.3	0.511
BMD Z-score (N: >-2)*	–1.28 ± 1.64	–1.86 ± 1.51	0.229
Vitamin D (nmol/L) (N: 50-100)*	47.1 ± 18.8	42.6 ± 12.0	0.319
Gender†			
Male	20 (69.0)	9 (31.0)	0.404
Female	7 (87.5)	1 (12.5)	
Tanner stage†			
Prepubertal	15 (88.2)	2 (11.8)	0.073
Pubertal	12 (60.0)	8 (40.0)	
Calcium treatment†			
Present	16 (84.2)	3 (15.8)	0.151
Absent	11 (61.1)	7 (38.9)	
Vitamin D treatment†			
Present	5 (100)	0 (0)	0.295
Absent	22 (68.8)	10 (31.3)	
Sun exposure†			
Present	7 (58.3)	5 (41.7)	0.240
Absent	20 (80.0)	5 (20.0)	
Pamidronat treatment regularity†			
Regular	10 (58.8)	7 (41.2)	0.136
Irregular	17 (85.0)	3 (15.0)	

***:** mean±SD (Mann–Whitney U test), **†:** n(%) (Fisher's exact test), **SDS:** standard deviation score, **BMI:** body mass index, **Ca:** calcium, **mg:** milligrams, **dL:** deciliters, **N:** normal, **ALP:** alkaline phosphatase, **PTH:** parathyroid hormone, **nmol:** nanomoles, **L:** liters, **BMD:** bone mineral density*

Table V: Correlation analysis results

Variable / Model Correlation analysis	r	p
BMD Z-score – Total Ca	0.343	0.038
BMD Z-score – Corrected Ca	0.313	0.059
BMD Z-score – P	0.274	0.101
BMD Z-score – Mg	0.264	0.114
BMD Z-score – ALP	–0.191	0.258
BMD Z-score – PTH	–0.233	0.166
BMD Z-score – Vitamin D	0.274	0.100
BMD Z-score – Age	–0.061	0.718
BMD Z-score – Height SDS	–0.001	0.997
BMD Z-score – Weight SDS	0.067	0.693
BMD Z-score – BMI SDS	0.093	0.586
P – PTH	–0.484	0.002
Vitamin D – Total Ca	0.457	0.005
Vitamin D – Corrected Ca	0.367	0.026

***r:** Spearman's rank correlation coefficient, **SDS:** standard deviation score, **BMI:** body mass index, **Ca:** calcium, **P:** phosphorus, **Mg:** magnesium, **ALP:** alkaline phosphatase, **PTH:** parathyroid hormone, **BMD:** bone mineral density*

did not reach statistical significance (p=0.229). A total of 48.6% of patients were receiving Ca therapy, while 86.5% were receiving vitamin D therapy. A history of regular sun exposure was reported in 67.6% of cases, and treatment

Table VI: Multiple linear regression analysis predicting BMD Z-score

Predictor	B	SE B	β	t	p	95% CI for B
Total calcium	1.014	0.634	0.295	1.599	0.119	–0.276 to 2.305
PTH	–0.014	0.018	–0.138	–0.812	0.422	–0.050 to 0.022
Vitamin D	0.007	0.018	0.074	0.387	0.701	–0.029 to 0.043

*R^2=0.158; adjusted R^2=0.081; F(3, 33)=2.065; p=0.124. **B:** unstandardized regression coefficient; **SE B:** standard error; **β:** standardized regression coefficient; **CI:** confidence interval; **PTH:** parathyroid hormone*

adherence was observed in 54.1%. Similarly, there were no significant differences between the groups concerning gender (p=0.404), Tanner stage (p=0.073), Ca treatment status (p=0.151), vitamin D treatment status (p=0.295), sun exposure (p=0.240), or pamidronate treatment regimen (p= 0.136) (Table IV).

Correlation analysis results are summarized in Table V. A statistically significant positive correlation was observed between BMD Z-score and serum total calcium levels (r=0.343; p=0.038). In addition, serum phosphorus was negatively correlated with PTH (r=–0.484; p=0.002) and positively correlated with vitamin D (r=0.454; p=0.005). Vitamin D was also positively correlated with total calcium (r =0.457; p =0.005) and corrected calcium levels (r=0.367; p =0.026) (Table V).

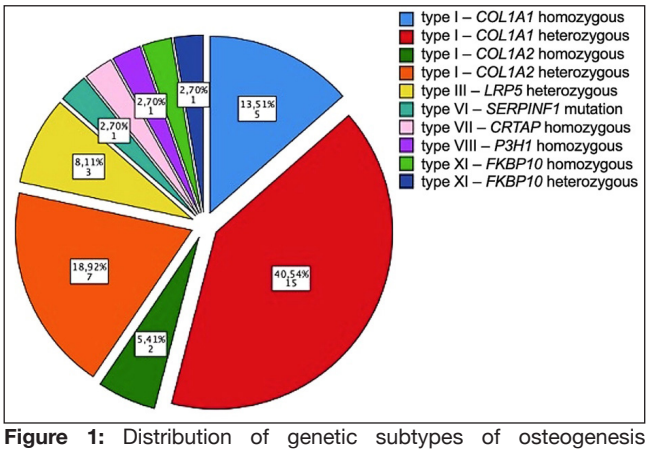

Figure 1: Distribution of genetic subtypes of osteogenesis imperfecta in the study population.

Multiple linear regression analysis results are presented in Table VI. The overall regression model was not statistically significant (R^2=0.158, adjusted R^2 =0.081; F[3,33] = 2.065; p =0.124). Serum total calcium (B=1.014; p=0.119), PTH (B = –0.014; p=0.422), and vitamin D (B=0.007; p=0.701) were not independently associated with BMD Z-score (Table VI).

Discussion

This study examines the bone health of pediatric patients diagnosed with OI who presented to a pediatric orthopedic clinic for fractures from a pediatric endocrinology perspective. Our results support the concept that reduced BMD and the relatively high frequency of vertebral fractures in OI mainly reflect the underlying abnormalities of the bone matrix, with mechanical trauma serving a secondary role (13). Additionally, disparities in access to antiresorptive therapy and variations in treatment continuity have facilitated a comparative analysis of the disease's natural progression versus the effects of therapeutic interventions (14,15).

Growth retardation, low BMD, and a high rate of vertebral fractures (27%) are significant findings in the study group (16). Recent longitudinal studies indicate that the annual incidence of new vertebral fractures or deformities in children with OI ranges from about 10% to 25%, is higher in severe phenotypes, and is notably decreased by bisphosphonate therapy (9,13). Vitamin D deficiency and low treatment adherence highlight the importance of modifiable factors affecting bone health (17). However, no notable link was found between biochemical parameters and the anthropometric indicators measured alongside BMD (18). This implies that BMD alone might be limited in its ability to reflect disease severity and metabolic status in OI (13,19). A comparison between patients who are able to regularly receive antiresorptive therapy and those who are unable to do so may suggest clinical differences in fracture burden and vertebral involvement, independent of the absolute change in BMD (13). This observation emphasizes that access to treatment and continuity of care are at least as vital as pharmacological efficacy in the management of OI (9,20). It is anticipated that the increase in BMD in patients with OI is less pronounced than in secondary osteoporosis, given that the underlying pathology involves deterioration in bone quality rather than bone mass (13). Consequently, even if bisphosphonate therapy yields only a modest increase in BMD, it is well established that clinical benefits predominantly include reduced pain, enhanced mobility, and improved functional capacity (13,21).

The fact that the biochemical parameters obtained in our study mainly fall within reference ranges supports the idea that the risk of fracture primarily stems from primary osteoporosis rather than secondary metabolic disorders (9). Reviewing the hospital records of patients who came to our center due to fractures revealed that many of these patients had already been receiving treatment and follow-up. However, the frequency and consistency of their follow-up varied. This may partly explain why biochemical parameters appeared within reference ranges at the time of assessment (22). Nevertheless, the fluctuations in vitamin D levels and sun exposure emphasize the role of environmental and metabolic factors in fracture risk, especially when access to treatment is limited (17,18).

The lack of major differences in biochemical, clinical, and densitometric parameters between patients with and without vertebral fractures indicates that vertebral fractures often progress quietly without obvious symptoms (23). This supports the idea that focusing only on symptomatic fractures in children with OI is insufficient and highlights the importance of regular radiological follow-up (13,23). Early identification of vertebral deformities is crucial not only for assessing the disease burden but also for optimizing the timing of antiresorptive therapy (7).

Bisphosphonates reduce bone resorption primarily by suppressing osteoclast-mediated bone turnover. They may also increase osteoblastic activity, which could indirectly speed up healing in osteoporosis (9). However, because osteoclastic activity is important during fracture healing—especially in the remodeling phase—it is more sensible to plan treatment at least 4 weeks after a fracture rather than immediately after (9). This advice does not mean treatment should be completely delayed; instead, it emphasizes the importance of personalized planning that considers fracture healing processes (20). Since hospital stays due to fractures can interrupt antiresorptive therapy, this highlights the need for coordinated follow-up care between pediatric orthopedics and pediatric endocrinology (9).

In the long-term follow-up of children with OI, it is important to assess not only the number of fractures and BMD measurements but also clinical parameters such as bone pain, functional capacity, and daily activity levels. Regularly monitoring these factors throughout clinical follow-up provides a more complete understanding of treatment effectiveness and helps prevent early functional decline (9,13). Furthermore, integrating personalized physical therapy programs and lifestyle modifications into the treatment plan is crucial for boosting bone health and improving patients' quality of life (4,6).

Given the genetic heterogeneity and the varying clinical courses of OI subtypes, the importance of a multidisciplinary approach becomes even clearer. Collaboration among pediatric endocrinologists, orthopedic surgeons, and rehabilitation specialists plays a vital role in reducing fracture risk, enhancing treatment adherence, and ensuring

long-term functional improvements (24). In this context, future studies exploring genotype-phenotype relationships and assessing subtype-specific treatment responses will help develop more targeted strategies for OI management.

Limitations

This study has certain limitations. The relatively small sample size may have limited the statistical power of subgroup analyses and reduced the ability to detect weaker associations. Because of the limited number of cases with OI subtypes other than Type 1 OI, meaningful comparisons of osteoporosis diagnostic parameters might not have been possible in these groups; differences related to genetic variation are known (2,3), and studies with larger patient groups could help clarify these differences more effectively.

Another limitation of the study is that although serum Ca, corrected Ca, P, Mg, and ALP levels were assessed, these parameters could not be analyzed separately using age- and puberty-specific reference ranges. Since ALP levels in childhood are linked to growth and bone turnover rates, not assessing ALP isoenzymes (e.g., bone-specific ALP) may have made it difficult to clearly identify bone-related activity. Additionally, because ALP is released from the bone, liver, intestines, and other tissues, this could restrict the accuracy of total ALP levels in reflecting bone metabolism. Nevertheless, the inclusion of recent biochemical data, along with densitometric and radiological records, can be seen as a strength of the study (25).

Conclusion

Evaluation of bone health in children with OI should not rely solely on BMD measurements; it should also include vertebral fractures, biochemical parameters, growth data, environmental factors, and access to treatment. The goals of management extend beyond improving BMD and also include reducing pain, improving function, and supporting quality of life. Incorporating a pediatric endocrinology approach into pediatric orthopedic care and ensuring continuous access to antiresorptive therapy will help children with OI lead more active and sustainable lives.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (04.03.2026, reference number: 2-26-2063).

Contribution of the authors

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

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Original Article

Altered heart rate variability and ventricular repolarization in children with mitral valve prolapse

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Received : 09.05.2026, Accepted : 25.08.2026 DOI: 10.12956/TJPD.2026.1365

ABSTRACT

Objective: The aim of this study was to evaluate heart rate variability (HRV) parameters and ventricular repolarization abnormalities in children with mitral valve prolapse (MVP) compared with healthy controls.

Materials and Methods: This retrospective single-center study included 78 children with MVP and 92 healthy controls with similar age and gender distributions. Demographic characteristics, 24-hour Holter-derived HRV parameters, and electrocardiographic measurements were analyzed. HRV indices included SDNN, SDANN, SDANNi, rMSSD, pNN50, total power, VLF, LF, HF, LF/HF ratio, and triangular index. Multiple comparisons were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. Multivariable linear regression analyses adjusted for age and sex were performed for selected representative variables.

Results: Children with MVP demonstrated significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values compared with controls after FDR correction. Maximum QTc values were significantly higher in the MVP group. In multivariable regression analysis, MVP remained independently associated with lower HF and rMSSD values and higher maximum QTc values after adjustment for age and gender. No significant differences were observed for LF/HF ratio, SDNN, SDANN, or pNN50 after FDR correction.

Conclusion: Children with MVP exhibit reduced parasympathetic modulation together with prolonged ventricular repolarization independently of age and gender. These findings suggest that pediatric MVP may be associated with autonomic and electrophysiological alterations.

Keywords: Autonomic nervous system, child, electrocardiography, heart rate variability, mitral valve prolapse

Introduction

Mitral valve prolapse (MVP) is characterized by the displacement of one or both mitral valve leaflets above the atrioventricular junction during ventricular systole (1). It is often asymptomatic but may present with a wide spectrum of symptoms, including atypical chest pain, palpitations, dyspnea, presyncope, reduced exercise tolerance, migraine-like headaches, anxiety, and depression (2).

Overall, MVP is generally associated with a favorable prognosis; however, complications such as ventricular arrhythmias and sudden cardiac death have been reported in a subset of patients (3,4).

Several studies have investigated autonomic function in patients with MVP using heart rate variability (HRV) analysis, yielding inconsistent results. While some reports have demonstrated reduced parasympathetic activity and impaired autonomic regulation, others have reported no significant differences, and the underlying mechanisms remain incompletely understood (5,6).

Given the potential link between autonomic dysfunction and arrhythmic risk in MVP, further evaluation of HRV parameters may provide valuable insights into the pathophysiology of this condition. Therefore, in this study, we aimed to assess HRV parameters in patients with MVP and compare them with those of healthy controls in order to better characterize autonomic function in this population.

Materials and Methods

This retrospective study was conducted in the pediatric cardiology outpatient clinic of Ankara Bilkent City Hospital as requested and included 78 pediatric patients diagnosed with MVP between January 2022 and September 2025. A total of 92 healthy children with normal echocardiographic findings and similar age distribution were included as the control group.

Inclusion criteria were adequate echocardiographic imaging, displacement of the anterior and/or posterior mitral valve leaflets more than 2 mm beyond the mitral annulus during systole, structurally normal hearts without congenital heart disease, and no use of antiarrhythmic medications. Patients with MVP secondary to conditions such as Marfan syndrome, rheumatic heart disease, Ehlers–Danlos syndrome were excluded from the study.

Twenty-four-hour Holter monitoring recordings were analyzed in all participants. The evaluated HRV parameters included time-domain indices such as SDNN, SDANN, SDANNi, rMSSD, pNN50, triangular index, minimum heart rate, maximum heart rate, and average heart rate, as well as frequency-domain parameters including total power, very low frequency (VLF), low frequency (LF), high frequency (HF), and LF/HF ratio. Maximum corrected QT interval (QTc) values were obtained from 24-hour Holter recordings using CardioScan 12 Holter analysis software (DM Software, USA). QTc values were automatically calculated using Bazett's correction formula, and the maximum QTc value recorded during the monitoring period was used for statistical analysis.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were presented as frequency and percentages and subsequently subjected to comparison through the utilisation of the Pearson chi-square test. To account for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method, which was preferred over more conservative methods because HRV parameters are physiologically interrelated. In addition, multivariable linear regression analyses adjusted for age and gender were performed for selected representative variables. A p-value <0.050 was considered statistically significant.

Results

A total of 170 children were included in the study, consisting of 78 patients with MVP and 92 healthy controls. The median age was 9.5 years in the MVP group and 10.1 years in the control group, with no significant difference between the groups (p=0.536). Female gender was present in 88.5% of the MVP group and 84.7% of the control group, with no significant difference between the groups (p=0.905).

Comparisons of HRV parameters between the groups are presented in Table I. Patients with MVP demonstrated significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values after FDR correction. In addition, maximum QTc values were significantly higher in the MVP group. No significant differences remained after FDR correction for SDNN, SDANN, pNN50, VLF, LF/HF ratio, minimum heart rate, maximum heart rate, or average heart rate.

Given the interrelated nature of HRV parameters, representative variables reflecting parasympathetic modulation and ventricular repolarization were selected for multivariable regression analysis. MVP remained independently associated with lower HF and rMSSD values after adjustment for age and gender (p=0.001 and p=0.012, respectively). Maximum QTc also remained significantly associated with MVP after adjustment (p=0.026). In addition, age and gender were independent predictors of QTc (Table II).

Table I: Comparison of HRV parameters between MVP and control groups

	MVP	Control	p	p (FDR)
Age*	9.5 (6.4)	10.1 (4.2)	0.536	0.573
Female†	69 (88.5)	78 (84.7)	0.905	-
SDNN*	121 (53)	137 (45)	0.075	0.086
SDANN	110 (47)	120 (45)	0.215	0.246
SDANNi*	58 (26)	66 (18)	0.009	0.029
rMSSD*	38 (14)	48 (19)	0.015	0.034
pNN50*	15 (10)	18 (13)	0.044	0.078
Total Power*	2964 (2902)	4298 (2123)	0.005	0.020
VLF*	1735 (1646)	2543 (1207)	0.072	0.086
LF*	711 (541)	974 (400)	0.005	0.020
HF*	452 (318)	607 (444)	0.002	0.016
LF/HF*	1.49 (0.94)	1.65 (0.77)	0.388	0.414
Triangular index*	31.8 (10.6)	34.7 (11.9)	0.011	0.029
Max QTc*	469 (60)	415 (75)	<0.001	0.008
Min HR*	51 (8)	51 (7)	0.624	0.624
Max HR*	154.5 (17)	161 (26)	0.229	0.262
average HR*	86 (13)	84 (7)	0.037	0.074

***:** median (IQR) (Mann–Whitney U test), **†:** n(%) (Pearson chi-square test), **HRV:** heart rate variability, **MVP:** Mitral valve prolapse, **QTc:** corrected QT interval, **HR:** heart rate. **p (FDR):** p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method.*

Discussion

In the present study, children with MVP demonstrated significant alterations in HRV parameters together with prolonged maximum QTc values compared with healthy controls. The main finding of our study is that pediatric MVP patients exhibit impaired autonomic modulation, particularly reduced parasympathetic (vagal) activity. Given the interrelated nature of HRV parameters, representative variables reflecting parasympathetic modulation and ventricular repolarization were selected for multivariable regression analysis. In this analysis, MVP remained independently associated with lower HF and rMSSD values as well as higher maximum QTc values after adjustment for age and gender.

Our analysis demonstrated that patients with MVP had significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values compared with healthy controls. Among these, HF and rMSSD are considered reliable indicators of parasympathetic modulation and reflect short-term beat-to-beat variability (7,8). Interestingly, SDANNi was significantly reduced whereas SDANN remained unchanged. Since SDANNi reflects short-term fluctuations in autonomic modulation, this finding may suggest that autonomic impairment in MVP predominantly affects short-term HRV dynamics rather than longer-term variability (7,9). The independent association of HF and rMSSD, two established markers of parasympathetic modulation, with MVP in our

Table II: Multivariable linear regression analyses adjusted for age and gender

Predictor	B	SE B	β	t	p	95% CI for B	R^2
HF							
Gender	226.783	76.160	0.221	2.978	0.003	76.415-377.151	0.121
Age	1.958	8.229	0.017	0.238	0.812	-14.288-18.205	
MVP vs. control	187.098	57.061	0.241	3.279	0.001	74.439-299.758	
rMSSD							
Gender	16.161	3.874	0.305	4.171	<0.001	8.512–23.809	0.144
Age	-0.115	0.419	-0.020	-0.274	0.784	-0.94-0.712	
MVP vs. control	7.353	2.903	0.184	2.533	0.012	1.622-13.083	
Maximum QTc							
Gender	-53.850	11.536	-0.342	-4.668	<0.001	-76.634-31.066	0.186
Age	-3.383	1.239	-0.198	-2.730	0.007	-5.831-0.936	
MVP vs. control	-19.813	8.786	-0.164	-2.255	0.026	-37.165-2.460	

***HF:** high frequency, **MVP:** mitral valve prolapse, **rMSSD:** root mean square of successive differences, **QTc:** corrected QT interval, **B:** unstandardized regression coefficient, **SE:** standard error, **β:** standardized regression coefficient, **CI:** confidence interval, **R^2:** coefficient of determination*

regression analysis supports the presence of reduced vagal activity in these patients (10,11). These findings are consistent with the study by Han et al. (12), which reported significantly lower time-domain and frequency-domain HRV indices, including HF, LF, and rMSSD, in children with MVP.

Similarly, Ahmadi et al. (6) demonstrated a decline in several HRV parameters, including SDNN, SDANN, rMSSD, and pNN50, in children with MVP, suggesting autonomic dysfunction in these patients. In contrast, Beyazal et al. (13) did not find significant differences in overall time- and frequency-domain HRV parameters between MVP patients and controls, reporting only a lower minimum heart rate and a higher prevalence of low LF values in the MVP group. The relatively large sample size of our study, together with the use of FDR correction and multivariable regression analysis, strengthens the evidence supporting impaired parasympathetic modulation in pediatric MVP.

Previous studies evaluating ventricular repolarization in MVP have reported heterogeneous findings. While several studies demonstrated prolonged QTc intervals and increased QT dispersion in pediatric MVP patients, others failed to detect significant QTc prolongation compared with healthy controls (6,13-15). In our cohort, maximum QTc values were significantly higher in the MVP group and remained independently associated with MVP after adjustment for age and gender. The QT interval and its corrected value (QTc) reflect ventricular depolarization and repolarization, and QTc prolongation is a recognized marker associated with an increased risk of ventricular arrhythmias (16,17). Taken together, our findings suggest that autonomic dysregulation and ventricular repolarization abnormalities may coexist in children with MVP.

Our multivariable regression analysis identified age and gender as independent predictors of QTc. Physiological maturation and gender-related differences are known to influence autonomic tone, HRV parameters, and ventricular repolarization in children (18,19). Therefore, adjustment for these variables is important when evaluating autonomic function and repolarization abnormalities in pediatric MVP populations.

Interestingly, although some previous studies reported increased LF/HF ratios in MVP patients, suggesting altered sympathovagal balance, other studies failed to demonstrate significant differences in HRV parameters between MVP patients and controls (12,20,21). In our cohort, LF/HF ratio was not significantly different after FDR correction. Similarly, SDNN, SDANN, and pNN50 values were not significantly different between groups. These findings may suggest that autonomic alterations in our pediatric MVP cohort are more closely related to reduced parasympathetic modulation rather than sympathetic predominance.

Limitations

Our study has several limitations. First, the retrospective design limits the ability to establish causal relationships between the observed autonomic and repolarization abnormalities and future clinical outcomes. In addition, long-term prospective follow-up studies are needed to determine whether reduced HRV parameters and prolonged QTc values in pediatric MVP patients are associated with clinically significant arrhythmic events or syncope later in life.

Conclusion

In conclusion, children with MVP demonstrated altered parasympathetic modulation and prolonged ventricular repolarization independently of age and gender. These findings suggest that pediatric MVP may be associated with autonomic and electrophysiological alterations, highlighting the potential importance of cardiac autonomic assessment and electrocardiographic evaluation in this population. Although these findings do not warrant changes in current clinical management, they may provide additional information in the clinical evaluation of children with MVP. Whether these abnormalities predict future arrhythmic events and should influence follow-up strategies remains to be determined.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (01.10.2025, reference number: TABED 2-25-1546).

Contribution of the authors

UP: conceived and designed the study, collected the data, and drafted the initial manuscript, İİÇ: critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Source of funding
The authors declare the study received no funding.

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

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Turkish Journal of Pediatric Disease

Original Article

Pediatricians' knowledge of pediatric *Mycoplasma pneumoniae* infection in the post–COVID-19 period: A single-center cross-sectional survey from Türkiye

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Received : 07.05.2026, Accepted : 25.08.2026
DOI:10.12956/TJPD.2026.1362

ABSTRACT

Objective: *Mycoplasma pneumoniae* (MP) remains an important cause of respiratory tract infections and community-acquired pneumonia in children and has regained prominence in the post–COVID-19 period. We aimed to evaluate pediatricians' knowledge of pediatric MP infection across key clinical domains and to compare knowledge according to professional experience.

Materials and Methods: This single-center, cross-sectional, questionnaire-based study was conducted in November–December 2025. A literature-based, face-to-face survey with 29 multiple-choice items (single best answer) assessed knowledge in four domains: risk factors (5 items), clinical manifestations/complications (8 items), diagnostic tests (6 items), and treatment (10 items). Participants were stratified by experience (0–5 years vs. ≥6 years). Item-level correct response rates were compared using chi-square/Fisher's exact tests, and domain scores were compared using the Mann–Whitney U test.

Results: A total of 126 physicians participated (0–5 years: n=93; ≥6 years: n=33). Domain-level knowledge scores were comparable between groups across risk factors, clinical manifestations/complications, diagnostic tests, and treatment. However, several item-level differences were observed; these item-level comparisons were exploratory. Physicians with ≥6 years of experience more frequently answered correctly questions related to the incubation period, cutaneous manifestations, limitations of serologic testing, and identification of an antibiotic ineffective against *M.pneumoniae* infection. In contrast, physicians with 0–5 years of experience more frequently answered correctly items concerning post-infection immunity, the most commonly affected age group, *M.pneumoniae*-associated CNS disease, hospitalization-related knowledge, and management of MP-associated hemolytic anemia.

Conclusion: Overall knowledge of pediatric *M.pneumoniae* infection was comparable across experience strata at the domain level; however, item-level findings should be interpreted cautiously as exploratory. These findings support an institution-wide, high-yield educational package prioritizing diagnostic test interpretation (particularly serology), recognition of extrapulmonary manifestations, and evidence-based antimicrobial selection in the post–COVID-19 period.

Keywords: *Mycoplasma pneumoniae*, children, community-acquired pneumonia, knowledge, pediatricians, surveys and questionnaires

Introduction

Mycoplasma pneumoniae (MP) is an important bacterial pathogen causing respiratory tract infections in children, with a clinical spectrum ranging from mild upper respiratory tract infection to tracheobronchitis and community-acquired pneumonia (CAP) (1,2). Although many infections are self-limited and present as so-called "walking pneumonia," *M. pneumoniae* infection may also cause moderate-to-severe lower respiratory tract disease requiring hospitalization. Common clinical manifestations include fever, persistent cough (often initially non-productive), and dyspnea, while rhinorrhea, pharyngitis, otitis, headache, and chest pain may also accompany the infection. In some children, cough may be prolonged for weeks after the acute phase (3,4).

Mycoplasma pneumoniae is classically recognized as a pathogen affecting school-aged children and adolescents more frequently than younger children, and it is among the leading causes of pediatric CAP in this age group. However, recent surveillance data indicate that age patterns may shift during resurgence periods, with increased detection also

reported in younger children after the COVID-19 pandemic era (5,6). This changing epidemiology is clinically relevant because it broadens the age range in which pediatricians should consider *M. pneumoniae* infection in the differential diagnosis of respiratory infections (7).

The epidemiology of *M. pneumoniae* infection is characterized by cyclical outbreaks, typically occurring every 3–7 years, partly related to changes in circulating strains and the accumulation of susceptible individuals as post-infection immunity wanes (8,9). In addition, outbreaks tend to be facilitated in crowded settings such as schools and households, and transmission can be sustained by the organism's relatively long incubation period. *M. pneumoniae* infections can occur year-round, but many datasets indicate increased activity in summer and early autumn, with subsequent seasonal spillover into colder months depending on region and outbreak dynamics (10). Beyond respiratory disease, *M. pneumoniae* infection is increasingly recognized as a cause of extrapulmonary manifestations, which may occur with or without prominent respiratory symptoms. Reported manifestations most commonly involve the gastrointestinal and dermatologic systems (e.g., vomiting, diarrhea, non-specific rash), but neurologic and cardiovascular complications have also been described (11,12). Rare but clinically significant presentations such as hepatitis, pancreatitis, and mycoplasma-induced rash and mucositis (MIRM) have been reported. The broad clinical spectrum and the potential for immune-mediated complications make early recognition and appropriate management particularly important in pediatric practice (13).

The COVID-19 pandemic substantially altered the epidemiology of respiratory pathogens, including *M. pneumoniae* infection. Non-pharmaceutical interventions (e.g., masking, distancing, school closures) were associated with a marked decline in *M. pneumoniae* infection circulation during 2020–2022. Following the relaxation of these measures, several countries reported re-emergence and surges of *M. pneumoniae* infections, beginning in 2023 and extending into 2024, likely in part due to an expanded susceptible population after a prolonged period of reduced exposure (5,14). Public health surveillance data from multiple systems have documented this post-pandemic resurgence and highlighted its implications for pediatric respiratory care. From a therapeutic perspective, *M. pneumoniae* infection is clinically important because it lacks a cell wall, rendering beta-lactam antibiotics ineffective. Macrolides remain the first-line treatment in children in many settings, particularly for suspected or confirmed *M. pneumoniae*; however, macrolide resistance has become an important global concern, with substantial geographic variation (5,15). In severe, refractory, or complicated cases, treatment decisions may require escalation and multidisciplinary evaluation, especially when significant neurologic, mucocutaneous, or other extrapulmonary involvement is suspected. These diagnostic and therapeutic complexities underscore the need for pediatricians to maintain updated knowledge on *M. pneumoniae* infection epidemiology, clinical manifestations, diagnostic testing, and treatment principles.

In the post-pandemic period, timely recognition and appropriate management of *M. pneumoniae* infections have become even more critical for pediatricians. Accordingly, this study aimed to evaluate pediatricians' knowledge regarding risk factors, clinical manifestations and complications, diagnostic tests, and treatment approaches for *M. pneumoniae* infection, and to compare knowledge levels according to professional experience in a single-center setting. The questionnaire-based analysis was structured across these four domains, enabling a focused assessment of strengths and knowledge gaps relevant to routine pediatric care.

Materials and Methods

Study design and setting

This was a single-center, cross-sectional, questionnaire-based study conducted to assess pediatricians' knowledge regarding *M. pneumoniae* infection in children. The study evaluated knowledge in four predefined domains: risk factors, clinical manifestations/complications, diagnostic testing, and treatment approaches. The study was conducted over a 2-month period, between November 2025 and December 2025.

Participants

A total of 126 physicians participated in the study. Participants were recruited on a voluntary basis, and only physicians who agreed to participate were included. The study population consisted of pediatrics residents and board-certified pediatric specialists. Physicians with 0–5 years of professional experience were residents, whereas those with ≥6 years of experience were pediatric specialists. The draft questionnaire items were reviewed by a pediatric infectious diseases specialist and a general pediatrics specialist for clinical accuracy, content relevance, and clarity; items were revised by consensus to minimize ambiguity and ensure alignment with current evidence. For comparative analyses, participants were stratified according to professional experience into two groups: 0–5 years and ≥6 years.

Questionnaire development and administration

The questionnaire was developed based on the existing literature on pediatric *M. pneumoniae* infection and was designed to assess knowledge across key domains, including epidemiology, risk factors, clinical manifestations and complications, diagnostic methods, and treatment approaches. To ensure methodological rigor, questionnaire development followed a structured, stepwise process. First, we performed a focused review of post–COVID-19 pediatric *M. pneumoniae* literature emphasizing changes in incidence, emerging treatment challenges (including concerns about antimicrobial resistance), and extrapulmonary manifestations. Second, an a priori content blueprint was created across four domains (risk factors; clinical manifestations/complications; diagnostic tests; treatment), and an initial pool of items was drafted accordingly. Third, the draft questionnaire was reviewed for clinical accuracy, relevance, and clarity by a panel consisting of a pediatric infectious diseases specialist and a general pediatrics specialist; items were refined by consensus to reduce ambiguity and align wording with current evidence and routine clinical decision points. Fourth, the revised version was pilot-tested face-to-face in a small group of physicians not included in the final analysis to assess feasibility, comprehension, and completion time; minor wording revisions were made based on feedback.

The final instrument consisted of 29 multiple-choice questions, each with a single best correct answer, and was organized into four domains. The risk factor domain (5 items) included questions on epidemiologic and transmission-related characteristics, such as age groups at higher risk, outbreak periodicity, and factors associated with increased susceptibility. The clinical manifestations and complications domain (8 items) covered both common respiratory findings (e.g., fever, persistent cough, and dyspnea) and extrapulmonary involvement, including dermatologic, gastrointestinal, and neurologic complications. The diagnostic tests domain (6 items) assessed knowledge of commonly used diagnostic approaches, including PCR-based testing, serologic methods, and considerations related to test timing and interpretation. The treatment domain (10 items) evaluated knowledge of first-line antimicrobial options, the ineffectiveness of beta-lactam antibiotics due to the absence of a cell wall, and management considerations in severe, refractory, or complicated cases.

Because the instrument was designed as a domain-based knowledge assessment sampling multiple content areas rather than a unidimensional psychometric scale, formal scale validation was not the primary aim; accordingly, content coverage and clarity were ensured through the blueprinting, expert review, and pilot testing steps described above.

The questionnaire was administered face-to-face. There were no missing responses in the completed questionnaires; therefore, no imputation or missing-data handling procedure was required.

Scoring and outcome measures

Each questionnaire item had one correct answer. For item-level analyses, the number and percentage of correct responses were calculated for each participant group.

For domain-level analyses, the number of correctly answered items was calculated separately for each participant in each of the four domains (risk factors, clinical manifestations/complications, diagnostic tests, and treatment). These domain scores were compared between experience groups.

The primary outcome was the difference in domain-specific knowledge scores between the two experience groups. Secondary outcomes included item-level differences in correct response rates.

Statistical analysis

All statistical analyses were performed to compare knowledge performance between physicians with 0–5 years and ≥6 years of professional experience. Descriptive statistics were used to summarize participant characteristics and questionnaire performance. For item-level analyses, responses were coded as correct or incorrect, and each item was summarized as number (n) and percentage (%) of correct responses in each experience group. Between group comparisons for categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate according to expected cell counts.

For domain-level analyses, a score was calculated for each participant in each of the four questionnaire domains (risk factors, clinical manifestations/complications, diagnostic tests, and treatment) by assigning 1 point for each correct answer and 0 points for each incorrect answer, with no penalty for incorrect responses. Thus, higher scores indicated greater knowledge within the relevant domain. The normality of distribution for continuous variables was assessed using the Shapiro–Wilk test. Because domain scores were discrete and not normally distributed, they were summarized as median and interquartile range (IQR) and compared between the two experience groups using the Mann–Whitney U test. If a total knowledge score was also analyzed, it was calculated as the sum of all correctly answered items (possible range: 0–29) and summarized similarly as median (IQR), with between-group comparisons performed using the Mann–Whitney U test. All tests were two-tailed, and a p value <0.050 was considered statistically significant. Statistical significance was interpreted in conjunction with the magnitude and direction of between-group differences in correct response rates and score distributions. Item-level analyses were exploratory and intended to generate hypotheses regarding topic-specific knowledge gaps. There were no missing responses in the completed questionnaires; therefore, complete-case analysis was performed and no imputation method was required.

Results

A total of 126 physicians were included in the study, including 93 with 0–5 years of professional experience and 33 with ≥6 years. As shown in Table I, although overall performance was similar across many items, several significant item-level differences were identified between the two experience groups. In the risk factor domain, physicians with ≥6 years of experience had a higher correct response rate for the question on the average incubation period of *M. pneumoniae* infection (100.0% vs. 67.7%, p<0.001), whereas physicians with 0–5 years of experience performed better on the item regarding immunity to *M. pneumoniae* (80.6% vs. 42.4%, p<0.001). A significant difference was also observed for the question on the age group in which *M. pneumoniae* most commonly causes community-acquired pneumonia, with correct responses observed only in the 0–5 years group (21.5% vs. 0.0%, p=0.009). In the clinical manifestations/complications domain, the 0–5 years group had a higher correct response rate for the item related to *M. pneumoniae*-associated central nervous system disease (90.3% vs. 66.7%, p=0.004), while the ≥6 years group performed better on the item regarding cutaneous manifestations (87.9% vs. 66.7%, p=0.035). In the diagnostic tests domain, the ≥6 years group showed higher correct response rates for the item on laboratory findings not expected in *M. pneumoniae* pneumonia (90.9% vs. 72.0%, p=0.049) and the item assessing knowledge of the limitations of serologic tests (87.9% vs. 61.3%, p=0.009). In the treatment domain, the 0–5 years group had higher correct response rates for the questions on hospitalization rates (73.1% vs. 42.4%, p=0.003) and management of *M. pneumoniae*-associated hemolytic anemia (75.3% vs. 45.5%, p=0.003), whereas the ≥6 years group performed better on the item identifying an antibiotic ineffective against *M. pneumoniae* (100.0% vs. 80.6%, p=0.003).

As presented in Table II, despite these item-specific differences, domain-based knowledge scores did not differ significantly

Table I: Item-level correct response rates to the *Mycoplasma pneumoniae* knowledge questionnaire according to physicians' professional experience

Domain / Questionnaire item	0–5 years (n=93)*	≥6 years (n=33)*	p*
Risk factors			
Transmission route	93 (100.0)	33 (100.0)	–
Household transmission rate	34 (36.6)	13 (39.4)	0.936
Incubation period	63 (67.7)	33 (100.0)	<0.001
Post-infection immunity	75 (80.6)	14 (42.4)	<0.001
Age group most associated with CAP	20 (21.5)	0 (0.0)	0.009
Clinical manifestations and complications			
Most prominent symptom	72 (77.4)	19 (57.6)	0.050
Most common accompanying condition	78 (83.9)	25 (75.8)	0.439
Not an extrapulmonary manifestation	72 (77.4)	22 (66.7)	0.324
CNS involvement (true statement)	84 (90.3)	22 (66.7)	0.004
Least common neurologic complication	63 (67.7)	23 (69.7)	>0.999
Cutaneous manifestations (true statement)	62 (66.7)	29 (87.9)	0.035
Serious cardiac complication	–	–	–
System with most common extrapulmonary complication	6 (6.5)	–	0.339
Diagnostic tests			
Not expected laboratory finding	67 (72.0)	30 (90.9)	0.049
Fastest/most sensitive test	48 (51.6)	19 (57.6)	0.699
Not sufficient alone to confirm diagnosis	39 (41.9)	13 (39.4)	0.961
Incorrect radiologic statement	63 (67.7)	24 (72.7)	0.754
Testing approach for suspected encephalitis without respiratory symptoms	64 (68.8)	19 (57.6)	0.339
Main limitation of serology	57 (61.3)	29 (87.9)	0.009
Treatment			
Hospitalization rate (true statement)	68 (73.1)	14 (42.4)	0.003
When to initiate antibiotics	85 (91.4)	30 (90.9)	>0.999
First-line antibiotic	87 (93.5)	30 (90.9)	0.696
Antibiotic not effective against MP	75 (80.6)	33 (100.0)	0.003
Management of MP-associated CNS disease	79 (84.9)	29 (87.9)	0.780
Management of MP-associated hemolytic anemia	70 (75.3)	15 (45.5)	0.003
Reason for beta-lactam non-susceptibility	69 (74.2)	23 (69.7)	0.786
Trigger of acute chest syndrome	42 (45.2)	16 (48.5)	0.900
Group for which prophylaxis may be considered	59 (63.4)	21 (63.6)	>0.999
Steroid indication	84 (90.3)	33 (100.0)	0.110

***:** *n(%) (Pearson's chi-square test or Fisher's exact test)*

Table II: Domain-based knowledge scores according to physicians' professional experience

Domain	0–5 years (n=93)*	≥6 years (n=33)*	p
Risk factors	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.195
Clinical manifestations and complications	5.0 (4.0–6.0)	5.0 (3.0–5.0)	0.085
Diagnostic tests	4.0 (2.0–5.0)	4.0 (3.0–4.0)	0.761
Treatment	8.0 (7.0–9.0)	7.0 (7.0–8.0)	0.052

***:** *median (interquartile range [IQR]), Mann–Whitney U test*

between the two experience groups. Median (IQR) scores in the 0–5 years and ≥6 years groups were 3.0 (2.0–4.0) vs. 3.0 (2.0–4.0) for risk factors (p=0.195), 5.0 (4.0–6.0) vs. 5.0 (3.0–5.0) for clinical manifestations/complications (p=0.085), 4.0 (2.0–5.0) vs. 4.0 (3.0–4.0) for diagnostic tests (p=0.761), and 8.0 (7.0–9.0) vs. 7.0 (7.0–8.0) for treatment (p=0.052), respectively.

Discussion

In this study, we evaluated pediatricians' knowledge of *M. pneumoniae* infection according to years of professional experience. To the best of our knowledge, this is the first study conducted in Türkiye to assess clinicians' *M. pneumoniae* infection -related knowledge in this manner. Although no statistically significant differences were observed between experience groups in the domain-based scores, several differences emerged at the individual item level. Given the absence of significant domain-level differences, these item-level findings should be interpreted cautiously as topic-specific variability rather than evidence of overall superiority of one group over another. Physicians with ≥6 years of experience achieved higher correct response rates on items addressing the incubation period, cutaneous manifestations, limitations of serologic tests in diagnosis, and identification of an antibiotic ineffective against *M. pneumoniae* infection. In contrast, physicians with 0–5 years of experience performed better on questions related to post-infection immunity, the most commonly affected age group, the most prominent symptom, *M. pneumoniae* -associated central nervous system disease, hospitalization rates, and the management of *M. pneumoniae* -associated hemolytic anemia. Items regarding the route of transmission, when to initiate antibiotic therapy, treatment approach for *M. pneumoniae* -associated CNS disease, indications for steroid therapy, and overall diagnostic approaches were among the most frequently answered correctly in both groups. Item-level differences should be considered exploratory.

In the post–COVID-19 period, heightened awareness of transmission pathways and diagnostic methods (including radiologic evaluation, serology, and PCR) has likely

increased clinicians' overall alertness to these aspects not only for *M. pneumoniae* infection but also for other respiratory infections, which may partly explain the high correct response rates observed for these items across both experience groups (14).

Although domain-level knowledge scores were comparable between experience groups, the observed item-level differences likely reflect the well-described pattern that certain competencies are strengthened primarily through cumulative clinical exposure, whereas others are reinforced through recent, guideline-oriented training. Importantly, because both experience groups practiced during the COVID-19 era, attributing differences solely to "pandemic exposure" versus "years of practice" would be overly simplistic. For example, higher correct response rates among physicians with ≥6 years of experience for the incubation period, cutaneous manifestations, serologic limitations, and identification of an antibiotic ineffective against *M. pneumoniae* may be explained by repeated real-world encounters requiring test selection and interpretation and basic antimicrobial decision rules (16). Contemporary reviews emphasize that *M. pneumoniae* infection diagnostics are highly timing-dependent and that serology has important limitations (e.g., need for paired samples and interpretive pitfalls), while PCR is generally the most accurate approach when available—topics that often become more salient with longitudinal clinical practice and repeated diagnostic stewardship decisions (17). Current recommendations emphasize that PCR is the most accurate routine diagnostic method for *M. pneumoniae*; however, clinicians should interpret a positive PCR result in the clinical context because molecular detection may also occur in asymptomatic carriage or in co-infections. Conversely, serology is limited by timing (particularly early false-negatives) and by prolonged antibody positivity; therefore, single-sample serology may be misleading and paired serology can be required for confirmation in selected scenarios. Importantly, several guidance documents recommend restricting *M. pneumoniae* infection testing to situations in which the result is likely to change management (e.g., severe disease, outbreak settings, or treatment failure), reinforcing the need for targeted clinician education on test selection and interpretation (3,18).

Conversely, better performance of the 0–5 year group on items related to immunity, the most commonly affected age group, hallmark symptoms, *M. pneumoniae* -associated CNS disease, hospitalization-related knowledge, and hemolytic anemia management may reflect the effect of more recent curricula and exam-focused updates, particularly in the post–COVID-19 period when atypical pathogens and extrapulmonary complications have regained prominence. This interpretation is supported by outbreak-era literature documenting post-pandemic *M. pneumoniae* infection resurgences with notable mucocutaneous disease signals (including increased *M. pneumoniae* -induced rash and mucositis) and evolving epidemiologic patterns that necessitate rapid knowledge refresh across all physician strata (19). In this setting, structured continuing medical education has been shown to improve physicians' application of knowledge, especially when delivered with repeated exposures, suggesting that targeted, institution-wide updates could help harmonize these item-level gaps regardless of seniority (20). Overall, the item-level findings should be considered exploratory signals for potential educational targets rather than definitive evidence of group-level superiority.

This study offers a structured, domain-based assessment of pediatricians' knowledge on pediatric *M. pneumoniae* infection and is, to our knowledge, the first such clinician-focused study from Türkiye. Face-to-face administration and complete questionnaires (no missing data) strengthened data quality, while item- and domain-level analyses enabled identification of topic-specific gaps.

Limitations

The single-center, cross-sectional, voluntary design and the relatively small sample size—particularly in the ≥6 years group—may limit generalizability and introduce selection bias. Knowledge was assessed using a domain-based multiple-choice questionnaire rather than observed clinical practice; therefore, the instrument was intended as a pragmatic knowledge assessment tool rather than a formally validated psychometric scale. Multiple item-level comparisons were conducted without formal adjustment for multiple testing; thus, some statistically significant findings—especially borderline results—may reflect type I error. Accordingly, item-level analyses were exploratory and should be interpreted cautiously, with primary emphasis placed on domain-level comparisons. In addition, participant-level factors such as age, subspecialty exposure, guideline use, and academic affiliation were not measured and may have influenced knowledge performance independently of professional experience. Some epidemiologic items relied on specific numeric estimates (e.g., hospitalization rates), which may partially assess recall of statistics rather than clinically actionable knowledge; future iterations will prioritize clinically oriented phrasing over exact values. Finally, because the questionnaire was administered before peer review, items and the predefined answer key could not be modified retrospectively; therefore, a small number of items (e.g., the cardiac-complication item) may be sensitive to variation in literature emphasis and should be interpreted cautiously.

Conclusion

In this single-center, cross-sectional survey, pediatricians with 0–5 years and ≥6 years of professional experience demonstrated comparable overall knowledge of pediatric *M. pneumoniae* infection across the domains of risk factors, clinical manifestations/complications, diagnostic testing, and treatment. Although several item-level differences were observed, these findings should be interpreted cautiously and do not indicate overall superiority of either group, particularly given the absence of statistically significant domain-level differences. These findings support the need for institution-wide, targeted educational updates focusing on high-yield areas such as diagnostic test interpretation (particularly serology), recognition of extrapulmonary manifestations, and evidence-based antimicrobial selection. Because item-level

analyses were exploratory and multiple comparisons were performed without formal adjustment, borderline findings may reflect chance and should be interpreted alongside the domain-level results. Multicenter studies are warranted to confirm these results and to evaluate whether structured training improves knowledge and clinical decision-making in pediatric practice.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (12 November 2025, reference number: TABED 2-25-1625).

Contribution of the authors

Data collection, Literatüre search: BD, AÖP, DG, EGE, Data analysing: SPY Manuscript editing and review: BD, AÖP

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Turkish Journal of Pediatric Disease

Case Report

Foreign body reaction following social media-driven skincare trend: A case report in an adolescent

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Received : 13.03.2026, Accepted : 24.06.2026 DOI: 10.12956/TJPD.2026.1328

ABSTRACT

Social media has become a major channel for the rapid spread of unverified health information. Hyaluronic acid (HA), widely used as a dermal filler under controlled conditions, is also promoted in skincare content online. Improper or unsupervised administration may result in foreign-body reactions and infectious complications, posing a risk especially to adolescents influenced by such trends.

A 16-year-old female presented with acute facial swelling and erythema after self-injecting a commercially available topical serum containing 1% hyaluronic acid into the nasal dorsum using a 21G syringe, imitating a social media video. Examination revealed multiple nasal injection sites with marked edema extending to the eyelids and infraorbital region, while systemic findings and laboratory tests were normal. She was treated with intravenous corticosteroid and antihistamine, followed by oral methylprednisolone, cetirizine, and amoxicillin–clavulanate. During the two-week follow-up, inflammatory findings had regressed without sequelae.

This case emphasizes the dermatological risks of unscientific cosmetic practices promoted on social media. Adolescents represent a particularly vulnerable group, underscoring the need for clinician awareness and preventive education regarding unsafe procedures outside medical supervision.

Keywords: Adolescent, foreign-body reaction, skin care, social media

Introduction

Hyaluronic acid (HA) is a volume-enhancing glycosaminoglycan with viscoelastic properties, widely used in dermatologic filler procedures under sterile and controlled conditions (1). It is commonly included in topical skincare products due to its moisturizing properties. However, the administration of non-sterile preparations, especially when administered with improper injection techniques may lead to serious adverse events such as local tissue reactions, cellulitis, abscess formation, granulomatous inflammation and, rarely, necrotizing complications (2). Beauty and care trends that have spread rapidly on social media platforms in recent years have led to practices that are far from medical supervision, especially in individuals in the adolescent age group, and can lead to serious dermatological complications (3). Short video-based platforms may increase interest in skin care and aesthetic procedures among young individuals, leading to an increase in aesthetic procedures outside of medical supervision (4). A significant proportion of this content is not compatible with scientific guidelines and are applied without professional consultation.

In this report, we present a case of severe dermatologic complications in an adolescent patient who applied HA without medical supervision under the influence of social media.

Case Report

A 16-year-old female patient, with no known chronic disease or allergy history presented to the pediatric emergency department with complaints of facial swelling and erythema. A detailed history revealed that, after watching a video on a

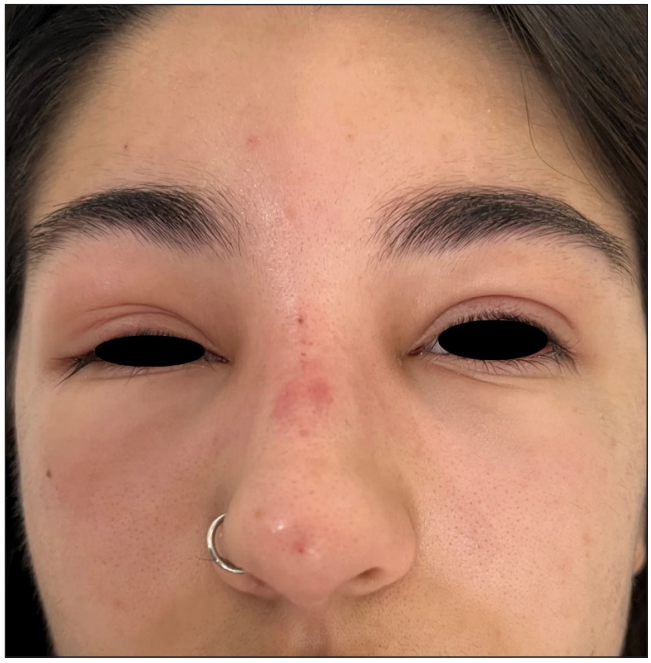

Figure 1: Marked edema of the nasal dorsum, erythema at the injection sites, and diffuse periorbital swelling observed during physical examination.

social media platform, the patient had injected a commercially available topical HA serum into the nasal dorsum using a 21G syringe, with the intention of performing a filler-like procedure. According to the available product information, the serum was intended for external topical use and contained 1% multi-molecular hyaluronic acid/sodium hyaluronate. The listed excipients included aqua, propanediol, xanthan gum, hydroxyacetophenone, and sodium phytate. The product was not an injectable dermal filler and was not labeled for sterile intradermal or subcutaneous administration. Physical examination revealed four separate injection sites on the dorsum of the nose, marked erythema and edema in these areas, as well as widespread edema and tenderness in both upper eyelids and the infraorbital region (Figure – 1). The lesions detected on physical examination began on the nose approximately 2–3 hours after the application and then spread to the surrounding face. Systemic examination revealed no pathological findings, and her vital signs were within normal limits. There were no abnormal findings in the patient's laboratory examination.

The patient did not meet the diagnostic criteria for anaphylaxis and with a preliminary diagnosis of acute hypersensitivity reaction and foreign body reaction, the patient was administered 1 mg/kg intravenous methylprednisolone and 44.5 mg intravenous pheniramine (1 mg/kg). The patient was also consulted with the dermatology department, and a possible early secondary infection related to the non-sterile injection procedure was also considered. Treatment was initiated with 1 mg/kg/day oral methylprednisolone, 10 mg/day oral cetirizine for 3 days, and 2000 mg/day amoxicillin-clavulanate for 10 days. At the outpatient clinic check-up two weeks later, it was observed that the findings of infection and inflammation had significantly regressed.

Discussion

In this report, we presented an adolescent patient who developed an acute inflammatory reaction following the intradermal injection of a topical HA product, influenced by skincare content shared on social media platforms.

Several diagnostic possibilities should be considered in such presentations. An acute allergic or irritant reaction may present with rapid-onset erythema and edema, particularly when cosmetic ingredients are introduced into the dermis rather than applied topically. In contrast, a foreign-body-type inflammatory reaction is supported by the direct intradermal deposition of HA and cosmetic excipients into tissue, especially when the preparation is not designed or validated for injection. Early bacterial infection is also an important consideration after any non-sterile injection, particularly in the centrofacial region; however, in our patient, the very rapid onset, absence of fever or purulent discharge, normal laboratory parameters, and favorable clinical course without abscess formation suggested that acute inflammation predominated over established infection. Because histopathological examination and microbiological culture were not performed, the diagnosis should be interpreted as a clinical foreign-body-type inflammatory reaction with possible early secondary infection rather than histologically proven granulomatous inflammation.

Over the past decade, social media usage among children and adolescents has increased substantially. Alongside this rise, skincare products have become widely marketed across these platforms, particularly through short-form video applications such as TikTok. Recent studies have noted a growing interest in pediatric skincare routines within this demographic, often driven by influencers and unverified online content (5,6). These trends have led to the unsupervised use of dermatological products, posing potential clinical risks.

Brinks et al. (5) highlighted that skincare products disseminated on social media—especially among adolescents—are frequently adopted without medical guidance or safety evaluation. Similarly, Hales et al. (4) reported that many pediatric skincare videos shared on TikTok promoted products unsuitable for children's skin physiology, with only 26.2% recommending sunscreen use. In their content analysis, a significant number of potential contact allergens were identified, raising concerns regarding allergic contact dermatitis and irritant reactions. While the 2023 guidelines from the American Academy of Pediatrics (AAP) emphasize that pediatric skincare products should be fragrance-free, dye-free, and hypoallergenic, current online content rarely reflects these evidence-based recommendations (7).

The clinical presentation in our case—marked facial erythema and periorbital edema following the injection of a topical HA serum—illustrates an emerging and underrecognized risk pattern. The use of a product not intended for injections, combined with non-sterile technique and lack of training, resulted in a significant inflammatory response requiring systemic therapy. This type of application appears to align with "do-it-yourself filler" videos that have gained

popularity on TikTok (8). While filler-related complications are more frequently reported in adults, the imitation of these procedures by adolescents introduces new safety concerns in the pediatric population (6,9).

Our patient stated that she had seen this procedure in a TikTok video, had never performed such an injection before, and was unaware of the exact composition of the substance she was administering. This emphasizes not only the vulnerability of adolescents to misleading content but also the absence of appropriate filters or warnings on widely accessed platforms. The case exemplifies how unregulated aesthetic experimentation can lead to serious dermatologic complications and necessitate emergency care.

Raising awareness among parents, educators, and healthcare professionals is critical in addressing these emerging trends. Promoting evidence-based skincare education and improving the visibility of pediatric-specific recommendations on digital platforms may serve as an effective preventive strategy (4). Furthermore, clinicians should remain vigilant about nontraditional causes of dermatologic presentations in adolescents and proactively inquire about social media influences during history-taking.

Conclusion

In conclusion, this case highlights the clinical risks associated with unsupervised, social media-driven skincare behaviors in adolescents. Pediatricians and pediatric emergency physicians should adopt an education-centered approach and remain alert to the evolving impact of digital media on health behaviors. Documenting and sharing similar cases will enhance clinical awareness and help address existing gaps in literature.

Contribution of the authors

Study concept and design: FŞE, AG, OA; Analysis and interpretation of data: FŞE, BA; Drafting of the manuscript: FŞE, AG; Critical revision of the manuscript for important intellectual content: FŞE, NT.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Consent for publication

Written informed consent for publication was obtained from the patient's parents.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Levetiracetam in childhood epilepsy: Expanding the evidence base"

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Received : 26.04.2026, Accepted : 06.05.2026 DOI: 10.12956/TJPD.2026.1354

Introduction

We read with genuine interest the article by Toksöz and Teber recently published in the Turkish Journal of Pediatric Disease, which presents long-term efficacy and safety data on levetiracetam (LEV) monotherapy in 101 children managed at a tertiary pediatric neurology centre (1). The reported seizure-response rate of 72.3%, with complete seizure freedom in 38.0% of patients, positions this study squarely within the broader real-world evidence base and confirms LEV's standing as a first-line antiseizure medication (ASM) in childhood epilepsy. Particularly clinically useful is the identification of age over four years and low pre-treatment seizure frequency as independent predictors of a favourable response—two stratification criteria that translate directly into day-to-day prescribing decisions. Yet, precisely because this paper contributes to a growing corpus of retrospective evidence on LEV, it also highlights several dimensions that deserve more rigorous prospective investigation.

To begin with, situating the results of Toksöz and Teber within the comparative effectiveness literature raises questions that a single-arm retrospective design cannot resolve. A systematic review and meta-analysis of four randomised controlled trials including 381 children demonstrated that LEV monotherapy was associated with a significantly lower frequency of at least one seizure and a 76% reduction in dermatological adverse events relative to carbamazepine (CBZ), while seizure-freedom rates did not differ significantly between the two agents (2). This context matters: an overall response rate of 72.3% is meaningful, but without a comparator arm—whether historical or concurrent—it remains difficult to determine whether this figure reflects a drug effect, a patient-selection effect, or an institutional effect. A large Turkish tertiary centre cohort of 281 children treated with LEV monotherapy across a decade found seizure reduction rates that, while broadly consistent with the current paper, varied substantially by epilepsy aetiology—ranging from idiopathic to symptomatic and cryptogenic forms (3). Heterogeneity in patient mix is therefore a critical variable, and its underreporting limits how far the findings of Toksöz and Teber can be generalised to other settings, Table I summarises the efficacy and adverse-event profiles across the major cohorts and meta-analyses cited in this commentary, placing the index study in comparative perspective.

A closely related limitation concerns the absence of structured epilepsy syndrome classification in the cohort. The International League Against Epilepsy (ILAE) 2017 framework—distinguishing focal, generalised, combined generalised-and-focal, and unknown epilepsies—is not a bureaucratic formality; it carries direct and differential therapeutic implications (4). LEV holds regulatory approval as adjunctive therapy for focal-onset seizures and juvenile myoclonic epilepsy, but its behaviour across syndrome subtypes diverges in ways that aggregate response rates flatten into invisibility. A head-to-head systematic review and meta-analysis comparing LEV versus oxcarbazepine in children found that focal epilepsy subgroups drove most of the seizure-free advantage observed with LEV, while outcomes in other syndromic categories were considerably narrower (5). The clinical decision that a practitioner makes when initiating LEV in a child with Rolandic epilepsy—a syndrome with a favourable natural history regardless of treatment—should not be conflated with the decision made for a child with drug-resistant generalised epilepsy. Disaggregating outcomes by ILAE-classified syndrome type is not merely a methodological nicety; it is the minimum granularity needed to transform observational data into actionable prescribing evidence. Future work from this group should prioritise syndrome classification at enrolment.

The adverse-event profile documented by Toksöz and Teber —45.5% of patients affected, with drowsiness, irritability, and fatigue predominating—is numerically consistent with prior series (6). The published literature, however, draws attention to a dimension of LEV toxicity that chart-based retrospective ascertainment systematically underestimates: the neuropsychiatric spectrum. Behavioural dysregulation under LEV, encompassing irritability, emotional lability, hyperactivity, and, in a minority of cases, frank psychotic symptoms, has been documented in up to 37.6% of pediatric patients in series that used structured ascertainment methods (7). A systematic

Table I: Comparison of levetiracetam efficacy and adverse-event profiles across selected pediatric epilepsy cohorts and meta-analyses cited in this commentary.

Study / Country	N	Design	Mean age	Efficacy (%)	Seizure freedom (%)	Adverse events (%)
Martins et al. (2) Brazil	381 (4 RCTs)	SR & meta-analysis	7.3–9.3 yr	LEV = CBZ (seizure freedom)	~85% vs ~75% (ns)	Derm. AE: LEV < CBZ*
Liu et al. (5) China	Pooled RCTs	SR & meta-analysis	Children	LEV > OXC (focal subgroup)†	NR	No significant difference
Halma et al. (8) Netherlands	727 (13 studies)	Systematic review	1 mo – 18 yr	Not primary outcome	Not reported	Behav. AE: RR 2.18 vs placebo‡
Toksöz and Teber (1) Türkiye	101	Retrospective cohort	NR (>4 yr: predictor)	72.3	38.0	45.5
Yıldırım et al. (3) Türkiye	281	Retrospective cohort	Mean 9 yr	~74%	~40%	~18%
Hadzagic Catibusic et al. (6) Bosnia-Herzegovina	NR (15-yr cohort)	Prospective cohort	>1 month	NR	NR	Comparable to (1)
Ganjikunta et al. (7) India	Case series	Retrospective	Mixed	—	—	Psychiatric AE: up to 37.6%
Verrotti et al. (10) Italy	Review	Narrative review	Children	Summary of cohort data	Variable	PK: faster clearance <4 yr

:** *Dermatological adverse events: RR 0.24 (95% CI 0.09–0.64; p<0.010) in favour of LEV,* **†:** *LEV showed superior seizure-free rates vs. OXC in the focal epilepsy subgroup; no significant difference in generalised epilepsy subgroups,* **‡:** *Behavioural adverse events vs. placebo across 13 studies (n=727); hostility, nervousness, and aggression predominated.* ***N: *sample size,* ***NR :*** *not reported,* ***OXC:*** *oxcarbazepine,* ***CBZ:*** *carbamazepine,* ***LEV:*** *levetiracetam,* ***RCT:*** *randomised controlled trial,* ***SR****: systematic review,* ***AE:*** *adverse event,* ***Derm.:*** *dermatological,* ***Behav.:*** *behavioural,* ***PK:*** *pharmacokinetic,* ***ns:*** *not significant,* ***mo:*** *months,* ***yr:*** *years.*

review specifically examining behavioural side effects in children on LEV confirmed a statistically significant relative risk of 2.18 for total behavioural adverse events compared to placebo—hostility, nervousness, and aggression being the most frequently reported domains (8). These reactions are not trivial. A child whose seizures are controlled but who becomes aggressive, oppositional, or emotionally dysregulated has not simply 'tolerated' the drug; the family's quality of life has been exchanged for seizure freedom, which is a different clinical outcome entirely. Neurodevelopmental comorbidities magnify this risk: children with pre-existing cognitive or psychiatric vulnerabilities are disproportionately susceptible to LEV-related behavioural deterioration, a factor impossible to fully control for in retrospective designs (9). Integrating standardised tools—the Child Behavior Checklist (CBCL) or the Strengths and Difficulties Questionnaire (SDQ)—at baseline and at each scheduled visit would allow future studies to detect these effects early and systematically, before they become reasons for treatment discontinuation rather than data points in the record.

A dimension not discussed by Toksöz and Teber, yet central to understanding long-term LEV performance in children, is the concept of treatment retention as an integrated measure of efficacy and tolerability. In a real-world European pediatric cohort, the one-year LEV continuation rate was estimated at 72%, with insufficient efficacy—rather than adverse events—accounting for the majority of discontinuations. This architecture of drug attrition carries a practical message: achieving initial seizure control is necessary but not sufficient; sustaining it without accumulated tolerability burden is the harder clinical problem. Age-specific pharmacokinetic variability compounds this challenge. LEV clearance in young children is substantially faster than in adults, resulting in lower plasma concentrations at standard weight-based doses and potentially explaining some of the apparent efficacy ceiling observed in younger age groups—a finding that aligns with the age-related predictor identified by Toksöz and Teber (10). Prospective designs incorporating therapeutic drug monitoring would allow disentanglement of pharmacokinetic from pharmacodynamic sources of treatment failure, a distinction with direct therapeutic implications for dose adjustment strategies in the under-four age group.

A final perspective, critical from a global pediatric neurology standpoint, concerns the generalisability of these findings beyond well-resourced tertiary settings. A systematic review and meta-analysis estimated the prevalence of childhood epilepsy in sub-Saharan Africa at 7.8 per 1000 population, with treatment gaps exceeding 80% in several regions (11). The recent inclusion of LEV on the WHO Essential Medicines List was a meaningful step, yet access remains constrained in low-and middle-income countries (LMICs) by drug cost, cold-chain logistics, and the scarcity of trained pediatric neurologists (12). A scoping review of epilepsy care outcomes in LMICs underscored that real-world effectiveness data generated in Turkish or European tertiary centres cannot be uncritically transposed to contexts where EEG is unavailable, neuroimaging is sporadic, and the interval between seizure onset and specialist consultation may span years (13). The cohort of Toksöz and Teber does not report on diagnostic delays, socioeconomic stratification, or access-related variables—all of which shape LEV outcomes in resource-limited settings in ways that standard efficacy metrics do not capture. Collaborative networks linking high-income and LMIC centres could help establish globally representative benchmarks and identify which elements of current management protocols are feasibly exportable, Figure 1 proposes a syndrome-stratified, neurobehaviourally monitored prospective framework that could serve as a blueprint for such collaborative efforts.

In summary, the study by Toksöz and Teber makes a genuine and valuable contribution: it provides real-world evidence of LEV's efficacy in a sizeable pediatric cohort, documents the adverse-event landscape with clinical honesty, and offers two stratification criteria with immediate utility at the point of prescribing. The path to a more complete understanding of LEV in childhood epilepsy runs through syndrome-specific

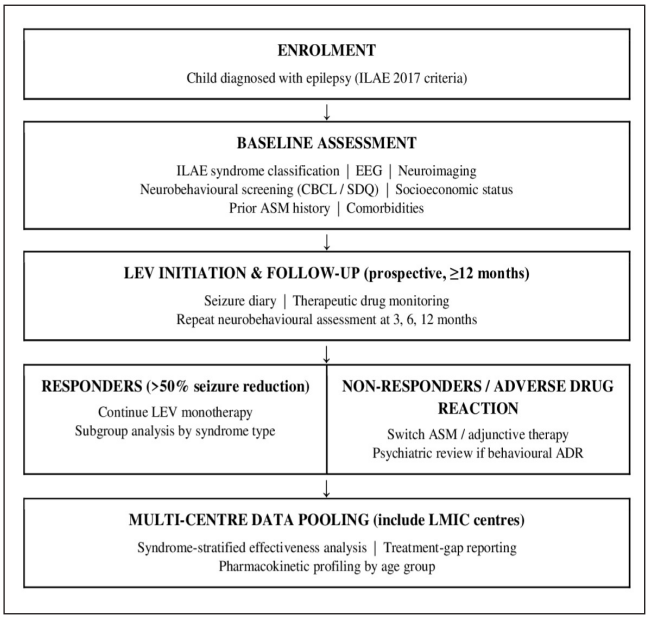

Figure 1: Proposed framework for a syndrome-stratified, neurobehaviourally monitored prospective evaluation of levetiracetam in pediatric epilepsy. **ILAE:** International League Against Epilepsy, **EEG:** electroencephalogram, **ASM:** antiseizure medication, **LEV:** levetiracetam, **ADR:** adverse drug reaction, **CBCL:** Child Behavior Checklist, **SDQ:** Strengths and Difficulties Questionnaire, **LMIC:** low- and middle-income country

prospective designs, standardised neurobehavioural monitoring incorporated from enrolment, retention and therapeutic drug monitoring analyses, and deliberate cross-centre collaboration that places these findings within a global epidemiological frame. Levetiracetam has more than justified its first-line status; the question of for whom, at what dose, and at what neuropsychiatric cost remains, in meaningful ways, open.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Prevalence and clinical predictors of sleep disturbances in children with seasonal allergic rhinitis"

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Received : 14.07.2026, Accepted : 24.08.2026 DOI: 10.12956/TJPD.2026.1408

Introduction

In the latest issue of the Turkish Journal of Pediatric Disease, Aytekin Güvenir et al. (1) evaluated the prevalence and clinical predictors of sleep disturbances in children with seasonal allergic rhinitis (SAR). The authors reported that 44.3% of children with SAR had clinically significant sleep disturbances and that the total and subscale scores of the Sleep Disturbance Scale for Children (SDSC) were higher in children with SAR than in healthy controls. In the multivariate analysis, a higher nasal visual analogue scale (VAS) score remained independently associated with sleep disturbances. The study offers useful insight into sleep disturbances among children with SAR. The evaluation of different SDSC subscales also provides valuable information by demonstrating that sleep-related difficulties in these children may extend beyond sleep-related breathing disorders.

Apart from the study limitations acknowledged by the authors, we would like to highlight several points that may be relevant when interpreting the findings. The relationship between the ARIA severity classification and sleep outcomes may merit consideration. Since impaired sleep quality is itself one of the criteria used to classify rhinitis as moderate-to-severe, some children may have been assigned to the more severe category partly or solely on the basis of impaired sleep quality. Although the grouping variable in Table III is labelled as "sleep disorders," the identical number of affected children reported according to the SDSC threshold and in Table III (n=51) suggests that the groups were defined on the basis of SDSC-defined sleep disturbance. This definitional overlap may have contributed to the observed association between rhinitis severity and SDSC-defined sleep disturbance. We would therefore be interested to know how many children met the moderate-to-severe classification because of impaired sleep quality alone or together with other ARIA criteria. It would also be informative to know whether the association was explored after excluding the sleep-related criterion from the severity classification. Clarification of these points would help contextualize the reported association between rhinitis severity and sleep disturbance.

Although the SDSC captures different manifestations of sleep disturbance, contemporary pediatric sleep-health frameworks conceptualize sleep as a product of interacting biological, behavioral, developmental, familial, environmental, and social influences. Children's sleep occurs within a dynamic socioecological system in which the child may have limited control over sleep schedules, routines, environmental conditions, and opportunities for healthy sleep (2, 3). In this context, we would be interested to know whether other factors that may influence pediatric sleep, such as screen exposure, physical activity, sleep schedules and bedtime routines were also considered or recorded during the study (4-6). Such factors may contribute to sleep outcomes independently or may form part of the pathway linking allergic symptoms to sleep; for example, children with more severe symptoms may spend less time outdoors, engage in less physical activity, or experience changes in screen use and bedtime routines. Any available information regarding these variables could provide further context for interpreting the finding that nasal VAS score was the only independently associated factor in the model.

The broad age range of 6–16 years may also deserve consideration, as sleep patterns and their determinants differ between school-aged children and adolescents. Age-related differences in circadian timing, bedtime autonomy, school demands, screen use, and pubertal development may influence both baseline sleep characteristics and the association between allergic symptoms and sleep disturbance (7). We would therefore be interested to know

whether sleep outcomes and their clinical associations were also explored separately in school-aged children and adolescents. Such information, if available, could provide additional context regarding the consistency of the findings across developmental stages.

Irrespective of these considerations, the study provides valuable evidence supporting the routine assessment of sleep health in children with SAR. Following the identification of a sleep concern, extending the clinical evaluation beyond allergic symptoms to include relevant child-, family-, behavioral-, and environmental factors may enable a more comprehensive understanding of the child's sleep difficulties.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Response to comments " Prevalence and clinical predictors of sleep disturbances in children with seasonal allergic rhinitis"

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Received : 30.07.2026, Accepted : 25.08.2026 DOI: 10.12956/TJPD.2026.1417

We sincerely thank the authors for their thoughtful comments and for their interest in our article entitled "Prevalence and Clinical Predictors of Sleep Disturbances in Children with Seasonal Allergic Rhinitis." We appreciate their constructive observations, which provide an opportunity to further clarify the interpretation of our findings.

The authors raise an important methodological point regarding the potential conceptual overlap between the Allergic Rhinitis and its Impact on Asthma (ARIA) severity classification and the Sleep Disturbance Scale for Children (SDSC). We agree that impaired sleep is one of the components considered when classifying allergic rhinitis as moderate-to-severe according to the ARIA guidelines, and therefore some degree of overlap between disease severity and sleep outcomes is theoretically possible. Regarding the specific question of how many children fulfilled the moderate-to-severe ARIA classification solely because of sleep impairment, this information was unfortunately not available, as we evaluated only the overall ARIA severity classification and did not record the individual criteria contributing to disease severity separately. We agree that evaluating disease severity after excluding the sleep-related criterion would represent a valuable methodological approach and could further clarify this relationship in future studies.

The authors also appropriately emphasize that pediatric sleep health is influenced by multiple biological, behavioral, familial, environmental, and developmental factors. We fully agree with this broader perspective. Variables such as screen exposure, physical activity, bedtime routines, and sleep hygiene were not systematically collected, as they were beyond the predefined scope of our study, which primarily focused on the relationship between allergic disease characteristics and sleep disturbances. We acknowledge that these factors may influence sleep quality independently or interact with allergic symptoms, and their inclusion in future prospective studies would provide a more comprehensive understanding of sleep health in children with seasonal allergic rhinitis.

Similarly, we appreciate the authors' comments regarding the broad age range of our study population. We agree that sleep characteristics and their determinants may differ between school-aged children and adolescents owing to developmental and behavioral changes. Participants aged 6–16 years were included in the study because the assessment tool used has been validated for this age range. Furthermore, 78 of the 115 participants (67.8%) were aged 10 years or older, indicating that the study population predominantly consisted of older children and adolescents. Although age was recorded as a demographic variable, age-stratified analyses were not prespecified in our study, and the age groups were therefore not analyzed separately. We believe that future studies specifically designed to evaluate developmental differences across age groups would provide valuable additional insight into the relationship between allergic rhinitis and sleep disturbances.

Once again, we thank the authors for their insightful comments and for highlighting important considerations regarding the interpretation of pediatric sleep research. We believe these observations complement our findings and further emphasize the importance of adopting a comprehensive approach when evaluating sleep health in children with seasonal allergic rhinitis.