Turkish Journal of Pediatric Disease

Volume 20 Number 4 July 2026

TJPD Turkish Journal of Pediatric Disease

Turkish Journal of Pediatric Disease

Türkiye Çocuk Hastalıkları Dergisi

Turk J Pediatr Dis

Volume 20 • Number 4 • July 2026

https://turkjpediatrdis.org

ISSN 1307-4490
E-ISSN 2148-3566

Turkish Journal of Pediatric Disease

ISSN: 1307-4490
E-ISSN 2148-3566

Vol.20, No.4, July 2026

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

Vol.20, No.4, July 2026

Turkish Journal of Pediatric Disease

TJPD

Owner on Behalf of the Ankara Bilkent City Hospital Children's Hospital

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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 : 24.07.2026

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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Turkish Journal of Pediatric Disease

Original Article

Bronchoalveolar lavage: A key tool in pulmonary fungal infection management

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Received : 23.10.2025, Accepted : 02.03.2026
DOI: 10.12956/TJPD.2026.1255

ABSTRACT

Objective: Bronchoalveolar lavage (BAL) is a widely used diagnostic tool for evaluating lower respiratory tract infections and pulmonary pathologies in children. BAL provides valuable diagnostic information and can significantly influence management strategies, particularly in patients with malignancy, immunodeficiency (ID), or critical illness. This study aimed to assess the diagnostic and therapeutic value of BAL in pulmonary fungal infections.

Material and Methods: This retrospective study analyzed BAL samples obtained by flexible fiberoptic bronchoscopy (FFB) between 2019 and 2024 in the Pediatric Pulmonology Department of a tertiary referral center. Among 668 patients who underwent FFB, those with BAL fungal culture, BAL *Aspergillus* DNA PCR, and BAL galactomannan antigen (GM) testing were included. Demographic, clinical, radiological, and bronchoscopic findings, as well as antifungal treatment modifications based on BAL results, were evaluated.

Results: BAL results from 668 patients were reviewed. Fungal culture was performed in 236 (35.3%), *Aspergillus* DNA PCR in 127 (19%), and GM in 121 (18.1%) patients. Among those tested for fungal culture, 58.9% were male, with a mean age of 7.0 years (±5.7). Fungal culture positivity was found in 26 (11%) patients: *Candida albicans* (n=14), *Aspergillus spp.* (n=5), *Candida dubliniensis* (n=3), *Aspergillus* fumigatus (n=3), and *Penicillium spp.* (n=1). Culture positivity was significantly higher in patients with malignancy (p=0.011). BAL *Aspergillus* DNA PCR was positive in two patients, and BAL GM in five. Based on BAL results, antifungal therapy was modified in seven patients.

Conclusion: BAL fungal culture, BAL GM, and *Aspergillus* PCR testing are valuable diagnostic tools for pulmonary fungal infections in children, especially those with malignancy or immunodeficiency (ID). The observed treatment modifications following BAL results emphasize their clinical importance not only in establishing diagnosis but also in guiding and optimizing antifungal therapy.

Keywords: *Aspergillus, candida,* bronchoalveolar lavages, bronchoscopy, pulmonary fungal infections

Introduction

Bronchoalveolar lavage (BAL) is a commonly used and relatively safe diagnostic procedure for evaluating patients with lung disease. When conventional assessments such as clinical history, physical examination, laboratory tests, pulmonary function testing, and imaging are inconclusive, BAL provides valuable diagnostic information (1-3). In children with underlying conditions such as ID, critical illness, or malignancy—where the incidence of opportunistic infections is increased—BAL plays a crucial role in guiding management strategies (4-6).

Bronchoalveolar lavage provides valuable etiological information in suspected pulmonary infections when noninvasive diagnostic methods are inconclusive. Microbiological analysis of bronchoalveolar lavage fluid supports targeted antimicrobial therapy and informs clinical management (7-9). Fungal infections represent a significant proportion of pulmonary infections in high-risk patients, and

bronchoalveolar lavage fluid analysis plays an important role in their diagnosis (10).

Fungal infections are becoming increasingly prevalent, particularly among immunocompromised patients and those with malignancies. Despite the availability of new drugs, mortality rates from fungal infections remain high in these patient groups (11). In various population-based studies, the positivity rate of fungal cultures from BALF obtained through FFB has been reported to range from 16% to 73% (12,13). In these studies, Candida species have been consistently reported as the most commonly isolated organisms in patients with positive fungal cultures from BALF (5,6). Immunocompromised patients with candidemia have a 40% mortality rate. The mortality rate attributable to invasive aspergillosis ranges from 30% to 70% (14,15).

Although fungal culture samples are sent from BALF for diagnosis of fungal infections, the newly developed polymerase chain reaction (PCR) method has provided a powerful tool to improve the detection and identification of fungal pathogens in clinical microbiology practice (16). The galactomannan antigen (GM) assay is essential for diagnosing invasive fungal infections, particularly in immunocompromised patients and those with hematological malignancies (14).

This study aimed to highlight the role of BALF in the diagnosis and assessment of pulmonary fungal infections.

Materials and Methods

This study retrospectively evaluated BALF results obtained via FFB in the Pediatric Pulmonology Ankara Bilkent City Hospital between January 2019 and December 2024. The BALF results of 668 patients who underwent FFB during this period were analyzed. The study included those for whom BAL fungal culture, BAL *Aspergillus* DNA PCR, and BAL GM tests were performed. The demographic data, clinical findings, laboratory results, radiological examination results, treatment, and follow-up of these patients were examined using the hospital's digital record system. The indications for FFB were evaluated and grouped according to etiology. The patients' BAL fungal culture, BAL *Aspergillus* DNA PCR, and BAL GM results, as well as the antifungal treatments or prophylaxis they received, were evaluated. All bronchoscopy procedures and clinical decisions regarding the indication for bronchoscopy were made and performed by the same experienced team throughout the study period in order to ensure consistency. In patients with significant underlying comorbidities such as ID or malignancy, prolonged hospitalization, or strong clinical suspicion of fungal infection, additional tests including fungal culture, *Aspergillus* PCR, and GM assay were requested from BAL fluid. Furthermore, in patients hospitalized due to malignancy who had positive serum GM or serum *Aspergillus* PCR results, BAL *Aspergillus* PCR and BAL GM testing were also specifically performed.

Informed consent for bronchoscopy procedure was obtained from the parents of all patients. Prior to the procedure, informed preoperative anesthesia consent was obtained and a fasting period of at least eight hours was ensured. The procedure was performed under operating room conditions. General anesthesia was administered by an anesthesiologist, and ventilation was maintained using a laryngeal mask airway. A fiberoptic bronchoscope appropriate for the patient's age and body weight was selected and advanced through the laryngeal mask airway to perform the FFB.

Statistical analysis

Statistical analysis were performed using the IBM Statistical Package, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Numerical data with a normal distribution were expressed as the mean and standard deviation. Percentages (%) and numbers (n) were used to express categorical variables. Categorical variables were analyzed using the Chi-Square test. Age was analyzed using the Independent Samples t-test. In all statistical tests, $p < 0.050$ was considered statistically significant.

Results

Patient characteristics and sample overview

BAL results from 668 patients who underwent FFB during the study period were evaluated. BAL fungal culture was requested for 236 (35.3%), BAL *Aspergillus* DNA PCR for 127 (19%), and BAL GM for 121 (18.1%) patients. Of the 236 patients tested for fungal culture, 139 (58.9%) were male and 97 (41.1%) were female, with a mean age of 7.0±5.7 years. The mean ages of female and male patients were 7.6±5.9 years and 6.5±5.2 years, respectively, with no significant age difference between the genders (p=0.960).

FFB indications and underlying diseases

The indications for FFB and the underlying diagnoses of the 236 patients who underwent BAL for fungal culture were analyzed. Among these, 35 (14.8%) patients had ID, 22 (9.3%) had malignancy, and 56 (23.7%) presented with atelectasis. A history of lower respiratory tract infection (LRTI) was documented in 78 (33.0%) patients, and 33 (13.9%) were evaluated for suspected interstitial lung disease or bronchiolitis obliterans (ILD/BO). FFB was also performed in six (3.2%) patients with a history of tracheoesophageal fistula (TEF), in three (1.6%) patients due to extubation intolerance, and in three (1.6%) patients presenting with stridor.

Radiological imaging findings of patients undergoing FFB

Thoracic computed tomography (CT) was available for 197 out of the 236 patients who underwent BAL fungal culture testing. Radiological findings included fibroatelectatic changes (n=76), ground-glass opacities (n=61), bronchiectasis (n=57), consolidation (n=29), nodular infiltrates (n=18), mosaic perfusion pattern (n=9), pleural

effusion (n=6), and mass-like lesions (n=5). Several patients demonstrated multiple radiological findings. CT scans were reported as normal in seven (2.9%) patients.

FFB findings of patients undergoing FFB

The FFB findings of the 236 patients who underwent BAL fungal culture were classified. Purulent or seropurulent secretions were observed in 115, tracheomalacia/bronchomalacia in 31, anatomical airway stenosis in 28, increased vascularity in 12, postoperative findings related to TEF in six, mucosal pallor in five, and granulation tissue in four patients. Other, less common findings (seen in a total of 18 patients) included epiglottic edema, tracheal mucosal folds, tracheal dyskinesia, hemorrhage, subglottic stenosis, polypoid structures, mucosal lesions, pulsatile masses, white mucosal plaques, and fibrinoid tissue.

Evaluation of fungal culture results according to ffb indications, ct findings, and FFB findings

Fungal culture positivity was detected in 26 of the 236 patients for whom BAL fungal culture testing was requested (11%). *Candida albicans* was identified in 14 patients, *Aspergillus* species in five, Candida dubliniensis in three, *Aspergillus* fumigatus in three patients, and Penicillium species in one patient.

Among these 26 patients, malignancy was the most frequent underlying condition (six patients, 23%), followed by atelectasis and LRTI (five patients each, 19.3%). ID and bronchiectasis were present in three patients each (11.6%), and hemoptysis in two patients (7.6%). Tuberculosis and sarcoidosis were each diagnosed in one patient (3.8%). In patients who underwent FFB due to malignancy, BAL fungal culture positivity was more frequent compared to other indications (72.7% vs. 27.3%, p=0.011). There was no significant difference in the distribution of cultured fungal pathogens between immunodeficient patients and those with malignancies. BAL fungal culture positivity according to FFB indications and underlying diseases are summarized in Table I.

Fungal culture positivity varied according to thoracic CT findings: 55.5% (10/18) in patients with nodular infiltration, 33.3% (2/6) with pleural effusion, 8.7% (5/57) with bronchiectasis, 11.4% (7/61) with ground-glass opacities, and 7.9% (6/76) with atelectasis. Patients were then grouped based on the presence or absence of nodular infiltration and/or ground-glass opacities. BAL fungal culture positivity was significantly higher in patients with these findings compared to those without (60.9% vs. 39.1%, p <0.010).

Table I: BAL fungal culture positivity according to FFB indications and underlying diseases

Bronchoscopy indications	BAL Fungal Culture		p†
	Positive	Negative	
Malignancy*	6 (27.3)	16 (72.7)	0.011
ID*	3 (8.6)	32 (91.4)	0.617
Atelectasis*	3 (5.4)	53 (94.6)	0.147
Recurrent LRTI*	10 (12.8)	68 (87.2)	0.517
Suspected ILD/BO*	3 (9.1)	30 (90.9)	0.703

:** *n(%),* **†:** *Chi-Square test,* ***LRTI: *Lower Respiratory Tract Infection,* ***ILD:*** *Interstitial Lung Disease,* ***BO:*** *Bronchiolitis Obliterans,* ***ID:*** *Immunodeficiency*

Table II: BAL fungal culture positivity according to FFB findings

Bronchoscopic findings	BAL fungal culture		p‡
	Positive	Negative	
Purulent or seropurulent secretions*	20 (17.4)	95 (82.6)	0.002
Tracheomalacia/bronchomalacia*	2 (6.5)	29 (93.5)	0.384
Anatomical airway stenosis*	3 (10.7)	25 (89.3)	0.957
Mucosal pallor*	0 (0.0)	5 (100.0)	0.426
Postoperative findings related to TEF*	0 (0.0)	6 (100.0)	0.383
Granulation tissue*	1 (25.0)	3 (75.0)	0.368
Increased vascularity*	0 (0.0)	12 (100.0)	0.211
Other*†	0 (0.0)	18 (100.0)	0.120

:** *n(%),* **†:** *Epiglottic edema, tracheal mucosal folds, tracheal dyskinesia, hemorrhage, subglottic stenosis, polypoid structures, mucosal lesions, pulsatile masses, white mucosal plaques, fibrinoid tissue etc,* **‡:** *Chi-Square test,* ***TEF: *tracheoesophageal fistula*

BAL fungal culture positivity was evaluated according to FFB findings. Patients in whom purulent or seropurulent secretions were observed on FFB had a higher frequency of positive fungal cultures compared to those with other findings (82.6% vs. 17.4%, p=0.002). BAL fungal culture positivity according to FFB findings is summarized in Table II.

Antifungal prophylaxis and treatment use at the time of FFB

Among patients for whom BAL fungal cultures were requested, 21 (8.9%) were receiving antifungal prophylaxis at the time of FFB (10 on fluconazole, seven on voriconazole, and four on itraconazole). Of these, 13 had ID and eight had malignancy. BAL fungal cultures were negative in 17 patients receiving prophylaxis. In four patients receiving prophylaxis, BAL fungal culture positivity was detected; therefore, prophylaxis was discontinued, and a new antifungal treatment was initiated.

Additionally, 25 (10.5%) patients were receiving antifungal treatment at the time of FFB. Among these, 23 (92%) had negative fungal cultures. Antifungal treatment decisions were made collaboratively with the pediatric infectious diseases team based on clinical status, infection markers, and lung imaging. Antifungal treatment was modified in two patients due to positive fungal cultures with *Aspergillus* species, specifically *Aspergillus* fumigatus. Out of 26 patients with positive fungal culture, three (11%) died; two of them had ID, and one had an underlying malignancy.

BAL *Aspergillus* DNA PCR and BAL galactomannan antigen test results

BAL *Aspergillus* DNA PCR was positive in two patients. One patient, diagnosed with acute lymphoblastic leukemia and not on antifungal treatment or prophylaxis, started voriconazole after the positive PCR result; this patient also had fungal culture positivity. The other patient, diagnosed with chronic granulomatous disease analysis and not receiving antifungal therapy, was started on voriconazole following PCR positivity despite a negative fungal culture. Both patients had purulent or seropurulent secretions observed during FFB and nodular infiltrates on thoracic CT. Their BAL GM tests were also positive.

In addition to these two patients, three more had positive BAL GM results. One patient with ID was started on amphotericin B after the positive outcome. Another patient with malignancy and fungal culture positivity was receiving voriconazole at the time of FFB; treatment was not changed due to clinical stability. The third patient, also with malignancy and on voriconazole, continued treatment as clinical status remained stable.

Discussion

In our study, we demonstrate that BAL findings significantly influenced treatment decisions in patients evaluated for pulmonary fungal infections. Notably, BAL fungal culture positivity was significantly more frequent in patients undergoing FFB for malignancy than in other patient populations. Evaluation of culture positivity based on FFB findings revealed that patients with observed purulent or seropurulent secretions had a significantly higher rate of BAL fungal culture positivity. Fungal culture positivity was more frequent in patients presenting with nodular infiltration and/or ground-glass opacities on thoracic CT. Despite receiving antifungal prophylaxis, some patients required modifications in antifungal therapy due to positive BAL fungal culture results.

A study involving 35 pediatric patients in the intensive care unit (ICU) evaluated BAL fungal cultures, *Aspergillus* PCR, GM and Candida mannan antigen. The majority of patients had malignancies and had been hospitalized in the ICU for more than one week. Chest radiography was the primary imaging modality, with patchy consolidations and nodular lesions being the most common findings (17). BAL fungal cultures were positive in 15 patients: *Candida spp*. in 12, *Aspergillus spp*. in one, and both in two patients (17). In our study, similar to the referenced study, culture positivity was more frequent in patients with malignancy, and *Candida spp*. was the most commonly isolated organism. However, the BAL culture positivity rate in our study was slightly lower than that reported in other studies (12,13,17). This difference may be attributed to variations in patient populations, as our cohort included not only hospitalized patients but also clinically stable outpatients who underwent FFB. Also, some patients who underwent FFB may have had no detectable pathogens due to antifungal therapy at the time of the procedure.

In a study involving 101 patients with malignancy who were evaluated for suspected pulmonary fungal infection, 24 patients underwent BAL, 31 underwent biopsy (27 lung, 4 sinus), and 46 were assessed by thoracic CT for diagnostic purposes (18). Among the 38 patients with thoracic CT findings suggestive of fungal infection, antifungal treatment was modified in 30 cases. Treatment changes were also made in two of the six patients with positive BAL fungal cultures and in four of the 12 patients with biopsy-confirmed fungal infection (19). In another study conducted on adult patients, fungal growth was detected in 16% of cases; antifungal therapy was initiated in 15% of these patients, and treatment was modified in 7% (13). Similar to the referenced studies, our cohort also exhibited changes in antifungal treatment in a total of seven (26%) patients due to BAL results. These changes demonstrate the impact of BAL results on the regulation of treatment.

In a study conducted on adult solid organ transplant recipients, 131 BAL samples were evaluated. BAL fungal cultures were positive in 24 patients, and BAL *Aspergillus* PCR was positive in nine patients (13). None of the BAL GM tests were positive. Based on clinical and radiological findings, BAL *Aspergillus* PCR demonstrated moderate sensitivity and high specificity for the diagnosis of fungal infections (13). In another study, BAL samples obtained from 1736 FFB procedures in 688 ICU patients diagnosed with pneumonia were evaluated (20). *Aspergillus spp* was identified in 18 of 968 BAL fungal cultures, and 53 of 1146 BAL GM samples tested positive. Due to technical limitations, *Aspergillus* PCR was not performed (20). While the BAL GM positivity rate in that study was comparable to that observed in our cohort, the proportion of patients with *Aspergillus spp* in BAL fungal cultures was slightly higher in our center (3.4% vs. 1.9%). This difference may be attributed to variations in patient selection and the underlying burden of comorbidities. The findings highlight the importance of not only BAL fungal culture but also BAL GM and BAL *Aspergillus* PCR tests in supporting the diagnosis of suspected pulmonary fungal infections.

Our findings support the diagnostic value of BAL samples in the assessment of pulmonary fungal infections. BAL fungal culture, BAL GM, and BAL *Aspergillus* PCR tests are particularly relevant in managing patients with malignancy or ID. Treatment adjustments based on BAL findings appear to improve clinical outcomes. However, large-scale, longitudinal studies with comprehensive data are required to validate these observations.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Bilkent City Hospital (25.06.2025, reference number: TABED-2-25-1337).

Contribution of the authors

Study conception and design: HY, GDT, DAT, SEP, GC; data collection: HY, ÇY, SÖT; analysis and interpretation of results: HY, ŞSAS, IB, MKÇ; draft manuscript preparation: HY, BET, GAD, AÜ. 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

Transcatheter atrial septal defect closure in children weighing ≤15 kg: A single-center experience

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Received : 22.11.2025, Accepted : 02.03.2026
DOI: 10.12956/TJPD.2026.1273

ABSTRACT

Objective: The aim of this study was to assess the feasibility, safety, and outcomes of transcatheter atrial septal defect (ASD) closure in children weighing ≤15 kg, a group in whom transcatheter intervention is often deferred due to limited evidence and perceived procedural risks.

Materials and Methods: This retrospective single-center study included 34 children weighing ≤15 kg who underwent transcatheter ASD closure. Demographic, echocardiographic, procedural, and post-procedural follow-up data were analyzed.

Results: The mean age was 4.14±1.16 years, and the mean ASD diameter on transthoracic echocardiography was 10.41± 2.96 mm. The median balloon-sized ASD diameter was 14.30 mm (IQR: 12–17). All procedures were performed using Amplatzer Septal Occluder devices, with a 100% procedural success rate. The mean pulmonary artery pressure was 19.50±5.01 mmHg, and median pulmonary vascular resistance was 0.97 Wood units (0.44-1.20). A transient episode of supraventricular tachycardia occurred in one patient (2.94%), with no device embolization or other major complications observed. In most patients, right ventricular dimensions normalized and no residual shunt was observed by the first postoperative day.

Conclusion: Transcatheter ASD closure in carefully selected children weighing ≤15 kg appears to be a safe and effective procedure, achieving high procedural success and low complication rates comparable to those observed in heavier patients. Early right ventricular remodeling and the absence of major adverse events further support the feasibility of this approach in appropriately selected cases.

Keywords: Atrial septal defect, body weight, cardiac catheterization, child

Introduction

Transcatheter closure of atrial septal defects (ASD) was first introduced in 1974 and has since become the preferred treatment modality over surgical repair in appropriately selected patients (1). Current guidelines, however, generally do not recommend transcatheter ASD closure in children weighing less than 15 kg due to the limited body of evidence and concerns regarding higher complication rates in this subgroup (2). In line with these concerns, both a large multicenter French study and a multicenter Swedish study have reported relatively frequent complications in children weighing under 15 kg (3, 4). Consequently, published studies focusing on transcatheter ASD closure in infants and small children remain scarce. The present study aimed to present our institutional experience with transcatheter ASD closure in patients weighing less than 15 kg, evaluating both procedural outcomes—including technical success, complication rates, and residual shunt—and outpatient follow-up findings, such as changes in right ventricular size, pulmonary artery pressure, and electrocardiographic abnormalities.

Materials and Methods

This retrospective, single-center study was conducted at a Ankara Bilkent City Hospital. Medical records of patients weighing less than 15 kg who underwent transcatheter ASD closure between January 2022 and August 2025 were reviewed. All procedures were performed under general anesthesia with transthoracic echocardiographic guidance,

and in selected cases, transesophageal echocardiography was additionally utilized. Pre-procedural echocardiography, electrocardiography (ECG), catheterization reports, and post-procedural echocardiographic and ECG findings were systematically collected and analyzed.

Statistical analysis

The data obtained in the study were evaluated using descriptive statistics. Continuous variables were presented as mean and standard deviation (SD) if normally distributed, and as median (minimum–maximum or interquartile range [IQR]) if not normally distributed. Categorical variables were expressed as numbers and percentages. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 147 patients underwent transcatheter ASD closure during the study period, of whom 34 weighed ≤15 kg. The mean age was 4.14±1.16 years, and the median weight was 14.25 kg (range: 12–15). Of the cohort, 15 were male and 19 were female. The primary indications for transcatheter ASD closure were failure to thrive in 15 patients, recurrent respiratory tract infections in five patients, and a history of transient ischemic attack (TIA) in one patient, as summarized in Table I. The remaining patients were older than four years of age and weighed close to 15 kilograms, for whom the decision for closure was made based on clinical and echocardiographic findings. The mean ASD diameter measured by transthoracic echocardiography was 10.41±2.96 mm and the mean preprocedural right-to-left ventricular end-diastolic diameter ratio was 1.13±0.02. Tricuspid regurgitation was moderate in three patients. Rim deficiencies were observed in five aortic, three inferior vena cava, and one posterior rim.

Table I: Baseline demographic and echocardiographic characteristics

Total number of patients	34
Gender	
Female	19
Male	15
Age, years*	4.14±1.16
Weight, kg†	14.25 (12-15)
ASD diameter, mm TTE*	10.41±2.96
Deficient rims‡	
Aortic	5 (14.70)
IVC	3 (8.82)
Posterior	1 (2.94)
Clinical indications‡	
Failure to thrive	15 (44.11)
Frequent respiratory infections	5 (14.70)
History of transient ischemic attack	1 (2.94)
RA/RV enlargement in echocardiography‡	33 (97.06)
Associated congenital cardiac findings‡	3 (8.82)
Small additional ASD	3 (8.82)
Pulmonary valve stenosis	1 (2.94)
Ventricular septal defect (muscular, small)	
PDA (small)	1 (2.94)
Bicuspid aortic valve	1 (2.94)
APCA (small)	1 (2.94)

: mean±SD, †: median (IQR), ‡: n(%), **ASD: atrial septal defect, **TTE:** transtorasic echocardiography, **IVC:** inferior vena cava, **RA/RV:** right atrium/right ventricle, **PDA:** patent ductus arteriosus, **APCA:** aortopulmonary collateral artery*

Associated cardiac and extracardiac findings

Additional cardiac anomalies were present in 16 patients. These included small ASDs (n=3), pulmonary valve stenosis (n=3), small muscular ventricular septal defect (n=1), mild mitral regurgitation (n=3), mitral valve prolapses (n=1), bicuspid aortic valve (n=1), trivial aortic regurgitation (n=1), small patent ductus arteriosus (PDA, n=1), previously closed PDA (n=1), and a small aortopulmonary collateral artery (n=1). Extracardiac comorbidities included Down syndrome (n=2), biotinidase deficiency (n=1), and operated omphalocele (n=1).

Electrocardiographic findings

Right axis deviation was present in 10 patients, and signs of right ventricular hypertrophy were observed in 2 patients. At baseline, one patient had a diagnosis of junctional ectopic tachycardia (JET), confirmed by Holter monitoring and electrophysiological study, demonstrating atrioventricular dissociation with a ventricular rate of approximately 100 bpm, and no significant QT prolongation or ST–T changes. The patient had been managed with a triple antiarrhythmic regimen consisting of amiodarone, propranolol, and flecainide, and ASD closure was planned during follow-up. After device implantation, ivabradine therapy was initiated, and the patient subsequently showed marked rhythm improvement, achieving near-normal sinus rhythm.

Procedural characteristics

The median procedure duration was 40 minutes (IQR: 35–65), and fluoroscopy time was 11.90 minutes (IQR: 8.60–19.45). The median radiation dose was 1.37 Gy·cm² (IQR: 0.83–2.19). Transesophageal echocardiography was used in 6 patients (Table II).

All procedures were performed using Amplatzer Septal Occluder devices (Abbott, Plymouth, MN, USA), and the overall procedural success rate was 100%. Pulmonary artery pressure was ≥20 mmHg in 17 patients, and the mean pulmonary artery pressure across the cohort was 19.50±5.01 mmHg. The median pulmonary-to-systemic flow ratio was 2.16 (IQR: 1.75–2.84), the median pulmonary vascular resistance (PVR) was 0.97 Wood units (IQR: 0.44–1.20).

The median balloon-sized ASD diameter was 14.30 mm (IQR: 12–17), and the mean device size was 15.16±4.11 mm, with a mean ASD diameter-to-device ratio of 1.02±0.26 and a device-to-weight ratio of 1.05±0.27.

Among patients with multiple ASDs, one hemodynamically insignificant 5-mm defect was left open, while two smaller defects were closed simultaneously by the main occluder device. Balloon valvuloplasty was performed in all three cases of pulmonary stenosis.

In two patients, the device was delivered via the right superior pulmonary vein, and in one 3-year-old patient with a 3-mm

Table II: Procedural and follow-up characteristics of the patients

Variables	Values
Balloon-sized ASD diameter, mm*	14.30 (12-17)
PA pressure, mmHg†	19.50±5.01
Patients with PH‡	17 (50)
Qp/Qs*	2.16 (1.75–2.84)
PVR, WU*	0.97 (0.44-1.20)
TEE used‡	6 (17.64)
Amplatzer occluder size, mm†	15.16±4.11
Fluoroscopy time, min*	11.90 (8.60–19.45)
Procedure time, min*	40 (35–65)
Radiation dose, Gy·cm²*	1.37 (0.83-2.19)
Concomitant procedure‡	
Balloon pulmonary valvuloplasty	3 (8.82)
Complications‡	
Transient SVT	1 (2.94)
Postprocedure follow-up	
Residual shunt closure time, days§	1 (1-30)
RV diameter normalization time*	1 (1-30)

: median (IQR), †: mean±SD, ‡: n(%), §: median (range), **ASD: atrial septal defect, **PA:** pulmonary artery, **PH:** pulmonary hypertension, **Qp/Qs:** Pulmonary-to-systemic flow ratio, **PVR:** pulmonary vascular resistance, **WU:** Wood units, **TEE:** transesophageal echocardiography, **SVT:** supraventricular tachycardia, **RV:** right ventricle*

ASD and prior TIA, device closure with a 4-mm occluder was performed after neurology consultation.

Post-procedural outcomes

The median time to residual shunt closure was 1 day (IQR: 1–1; range: 0–30 days). The median time for normalization of right ventricular dimensions was also 1 day (IQR: 1–30). In most patients, remodeling occurred within the first few days; however, in two cases the process was delayed, with one patient showing improvement at 1 month and another not achieving full normalization even at 6 months.

A brief episode of supraventricular tachycardia (four beats) was detected on Holter monitoring in one patient during the early post-procedural period. No antiarrhythmic therapy was required, and subsequent Holter recordings at one week and one month were normal. In patients with normal baseline ECG, no new conduction abnormalities developed after device closure. In those with right axis deviation, axis normalization occurred in most during early follow-up. One patient persisted with right axis deviation at 1 month, another until 4–5 months, and one still showed deviation at 6 months. Additionally, one patient with JET achieved near-normal sinus rhythm under ivabradine therapy.

Discussion

Traditionally, transcatheter closure of atrial septal defects has been recommended for children older than 4 years and weighing more than 15 kilograms, as higher complication rates in smaller patients have led to the suggested deferral of the procedure in this group (2,5). This recommendation primarily stems from concerns regarding the relative size of the occluder device to cardiac structures, vascular access challenges, the higher risk of procedural complications in smaller patients, and the spontaneous closure potential of atrial septal defects smaller than 8 mm (6,7). However, in symptomatic patients with significant left-to-right shunting, recurrent respiratory infections, or growth failure, earlier closure may be considered. In such cases, surgical repair is often contemplated as the preferred approach. Nevertheless, data on transcatheter ASD closure in symptomatic children weighing less than 15 kg remain limited, and current guidelines generally discourage this approach due to the increased risk of technical and procedural complications (2). In our cohort, all patients were symptomatic, with the primary indications for intervention being failure to thrive in 15 patients, recurrent respiratory tract infections in 5 patients, and a history of transient ischemic attack in 1 patient. These proportions were higher than those reported in previous studies, likely because most published series have included patients in whom right ventricular enlargement alone was considered an indication for closure (8). In contrast, in our study, right ventricular enlargement was accepted as an indication only in patients aged over 4 years and weighing around 15 kg, which may explain the higher rate of symptomatic presentation in our cohort.

In our study, the mean ASD diameter measured by transthoracic echocardiography was 10.41±2.96 mm, and the median diameter determined by balloon sizing was 14.30 mm (IQR: 12–17), indicating that these defects were unlikely to close spontaneously without intervention (9).

The procedural success rate in our study was 100%, consistent with previously published series that generally report success rates above 90%. This high success rate may be attributed to meticulous pre-procedural assessment of defect morphology and surrounding rims, as well as the routine use of balloon sizing prior to device selection, which facilitates accurate device sizing and stable implantation (10, 11). Another factor contributing to the high procedural success in our cohort may be the careful selection of patients, in line with the widely accepted recommendation to avoid transcatheter closure when the defect-to-weight ratio exceeds two. In our study, the mean ASD diameter-to-device ratio was 1.02±0.26, and none of the patients had values above this threshold (12).

In small children, suboptimal device positioning may occur due to the relatively small size of the left atrium, which can prevent the device from opening symmetrically and may necessitate the use of technical modifications (13). In our cohort, the mean device-to-weight ratio was 1.05±0.27, indicating that device size was not disproportionately large for patient body size. Consequently, transcatheter closure was successfully performed through the left upper pulmonary vein in all but one

patient, in whom the device was delivered via the right upper pulmonary vein. None of the patients required balloon-assisted device implantation.

Beyond the conventional 15 kg threshold, accumulating evidence from recent studies indicates that transcatheter ASD closure can also be safely and effectively performed in carefully selected children weighing under 10 kg, with high procedural success rates (14,15). In a comparative study including 96 symptomatic children under 10 kg, device closure was shown to be both feasible and safe, with significant post-procedural improvement in symptoms and growth parameters. The authors reported a 99% procedural success rate, with only one case of device embolization requiring surgical retrieval (14). Similarly, another series involving 28 infants weighing ≤10 kg reported a 93% procedural success rate, with only minor transient complications such as self-limited arrhythmias and post-procedural fever, and no long-term conduction abnormalities during follow-up (15). In our study, the lowest patient weight was 12 kg, and the smaller device-to-defect and device-to-weight ratios compared with those reported in studies involving <10 kg children may have contributed to the absence of such serious complications, including embolization.

Residual shunt findings were consistent with previous reports, as no residual flow was observed in 29 of the 33 patients on the first postoperative day (8). At the 1-month follow-up, residual shunt persisted in only one patient; however, the exact timing of spontaneous closure could not be determined because the patient did not attend subsequent follow-up visits.

Right ventricular dimensions returned to normal in 27 of the 33 patients, mostly within the first postoperative day and by 1 month in all of these cases. In five patients, normalization occurred within 6 months, whereas in one patient, mild right ventricular dilation persisted at the 6-month follow-up.

Only one patient (2.94%) experienced a procedural complication, which is consistent with the reported 3–4% complication rates in both <15 kg and ≥15 kg cohorts (8,16,17). This event consisted of a brief, self-limiting episode of supraventricular tachycardia (four beats) occurring immediately after device deployment. No medical intervention was required, and follow-up Holter monitoring at 1 week and 1 month demonstrated complete resolution. In our cohort, one patient—a 2.7-year-old girl—underwent ASD closure following a confirmed ischemic attack on magnetic resonance imaging of the brain. During the etiological evaluation, a small atrial septal defect was identified, and, upon consultation with the pediatric neurology team, transcatheter closure was recommended and performed using a 4-mm Amplatzer occluder device. Previous studies have demonstrated that percutaneous closure of interatrial communications is superior to medical therapy in preventing recurrent ischemic events, particularly in patients with paradoxical embolism (18, 19). However, the number of reports describing device closure in very young and low-weight children remains limited, as most published studies have focused on adolescent or adult populations (20). In this regard, our case is noteworthy, given that it is characterised by a significant age and a substantial weight of 15 kilograms.

Limitations

This study has several limitations. First, it was a retrospective, single-center study with a relatively small sample size, which may limit the generalizability of the findings. Second, although all patients were followed clinically and echocardiographically, long-term follow-up data beyond six months were not available for every patient. Finally, subtle hemodynamic or electrical changes that may occur in the long term could not be fully assessed due to the limited observation period.

Conclusion

This study demonstrates that in carefully selected children weighing less than 15 kg—particularly those with favorable echocardiographic anatomy and without excessive defect-to-body or device-to-body ratios—transcatheter ASD closure can be performed safely with high procedural success and complication rates comparable to those in heavier patients. Appropriate case selection, accurate device sizing, and operator experience appear to be key factors for procedural success. Further studies with larger cohorts and long-term follow-up are warranted to validate these findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital Ethics Committee (date: 08.10.2025, number: TABED 1-25-1752).

Contribution of the authors

UP conceived and designed the study, collected the data, and drafted the initial manuscript; HAG. coordinated and supervised data collection, contributed to study design, and critically reviewed and revised the manuscript; EA. contributed to study design and provided critical revisions to the manuscript; YÖŞ. provided critical revisions to the 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

Evaluation of clinical, demographic, and echocardiographic characteristics of patients with acute rheumatic fever diagnosed in the secondary care hospital

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Received : 09.12.2025, Accepted : 23.03.2026
DOI: 10.12956/TJPD.2026.1279

ABSTRACT

Objective: Acute rheumatic fever remains a significant cause of morbidity and mortality, particularly in developing countries. According to the Modified Jones Criteria updated by the American Heart Association in 2015, populations with an annual incidence of fewer than 2 new cases per 100,000 individuals are considered low-risk. A nationwide multicenter study conducted in Türkiye reported an annual incidence of 8.8 per 100,000, classifying the country as being within the moderate–to–high–risk category. In this study, we aimed to evaluate the clinical, demographic, and echocardiographic characteristics of patients diagnosed with acute rheumatic fever at a secondary healthcare center.

Material and Methods: The clinical and demographic data of patients diagnosed with acute rheumatic fever at Denizli State Hospital between March 2015 and December 2024 were retrospectively evaluated. Patient records were accessed through the hospital's electronic database.

Results: A total of 60 patients were diagnosed with acute rheumatic fever during the study period. The most common presenting complaint was joint pain. Carditis and joint involvement (91.6% and 92.8%, respectively) were the most frequently observed major manifestations, while Sydenham chorea was diagnosed in 30% of the patients. According to the most recently modified criteria, the frequencies of polyarthritis, monoarthritis, and polyarthralgia as major manifestations were similar (30.1%, 28.6%, and 33.3%, respectively). Treatment-related complications included hepatotoxicity in four patients, and epistaxis, peptic ulcer, steroid-induced myopathy, esophageal candidiasis, and hyponatremia in one patient each.

Conclusion: Acute rheumatic fever remains a commonly encountered disease in Türkiye. With the recent updates to the Jones Criteria, the proportion of missed acute rheumatic fever cases in moderate-to-high–risk populations is expected to decline substantially. The high frequency and clinical significance of both the disease itself and its treatment-related complications underscore the importance of effective streptococcal eradication and early diagnosis.

Keywords: Acute rheumatic fever, arthritis, carditis, child, Sydenham chorea

Introduction

Acute rheumatic fever (ARF) is an autoimmune inflammatory reaction to pharyngitis and possibly superficial skin and skin structure infections in susceptible individuals after infection with group A β-hemolytic streptococcus. It is a serious but preventable public health problem in low- and middle-income countries and in indigenous populations of high-income countries (1,2). In 2021, rheumatic heart disease (RHD) affected an estimated 55 million people globally and caused 360,000 deaths (3-5).

There is currently no definitive diagnostic method, and diagnosis is made using the Jones criteria, first accepted in 1946 and last revised by the American Heart Association (AHA) in 2015 (3). Low risk is defined as an ARF incidence of <2 per 100,000 school-age children (usually 5–14 years of age) per year or a prevalence of RHD in the entire age group of ≤1 per 1000 population per year, where reliable epidemiological data are available. In Australia, the indigenous population has one of the highest reported incidences of ARF in the world, with 153 to 380 cases per 100,000 people per year

in the 5-14 age group, while in other Australian populations, the incidence is approaching European and North American levels (6). In a multicenter study covering the whole of Türkiye, the incidence was reported as 8.8 per 100,000 people, and it was determined as a moderate-high risk population (7).

The AHA made two main changes in the recent revision: First, different diagnostic criteria were defined for different incidence (risk) groups to prevent underdiagnosis in high-incidence populations and to reduce overdiagnosis in low-incidence populations. In moderate/high-risk populations, monoarthritis and polyarthralgia were considered major risk factors if other diagnoses were excluded. Second, valvular insufficiency detected by Doppler echocardiography was considered subclinical carditis in the diagnosis of carditis and was included among the major criteria (3).

Our study aimed to examine patients diagnosed with ARF according to the latest updated Jones Criteria in a secondary care hospital.

Material and Methods

Total of 60 patients diagnosed with a first episode of ARF at Denizli State Hospital between May 2015 and December 2024 were included in the study. All patients were evaluated by the same pediatric cardiologist. Data about age, gender, history of upper left respiratory tract infection, presenting symptoms, major and minor manifestations, supportive findings, and seasonal factors were collected from the medical records.

Laboratory tests (blood count, sedimentation rate, C-reactive protein, antistreptolysin O titers), telecardiography, and electrocardiography were obtained from the patients' hospital records.

The diagnosis of ARF was based on the Jones criteria as modified by the AHA in 2015 (3). Since our country is in the moderate-high risk group, we used the latest modified diagnostic criteria recommended by the AHA for these groups. The major criteria are arthritis, carditis, chorea, a characteristic rash called erythema marginatum, and subcutaneous nodules. The minor criteria include fever, arthralgia, elevated acute-phase reactants, and a prolonged PR interval on the electrocardiogram. Arthritis was defined either by redness, swelling, and hotness of joints, or by limitation in the range of joint movement due to tenderness and limping. Since our country is among the medium/high-risk countries, monoarthritis and polyarthralgia were accepted as major criteria in addition to polyarthritis in terms of joint findings. Carditis was characterized by the demonstration of valve involvement by echocardiography, with or without an audible murmur on physical examination. Sydenham chorea diagnosis was based on the exclusion of other possibilities and the presence of arthritis and/or carditis, together with evidence of a precedent group A streptococcal throat infection. The subcutaneous nodules were defined as small, varying in size from millimeters to 2 cm, and as firm, painless, freely movable lesions under the skin, mainly found on the extensor surface of the joints. Erythema marginatum, an uncommon manifestation, presented as a macular rash, sometimes coalescent with a serpiginous or circular form, and was almost coppery pink at the border. It was mainly located on the trunk and inner surface of the proximal limbs, with a light-colored center. The diagnosis of recurrence of rheumatic fever in children with rheumatic heart disease was based on the presence of one major criterion, apart from carditis, or two minor criteria, in addition to the evidence of preceding streptococcal infection (1, 3, 8).

The pathological valve levels determined by echocardiography by the American Heart Association are as follows: in mitral valve regurgitation, a color jet length of >2 cm, the presence of a defined color jet in at least two planes, and the presence of a mosaic color jet with a peak velocity of >3 m/sec. In aortic valve regurgitation, holodiastolic regurgitation, a color jet length of >1 cm, the presence of a defined color jet in at least two planes, and the presence of a mosaic color jet with a peak velocity of >3 m/sec (9).

Patients whose ages were not between 5 and 15 years during the acute attack, and patients with recurrent attacks, were excluded from the study. All statistical analyses were performed using Systat statistical software (version 17.0 for Windows; SPSS Inc., Chicago, IL, USA). All variables were presented as the mean, standart deviation, range, frequency, and percentage. Data were tested for homogeneity of variance with the Kolmogorov–Smirnov test.

Results

Sixty patients met the Modified Jones Criteria, last modified in 2015. Of these patients, 29 (48.3%) were female, and 31 (51.6%) were male (male-to-female ratio: 1.07). The ages of the patients ranged from 7 to 18 years, with a mean age of 11.8±2.1 years. Among those diagnosed with ARF, 25.0% presented during winter, 25.0% in spring, 26.7% in summer, and 23.3% in autumn. A total of 66.6% (40/60) of the patients presented with joint pain, 30.0% (18/60) with choreiform movements, one patient with isolated palpitations, and one patient with severe carditis presented with complaints of easy fatigability and dyspnea. Except for patients with chorea, all had elevated antistreptolysin-O (ASO) titers as evidence of streptococcal infection; however, none had a positive throat culture for group A β-hemolytic streptococcus.

Carditis was the most common major criterion of ARF, observed in 55 of 60 patients (91.6%), and 67.2% (37/55) of these had clinical carditis. The frequencies of other major manifestations—polyarthritis, aseptic monoarthritis, polyarthralgia, and Sydenham chorea—were 14/60 (23.3%),

Table I: Prevalence of carditis and associated joint manifestations

Findings	Count / Total	Rate (%)
Carditis	55/60	91.6
Clinical carditis	37/55	67.3
Subclinical carditis	18/55	32.7
Isolated carditis	16/55	29.1
Carditis + polyarthritis	14/55	25.4
Carditis + monoarthritis	12/55	21.8
Carditis + polyarthralgia	13/55	23.6

Table II: Valvular regurgitation profiles and subclinical carditis in acute rheumatic fever patients

Findings	Cases / Total	Rate (%)	Subgroups	Subgroup Rate (%)
Mitral regurgitation	55/60	91.7	Isolated mitral regurgitation	29/55 (52.7%)
Aortic regurgitation	27/60	45.0	Isolated aortic regurgitation	1/27 (3.7%)
Mitral + aortic regurgitation	26/60	43.3	—	—
Mitral regurgitation severity	—	—	Mild / Moderate / Severe	63.6 / 25.4 / 10.9
Aortic regurgitation severity	—	—	Mild / Moderate / Severe	85.1 / 11.1 / 3.7
Subclinical carditis	18/60	30.0	Mitral / Aortic / Both	94.4 / 11.1 / 5.5

Table III: Articular findings and their relationship to carditis in acute rheumatic fever

Findings	Case Count / Total	Rate (%)	Subgroups	Subgroup Rate (%)
Arthritis / Polyarthralgia	39/42	92.8	Isolated / With carditis	10.3 / 89.7
Isolated arthritis/polyarthralgia	4/39	10.3	—	—
Arthritis/polyarthralgia with carditis	35/39	89.7	—	—
Polyarthritis	13/42	30.1	With / Without carditis	83.3 / 16.7
Aseptic monoarthritis	12/42	28.6	With / Without carditis	91.6 / 8.4
Polyarthralgia	14/42	33.3	With / Without carditis	92.8 / 7.2

12/60 (20.0%), 15/60 (25.0%), and 18/60 (30.0%), respectively. The proportion of isolated carditis without joint involvement was 29.1% (16/55), while arthritis/polyarthralgia accompanied carditis in 70.9% (39/55). Carditis was accompanied by polyarthritis in 25.4% (14/55), by aseptic monoarthritis in 21.8% (12/55), and by polyarthralgia in 23.6% (13/55) of the patients as a major criterion Table I.

Mitral regurgitation was detected in 55/60 (91.7%) patients, and in 29 of 55 patients (52.7%), it was isolated mitral regurgitation. For aortic regurgitation, these rates were 27/60 (45.0%) and 1/27 (3.7%), respectively. A total of 26 patients (43.3%) had coexisting mitral and aortic regurgitation. The severity of mitral regurgitation was mild in 35/55 (63.6%), moderate in 14/55 (25.4%), and severe in 6/55 (10.9%) patients. For aortic regurgitation, the corresponding rates were 23/27 (85.1%), 3/27 (11.1%), and 1/27 (3.7%). Subclinical carditis was present in 18 (30%) patients, of which mitral regurgitation was found in 17/18 (94.4%) and aortic regurgitation in 2/18 (11.1%) patients, and only one patient (5.5%) had both mitral and aortic regurgitation Table II.

Among patients diagnosed with ARF, the rate of arthritis/poliarthlalgia was 39/42 (92.8%). Of these, 10.3% (4/39) had isolated arthritis/poliarthlalgia, while 89.7% (35/39) had arthritis/poliarthlalgia associated with carditis. Polyarthritis was present in 13/42 (30.1%) patients; two (16.7%) of them had no carditis, while 10 (83.3%) had concomitant carditis. Aseptic monoarthritis was identified in 12/42 (28.6%) patients, 11 (91.6%) of whom had clinical carditis, while one patient (8.4%) did not. Polyarthralgia, another major criterion, was present in 14/42 (33.3%) patients; 13 (92.8%) had clinical carditis, and one (7.8%) did not Table III.

Sydenham chorea was identified in 18 patients (30.0%), with 10 (55.5%) being female and eight (44.5%) male. All patients with chorea had accompanying carditis. None had erythema marginatum or subcutaneous nodules. About 14.3% (6/42) of patients with ARF showed a prolonged PR interval (first-degree atrioventricular block). Fever was present at admission in 4/42 (9.5%) patients, and only one (2.3%) experienced monoarthralgia. Acute-phase reactants were elevated in all patients except those diagnosed with chorea. One patient had Wenckebach-type second-degree Mobitz I AV block, and another had inappropriate sinus tachycardia upon admission. One patient with moderate morphologic carditis had mitral stenosis, and another had a history of surgery for a ventricular septal defect. Both erythrocyte sedimentation rate and C-reactive protein levels were elevated in all patients except those with chorea. The average sedimentation rate was 83.9 ± 25.6 mm/h, and the average CRP level was 77.4 ± 48.6 mg/dL (normal <5 mg/dL). The mean ASO titer was 814.2 ± 514.2 IU/mL. Acetylsalicylic acid (ASA) was started in patients with isolated arthritis or mild cardiac involvement. Prednisolone was given as initial therapy for patients with moderate or severe carditis. ASA was prescribed to 45.2% (19/42) and prednisolone to 54.8% (23/42). Nine patients experienced treatment-related complications necessitating therapy adjustments, including hepatotoxicity in four patients, and epistaxis, steroid-induced myopathy, esophageal candidiasis, peptic ulcer, and hyponatremia in one patient each.

Discussion

Our study evaluates patients diagnosed with ARF at a secondary-care hospital. The AHA defines high-risk populations as those with an annual incidence greater than 2 per 100,000 people (3). In studies previously conducted in Türkiye, the incidence of ARF was shown to decline from 56.6 to 21 per 100,000 over a decade (10,11). A multicenter study conducted in Türkiye in 2015 reported an annual incidence of 8.8 per 100,000 (7). In a recent study from Uganda, the incidence was reported to be 25 and 47.9 per 100,000 in two different cities (12). In Australia, the age-standardized incidence of ARF was markedly higher among the Indigenous population (71.9/100,000) compared with the non-Indigenous

population (0.6/100,000) (13). A very high incidence has also been reported in Malaysia (74.4/100,000) (14).

Denizli, where this study was conducted, is located in the Aegean Region of Türkiye. Therefore, we compared our data with the Aegean Region and national data. In this study, the frequency of carditis was similar to the average reported for the Aegean Region but higher than the national average (67.2%,62.1%, and 53.5% respectively) (7). However, it was comparable to the global average reported by the World Health Organization (WHO) (67.2% and 59.5%) (5). The prevalence of subclinical carditis—defined as carditis without an audible murmur—was consistent with national data. The frequency of arthritis also aligned with WHO global estimates. While the prevalence of polyarthritis was lower than the averages reported for both the Aegean Region and Türkiye, the rates of aseptic monoarthritis and polyarthralgia were higher in our cohort. The prevalence of Sydenham chorea was notably higher than figures reported for the Aegean Region, Türkiye, and the WHO (30.0%,6.0%,7.9%, and 12.9% respectively) (5,7).

Consistent with the literature, arthralgia was the most common presenting complaint in our study, followed by choreiform movements (15-17). Although some studies report arthritis as the most common major manifestation and others report carditis as the predominant finding, carditis was likewise the most frequently observed major criterion in our cohort. Similar to WHO results, arthritis and carditis occur at approximately the same frequency (~60%) (5). Following the widespread adoption of echocardiography—including its recognition of subclinical carditis as a major criterion—the rate of carditis diagnoses has increased. WHO reports that echocardiography is substantially more sensitive than cardiac auscultation in detecting RHD, identifying 12.9 cases per 1,000 individuals in endemic regions, compared with 2.9 per 1,000 by auscultation (5).

Güler et al. (18) reported that, between 2015 and 2018, they were able to diagnose nine of the 50 patients (18%) using the updated criteria. A similar study conducted in Italy reported this rate as 20.7% (6). This finding suggests that the latest update will reduce the diagnostic difficulty in populations where ARF is common (18). Interestingly, the prevalence of Sydenham chorea in our cohort (30%) was substantially higher than WHO estimates and national multicenter data, although comparable rates have been reported in a study from Kayseri (25%) (5,7,15). Because many conditions can mimic the major and minor criteria of ARF, a meticulous differential diagnosis is essential. The presence of a single pediatric cardiologist at our center allowed patients to be regularly followed by the same physician. This continuity may have facilitated careful evaluation of diagnostically challenging cases, helping to prevent overdiagnosis. In this study, the higher proportion of Sydenham Chorea compared to other major findings and the different distribution of the joint conclusions compared to national and international reports can be explained by close follow-up of cases with diagnostic uncertainty and subsequent confirmation or exclusion of the ARF diagnosis (5, 7).

In line with the literature, isolated mitral regurgitation was the most common valvular involvement in both clinical and subclinical carditis, followed by combined mitral and aortic valve regurgitation (5, 15-19). Before the most recent revisions of the Jones criteria, polyarthritis was exceedingly common; however, following the inclusion of monoarthritis and polyarthralgia as major criteria in certain populations, the proportion of polyarthritis appears to have decreased (18, 20).

Hepatotoxicity is a well-known complication of high-dose acetylsalicylic acid therapy. In this study, four patients developed hepatotoxicity, and their treatment was switched to naproxen. Other complications included epistaxis, steroid-induced myopathy, esophageal candidiasis, peptic ulcer disease, and hyponatremia in a patient with concurrent heart failure. In a study reported by researchers from Central Anatolia, 27.2% of patients had elevated liver function tests, 6.8% experienced gastrointestinal side effects, 2% reported tinnitus, 2% developed rash and fever, one patient developed serum sickness, and one patient had epistaxis (10).

Limitations

It has some limitations. The presence of two centers in the same city does not reflect the entire population. Because it does not include patients before the final modified criteria, we were unable to compare the additional diagnostic benefit of the latest criteria.

Conclusion

In conclusion, ARF remains prevalent in Türkiye and continues to pose a significant public health concern due to its potential to cause rheumatic heart disease. Because Türkiye is among the medium- to high-risk countries, monoarthritis and polyarthralgia should be considered major criteria to prevent potential oversight. Furthermore, active echocardiography evaluation can help identify subclinical carditis. In addition, we believe that primary and secondary healthcare facilities play a pivotal role in ARF control, particularly through the implementation of more effective and widespread preventive measures against streptococcal infections.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Pamukkale University (12.11.2024, reference number: E-60116787-020-624004).

Contribution of the authors

AE: concept and design, data collection, analysis and interpretation of results, preparation of draft 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 mineral density in pediatric celiac disease: Clinical, biochemical, and serologic profiles—a retrospective cohort study

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Received : 02.12.2025, Accepted : 24.03.2026
DOI: 10.12956/TJPD.2026.1274

ABSTRACT

Objective: The aim of this study was delineate the burden of low lumbar bone mineral density (BMD) in children with CD (celiac disease) and evaluate differences in BMD according to assessment timing and gluten-free diet (GFD) adherence, using concurrent tissue transglutaminase IgA (c-tTG-IgA), and describe accompanying anthropometric and biochemical profiles.

Materials and Methods: This retrospective cohort included CD patients (n=123) aged 5–18 years who underwent dual-energy X-ray absorptiometry (DEXA) between January 1, 2022, and December 31, 2024. Age-adjusted and height-adjusted BMD z-scores (BMD-AAz and BMD-HAz) were calculated. Patients were grouped as diagnosis or follow-up (≥12 months), and follow-up was subdivided into GFD-non-adherent follow-up group (FU-NonAdh) and GFD-adherent follow-up group (FU-Adh).

Results: Low BMD based on BMD-HAz (≤–1) was present in 37.4% (osteopenia 24.4%; osteoporosis 13.0%). Compared with diagnosis group, follow-up group had higher BMD-AAz and BMD-HAz (p=0.022 and p=0.011). BMD-HAz was higher in FU-Adh group than in diagnosis and FU-NonAdh group (p<0.001 and p=0.005), whereas FU-NonAdh group did not differ from diagnosis group. The low BMD group had a lower body mass index (BMI) z-score and shorter GFD duration (p<0.001 and p=0.010). Serum calcium levels were lower in the osteoporosis group than in the normal BMD group (p=0.003).

Conclusion: Lumbar BMD impairment is frequent in pediatric CD, with the most evident improvement in the GFD-adherent follow-up group. In secondary analyses, lower BMI z-scores and shorter GFD duration were observed in children with low BMD, which may help inform risk stratification.

Keywords: Body mass index, calcium, dual-energy x-ray absorptiometry, gluten-free diet, tissue transglutaminase

Introduction

Celiac disease (CD) is a systemic autoimmune condition characterized by immune-mediated small intestinal damage induced by gluten intake. In childhood, it may present not only with gastrointestinal symptoms but also with extraintestinal manifestations such as growth failure, anemia, and reduced bone mineral density (BMD) (1–3). Osteopenia and osteoporosis are prevalent and clinically significant conditions in children with CD due to their association with long-term fracture risk (4,5).

Multiple mechanisms contribute to the emergence of low BMD in CD, including malabsorption, chronic inflammation, and hormonal alterations. Malabsorption of calcium (Ca) and 25-hydroxyvitamin D_3 ($25(OH)D_3$) due to villous atrophy can predispose patients to the onset of secondary hyperparathyroidism and enhanced bone resorption, while growth retardation and malnutrition may hinder the attainment of optimal bone mass (6,7). Despite this, it remains unclear which clinical and biochemical profiles are more strongly associated with BMD impairment and which children should be prioritized for screening with dual-energy X-ray absorptiometry (DEXA) (8,9).

A gluten-free diet (GFD) is the mainstay for achieving both mucosal recovery and enhancement of bone health. However, the relationship between serologic response and bone mineralization has not been fully elucidated. Although tissue transglutaminase immunoglobulin A (tTG-IgA) levels are widely used indicators of dietary adherence, findings regarding their association with BMD remain inconsistent (4,10–12).

This study sought delineate the burden of low lumbar BMD in children with CD and to evaluate differences in BMD by assessment timing and GFD adherence, while describing accompanying anthropometric and biochemical profiles.

Materials and Methods

Study design and setting

This investigation was performed using the electronic medical records of CD patients followed in the Pediatric Gastroenterology Department of Gulhane Training and Research Hospital, University of Health Sciences. university hospital. All CD patients between 5 and 18 years of age who had BMD measurement with DEXA and had concurrent tissue transglutaminase immunoglobulin A (c-tTG-IgA) available at the time of BMD assessment between January 1, 2022, and December 31, 2024, were included.

Diagnosis and eligibility criteria

The diagnosis of CD was confirmed by upper gastrointestinal endoscopy and small intestinal biopsy according to European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2020 criteria (13). Patients diagnosed without biopsy, those with IgA deficiency, those with endocrine or other chronic diseases, and those using medications that could affect bone metabolism were excluded. A cohort of 123 patients meeting the study-defined requirements was incorporated into the analysis.

Data collection

Demographic and clinical data, including age, gender, height, weight, and body mass index (BMI), as well as Ca, phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25(OH)D_3 levels, were obtained from the medical records. Height z-score, weight z-score, and BMI z-score were calculated according to Neyzi growth references (14).

Dual-Energy X-ray absorptiometry and bone mineral density

BMD assessments were obtained at the lumbar vertebrae L2–L4 level using a Hologic QDR 4500 bone densitometer (Hologic Inc., Bedford, MA, USA). Age-adjusted BMD z-score (BMD-AAz) and height-adjusted BMD z-score (BMD-HAz) were calculated using reference curves derived from healthy Turkish children (15).

Grouping strategy

Participants were initially classified into two groups based on the timing of DEXA assessment: at diagnosis or at follow-up. The diagnosis group included patients assessed at diagnosis. The follow-up group included patients assessed ≥12 months after diagnosis. It was subdivided into two subgroups based on c-tTG-IgA status at the time of DEXA: the GFD-non-adherent follow-up group (FU-NonAdh), which was c-tTG-IgA positive, and the GFD-adherent follow-up group (FU-Adh), which was c-tTG-IgA negative (16).

For the secondary analysis, patients were categorized into three strata based on BMD-HAz: normal BMD group (BMD-HAz > –1), osteopenia group (–2 < BMD-HAz ≤ –1), and osteoporosis group (BMD-HAz ≤ –2) (17). Additionally, BMD-HAz ≤ –1 was defined as low BMD.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean andstandard deviation or median and interquartile range (IQR), and categorical variables as number and percentage. The distribution of continuous variables was assessed using the Shapiro–Wilk test and Q–Q plot. Between-group comparisons were performed using the independent samples t-test or Mann–Whitney U test, as appropriate. For comparisons across the three BMD categories, one-way ANOVA or the Kruskal-Wallis test was used, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. For subgroup analyses, pairwise comparisons were conducted as specified in the tables. A p-value < 0.050 was considered statistically significant in all analyses.

Results

BMD data from 123 children with CD were assessed. The mean age of the patients was 11.7±3.7 years, and 55.3% were female. The mean age at diagnosis was 8.7±3.8 years. Anthropometric assessment showed a mean height z-score of –0.40±1.08, a mean weight z-score of –0.62±1.22, and a mean BMI z-score of –0.54±1.19. Based on BMD-HAz values, 37.4% of the patients had low BMD (24.4% had osteopenia, and 13.0% had osteoporosis). Based on BMD-AAz values, 40.7% of the patients had low BMD (30.1% had osteopenia, and 10.6% had osteoporosis). In total, 38 patients were assessed at diagnosis and 73 at follow-up; an additional 12 patients were evaluated after diagnosis but within <12 months and were not included in either group. Compared with the diagnosis group, the follow-up group had significantly higher densitometric indices, with higher BMD-AAz and BMD-HAz (p=0.022 and p=0.011, respectively) (Table I, Figure 1). In contrast, age, gender distribution, and biochemical parameters Ca, P, ALP, PTH, and 25(OH)D_3 levels were comparable across groups (Table I).

When the diagnosis group and the follow-up subgroups were compared, the primary between-group differences were observed in BMD outcomes. BMD-HAz was higher in the GFD-adherent follow-up group than in the diagnosis group (p<0.001) and the GFD-non-adherent follow-up group (p=0.005). BMD-AAz was also higher in the GFD-adherent follow-up group than in the diagnosis group (p=0.005), whereas the difference between the two follow-up subgroups did not reach statistical significance (p=0.098) (Table II, Figure 2). BMI z-score was higher in the GFD-adherent follow-up group than in the diagnosis group (p=0.030). In contrast, age, gender distribution, and biochemical parameters Ca, P, ALP, PTH, and 25(OH)D_3 levels were comparable across the diagnosis group and follow-up subgroups (Table II). Compared with the normal BMD group, the low BMD group had a significantly lower BMI z-score (p<0.001) and shorter GFD duration (p=0.010). Age, gender distribution,

Table I: Comparison of clinical, biochemical, anthropometric, and densitometric parameters according to timing of assessment

Variable	Diagnosis Group	Follow-up Group	p
Total number of patients	38	73	-
BMD-AAz*	-0.98 ± 1.07	-0.45 ± 1.17	0.022§
BMD-HAz*	-1.05 ± 1.29	-0.41 ± 1.20	0.011§
Age (years)†	11.00 (9.00-14.75)	12.00 (9.00-15.00)	0.558¶
Gender (female)‡	22 (57.9)	46 (63.0)	0.749‖
Calcium (mg/dL)*	9.77 ± 0.40	9.84 ± 0.39	0.349§
Phosphorus (mg/dL)*	4.63 ± 0.65	4.52 ± 0.79	0.447§
Alkaline phosphatase (U/L)*	204.55 ± 74.53	203.80 ± 101.43	0.968§
Parathyroid hormone (pg/mL)†	35.50 (25.23-47.85)	34.30 (26.00-48.30)	0.936¶
25(OH)D_3 (ng/mL)†	20.61 (12.66-26.75)	22.00 (15.18-31.09)	0.291¶
Height z-score*	-0.35 ± 1.07	-0.38 ± 1.07	0.869§
Weight z-score*	-0.78 ± 1.13	-0.46 ± 1.28	0.194§
BMI z-score*	-0.82 ± 1.20	-0.35 ± 1.20	0.054§

:** *mean ± SD,* **†:** *median (IQR),* **‡:** *n(%),* **§:** *independent samples t-test,* **¶:** *Mann–Whitney U test,* **‖:** *chi-square test,* ***BMD-AAz: *Age-adjusted bone mineral density z-score,* ***BMD-HAz:*** *Height-adjusted bone mineral density z-score,* ***25(OH)D_3:*** *25-hydroxyvitamin D_3,* ***BMI:*** *Body mass index. The diagnosis group included patients assessed at diagnosis. The follow-up group included patients assessed ≥12 months after diagnosis.*

Table II: Comparison of clinical, biochemical, anthropometric, and densitometric parameters among the diagnosis group, the GFD-non-adherent follow-up group and the GFD-adherent follow-up group

Variable	Diagnosis Group	FU-NonAdh	FU-Adh Group	p^1	p^2	p^3
Total number of patients	38	24	49	-	-	-
BMD-AAz*	-0.98 ± 1.07	-0.78 ± 1.17	-0.29 ± 1.16	0.482§	0.005§	0.098§
BMD-HAz*	-1.05 ± 1.29	-0.96 ± 1.39	-0.14 ± 1.00	0.792§	<0.001§	0.005§
Age (years)†	11.00 (9.00-14.75)	12.50 (8.50–15.25)	12.00 (9.00–15.00)	0.896¶	0.468¶	0.621¶
Gender (female) ‡	22 (57.9)	11 (45.8)	35 (71.4)	0.506‖	0.276‖	0.061‖
Calcium (mg/dL)*	9.77 ± 0.40	9.77 ± 0.43	9.87 ± 0.37	0.963§	0.194§	0.294§
Phosphorus (mg/dL)†	4.70 (4.33–5.00)	4.75 (4.22–5.40)	4.50 (4.10–4.90)	0.669¶	0.288¶	0.223¶
Alkaline phosphatase (U/L)*	204.55 ± 74.53	188.88 ± 87.95	211.10 ± 107.51	0.455§	0.749t	0.383§
Parathyroid hormone (pg/mL)†	35.50 (25.23-47.85)	36.65 (25.93–51.20)	33.30 (26.60–45.00)	0.628¶	0.864¶	0.545¶
25(OH)D_3 (ng/mL)†	20.61 (12.66-26.75)	24.14 (16.65–30.92)	21.57 (14.70–31.09)	0.196¶	0.494¶	0.470¶
Height z-score†	-0.15 (-1.14–0.46)	-0.48 (-0.84–0.53)	-0.24 (-1.20–0.55)	0.691¶	0.952¶	0.738¶
Weight z-score*	-0.78 ± 1.13	-0.60 ± 1.12	-0.39 ± 1.36	0.546§	0.155§	0.507§
BMI z-score*	-0.82 ± 1.20	-0.58 ± 1.12	-0.24 ± 1.24	0.436§	0.030§	0.257§

:** *mean±SD,* **†:** *median (IQR),* **‡:** *n(%),* **§:** *independent samples t-test,* **¶:** *Mann–Whitney U test,* **‖:** *chi-square test,* ***GFD: *gluten-free diet,* ***BMD-AAz:*** *Age-adjusted bone mineral density z-score,* ***BMD-HAz:*** *Height-adjusted bone mineral density z-score,* ***25(OH)D_3:*** *25-hydroxyvitamin D_3,* ***BMI:*** *Body mass index,* ***p^1:*** *Diagnosis vs FU-NonAdh,* ***p^2:*** *Diagnosis vs FU-Adh;* ***p^3:*** *FU-NonAdh vs FU-Adh*

and biochemical parameters were otherwise comparable between groups (Table III).

Across BMD categories, BMI z-score decreased stepwise from the normal BMD group to osteopenia and osteoporosis, with significant overall differences (p=0.002). BMI z-score was lower in both the osteopenia (p=0.011) and osteoporosis (p=0.003) groups compared with the normal BMD group. Serum Ca levels also differed across groups (p=0.010) and was lower in the osteoporosis group than in the normal BMD group (p=0.003) (Table IV).

Discussion

In this study, a notable frequency of lumbar BMD loss assessed by DEXA was demonstrated in children with CD; based on BMD-HAz, low BMD was identified in 37.4% of cases. Compared with patients assessed at diagnosis, the most prominent improvement was observed in the follow-up group that was serologically negative and considered adherent to the GFD, in whom both BMD-AAz and BMD-HAz were significantly higher. In contrast, BMD measurements in patients who remained seropositive during follow-up and were considered non-adherent to the GFD did not differ from those in the diagnosis group. In secondary analyses, the low BMD group had a lower BMI z-score and a shorter GFD duration. These findings suggest that improvement in bone mineralization may be more closely related to seronegativity achieved through GFD adherence and a higher BMI during follow-up rather than to characteristics at diagnosis.

In our cohort, osteopenia was identified in 24.4% of patients and osteoporosis in 13.0%. Reported rates of osteopenia

Table III: Comparison of clinical, biochemical, and anthropometric parameters between normal BMD and low BMD groups

Variable	Normal BMD Group	Low BMD Group	p
Total number of patients	77	46	-
Age (years)*	12.00 (9.00–16.00)	11.00 (8.25–13.00)	0.178§
Gender (Female)†	50 (64.9)	27 (58.7)	0.618¶
GFD duration (months)*	26.00 (4.00–58.00)	10.50 (2.25–30.75)	0.010§
Calcium (mg/dL)‡	9.87 ± 0.34	9.73 ± 0.47	0.055‖
Phosphorus (mg/dL)*	4.70 (4.20–5.00)	4.60 (4.20–5.00)	0.904§
Alkaline phosphatase (U/L)*	208.00 (133.0–259.0)	188.00 (142.5–227.7)	0.340§
Parathyroid hormone (pg/mL)*	35.00 (26.80–47.90)	31.75 (24.25–50.33)	0.724§
25(OH)D_3 (ng/mL)*	22.00 (15.18–29.80)	24.40 (14.04–31.24)	0.427§
Height z-score*	–0.45 (–1.20–0.39)	0.03 (–1.08–0.54)	0.304§
Weight z-score*	–0.50 (–1.36–0.21)	–1.06 (–1.50––0.29)	0.047§
BMI z-score ‡	–0.25 ± 1.12	–1.02 ± 1.17	<0.001‖

: median (IQR), †: n(%), ‡: mean±SD, §: Mann–Whitney U test, ¶: chi-square test, ‖: independent samples t-test, **BMD: bone mineral density, **GFD:** gluten-free diet, **25(OH)D_3:** 25-hydroxyvitamin D_3, **BMI:** body mass index. Normal BMD comprised patients with BMD-HAz>–1. Low BMD comprised patients with BMD-HAz ≤ –1 (osteopenia or osteoporosis).*

Table IV: Comparison of clinical, biochemical, and anthropometric parameters across BMD categories

Variable	Normal BMD	Osteopenia	Osteoporosis	p^1	p^2
Total number of patients	77	30	16		
Age (years)*	12.00 (9.00–16.00)	11.00 (8.00–12.75)	13.00 (9.75–15.50)	0.048§	0.783§
Gender (Female)†	50 (64.9)	20 (66.7)	7 (43.8)	1.000¶	0.159¶
GFD duration (months)*	26.00 (4.00-58.00)	10.50 (3.00-29.00)	10.00 (1.75-39.25)	0.012§	0.180§
Calcium (mg/dL)‡	9.87 ± 0.34	9.83 ± 0.39	9.54 ± 0.57	0.567‖	0.003‖
Phosphorus (mg/dL)*	4.70 (4.20–5.00)	4.65 (4.20–5.07)	4.60 (4.30–4.83)	0.848§	0.603§
Alkaline phosphatase (U/L)*	208.00 (133.0–259.0)	193.50 (155.2–226.2)	178.50 (127.2–235.7)	0.579§	0.299§
Parathyroid hormone (pg/mL)*	35.00 (26.80–47.90)	30.95 (24.40–44.42)	35.15 (24.27–57.92)	0.579§	0.903§
25(OH)D_3 (ng/mL)*	22.00 (15.18–29.80)	23.36 (13.28–30.76)	25.36 (14.67–33.15)	0.672§	0.357§
Height z-score*	–0.45 (–1.20–0.39)	–0.29 (–1.12–0.29)	0.54 (–0.84–1.02)	0.994§	0.047§
Weight z-score*	–0.50 (–1.36–0.21)	–1.04 (–1.56––0.29)	–1.23 (–1.50––0.43)	0.059§	0.276§
BMI z-score*	–0.36 (–1.00–0.40)	–0.73 (–1.77––0.14)	–1.25 (–2.03––0.83)	0.011§	0.003§

: median (IQR), †: n(%), ‡: mean±SD, §: Mann–Whitney U test, ¶: Fisher's exact test, ‖: independent samples t-test, **BMD: bone mineral density, **GFD:** gluten-free diet, **25(OH)D_3:** 25-hydroxyvitamin D_3, **BMI:** body mass index, **p^1:** Normal BMD group vs osteopenia group **p^2:** Normal BMD group vs osteoporosis group Normal BMD group comprised patients with BMD-HAz > –1; Osteopenia group comprised patients with –2 < BMD-HAz ≤ –1; and Osteoporosis group comprised patients with BMD-HAz ≤ –2.*

and osteoporosis in the literature vary widely, largely due to methodological heterogeneity, including differences in study populations, timing of assessment, reference curves, and the use of alternative adjustment approaches based on age and/or height (10,12,18). At diagnosis, Kırsaçlıoğlu reported low BMD rates of 56.7% based on BMD-AAz and 21.6% based on BMD-HAz, while Çamtosun reported osteoporosis rates of 12.8% using BMD-HAz and 26.7% using BMD-AAz (12,19). Across studies from different regions, osteoporosis has been reported in 13–32% and low BMD in 22–78% of children with CD (4,11,20). Collectively, these findings indicate that osteopenia and osteoporosis can occur at clinically meaningful frequencies in pediatric CD, and that between-study variability is likely driven largely by methodological differences.

Several findings from our cohort underscore the importance of dietary adherence for bone recovery in pediatric CD. The GFD-adherent group had higher BMD-AAz and BMD-HAz than the diagnosis group, and BMD-HAz was also higher in the GFD-adherent group than in the GFD-non-adherent group, suggesting that sustained adherence to a GFD may be a key determinant of improvement in bone mineralization. Data from different populations likewise show that BMD tends to be lower in patients who have not yet initiated a GFD or who remain non-adherent, and that bone outcomes improve following dietary treatment (4,6,9,11,20). Moreover, pediatric series have reported BMD improvement as early as 6 months after diagnosis when vitamin D and Ca supplementation is appropriately provided, and have highlighted the first year

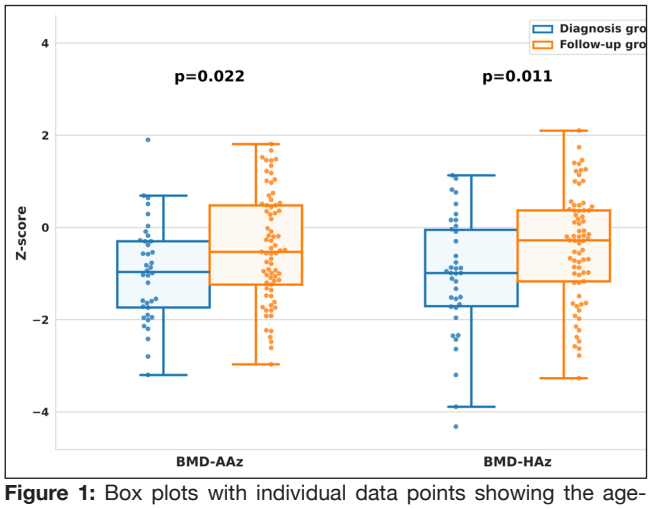

Figure 1: Box plots with individual data points showing the age-adjusted bone mineral density z-score (BMD-AAz) and height-adjusted bone mineral density z-score (BMD-HAz) in the Diagnosis and Follow-up groups. Boxes show the median (center line) and interquartile range (IQR), and points represent individual patient z-score values.

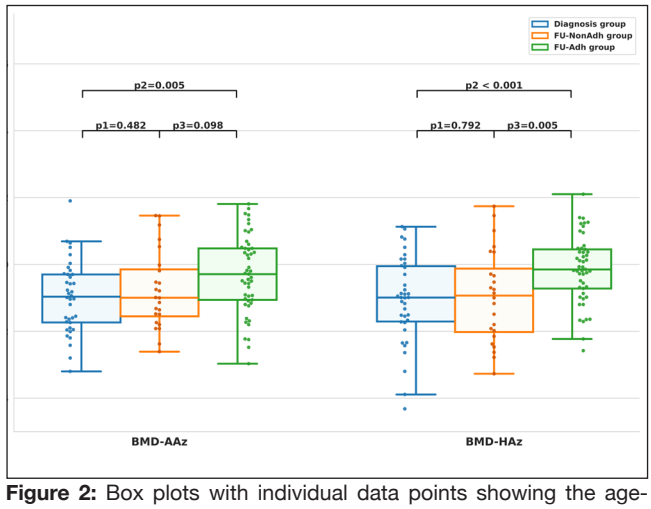

Figure 2: Box plots with individual data points showing the age-adjusted bone mineral density z-score (BMD-AAz) and height-adjusted bone mineral density z-score (BMD-HAz) in the diagnosis group, GFD-non-adherent follow-up group (FU-NonAdh group), and GFD-adherent follow-up group (FU-Adh group). Boxes show the median (center line) and interquartile range (IQR), and points represent individual patient z-score values. p1: Diagnosis group vs. FU-NonAdh group, p2: Diagnosis group vs. FU-Adh group, p3: FU-NonAdh group vs. FU-Adh group.

as a particularly critical period for recovery (19,21). Along the same lines, the longer GFD duration observed in the normal BMD group compared with the osteopenia group in our study supports a time-dependent benefit of remaining on a GFD. Overall, these results suggest that gains in bone health in pediatric CD may be more closely related to sustained GFD adherence during follow-up, together with intestinal healing and improved absorption, than to baseline characteristics at diagnosis.

In our cohort, the low BMD group had a lower BMI z-score than the normal BMD group, and BMI z-scores decreased stepwise from the normal BMD group to the osteopenia and osteoporosis groups, suggesting that impaired bone mineralization may accompany a less favorable anthropometric profile. This pattern is biologically plausible, as malabsorption and inadequate weight gain in CD may limit bone mass accrual, and lower body mass may reduce mechanical loading on the skeleton. Prior pediatric data have similarly suggested that a lower BMI may increase the likelihood of low BMD and that BMI could serve as a practical marker for clinical screening of reduced bone density (4,18). However, some pediatric series have reported BMD improvement shortly after diagnosis despite no clear differences in BMI SDS across BMD categories, implying that BMI-independent factors, such as mucosal healing and improved nutrient absorption, may also contribute to bone recovery (11,21). In this context, and as shown in our study, children with lower BMI z-scores during follow-up may warrant closer evaluation for low BMD, and BMI may be considered a pragmatic clinical indicator within risk-based monitoring strategies.

In our study, Ca, P, ALP, PTH, and 25(OH)D_3 levels were comparable across the diagnosis and follow-up groups and between follow-up subgroups; however, when analyses were stratified by BMD categories, serum Ca levels, while remaining within the normal reference range, were lower in the osteoporosis group than in the normal BMD group. In CD, impaired intestinal absorption of Ca and 25(OH)D_3 due to villous injury and secondary hyperparathyroidism are among the key mechanisms underlying bone loss, and several series have reported lower serum Ca levels in patients who have not yet initiated treatment (4,6,9,11). The absence of between-group differences in 25(OH)D_3 in our cohort may be related to the increasingly widespread use of vitamin D supplementation in the community and routine clinical practice.

Limitations

Limitations should be acknowledged. Due to the retrospective nature of the study, data on the use of supplements such as Ca and/or vitamin D, pubertal characteristics, and fracture history were not available. In addition, the limited sample size in the osteoporosis group may have reduced statistical power for certain comparisons, including those related to GFD duration.

Conclusion

Low BMD is common in children with CD, and the most prominent improvement is observed during follow-up in patients considered adherent to a GFD. Patients in the diagnostic period, those who remain non-adherent during follow-up, and children with a low BMI may be prioritized for closer monitoring. Although routine biochemical parameters are often comparable, lower Ca levels may serve as a warning sign for osteoporosis. Overall, our findings suggest that improvements in bone health during follow-up tend to accompany intestinal healing achieved through GFD adherence, better nutrition, and a higher BMI.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by University of

Health Sciences Gülhane Scientific Research Ethics Committee (03.06.2025, reference number: 2025-339).

Contribution of the authors

Study conception and design: ST; data collection: ST, EGB; analysis and interpretation of results: ST, EGB; draft manuscript preparation: ST. 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 extend our heartfelt thanks to Prof. Dr. Necati Balamtekin for his invaluable guidance, encouragement, and unwavering support throughout the course of this study.

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Turkish Journal of Pediatric Disease

Original Article

Evaluation of awareness and knowledge levels of pediatric residents on tuberculosis

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Received : 23.12.2025, Accepted : 31.03.2026 DOI: 10.12956/TJPD.2026.1287

ABSTRACT

Objective: Data on pediatric residents' awareness and knowledge of childhood tuberculosis in Türkiye are limited. This study aimed to evaluate the awareness and knowledge levels of pediatric residents regarding childhood tuberculosis at Ankara City Hospital.

Materials and Methods: This cross-sectional study was conducted between August and September 2023 among pediatric residents at Ankara Bilkent City Hospital. A 15-item online multiple-choice questionnaire assessed knowledge related to epidemiology and prevention, clinical–laboratory–imaging evaluation, treatment, and prophylaxis of childhood tuberculosis. Incomplete or unsubmitted questionnaires were excluded from the analysis.

Results: A total of 172 pediatric residents participated in the study, of whom 72.7% were female. Eighty-six residents (50.0%) were classified as junior and 86 (50.0%) as senior. Senior residents demonstrated significantly higher correct response rates than junior residents regarding incorrect statements about BCG vaccination (53.5% vs. 38.4%, p=0.047), definition of close contact in tuberculosis (91.9% vs. 79.1% p=0.017), interpretation of abnormal PPD values (93.0% vs. 76.7%, p=0.003), microbiological diagnostic methods (80.2% vs. 58.1%, p=0.002), and typical radiographic findings in childhood pulmonary tuberculosis (89.5% vs. 74.4%, p=0.010) ($p<0.050$ for all). Correct response rates increased progressively with advancing residency year (X^2 : 37.295, df:1, $p<0.001$).

Conclusion: Senior pediatric residents demonstrated significantly higher knowledge levels regarding childhood tuberculosis compared with junior residents. These findings highlight the importance of structured and continuous educational programs beginning early in residency and reinforced throughout training. Given the endemic nature of tuberculosis in Türkiye, targeted and regularly updated educational interventions may improve early recognition, diagnostic accuracy, appropriate treatment, and overall clinical outcomes. Future multicenter studies incorporating key domains of tuberculosis knowledge—epidemiology and prevention, clinical–laboratory–imaging evaluation, and treatment and prophylaxis—may help identify regional gaps and guide standardized educational strategies.

Keywords: Attitudes, child, internship and residency, health knowledge, practice, surveys and questionnaires, tuberculosis

Introduction

Childhood tuberculosis (TB) remains an important global public health problem due to diagnostic challenges, limited bacteriological confirmation, and the relatively higher frequency of extrapulmonary involvement in young children (1–4). Children under five years of age are at increased risk for rapid progression to severe disease, including miliary TB and TB meningitis, and therefore pediatric cases serve as indicators of recent transmission within the community (1,2). Transmission in children most commonly occurs from an infectious adult household contact, making accurate identification of close contacts, appropriate contact evaluation, and risk-based management essential components of TB control (1). Diagnosis relies on the combined assessment of clinical findings, radiological features, and evidence of infection. The tuberculin skin test is performed using purified protein derivative (PPD), and

throughout this manuscript, the term TST refers to PPD-based testing. Interpretation of these tests varies according to age, Bacillus Calmette–Guérin (BCG) vaccination status, and immunosuppression (1,2). Prolonged cough, unexplained fever, and weight loss or growth failure are the most common clinical manifestations, while unilateral hilar or mediastinal lymphadenopathy with ipsilateral parenchymal consolidation is the typical radiological finding (1,2). Given the paucibacillary nature of childhood TB, current guidelines recommend the combined use of smear microscopy, culture, and molecular tests such as Xpert MTB/RIF Ultra (1,2). Treatment is based on a standard six-month regimen, and successful outcomes depend on regular follow-up, early recognition of adverse drug effects, and appropriate preventive therapy for children with latent tuberculosis infection (LTBI) (1,2). Accurate knowledge of prophylaxis indications and risk-based management strategies is therefore essential in pediatric clinical practice. Despite the clinical importance of childhood TB, studies evaluating pediatric residents' knowledge and awareness remain scarce, with existing data largely derived from non-pediatric trainees or physicians from other specialties (5–8). This highlights a significant gap in the literature. The present study aimed to address this gap by comprehensively assessing pediatric residents' knowledge and awareness of childhood tuberculosis, including epidemiology, prevention, diagnosis, and treatment–prophylaxis practices, and to explore potential differences according to residency year and clinical exposure.

Materials and Methods

Study design and participants

This descriptive, cross-sectional study was carried out among pediatric residents with 0–48 months of training at Ankara Bilkent City Hospital, 172 pediatric residents in Türkiye during August–September 2023. The institution name has been anonymized to preserve the integrity of the double-blind peer-review process. Only residents who participated voluntarily and completed the entire questionnaire were included in the study. Those who declined participation or provided incomplete survey forms were excluded from the final analysis. All eligible residents during the study period were invited to participate, and no sampling method was applied.

Questionnaire

A 15-item, multiple-choice questionnaire was developed and distributed via Google Forms. The questionnaire consisted of three demographic items (age, year of residency, and type of institution) and 12 knowledge-based questions. The knowledge-based items assessed pediatric tuberculosis–related domains, including clinical manifestations, diagnostic approaches (laboratory and imaging findings), treatment protocols, and prophylactic practices. The questionnaire was developed by the authors based on current national and international tuberculosis guidelines and a comprehensive literature review. Content validity was evaluated by two pediatric infectious diseases specialists. The demographic items were not included in the knowledge score analysis; therefore, knowledge assessment tables begin with Question 4.

Procedures

Following administrative approval, the survey link was disseminated through official departmental communication channels and closed social media platforms used by pediatric residents. All eligible residents were invited to participate during the study period, and participation was entirely voluntary. Prior to accessing the questionnaire, participants were presented with an information and consent page outlining the study objectives, the voluntary nature of participation, and assurances of confidentiality. No personal identifiers were collected, and responses were recorded anonymously. Electronic informed consent was obtained before enrollment. To minimize response bias, correct answers were disclosed only after participants completed and submitted the questionnaire. Participants were allowed to complete the survey only once, and duplicate responses were restricted by the survey platform settings.

Classification of pediatric resident seniority

At the participating tertiary care university hospital, pediatric residents undergo a formal seniority examination at the 24th month of their training. Individuals who successfully pass this assessment are classified as senior pediatric residents. Accordingly, first- and second-year residents (0–24 months of training) are categorized as juniors, whereas those in their third and fourth years of training (25–48 months) are regarded as seniors. This classification was used to explore potential differences in tuberculosis-related knowledge according to clinical exposure and progression within the residency program.

Pediatric resident rotation framework

At the participating tertiary care university hospital, pediatric residents rotate systematically through both inpatient and outpatient services of the Pediatric Infectious Diseases Unit. Each of the two inpatient wards is staffed monthly by two senior and two junior residents. Additionally, two senior residents and one to two junior residents are assigned each month to the Pediatric Infectious Diseases outpatient clinics. This structured rotation model provides consistent exposure to the evaluation, management, and follow-up of pediatric infectious diseases—including tuberculosis—throughout the residency training period. The presence of both junior and senior residents within the same rotation framework enables progressive responsibility and cumulative clinical experience, which may influence tuberculosis-related knowledge and practical competence.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, and comparisons were performed using the chi-square test or Fisher's exact test when appropriate. Trends between residency year and correct answer rates were assessed using the linear-by-linear association test. For all analyses, two-tailed tests were applied, and a p value of < 0.050 was considered statistically significant. To ensure 80% statistical power at a 95% confidence level—assuming an anticipated response rate of 80%—the required sample

size was calculated as 170 participants. The sample size calculation was performed using standard formulas for cross-sectional studies evaluating proportions.

Results

A total of 172 pediatric residents completed the survey, meeting the predetermined sample size requirement. Of the participants, 72.7% were female. Half of the respondents were junior residents (n = 86; 1st year: 42; 2nd year: 44), while the remaining half were senior residents (n = 86; 3rd year: 43, 4th year: 43). The distribution of participants across residency years was balanced, allowing for comparative analysis between junior and senior groups.

Responses to the survey questions related to epidemiology and prevention of tuberculosis in children

The knowledge levels of pediatric residents regarding epidemiology and prevention of childhood tuberculosis are presented in Table I. Senior residents demonstrated higher correct response rates than junior residents for questions related to BCG vaccination and the definition of close contact. For the item assessing identification of the incorrect statement about the BCG vaccine, 38.4% of junior residents answered correctly compared with 53.5% of senior residents (p=0.047). Similarly, in the question evaluating the definition of close contact with an infectious tuberculosis case, 79.1% of junior residents responded correctly versus 91.9% of senior residents (p=0.017). For the question assessing the most common source of tuberculosis transmission in children, correct responses were 89.5% among junior residents and 94.2% among senior residents; this difference was not statistically significant (p=0.265). Overall, statistically significant differences between junior and senior residents were observed in items related to BCG vaccination and close contact definition, whereas no significant difference was found for knowledge of the primary transmission source.

Responses to questions on clinical-laboratory-imaging findings

The responses of pediatric residents to clinical, laboratory, and imaging-based questions regarding childhood tuberculosis are presented in Table I. Across most items, senior residents demonstrated higher correct response rates than junior residents. For the question assessing abnormal thresholds in TST interpretation, 76.7% of junior residents answered correctly compared with 93.0% of senior residents

Table I: Comparison of the correct response rates of pediatric residents according to seniority status to the survey questions

	Total*	Junior*	Senior*	p†
Total number of participants	172	86	86	-
Epidemiology and prevention	79 (45.9)	33 (38.4)	46 (53.5)	0.047
Question 4: Which of the following statements about the BCG vaccine is incorrect?	147 (85.5)	68 (79.1)	79 (91.9)	0.017
Question 5: Screening is required for individuals who have been in contact with a contagious tuberculosis patient. Which of the following does not meet the definition of close contact?	158 (91.9)	77 (89.5)	81 (94.2)	0.265
Question 6: From which source is tuberculosis most commonly transmitted to children?	146 (84.9)	66 (76.7)	80 (93.0)	0.003
Clinical, laboratory, and imaging findings	141 (82.0)	66 (76.7)	75 (87.2)	0.074
Question 7: Which of the following represents abnormal values in the interpretation of the TST?	156 (90.7)	74 (86.0)	82 (95.3)	0.036
Question 8: Which of the following corresponds to the definition of latent tuberculosis infection?	72 (41.9)	30 (34.9)	42 (48.8)	0.064
Question 9: Which of the following corresponds to the definition of tuberculosis disease?	119 (69.2)	50 (58.1)	69 (80.2)	0.002
Question 10: Which of the following is not one of the most common symptoms of pulmonary tuberculosis in children?	141 (82.0)	64 (74.4)	77 (89.5)	0.010
Question 11: In microbiological diagnosis of tuberculosis, which of the following tests must be performed on specimens such as sputum, gastric aspirates, tissue samples, cerebrospinal fluid, urine, pleural fluid, ascites, or synovial fluid?				
Question 12:What is the most common radiographic finding in childhood pulmonary tuberculosis?				
Treatment and prophylaxis	30 (17.4)	9 (10.5)	21 (24.4)	0.016
Question 13: Which of the following statements regarding tuberculosis prophylaxis is incorrect?	142 (82.6)	67 (77.9)	75 (87.2)	0.108
Question 14: Which of the following statements regarding childhood tuberculosis prophylaxis is incorrect?	141 (82.0)	67 (77.9)	74 (86.0)	0.165
Question 15: What is the standard traditional 6-month treatment regimen for tuberculosis?	125 (72.7	57 (66.3)	68 (79.1)	0.060
Question 16: In a patient receiving tuberculosis treatment, in which of the following adverse events should treatment not be discontinued?				

**: n(%), †: Chi Squared test was used*

(p=0.003). For the item defining latent tuberculosis infection, correct response rates were 76.7% among junior residents and 87.2% among senior residents; this difference was not statistically significant (p=0.074). In the question evaluating clinical findings of childhood tuberculosis, correct response rates were 86.0% among junior residents and 95.3% among senior residents (p=0.036). For the identification of extrapulmonary involvement sites, 34.9% of junior residents responded correctly compared with 48.8% of senior residents (p=0.064). A statistically significant difference was observed in the question addressing appropriate microbiological diagnostic methods—combining acid-fast bacilli (AFB) staining, culture, and molecular testing—where correct response rates were 58.1% among junior residents and 80.2% among senior residents (p=0.002). Senior residents also demonstrated higher accuracy in recognizing characteristic radiological findings (89.5% vs. 74.4%; p=0.010). Statistically significant differences between groups were observed in TST interpretation, microbiological diagnostic methods, radiological findings, and clinical findings, whereas differences in latent tuberculosis infection definition and extrapulmonary involvement did not reach statistical significance.

Responses to questions on treatment and prophylaxis

The responses of pediatric residents to questions regarding tuberculosis treatment and prophylaxis are presented in Table I. Senior residents demonstrated higher correct response rates than junior residents across all items; however, a statistically significant difference was observed for only one question. For the item assessing identification of an incorrect statement regarding tuberculosis prophylaxis, the correct response rate was 10.5% among junior residents and 24.4% among senior residents (p=0.016). For the second question related to childhood tuberculosis prophylaxis, correct response rates were 77.9% among junior residents and 87.2% among senior residents; this difference was not statistically significant (p=0.108). In the question evaluating knowledge of the conventional six-month tuberculosis treatment regimen, correct response rates were 77.9% among junior residents and 86.0% among senior residents (p=0.165). Regarding the question on which adverse effect during tuberculosis treatment does not require treatment discontinuation, correct response rates were 66.3% among junior residents and 79.1% among senior residents (p=0.060). A statistically significant difference between junior and senior residents was observed only for the item concerning identification of an incorrect statement about tuberculosis prophylaxis.

Trend by residency year

Figure 1 illustrates the correct response rates of pediatric residents to questions related to clinical findings, diagnostic evaluation, treatment, and prophylaxis of tuberculosis, stratified by seniority level. Senior residents achieved higher correct response rates than junior residents across all question categories. The differences were most pronounced in items related to diagnostic evaluation, including TST interpretation, microbiological diagnostic methods, and recognition of radiological findings. Similar patterns were observed in treatment and prophylaxis items. Figure 1 presents the distribution of correct response rates according to residency seniority without adjustment for additional variables.

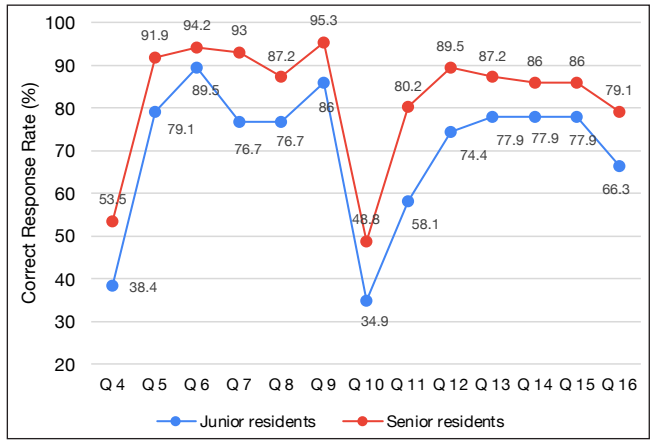

Figure 1: Comparison of correct response rates between junior and senior pediatric residents across survey questions.

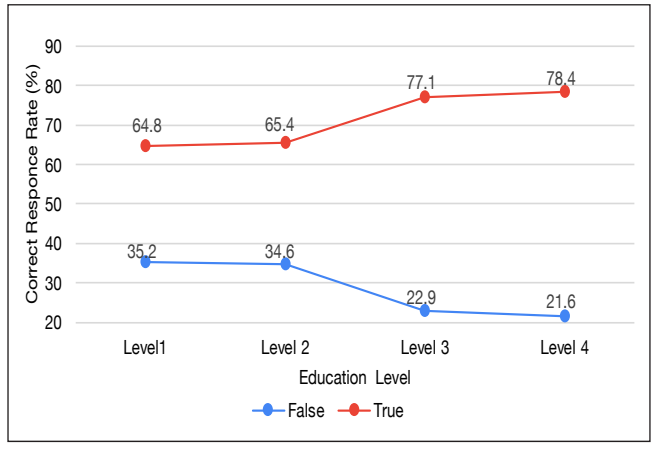

Figure 2: Linear-by-linear relationship between postgraduate year of pediatric residency and response accuracy.

Figure 2 demonstrates the relationship between postgraduate year of training and rates of correct and incorrect responses. According to the linear-by-linear association analysis, correct response rates were 64.8% and 65.4% among first- and second-year residents, respectively, increasing to 77.1% in third-year residents and 78.4% in fourth-year residents (p<0.001). Correspondingly, incorrect response rates decreased with advancing year of training. The linear-by-linear association test confirmed a statistically significant upward trend in correct response rates across residency years.

Discussion

This study provides a comprehensive evaluation of pediatric residents' knowledge and awareness regarding childhood tuberculosis across the domains of epidemiology and prevention, clinical–laboratory–imaging assessment, and treatment–prophylaxis practices. The findings reveal a consistent increase in correct response rates with advancing residency year, with senior residents outperforming junior residents in most knowledge domains. The differences were

particularly evident in areas requiring clinical judgment, such as interpretation of TST results, selection of appropriate microbiological diagnostic methods, and recognition of radiological findings. These results suggest that progressive clinical exposure and cumulative hands-on experience during residency contribute substantially to competency development in tuberculosis management. However, the presence of measurable knowledge gaps—especially among junior residents—indicates that reliance solely on experiential learning may be insufficient. For a disease that remains epidemiologically relevant and diagnostically complex, early incorporation of structured, competency-based tuberculosis education into residency curricula may help ensure more uniform knowledge acquisition across training levels.

Knowledge related to the epidemiology and prevention of childhood tuberculosis has been shown to vary according to level of training and clinical background. In Türkiye, one of the few studies focusing specifically on pediatric residents is that of Kara et al. (5), which identified substantial gaps in knowledge regarding national TB burden, BCG vaccination practices, and contact management; notably, post-BCG TST threshold interpretation was particularly problematic. Similarly, Akaslan Kara et al. (6) reported that even among pediatric infectious diseases physicians, although epidemiological awareness was relatively higher, deficiencies persisted in key preventive domains such as isolation measures and duration of infectiousness. Comparable patterns have been described in non-pediatric physician populations. Chida et al. (8) reported inconsistencies between theoretical knowledge and practical application in TB transmission dynamics and contact evaluation among internal medicine residents. Among primary healthcare providers, Aydemir et al. (9) and Kılıç et al. (10) demonstrated marked variability in knowledge related to transmission chains, contact tracing, and BCG-related preventive strategies. Ngo et al. (11) further highlighted inadequate screening of high-risk contacts and insufficient implementation of preventive strategies in private healthcare settings. Studies conducted among medical interns and students have likewise documented insufficient knowledge in prevention and prophylaxis domains (12–14). Moreover, investigations from low- and middle-income countries consistently report limited understanding of child contact management and preventive therapy indications despite recognition of household transmission as a key source (15–17). Within this broader literature, our findings align with prior evidence demonstrating variability in preventive knowledge across training levels. The higher performance of senior residents suggests that epidemiology- and prevention-related competencies may develop progressively through clinical exposure and cumulative patient contact. However, the persistence of knowledge gaps in foundational preventive topics—particularly BCG-related decision-making and close contact definitions—indicates that experiential learning alone may not ensure uniform competency acquisition. These findings support the integration of structured, curriculum-based tuberculosis education early in pediatric residency training to reinforce core preventive principles.

The existing literature indicates that while the clinical manifestations of childhood tuberculosis are generally well recognized, important gaps persist in key components of diagnostic algorithms, particularly in the interpretation of TST/IGRA results, microbiological confirmation strategies, and radiological evaluation. In the study conducted by Kara et al. among pediatric residents, recognition of clinical symptoms was high; however, interpretation of TST positivity thresholds was notably limited (5). Similarly, Akaslan Kara et al. reported relatively strong knowledge of conventional diagnostic tools such as mycobacterial culture and acid-fast bacilli smear among pediatric infectious diseases physicians, yet deficiencies were observed in more nuanced areas such as IGRA indications, highlighting heterogeneity within diagnostic competencies (6). International findings parallel these observations. Chida et al. (8) demonstrated suboptimal knowledge among internal medicine residents regarding the combined use of nucleic acid amplification tests (NAATs) and integrated diagnostic interpretation. Studies among medical interns and students likewise showed that, although recognition of clinical symptoms was adequate, interpretation of immunological tests and radiological findings represented consistent areas of weakness (12–14). In concordance with this body of evidence, our findings suggest that knowledge related to clinical presentation is comparatively well established across training levels, whereas more complex diagnostic reasoning—such as appropriate integration of microbiological tests and interpretation of radiological features—varies according to residency seniority. The stronger performance observed among senior residents may reflect cumulative clinical exposure and repeated engagement with diagnostic decision-making processes. However, the persistence of variability in algorithm-based diagnostic knowledge underscores the need for structured, guideline-oriented educational reinforcement rather than reliance solely on experiential learning.

Knowledge related to the treatment and prophylaxis of childhood tuberculosis has consistently been identified as a vulnerable domain across different physician groups. In Türkiye, Kara et al.(5) reported that although pediatric residents were generally familiar with first-line prophylactic agents and the standard duration of active tuberculosis treatment, more nuanced aspects —such as prophylaxis indications and management in special clinical scenarios— remained insufficiently understood. Similarly, Akaslan Kara et al. (6) observed relatively high familiarity with conventional treatment regimens among pediatric infectious diseases physicians, but heterogeneous knowledge regarding latent tuberculosis infection (LTBI) prophylaxis and alternative regimens. Comparable patterns were described by Altındiş et al. (7), who noted that while core treatment principles were recognized, gaps persisted in prophylaxis indications and follow-up strategies. International data reinforce these findings. Joshi et al. (18) demonstrated that healthcare workers' knowledge scores for treatment and prophylaxis were lower than those for epidemiology, particularly regarding identification of pediatric populations eligible for LTBI therapy. Studies by Vukugah et al. (16) and Kaumba et al. (17) similarly reported limited accuracy in recognizing preventive therapy indications, with improvement observed primarily among clinicians with greater tuberculosis-related clinical exposure. Among medical interns and students, treatment-related knowledge has also been shown to lag behind recognition

of clinical manifestations (19). In Indonesia, Main et al. (20) documented substantial deficiencies in understanding treatment duration and prophylaxis strategies among healthcare workers, including physicians. In alignment with this body of evidence, our findings indicate that while familiarity with the conventional six-month treatment regimen is relatively well established, knowledge gaps become more apparent in algorithm-based decision-making areas such as prophylaxis indications, duration of preventive therapy, and interpretation of adverse effects that do not necessitate treatment discontinuation. The comparatively stronger performance of senior residents suggests progressive knowledge acquisition through cumulative clinical exposure; however, the persistence of variability across training levels highlights that experiential learning alone may not be sufficient to ensure consistent competency in preventive decision-making. Given that preventive therapy plays a central role in interrupting transmission and reducing progression to active disease in high-risk pediatric populations, deficiencies in prophylaxis-related knowledge carry important public health implications. These findings support the need for structured, guideline-based, and case-oriented educational interventions—implemented early and reinforced longitudinally throughout residency—to standardize treatment–prophylaxis competencies in pediatric training programs.

Progression through residency is generally associated with increasing clinical responsibility and cumulative patient exposure, factors that may influence tuberculosis-related knowledge acquisition. The literature suggests that although both theoretical understanding and clinical competence tend to improve over time, such gains often occur through experiential learning rather than through formally structured curricula. Chida et al. (8) demonstrated that diagnostic knowledge among internal medicine residents improved with seniority, particularly in the application of diagnostic algorithms. Similarly, Vukugah et al. (16) reported higher diagnostic and treatment-related knowledge scores among clinicians with longer experience in tuberculosis-focused units. Joshi et al. (18) also observed progressive improvement across training years, while identifying notable deficiencies during the early stages of residency. Consistent with these reports, our findings demonstrate a statistically significant upward trend in correct response rates across residency years. This progressive pattern was particularly evident in domains requiring algorithm-based reasoning, including diagnostic integration, treatment selection, and prophylaxis decision-making. However, the presence of measurable knowledge variability in the early years of training suggests that experiential exposure alone may not ensure uniform competency acquisition. Taken together, these findings highlight the importance of complementing clinical exposure with structured, guideline-oriented educational strategies. Early integration of case-based learning, standardized teaching sessions on contact management and prophylaxis, and periodic reinforcement of diagnostic algorithms may facilitate more consistent knowledge development throughout residency. While seniority-related improvement is evident, systematic curricular design appears essential to minimize early-stage knowledge gaps and promote standardized competency in childhood tuberculosis management.

Limitations

This study has several limitations. First, the sample was drawn from pediatric residents at a single tertiary care institution, which may limit the generalizability of the findings to other training settings. Second, the cross-sectional design precludes assessment of causality between clinical exposure and knowledge acquisition. Additionally, the use of an online questionnaire introduces the possibility that respondents may have accessed external resources while completing the survey, potentially inflating correct response rates. Furthermore, knowledge was assessed using a structured questionnaire rather than direct observation of clinical practice; therefore, actual decision-making behaviors in real clinical settings may differ from self-reported knowledge levels. Despite these limitations, the study provides a focused evaluation of tuberculosis-related knowledge across different stages of pediatric residency training and offers insight into areas requiring targeted educational reinforcement.

Conclusion

In conclusion, this study demonstrates a clear association between residency seniority and tuberculosis-related knowledge among pediatric residents. Higher levels of competency were observed in senior trainees, particularly in domains requiring integrated diagnostic reasoning and prophylaxis decision-making. The progressive pattern across training years suggests that cumulative clinical exposure contributes to knowledge development; however, variability in early training stages indicates that experiential learning alone may not ensure standardized competency. These findings underscore the importance of incorporating structured, competency-based tuberculosis education into pediatric residency curricula from the early phases of training. In the context of Türkiye's ongoing tuberculosis burden and the inherent diagnostic complexity of pediatric cases, systematic reinforcement of guideline-based diagnostic and prophylaxis algorithms may support earlier recognition, more accurate clinical decision-making, and improved patient care outcomes. Future multicenter studies with larger and more diverse training settings are needed to validate these findings and to inform national strategies for strengthening pediatric tuberculosis education.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (16.08.2023, reference number: E2-23-4863).

Contribution of the authors

Concept: ÖG, AÖP; Design: ÖG, AÖP; Data Collection or Processing: AYG, SKY, BG; Analysis or Interpretation: FÜ, AYG; Database and Informatics Support: FÜ, AYG; Literature Search: ÖG, AYG, SKY, BG; Writing – Original Draft: ÖG, AÖP, AYG; Writing – Review & Editing: ÖG, AÖP, AYG, FÜ, BG, SKY

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

Maternal versus paternal rejection in adolescent suicidality: A study in a socioeconomically disadvantaged cohort

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Received : 15.12.2025, Accepted : 06.04.2026 DOI: 10.12956/TJPD.2026.1283

ABSTRACT

Objective: Parental acceptance–rejection is linked to adolescent mental health, yet its distinct maternal versus paternal associations with suicidality in disadvantaged youth remain underexplored. This exploratory study aimed to delineate these specific relationships, examining perceived parental rejection as a predictor for suicidal ideation (SI) intensity, non-suicidal self-injury (NSSI), and psychopathology in a high-risk cohort.

Materials and Methods: Forty-six adolescents (82.6% girls; M age = 15.7±1.1) hospitalized in an ICU following a serious suicide attempt completed the Parental Acceptance-Rejection/Control Questionnaire and Youth Self-Report. A clinician assessed suicidality using the Columbia-Suicide Severity Rating Scale. Bivariate and multivariate regression analyses were performed to identify key predictors.

Results: A clear dissociation emerged between maternal and paternal roles. Greater perceived maternal rejection—particularly indifference and neglect—was significantly associated with higher SI intensity ($B = 0.128$, $p < 0.001$), and a perceived lack of maternal warmth correlated with depressive symptoms ($r = 0.454$, $p = 0.002$). In contrast, paternal acceptance was unrelated to SI or internalizing problems; however, paternal hostility was significantly associated with externalizing behaviors ($r = 0.381$, $p = 0.013$). Additionally, conduct problems were the only significant predictor of lifetime NSSI (OR = 1.125, $p = 0.040$), and SI intensity predicted a history of multiple suicide attempts (OR = 1.559, $p = 0.016$).

Conclusion: In this high-risk cohort, maternal rejection appeared to be more closely linked to suicidal ideation and internalizing distress, whereas paternal hostility showed a stronger association with externalizing behaviors. These exploratory findings point to the potential value of family-centered prevention approaches that enhance maternal responsiveness and address behavioral dysregulation to help mitigate suicide risk.

Keywords: Adolescent, parent-child relations, self-injurious behavior, suicidal ideation, socioeconomic disparities in health

Introduction

Suicide represents a significant public health challenge and is one of the leading causes of mortality in the adolescent population (1,2). Non-fatal suicidal behaviors, including suicidal ideation (SI), suicide attempts, and other forms of self-harm, signal profound psychological distress and often reflect both individual vulnerabilities and systemic gaps in prevention and support services (3,4). Current understanding suggests that suicide is not an isolated event but the culmination of a complex trajectory shaped by familial, social, cultural, and psychological factors beginning early in life (5,6).

Attachment theory posits that early parent–child relationships shape internal working models that influence emotion regulation, self-perception, and interpersonal functioning across the lifespan (7). Secure attachment is associated with a foundational sense of safety and self-worth, facilitates effective emotion regulation, and promotes resilience to adversity (8). In the absence of stable parental support, adolescents may adopt maladaptive coping strategies, which can exacerbate existing psychological distress (9,10). Within this framework, suicidal behavior can emerge as a maladaptive response to perceived rejection or emotional invalidation, particularly among youth who feel unworthy or

unsupported in their familial or social environments (11,12). These relational disruptions contribute to dual vulnerabilities: impaired development of internal regulation capacities and reduced access to effective external support during crises.

Among adolescents experiencing socioeconomic adversity, chronic stressors such as financial instability, limited access to care, and social marginalisation further intensify emotional distress and elevate suicide risk (13,14). Within these high-risk contexts, parental acceptance–rejection may be especially salient in shaping adolescent's affective development and coping capacities (15).

Despite extensive evidence linking parental acceptance–rejection to youth mental health, research directly examining these dynamics among socioeconomically disadvantaged adolescents who attempt suicide remains limited. Clarifying how parental behaviors interact with economic adversity is essential for developing targeted interventions to reduce suicide risk in these vulnerable populations. Accordingly, this study aimed to (1) describe patterns of perceived maternal and paternal acceptance–rejection in socioeconomically disadvantaged adolescents who had recently survived a medically serious suicide attempt; (2) examine how these parental relationship dimensions were associated with psychopathology, and non-suicidal self-injury (NSSI); and (3) explore whether these associations differed by gender. Through this, we sought to deepen understanding of how parent–child relationship patterns contribute to suicidality in high-risk youth.

Materials and Methods

The study was conducted between June 2021 and December 2021. Written informed consent was obtained from parents and assent from all adolescents prior to participation.

Participants and recruitment

The final sample consisted of 46 adolescents (38 girls, 82.6%; 8 boys, 17.4%), with a mean age of 15.7±1.15. Participants were recruited from low- to middle-income households, classified using the Hollingshead-Redlich Socioeconomic Status Scale (16,17). All participants were admitted to the intensive care unit (ICU) following a medically serious suicide attempt, defined as an overdose or ingestion of a toxic substance.

Fifty-nine adolescents were screened; 13 were excluded due to insufficient contact with a non-custodial parent (n = 6), early parental loss (n = 3), or a history of severe psychological trauma (n = 4).

Inclusion criteria were belonging to a low- or middle-income household, clinically assessed intelligence, and living with both biological parents or maintaining regular contact with the non-custodial parent. Exclusion criteria included chronic medical illness, intellectual disability, autism spectrum disorder, psychotic or bipolar disorders, and documented severe trauma histories.

Measures

Socioeconomic status (SES): The Hollingshead-Redlich Scale, was used to calculate a composite index of SES based on parental occupational status and educational attainment (16,17).

Emotional and behavioral problems: The Youth Self-Report (YSR) assessed internalizing and externalizing problems (18). T-scores (M = 50±10) were used in analyses. The Turkish version of the YSR has shown good reliability and validity (19).

Perceived parental acceptance-rejection: The Parental Acceptance-Rejection/Control Questionnaire (PARQ) measured adolescents' perceptions of maternal and paternal warmth, hostility, indifference/neglect, and rejection (20). The Turkish adaptation has demonstrated good internal consistency (21).

Suicidality assessment: The Columbia Suicide Severity Rating Scale (C-SSRS) is a semi-structured interview used to assess the severity and intensity of SI, and NSSI (22). The Turkish version has also shown strong psychometric properties (23).

Procedure

Assessments took place within 48 hours of ICU discharge. A trained clinician administered the C-SSRS, followed by self-administered YSR and PARQ questionnaires completed under supervision. Demographic and clinical data were obtained from medical records and participant report. All adolescents were scheduled for psychiatric follow-up, and those identified as acutely at risk were referred for immediate inpatient evaluation.

Statistical analysis

All statistical analysis were performed using IBM Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive statistics were calculated for all variables. Normality was examined through the Shapiro–Wilk test and visual inspection. Group differences were evaluated using independent-samples t-tests. Fisher's exact test was used for categorical variables. Pearson's or Spearman's correlations were conducted to examine bivariate associations.

To address primary research questions:

Hierarchical multiple regression predicted suicidal ideation intensity from parental acceptance–rejection subscales, adjusting for age and gender. Binary logistic regression identified predictors of lifetime NSSI and multiple suicide attempts.

Model fit indices and 95% confidence intervals were reported. All statistical tests were two-tailed, and the alpha level for statistical significance was set at $p<0.050$.

Results

Sample characteristics

Regarding socioeconomic status, 21.7% (n=10) of participants belonged to middle-income families (Hollingshead-Redlich Class III), while the majority, 78.3% (n=36), originated from low-income households (Classes IV and V). The mean educational attainment was 6.5±3.1 for mothers and 8.3±3.0 years for fathers.

Psychiatric history and substance use behaviors

A significant proportion of the sample reported a history of psychiatric morbidity and risk behaviors. A majority (82.6%, n=38) had a history of prior psychiatric consultation. Nearly half of the adolescents reported current tobacco use (47.8%, n=22), one-third reported alcohol consumption (32.6%, n=15), and a smaller portion reported other substance use (8.7%, n=4). In

terms of suicidality, 73.9% (n=34) had a history of one or more previous suicide attempts, and 80.4% (n=37) had engaged in NSSI at least once in their lifetime (see Table I for detailed statistics).

Gender differences

A significant gender difference was observed for NSSI (Fisher's Exact Test, p=0.030), with girls reporting a higher lifetime prevalence (86.8%) than boys (50.0%). No other significant gender differences were found for previous attempts, psychiatric history, perceived maternal or paternal acceptance, SI severity or intensity, or internalizing and externalizing problems (Table I).

Comparison of single-attempt versus multiple-attempt groups

Adolescents with multiple attempts (n=34) had significantly higher SI severity and intensity than those with a single attempt (n=12; p = 0.002 and p = 0.004, respectively Table II). Although mean perceived maternal acceptance scores (higher scores indicate greater rejection) were numerically higher in the multiple-attempt group, this difference did not reach statistical significance (t(44) = -1.84, p=0.073). No significant group differences were observed for perceived paternal acceptance or internalizing and externalizing problems (p = 0.687, p = 0.153, and p = 0.183, respectively).

Correlates of suicidal ideation

Bivariate correlations were performed to examine the relationships between key variables. SI severity was significantly and positively correlated with a history of suicide attempts (r(44)=0.395, p=0.007, 95% CI [0.11, 0.62]) and with preparatory acts for suicide (r(44)=0.752, p<0.001, 95% CI [0.60, 0.85]). Furthermore, SI intensity showed strong positive correlations with maternal subscales indicative of greater perceived rejection: Warmth/Affection (higher scores reflect less warmth; r(44)=0.605, p<0.001, 95% CI [0.38, 0.76]), Indifference/Neglect (r(44) = 0.631, p<0.001, 95% CI [0.42, 0.78]), and Undifferentiated Rejection (r(44)=0.579, p < 0.001, 95% CI [0.35, 0.75]). SI intensity was also correlated with a history of previous attempts (r(44)=0.436, p=0.002, 95% CI [0.16, 0.65]). In contrast, no significant associations emerged between SI severity or intensity and any paternal acceptance scores.

Maternal acceptance-rejection and psychological correlates

Higher total maternal rejection was significantly associated with several YSR subscales, including withdrawn/depressed problems (r(44 =0.405, p=0.006, 95% CI [0.12, 0.63]), thought problems (r(44)=0.391, p=0.008, 95% CI [.10, .61]), total internalizing problems (r(44)=0.351, p=0.018, 95% CI [0.06, 0.59]), affective problems (r(44) =0.311, p=0.037, 95% CI [0.01, 0.56]), and post-traumatic stress problems (r(44)=0.298, p= 0.047, 95% CI [0.00, 0.55]).

Among the maternal acceptance subscales, reduced Warmth/ Affection showed the strongest correlation with withdrawn/ depressed problems (r(44)=0.454, p=0.002, 95% CI [0.19, 0.66]), while the Indifference/Neglect was positively correlated with both post-traumatic stress disorder (PTSD)-related problems (r(44)=0.394, p=0.007, 95% CI [0.11, 0.62]) and oppositional defiant behavior (r(44)= 0.341, p =0.022, 95% CI [0.05, 0.58]).

Paternal acceptance-rejection and psychological correlates

No significant associations were identified between the total paternal acceptance score and any YSR subscales. However, paternal Hostility/Aggression was negatively correlated with age (r(44) = -0.321, p = 0.038, 95% CI [-0.57, -0.02]) and positively associated with rule-breaking behavior (r(44) = 0.343, p = 0.026, 95% CI [0.05, 0.58]), aggressive behavior (r(44) = 0.376, p = 0.014, 95% CI [0.08, 0.60]), total externalizing problems (r(44) = 0.381, p = 0.013, 95% CI [0.09, 0.61]), and conduct problems (r(44) = 0.376, p = 0.014, 95% CI [0.08, 0.60]).

Predictors of NSSI: Binary logistic regression analysis

The logistic regression model predicting lifetime NSSI was statistically significant (Omnibus Test: p=0.014), explaining approximately 28.3% of the variance (Nagelkerke R^2 = 0.283). The Hosmer-Lemeshow test indicated good model fit (p= 0.599). As shown in Table III, conduct problems emerged as a significant predictor; each one-unit increase in the conduct

Table I: Clinical and psychosocial characteristics

Variables	Full Sample	Girls	Boys	p
Total number of patients	46	38	8	-
Clinical History*				
Prior psychiatric consultation*	38 (82.6)	31 (81.6)	7 (87.5)	0.570
History of multiple suicide attempts*	34 (73.9)	29 (76.3)	5 (62.5)	0.410
Lifetime non-suicidal self-injury (NSSI)*	37 (80.4)	33 (86.8)	4 (50.0)	0.030
Parental Rejection (PARQ)†				
Perceived Maternal Rejection (Total)	151.7±49.9	156±48	131.7±56.6	0.216
Perceived Paternal Rejection (Total)	151.3±50.4	155.2±49.6	134.8±53.6	0.309
Suicidality (C-SSRS) †				
SI Severity (0-5)	4.4±0.6	4.5±0.5	4.0±1.0	0.174
SI Intensity (5-25)	17.3±2.8	17.5±2.7	16.1±3.1	0.201
Psychopathology (YSR) †				
Internalizing Problems (T-Score)	75.0±9.1	75.2±9.3	74.0±8.7	0.733
Externalizing Problems (T-Score)	64.1±10.9	63.8±11.7	65.2±6.3	0.754
Withdrawn/Depressed (T-Score)	77.9±11.3	79.0±10.9	72.8±12.4	0.168

:** *n(%) (Fisher's Exact Test),* **†:** *mean±SD (Student T test),* ***C-SSRS: *Columbia-Suicide Severity Rating Scale,* ***PARQ:*** *Parental Acceptance-Rejection/Control Questionnaire,* ***YSR:*** *Youth Self-Report*

Table II: Comparison of adolescents with a single suicide attempt versus multiple suicide attempts

Variables	Single-attempt	Multiple-attempt	t	df	p	Cohen's d
Total number of patients	12	34	-	-	-	-
SI severity	4.0±0.8	4.65±0.4	-3.22	44	0.002†	1.25
SI intensity	15.3±2.8	18.0±2.5	-3.03	44	0.004†	1.02
Maternal rejection	128.2±54.3	159.2±46.7	-1.84	44	0.073	0.63
Paternal rejection	156.4±52.3	149.3±50.3	0.41	44	0.687	0.14
Internalizing prob.	72.6±7.8	76.6±9.8	-1.46	44	0.153	0.44
Externalizing prob.	62.5±11.5	65.2±10.5	-1.35	44	0.183	0.24

***:** *mean±SD,* **†:** *Student's T-Test*

Table III: Summary of binary logistic regression analysis predicting lifetime non-suicidal self-injury (NSSI)

Predictors	B	SE	Wald	p	OR	Lower*	Upper*
Conduct Problems	0.118	0.057	4.234		0.040	1.125	1.006
Total Competence	-0.085	0.048	3.098		0.078	0.919	0.836

:** *95% CI,* ***Omnibus Test of Model Coefficients: *$\chi^2(2)=8.52$, $p=0.014$,* ***Nagelkerke*** *$R^2 = 0.283$,* ***Hosmer-Lemeshow test:*** *$p=0.599$,* ***CI:*** *confidence interval,* ***OR:*** *odds ratio,* ***B:*** *unstandardized regression coefficient,* ***SE:*** *standard error.*

Table IV: Summary of binary logistic regression analysis predicting multiple suicide attempts

Predictors	B	SE	Wald	p	OR	Lower*	Upper*
SI Intensity	0.444		0.184	5.844	0.016	1.559	1.088
Attention Problems	0.080		0.042	3.597	0.058	1.083	0.997

:** *95% CI,* ***Omnibus Test of Model Coefficients: *$\chi^2(2) = 13.06$, $p = 0.001$,* ***Nagelkerke*** *$R^2 = 0.376$,* ***Hosmer-Lemeshow test:*** *$p = 0.103$*

Table V: Summary of multiple linear regression analysis predicting suicidal ideation intensity

Predictors	B	SE	β	t	p	VIF
(Constant)	14.962	1.583		9.452**	<0.001	
Maternal Indifference/Neglect	0.128	0.027	0.556	4.727**	<0.001	1.085
Previous Suicide History	1.784	0.780	0.780	2.287*	0.027	1.085

R^2** = 0.465,* ***Adjusted *$R^2 = 0.440$,* ***$F(2, 42)$*** *$= 18.26$, $p < 0.001$,* ***β*** *= standardized regression coefficient,* ***VIF :*** *Variance Inflation Factor*

problems score was associated with a 1.13-fold increase in the odds of having engaged in NSSI (Odds Ratio [OR] = 1.125, 95% CI [1.006, 1.259], p=0.040). Total competence showed a non-significant trend towards a protective effect (p=0.078).

Predictors of multiple suicide attempts: Binary logistic regression analysis

A second logistic regression model predicting a history of multiple suicide attempts (vs. a single attempt) was also significant (Omnibus Test: p=0.001), accounting for 37.6% of the variance (Nagelkerke R^2=0.376). The model demonstrated acceptable fit (Hosmer-Lemeshow p=0.103). As detailed in Table IV, SI intensity was a significant predictor, with each one-unit increase in the intensity score associated with a 1.56-fold increase in the odds of belonging to the multiple-attempt group (OR =1.559, 95% CI [1.088, 2.235], p=0.016). Attention problems showed a trend toward significance (p= 0.058).

Predictors of SI intensity: Multiple linear regression analysis

The multiple linear regression model significantly predicted SI intensity, F(2, 42)=18.26, p<0.001, and accounted for 44.0% of the variance in SI intensity (Adjusted R^2=0.440). Two predictors were significant in the final model (Table V). Perceived maternal Indifference/Neglect was a strong positive predictor of SI intensity (B =0.128, SE=0.027, β =0.556, t(42) = 4.73, p<0.001). Additionally, a history of previous suicide attempts also significantly predicted higher SI intensity (B =1.784, SE=0.780, t(42)=2.29, p=0.027). These results indicate that higher perceived maternal indifference and a personal history of attempts are substantial contributors to the intensity of current suicidal ideation.

Discussion

The findings of this study provide a nuanced perspective on the interplay between familial factors, psychopathology, and suicidal behaviors among socioeconomically disadvantaged adolescents who have survived a medically serious suicide attempt. Our results particularly underscore the distinct roles of maternal and paternal relationships, highlight key correlates of NSSI and repeated suicide attempts, and offer insights into potential gender-specific expressions of distress.

A key finding of this study is how the mother–child relationship relates to adolescent outcomes. Echoing prior research, higher levels of perceived maternal rejection were robustly

associated with greater SI intensity (24). More specifically, diminished maternal warmth was primarily related to internalizing symptoms such as depression, whereas maternal indifference and neglect were more strongly correlated with post-traumatic stress and oppositional behaviors. These results align with developmental literature suggesting that affectionate maternal relationships buffer against internalizing distress, whereas neglect is linked to more pervasive psychopathology (25-27). In socioeconomically disadvantaged contexts, where mothers often function as the main source of emotional support, maternal rejection may deprive adolescents of the essential emotional scaffolding required for adaptive coping and affect regulation, thereby further amplifying suicidal ideation (28,29).

By contrast, paternal acceptance showed no significant association with suicidal ideation in our sample. This finding diverge from several studies reporting that reduced paternal warmth and increased rejection predict greater suicidal thoughts in other cultural contexts (30,31). This discrepancy may reflect the specific sociocultural and economic context of our Turkish, low-income cohort, in which fathers traditionally assume primarily financial and disciplinary roles. In line with this interpretation, paternal acceptance was also unrelated to internalizing symptoms, despite broader literature suggesting that low paternal acceptance is typically linked to internalizing and externalizing problems (32). Notably, however, paternal hostility and aggression were significantly associated with rule-breaking and aggression in our sample, consistent with evidence that authoritarian or hostile fathering contributes to conduct problems (33). The stronger association of paternal hostility with difficulties in younger adolescents likely reflects normative patterns of stricter paternal control in early and mid-adolescence, suggesting that, negative paternal interactions may be more likely to manifest as outward behavioral dysregulation than as internalizing distress (34).

Regarding gender, girls in our study reported significantly higher rates of NSSI than boys, echoing broader international evidence that adolescent girls are more likely to engage in self-injurious behaviors (35). However, gender did not emerge as a significant factor in relation to SI severity or intensity, parental relationships, or internalizing and externalizing symptoms. This pattern suggests that while gender may shape the form through which distress is expressed (e.g., NSSI), the quality of parental relationships may represent a shared correlate of psychopathology for both girls and boys in this high-risk group (36).

Our regression analyses identified specific psychological correlates of risk behaviors. Conduct problems were the only significant predictor of lifetime NSSI, supporting models that view both NSSI and disruptive behaviors as expressions of shared vulnerabilities such as impulsivity and emotion dysregulation (37,38). Although the trend-level protective role of total competence did not reach statistical significance, it suggests that strengthening academic and social functioning might help buffer against engagement in NSSI (39).

In line with "ideation-to-action" framework, our data were in line with a high-risk trajectory (40). A history of prior attempts predicted greater current SI intensity, which, in turn, significantly increased the odds of multiple suicide attempts. The distinction between single and multiple attempters was substantial, with large effect sizes for SI severity and intensity. These differences are likely to be important for how clinicians assess risk in similar settings. The trend-level association between attention problems and repeat attempts may point to underlying neurocognitive vulnerabilities, such as impulsivity and executive dysfunction, although this requires confirmation in studies with direct cognitive assessment.

Clinically, these findings underscore the importance of routinely assessing adolescents' perceptions of both maternal and paternal behavior following a medically serious suicide attempt. Particular attention may be warranted to maternal emotional rejection and reduced warmth in adolescents presenting with severe SI or multiple attempts, and to paternal hostility in those with prominent conduct problems or externalizing problems and NSSI. In family meetings, explicitly addressing these relational patterns and actively engaging both fathers and mothers in emotion-focused and behaviorally oriented interventions may help align parental responses with the adolescent's needs and reduce escalating self-harm risk.

Limitations

This study has notable strengths. It targeted a clinically homogeneous, high-risk group of socioeconomically disadvantaged adolescents admitted to intensive care following medically serious suicide attempts, thereby enhancing the clinical relevance and contextual specificity of the findings. The use of a semi-structured clinical interview for suicidality alongside standardized measures of psychopathology, together with detailed assessments of both maternal and paternal acceptance–rejection within a narrowly defined cohort, strengthens both the internal validity and the practical applicability of the results for family-focused interventions.

Despite these strengths, several limitations should be considered when interpreting the findings. First, the sample consisted of adolescents from low-income families who had survived a medically serious suicide attempt requiring ICU care. This focus on a highly vulnerable and clinically relevant group restricts generalizability to adolescents with less severe self-harm or from more advantaged backgrounds. Second, we intentionally excluded adolescents with extensive trauma histories to reduce confounding of parent-related factors by trauma-related psychopathology; therefore, the findings may not directly apply to youth whose suicidality is primarily trauma-driven. Third, the predominance of girls in our cohort reflects national patterns in Turkish suicide attempts but reduces statistical power for gender-stratified analyses and warrants caution when extrapolating to boys. Fourth, the cross-sectional design precludes causal inference and does not allow determination of temporal ordering between parental rejection, psychopathology, and suicidal behavior. Finally, all key constructs were assessed via adolescent self-

report within 48 hours of ICU discharge, which may have introduced reporting biases due to acute distress; future research should incorporate multi-informant and longitudinal assessments.

Future longitudinal research with larger, cross-cultural samples is needed to clarify which aspects of the associations observed here are context-specific and which may represent more universal pathways. Integrating qualitative methods could also deepen understanding of adolescents' subjective experiences of maternal and paternal roles in the aftermath of suicidal behavior.

Conclusion

In conclusion, this study highlights the central role of perceived maternal relationships in shaping the severity of suicidal ideation and internalizing difficulties among high-risk, low-income adolescents, while paternal rejection appears more specifically linked to externalizing behaviors. These findings support the potential value of family-centered prevention and intervention efforts that strengthen maternal responsiveness and promote positive paternal engagement. More broadly, systematic screening for conduct and attention difficulties in school and community settings, combined with interventions targeting emotion regulation, may help prevent the escalation of self-injurious behaviors in this vulnerable population.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Aksaray University (03 June 2021, reference number: 05-SBKAEK).

Contribution of the authors

Study conception and design: GIE, MSD; data collection: GIE, MSD; analysis and interpretation of results: GIE; draft manuscript preparation: GIE; supervision: MSD. 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 changing etiology of NICU-Admitted neonatal viral pneumonia: A multiplex RT-PCR era snapshot

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Received : 02.01.2026, Accepted : 09.04.2026 DOI: 10.12956/TJPD.2026.1293

ABSTRACT

Objective: Viral pathogens are an important cause of lower respiratory tract infection (LRTI) leading to hospitalization in neonates and young infants. This study evaluated the etiologic distribution, clinical course, and management of multiplex RT-PCR–confirmed LRTI among neonatal intensive care unit (NICU) admissions.

Materials and Methods: Between September 2022 and November 2023, neonates admitted to the NICU with LRTI and a positive respiratory viral panel (multiplex RT-PCR) were retrospectively analyzed (n=44). Disease severity at admission was assessed using the Downes score. Demographics, seasonality, respiratory support, treatments, and outcomes were recorded. Correlations between Downes score, oxygen requirement (FiO_2), and length of stay were examined.

Results: Median age at admission was 17 days (range: 1–45). Admissions peaked in January (29.5%) and November (18.1%). The most common presenting findings were respiratory distress/tachypnea, cough, and feeding difficulties. Median Downes score was 2 (range: 1–8) and median FiO_2 requirement was 31% (range: 25–45%). Respiratory support was required in 32 infants: mechanical ventilation in 11.4% (n=5), non-invasive ventilation in 22.7% (n=10), and supplemental oxygen in 38.6% (n=17). The most common agents were SARS-CoV-2 (n=22; 50%) and respiratory syncytial virus (RSV) (n=14; 31.8%). Downes score correlated positively with FiO_2 (r=0.39, p=0.008) and length of hospital stay (r=0.42, p=0.004). Oseltamivir was administered to three infants with influenza. Median length of stay was 6 days (range: 2–56) and no mortality occurred.

Conclusion: In this multiplex RT-PCR era snapshot, SARS-CoV-2 and RSV predominated among NICU-admitted neonates and young infants with viral LRTI. Management was primarily supportive, and admission Downes score may help anticipate oxygen requirement and hospitalization duration.

Keywords: Neonate, NICU, respiratory syncytial virus, SARS-CoV-2, viral pneumonia

Introduction

Advances in perinatal and neonatal care have substantially improved survival for preterm and critically ill newborns; however, respiratory infections continue to impose a major clinical burden in early life. Viral respiratory diseases account for a large share of pediatric respiratory hospitalizations, and their impact is particularly relevant for the youngest and most vulnerable patients, including those requiring intensive care (1).

In hospitalized children, molecular studies consistently show that viral pathogens account for a substantial proportion of acute respiratory infections, supporting virus-focused diagnostics and management strategies (2).

Although respiratory viral infections (RVIs) are considered relatively infrequent during birth hospitalization, they can lead to significant short- and long-term morbidity in both term and preterm neonates. In the neonatal intensive care unit (NICU), RVIs have been associated with a more severe disease course, prolonged hospitalization, unnecessary antimicrobial exposure, and nosocomial outbreaks, partly because clinical presentations often overlap with bacterial infections (3). The COVID-19 pandemic further altered respiratory virus circulation patterns, and NICU surveillance

studies have shown that the epidemiology of viral detections during admission can shift across pre- and post-pandemic periods (4).

In this context, accurate etiologic identification is central to both clinical management and infection prevention. Modern molecular assays, particularly multiplex RT-PCR panels, enable timely detection of a broad range of respiratory viruses and support targeted cohorting and antimicrobial stewardship in NICU settings (3,4). Moreover, different viruses may be associated with distinct clinical and laboratory profiles, reinforcing the value of virologic confirmation when respiratory disease is suspected (5).

Therefore, this study aimed to evaluate the etiologic distribution, clinical course, and management approaches among neonates and young infants admitted to our NICU with multiplex RT-PCR-confirmed viral lower respiratory tract infection.

Materials and Methods

Study design, setting, and participants

This retrospective observational study evaluated term babies between 0-28 days and preterm babies with a postmenstrual age up to 44 weeks who were admitted to our NICU after presenting to the emergency department with respiratory distress between September 2022 and November 2023. During the study period, a respiratory viral panel using multiplex RT-PCR was performed in 72 patients with suspected viral lower respiratory tract infection (LRTI). Infants with a positive multiplex RT-PCR result (n=44) were included in the final analysis. Infants with severe congenital malformations were excluded.

Data collection

Clinical and demographic variables were extracted from the hospital electronic medical record system, including gestational age, mode of delivery, postnatal age at admission, sex, birth weight, number of siblings, number of household members, history of LRTI within the household, presenting symptoms, type of respiratory support at admission, oxygen requirement (FiO_2), chest radiography findings, laboratory results, administered treatments (including antiviral/antibacterial therapy), and length of hospital stay.

Severity assessment

On the day of admission, respiratory distress severity was assessed using the Downes score, a bedside clinical scoring system originally described for grading neonatal respiratory distress and correlating with physiologic derangements (6). On the day of initial presentation, the Downes score, a comprehensive scoring system applicable to neonates of any gestational age, was utilized to assess the severity of respiratory distress and to facilitate objective decision-making regarding the initiation of treatment (Table I) (7,8).

Table I: Downes scoring system

Downes Score	0	1	2
Respiratory Rate	<60/min	60–80/min	>80/min or apnea
Retractions	Absent	Mild	Severe
Cyanosis	Absent	In room air	>40% FiO_2
Air Entry	Good	Decreased	Barely audible
Grunting	Absent	Audible with stethoscope	Audible without stethoscope

≥4 points: *Clinical respiratory distress,* ***>7 points:*** *Respiratory failure*

Clinical management and treatment decisions

All patients received supportive management as clinically indicated, including supplemental oxygen, invasive mechanical ventilation and/or non-invasive ventilation, fluid and electrolyte support, inotropic therapy when required, and enteral/parenteral nutrition. Antibacterial and/or antiviral therapy was initiated according to the attending neonatologist's decision. In suspected influenza cases, antiviral treatment (oseltamivir) was considered/used per clinical judgment, consistent with prior NICU literature addressing influenza management considerations in newborns (9).

Criteria for initiating antibacterial therapy

Antibacterial therapy was initiated when bacterial pneumonia could not be excluded, based on one or more of the following: high fever; progressively increasing oxygen requirement to maintain target oxygen saturation (90–92% in preterm infants and 94–96% in term infants); worsening respiratory distress despite treatment; clinical deterioration; radiographic evidence suggestive of infiltration; positive blood culture and/or tracheal aspirate culture; leukocytosis (>15.000/mm (3)); and elevated C-reactive protein (CRP >5 mg/L).

Statistical analysis

Statistical analysis were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Chicago, IL, USA). Descriptive statistics were used throughout. Continuous variables were summarized as mean and standard deviation (SD) for approximately normally distributed data, and as median (min–max) for non-normally distributed data. Categorical variables were presented as counts (n) and percentages (%). Associations between the Downes score and (i) oxygen requirement (FiO_2) and (ii) length of hospital stay were assessed using Spearman's rank correlation coefficient. All tests were two-tailed, and a p value <0.050 was considered statistically significant.

Results

All patients were previously healthy newborns without known chronic comorbidities. The monthly distribution of admissions is shown in Figure 1, with the highest frequency in January (29.5%) and November (18.1%).

Baseline characteristics

Sociodemographic and clinical characteristics are summarized in Table II. Median maternal age was 26.5 (range: 17-32) years. Median birth weight was 2980 g (range: 1680-4500) and median gestational age was 36.45 weeks (range: 34-41). Delivery by cesarean section occurred in 61.4% (n=27), and 59.1% (n=26) of the infants were male. Median 5-minute APGAR score was 8.0 (range: 3–9). Median postnatal age at admission was 17 days (range: 1–45). No infant had a history of prolonged rupture of membranes (>18 h).

Table II: Sociodemographic and clinical characteristics of all patients

Variables	Values
Maternal age (years)*	26.5 (17-32)
Gestational age (weeks)*	36.45 (34-41)
Mode of delivery (cesarean section)†	27 (61.4)
Birth weight (g)*	2980 (1680-4500)
Gender (male)†	26 (59.1)
APGAR score (5th min)*	8.0 (3–9)
Age at admission (days)*	17 (1–45)
Downes score*	2.0 (1–8)
Respiratory support†	32 (72.7)
Mechanical ventilation (MV)	5 (11.4)
Non-invasive ventilation (NIV)	10 (22.7)
Supplemental oxygen	17 (38.6)
Duration of MV (days)*	0 (0-20)
Duration of NIV (days)*	2.5 (0-16)
Length of hospital stay (days)*	6 (2–56)

***:** median (min-max), **†:** n(%), **MV:** mechanical ventilation, **NIV:** non-invasive ventilation*

Clinical presentation and exposure history

At admission, 59.1% (n=26) of infants were afebrile. The most common presenting symptoms were respiratory distress/tachypnea (n=28; 63.6%), feeding difficulty (n=24; 54.5%), and cough (n=22; 50%). Median Downes score at admission was 2.0 (range: 1–8). The household history of LRTI exposure was reported in 45.5% (n=20). Having a sibling attending daycare/school was present in 61.3% (n=27), and 61.3% (n=27) lived in households with >3 persons.

Virologic findings and secondary bacterial pathogens

According to multiplex RT-PCR, the most frequently detected viruses were SARS-CoV-2 (n=22; 50%) and RSV (n=14; 31.8%) (Figure 2). Secondary bacterial pathogens were identified as Streptococcus pneumoniae (n=3; 6.8%) and Haemophilus influenzae (n=1; 2.3%).

Severity, respiratory support, and outcomes

A Downes score ≥4 was observed in 15 infants (34%), and >7 in 2 infants (4.5%). Downes score showed a positive correlation with FiO_2 requirement (r=0.39, p=0.008) and length of hospital stay (r=0.42, p=0.004) (Figures 3–4). Laboratory values at admission were: median CRP 1 mg/L (range: 0-45) , WBC 8440/mm^3 (range: 5020-12340), lymphocytes 4365/mm^3 (range: 1310–6160), MPV 10.25±2.06 fL, absolute neutrophil count 2345 (range: 1170-6570) and neutrophil-to-lymphocyte ratio 0.64 (0.27-2.37).

Chest radiography showed ground-glass opacities in 68.2% (n=30) and paracardiac infiltrates in 31.8% (n=14). Median FiO_2 on day 1 was 31% (range: 25–45). Overall, 32 infants required respiratory support: mechanical ventilation 11.4% (n=5), non-invasive ventilation 22.7% (n=10), and supplemental oxygen 38.6% (n=17). Intravenous fluids/electrolytes and nutritional support were provided when indicated. Oseltamivir was administered in three infants with influenza. Antibiotics (ampicillin+gentamicin or cefotaxime) were initiated in 32 infants due to suspected bacterial pneumonia and discontinued after viral etiology was identified.

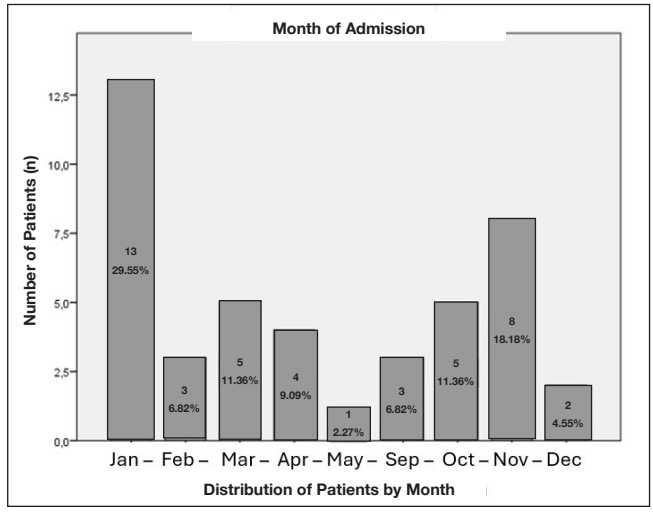

Figure 1: Monthly distribution of patient admissions

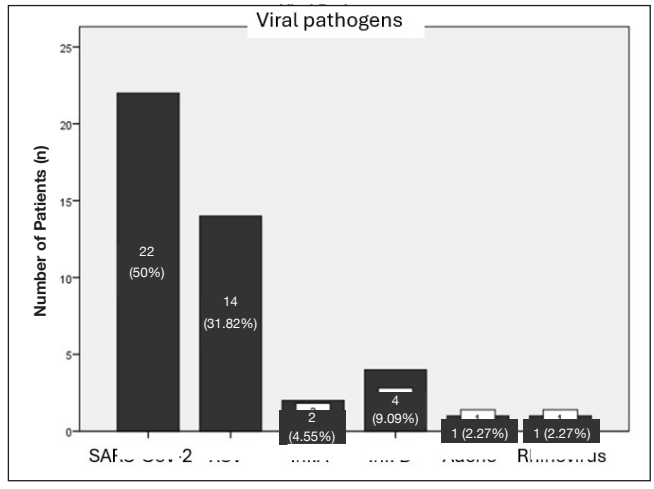

Figure 2: Distribution of viral pathogens

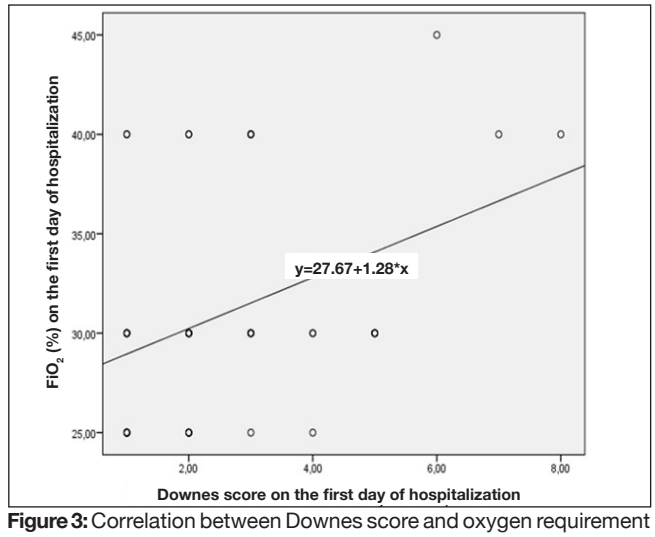

Figure 3: Correlation between Downes score and oxygen requirement (FiO_2)

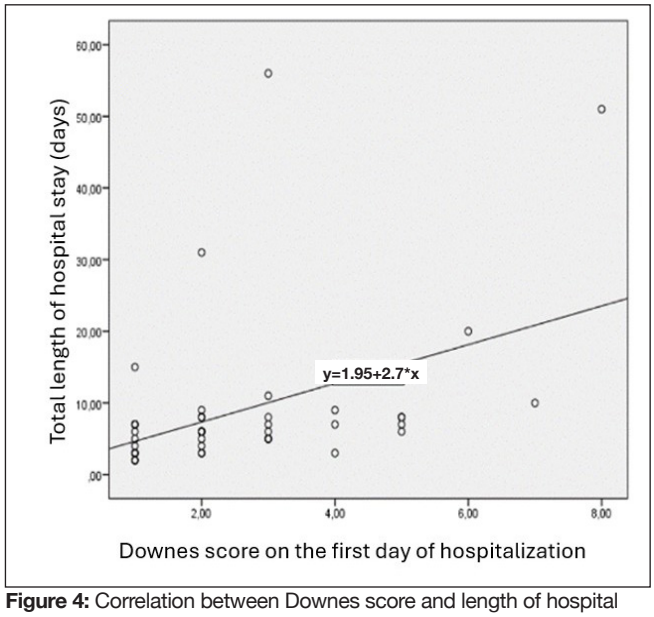

Figure 4: Correlation between Downes score and length of hospital stay

Median length of stay was 6 days (range: 2–56). No mortality occurred, and all infants were discharged with clinical and laboratory recovery.

Discussion

In this multiplex RT-PCR–era snapshot of NICU-admitted neonates and young infants with viral LRTI, admissions clustered in the colder months, with detections beginning in early autumn and peaking in winter. The rationale for etiologic confirmation with molecular testing and its relevance to infection prevention and antimicrobial stewardship in NICU settings have been emphasized in prior NICU-focused respiratory virus surveillance and review studies (3,4). Seasonality of respiratory viral infections is well described and reflects interactions between environmental conditions, host susceptibility, and viral transmission dynamics (10). NICU surveillance studies have shown that the burden and epidemiology of viral respiratory infections can change over time and shift under the influence of broader public health measures (4). Post-pandemic reports from several settings suggest altered timing and intensity of RSV activity and other respiratory viruses, and hospital-based analyses of recent respiratory seasons demonstrate that circulating viruses and clinical outcomes vary across years (11-13). Etiologic profiles of pediatric acute respiratory infection hospitalizations have also been reported to change after relaxation of COVID-19 non-pharmacological interventions, contributing to discussion around "immunity debt" and the need to sustain routine prevention strategies (14,15).

The most frequently detected pathogens in our cohort were SARS-CoV-2 and RSV. Surveillance data indicate that dominant etiologic agents can vary by population, testing practices, and pandemic/post-pandemic dynamics (4,13). Turkish NICU series evaluating neonatal viral LRTI admissions similarly highlight the persistent burden of viral respiratory disease and the common need for NICU-level monitoring and respiratory support (16,17). With respect to SARS-CoV-2, available evidence in maternal–neonatal outcome literature suggests a low likelihood of vertical transmission, while postnatal acquisition remains plausible, particularly via household exposure and close contact (18). In our cohort, household exposure markers (daycare/school-aged siblings and larger households) were common, supporting continued counseling for families of newborns and practical unit-level measures during periods of high community transmission.

RSV remains a major pathogen in neonatal and pediatric respiratory disease (19). In NICU settings, RSV transmission is facilitated by close contact and contaminated surfaces, and RSV has been detected within neonatal intensive care environments, supporting the need for rigorous infection-control practices (3,20). Globally, RSV contributes substantially to the burden of acute lower respiratory infection and mortality in young children, and severe disease is more likely in vulnerable populations and in those with important comorbidities, including HIV infection (21,22). In neonates requiring NICU admission, RSV pneumonia may present with significant respiratory distress, yet outcomes can be favorable with appropriate supportive care and monitoring, consistent with our zero-mortality findings (8).

Accurate etiologic identification is central to both clinical management and infection prevention. Routine clinical, laboratory, and radiographic findings may not reliably distinguish viral from bacterial disease early in the course, as emphasized in pediatric and NICU literature (3,23). It is important to acknowledge that the high sensitivity of multiplex molecular panels allows for the detection of organisms that may be part of the normal upper respiratory flora or represent colonization rather than active infection. Bacterial targets frequently included in these panels, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, are known to colonize the nasopharynx in young children. Consequently, the detection of bacterial nucleic acids does not always indicate a causal role in the acute illness. In the present study, we interpreted positive bacterial results in conjunction with clinical presentation, radiological findings, and inflammatory markers to distinguish true pathogens from bystanders, as recommended in recent literature (24). In our cohort, empiric antibiotics were commonly initiated due to this diagnostic uncertainty; similarly, prospective NICU data show that viral infections may be present among neonates evaluated for suspected late-onset bacterial sepsis, reinforcing the value of virologic testing in stewardship-focused care (25). Multiplex RT-PCR respiratory panels and other viral molecular panels can support patient cohorting/isolation and earlier discontinuation of avoidable antibiotics when bacterial infection is not supported (3,4,26). In addition, differential laboratory patterns across respiratory viruses have been reported; such parameters may complement clinical assessment but are insufficient alone for etiologic assignment (5). Our observations regarding risk factors align with local data reported by Çelik et al. (27), who identified the presence of siblings in the household (72%), family history of viral infection, lack of breast milk intake, Bronchopulmonary Dysplasia (BPD), and siblings attending school as major risk factors. Although RSV remains the predominant etiology of neonatal acute lower respiratory tract infections, it is crucial

to emphasize that the clinical impact of rare pathogens and co-infections must not be underestimated. Reducing unnecessary antibiotic exposure is particularly relevant because respiratory illness after NICU discharge remains an important cause of rehospitalization among preterm infants, and long-term respiratory vulnerability has also been described among survivors of early neonatal respiratory disease (28,29).

Most infants in our cohort required some form of respiratory support, underscoring that viral LRTIs can cause clinically meaningful respiratory compromise even in previously healthy neonates. National guidance emphasizes structured assessment and stepwise supportive management of respiratory distress in term neonates (7). Escalation to non-invasive ventilation or mechanical ventilation introduces additional risks, and consistent adherence to strategies for preventing ventilator-associated complications, including ventilator-associated pneumonia, is essential in NICU practice (30). The male predominance observed in our cohort is also consistent with broader neonatology references noting sex-related differences in susceptibility and clinical presentation in newborn infections (31).

We also observed that the admission Downes score correlated positively with oxygen requirement (FiO_2) and length of hospital stay. The Downes (Vidyasagar) score was originally described as a bedside clinical scoring system for grading neonatal respiratory distress, and its incorporation into routine pathways may assist early risk stratification and harmonize escalation decisions across providers (6,7).

Influenza was uncommon in our cohort; nevertheless, it remains clinically important because outbreaks in neonatal units have been described and targeted antiviral therapy may be considered in selected cases (9). Reviews of neonatal viral infections emphasize that supportive care is the cornerstone of management for most viral pathogens, while pathogen-specific therapy is limited to select viruses (e.g., influenza), and unnecessary antibiotics should be avoided in the absence of bacterial evidence (32).

Limitations

Limitations of this study include its retrospective single-center design, modest sample size, and selection of infants tested for suspected viral LRTI, which may limit generalizability. Multiplex RT-PCR turnaround time may have influenced antibiotic exposure and length of stay. The study was not designed to quantify viral–bacterial coinfection rates robustly or to compare outcomes with a PCR-negative control group.

Conclusion

In conclusion, NICU-admitted neonates and young infants with multiplex RT-PCR–confirmed viral LRTI showed clear winter predominance, with SARS-CoV-2 and RSV as the leading detected pathogens. These findings support continued emphasis on timely molecular diagnostics, infection prevention, and primarily supportive management, while structured bedside severity scoring may assist early clinical decision-making and stewardship-focused care (3,4,6,7,32).

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Etlik City Hospital Ethics Committee (03.09.2025, reference number: 2025-434).

Contribution of the authors

Conceptualization/Planning: AC, DD, HA, AO; Analysis/Interpretation: AC, DD, HA, SA; Data Acquisition: AC, DD, HA, AO, EO, SA, NYY, NF, FK; Writing: AC, DD, HA; Review and Editing: AC, DD, HA; Approval: AC, DD, HA

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 immunocompetent children with cytomegalovirus pneumonia: A single-center retrospective cohort study

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Received : 08.01.2026, Accepted : 16.04.2026
DOI: 10.12956/TJPD.2026.1297

ABSTRACT

Objective: Cytomegalovirus (CMV) pneumonia in immunocompetent children remains underrecognized, and standardized diagnostic criteria are lacking. We aimed to describe the clinical characteristics of immunocompetent children with CMV pneumonia and to evaluate the relationship between bronchoalveolar lavage (BAL) fluid and serum CMV DNA loads and laboratory results.

Materials and Methods: In this retrospective cohort study, medical records of 62 immunocompetent children who underwent flexible bronchoscopy for recurrent pneumonia or persistent wheezing between November 2023 and January 2025 were reviewed. CMV pneumonia was defined by detection of CMV DNA in BAL using real-time polymerase chain reaction (PCR). Quantitative CMV DNA load in BAL and serum were expressed as international units per milliliter (IU/mL). Demographic, clinical, laboratory, and radiological findings were recorded. Correlations between CMV DNA load in BAL and serum and blood indices were analyzed.

Results: Twenty patients (32.2%) were diagnosed with CMV pneumonia. The median age was six years (1.5-9.7), and 55% were male. The most common presenting symptom was chronic cough (85%). Patchy consolidation was the most frequent radiographic finding (45%), while chest computed tomography most commonly demonstrated consolidation (55%), often with bilateral (70%) and multilobar involvement (70%). Serum CMV PCR was positive in six patients (30%). No significant correlation was observed between BAL CMV DNA load (median; 2650 IU/mL; IQR; 311-16874) and serum CMV DNA load (median; 700 IU/mL; IQR; 443-2650) ($p > 0.963$). BAL CMV DNA load showed a strong positive correlation with serum monocyte count ($r = 0.861$, $p<0.001$) and mean platelet volume (MPV) ($r = 0.759$, $p < 0.001$). Eleven patients (55%) received intravenous ganciclovir at 5 mg/kg/per dose twice daily for 21 days, and demonstrated clinical and radiological improvement without documented significant adverse effects.

Conclusion: BAL CMV PCR demonstrated a higher detection rate than serum CMV PCR in immunocompetent children with recurrent pneumonia or persistent wheezing. Elevated monocyte count and MPV may reflect CMV-related pulmonary inflammation.

Keywords: Bronchoscopy, bronchoalveolar lavage, children, cytomegalovirus, pneumonia

Introduction

Cytomegalovirus (CMV) is a ubiquitous β-herpesvirus that infects a large proportion of the global population (1,2). In immunocompromised individuals, CMV is well recognized as a cause of severe pulmonary disease (3). However, the clinical significance of CMV pneumonia in immunocompetent children remains poorly understood (4). In children presenting with recurrent pneumonia, persistent wheezing, or unexplained radiological abnormalities, the differential diagnosis is often broad and includes infectious, inflammatory, and structural lung diseases. Increasing evidence suggests that CMV pneumonia may be an underrecognized contributor to such cases, and it is essential for clinicians to remain vigilant and include it in the differential diagnosis (5–7). The current literature underscores the lack of standardized diagnostic and therapeutic protocols for CMV pneumonia in otherwise

healthy pediatric populations, and randomized controlled trials are lacking to guide clinical practice (2,7,8). The diagnosis relies on a combination of respiratory symptoms, radiological findings consistent with infection, and virological confirmation of CMV infection.

Polymerase chain reaction (PCR) assays detecting CMV DNA in bronchoalveolar lavage (BAL) fluid or serum are frequently employed as diagnostic molecular methods, yet the interpretation of positive results in immunocompetent hosts remains challenging. Previous studies have suggested that CMV DNA detection in BAL fluid is considered the most sensitive and reliable specimen for detecting CMV DNA in the lungs, and may provide diagnostic value in wheezy infants or children with unexplained respiratory symptoms (5,6,9,10). However, the correlation between viral load and clinical severity, radiological manifestations, or treatment outcomes is still uncertain. Additionally, the role of serum CMV PCR remains controversial, as many children with CMV pneumonia may test negative in peripheral blood despite having positive BAL results (5,6).

The cornerstone of treatment for severe CMV infections is intravenous ganciclovir (8,11). Data on its use in immunocompetent children with CMV pneumonia are limited, and potential benefits must be weighed against the risk of toxicity (12). Understanding whether CMV viral load in BAL or serum predicts response to ganciclovir may help guide treatment decisions in this context.

In this retrospective study, we aimed to examine the clinical characteristics of immunocompetent children with CMV pneumonia and identify the relationship between BAL and serum CMV DNA loads.

Materials and Methods

This retrospective cohort study was conducted at the Departments of Pediatric Pulmonology and Pediatric Infectious Diseases at İzmir City Hospital between November 2023 and January 2025.During the study period, a total of 62 children (aged <18 years) underwent flexible bronchoscopy due to recurrent pneumonia or persistent wheezing. Among them, 25 patients were found to have CMV DNA positivity in bronchoalveolar lavage (BAL) fluid by PCR and were considered eligible for the study. Five patients were excluded due to immunodeficiency (n=2), congenital CMV infection (n=1), and malignancy (n=2). Thus, the final study population consisted of 20 patients. The study flowchart is presented in Figure 1. Patients were eligible if CMV DNA was detected in BAL fluid by PCR. Children with known primary or secondary immunodeficiency, malignancy, congenital CMV infection, and those receiving immunosuppressive therapy were excluded.

Clinical data were extracted from the institutional electronic medical system and compared between patients with positive and negative serum CMV DNA results.

Clinical data collection

Demographic and clinical data included age, sex, age at onset of symptoms, presenting symptoms (cough, wheezing, dyspnea, fever, recurrent pneumonia, and diarrhea), anthropometric measurements, physical examination findings (tachypnea, respiratory distress, rhonchi, rales, and hypoxemia), laboratory

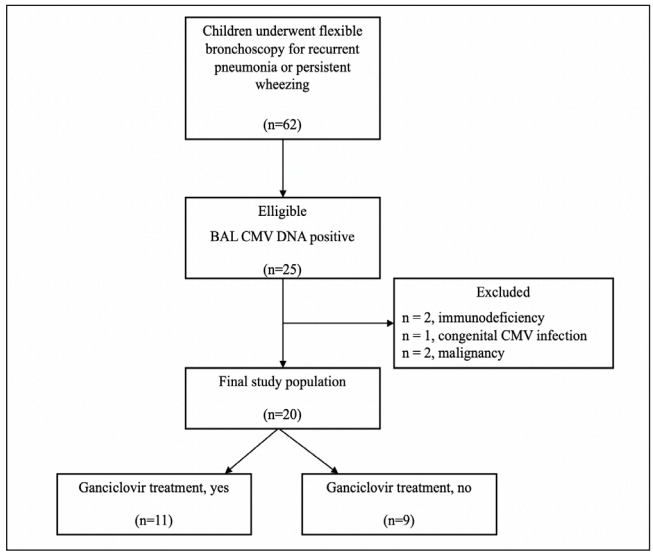

Figure 1: Flowchart of participants included in the study.

results, radiological findings (chest radiographs and computed tomography (CT) scans), and BAL analyses (microbiological and cytological).

Weight and height z-scores were calculated according to the Centers for Disease Control and Prevention (CDC) growth charts. Body mass index (BMI) was calculated using the weight (kg)/height (m^2) formula for children older than 2 years, and BMI z-scores were also determined using the CDC growth charts (13).

Chest radiographs obtained at admission were retrospectively reviewed for the presence of interstitial infiltrates, consolidation, atelectasis, hyperinflation, and pleural effusion.

Chest CT findings, as previously reported by a pediatric radiologist, were retrospectively extracted from the patients' medical files. Lobar involvement was recorded separately for each pulmonary lobe (right upper, right middle, right lower, left upper, and left lower lobes). The number of involved lobes was documented for each patient. Bilateral involvement was defined as the presence of parenchymal abnormalities affecting both lungs. Multilobar involvement was defined as involvement of two or more lobes. In addition to distribution, specific radiological patterns—including consolidation, atelectasis, mosaic perfusion, ground-glass opacities, bronchiectasis, pleural effusion, centrilobular small nodules, interlobular septal thickening, and tree-in-bud pattern, were noted.

Laboratory Data

Complete blood count (CBC) parameters, including leukocyte count (×10³/μL), neutrophil count (×10³/μL), lymphocyte count (×10³/μL), monocyte count (×10³/μL), eosinophil count (×10³/μL), platelet count (×10³/μL), mean platelet volume (MPV, fL), plateletcrit (PCT, %), and platelet distribution width (PDW, %), were retrospectively extracted from the electronic medical record system. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated by dividing the absolute neutrophil and platelet counts, respectively, by the absolute lymphocyte count.

Inflammatory markers, including C-reactive protein (CRP, mg/L) and serum immunoglobulin G (IgG, g/L), were also retrieved from the same database.

Quantitative CMV DNA levels from both serum and BAL samples (hereafter referred to as CMV DNA load) were recorded from the hospital's microbiology laboratory database, which had been analyzed by real-time PCR assay. Results were expressed as international units per milliliter (IU/mL). The lower limit of detection was 150 IU/mL, with a quantification range of 150–1×10^7 IU/mL. No predefined viral-load cut-off was used for the diagnosis of CMV pneumonia (5,7,8). CMV DNA results were interpreted in conjunction with clinical presentation and radiological findings.

All laboratory analyses were performed in the hospital's central laboratory according to standardized operating procedures and internal quality control protocols.

Bronchoscopy and BAL procedure

Flexible bronchoscopy was performed under general anesthesia using an appropriately sized flexible bronchoscope (EB-530P, Fujifilm Corporation, Tokyo, Japan). The procedure was conducted in a dedicated operating room by the same pediatric pulmonologist (14). After airway inspection, BAL was performed by instilling sterile 0.9% saline solution (1 mL/kg, with a maximum of 20 mL per aliquot) into the most affected segment, as determined radiologically, or the right middle lobe/lingula in cases of diffuse disease. The instilled fluid was immediately aspirated with gentle suction and collected into sterile mucus traps.

The first aliquot was sent for bacterial, fungal, and mycobacterial cultures. The remaining pooled aliquots were divided as follows: one portion for cytological examination (differential cell count and cytopathology) and one for viral PCR analysis (including CMV and other respiratory viruses). Samples were transported to the laboratory within 30 minutes of collection and processed immediately under sterile conditions, following standardized operating protocols. BAL differential cell counts were interpreted according to established pediatric reference values. Neutrophilia was defined as neutrophils >5% of total cells, and eosinophilia as eosinophils >1%, based on previously published reference ranges (15).

Treatment protocol

Intravenous ganciclovir was initiated in patients with high BAL CMV DNA load and/or positive serum CMV PCR results, particularly in the presence of severe or persistent respiratory symptoms and significant radiological abnormalities. It was administered at a dose of 5 mg/kg/per dose twice daily. The planned treatment duration was 21 days. Treatment decisions were made by a multidisciplinary team including pediatric pulmonology and infectious diseases specialists.

After the initial 14 days of therapy, patients were reassessed for clinical response and potential adverse effects. Clinical response was defined as improvement in baseline respiratory symptoms (wheezing, cough, or dyspnea) and/or radiological stabilization or improvement on chest imaging. In the absence of drug-related toxicity, treatment was continued and completed for a total duration of 21 days.

Statistical analysis

Descriptive data are presented as numbers for categorical variables and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, depending on the data distribution, as assessed by the Shapiro–Wilk test. Group comparisons were conducted using the Pearson χ^2 test or Fisher's exact test for categorical variables, and the Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Correlations between viral load and clinical characteristics were assessed with Spearman's correlation coefficient. A p-value <0.050 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY).

Results

Patient characteristics

The medical records of 62 pediatric patients who underwent flexible bronchoscopy for recurrent pneumonia or persistent wheezing were retrospectively assessed. The median age was six years (1.5-9.7), and 11 patients (55%) were male. The median age at onset of symptoms was 2.5 years (0.8-4.3). The most frequent presenting symptom and physical examination finding were chronic cough (85%), respectively. The demographic and clinical characteristics of the study population are presented in Table I.

Hematologic parameters, chest CT findings, and flexible bronchoscopy results

The median serum leukocyte count was 8.74x10^3/µL (7.02-12.04), the monocyte count was 0.74x10^3/µL (0.54-1.11), and MPV was 9.9 fL (9.4-10.5). The hematologic parameters of the study population are presented in Table II.

On chest radiography, patchy consolidations were observed in 9 patients (45%), hyperinflation in 7 (35%), atelectasis in 6 (30%), interstitial infiltrates in 2 (10%), and pleural effusion in 1 (5%).

All patients exhibited pathological abnormalities on chest CT. The most frequent CT findings were consolidation (55%)

Table I: Demographic characteristics of immunocompetent children diagnosed with CMV pneumonia

Symptom*	
Cough	17 (85)
Wheezing	13 (65)
Recurrent pneumonia	13 (65)
Dyspnea	8 (40)
Fever	2 (10)
Diarhea	1 (5)
Physical examination	
Weight (kg)†	18.5 (10.5-30)
Height (cm)†	110.5 (79-134)
BMI†	16.9 (15.2-19.5)
zWeight (kg)†	-0.56 (-1.37-0.03)
zHeight (cm)†	-0.38 (-1.6-0.22)
zBMI†	-0.3 (-1-0.43)
Rhonchi*	10 (50)
Rales*	8 (40)
Tachypnea*	7 (35)
Respiratory distress*	6 (30)
Hypoxemia*	2 (10)

:** *n(%),* **†:** *median (IQR),* ***BMI: *body mass index,* ***IQR:*** *interquartile range*

Table II: Hematologic parameters, chest CT findings, and flexible bronchoscopy results of immunocompetent children diagnosed with CMV pneumonia

Hematologic parameters*	
Leukocytes (10^3/μL)	8.74 (7.02-12.04)
Neutrophil (10^3/μL)	4.16 (2.87-6.84)
Lymphocyte (10^3/μL)	2.95 (2.56-5.72)
Monocytes (10^3/μL)	0.74 (0.54-1.11)
Eosinophil (10^3/μL)	0.26 (0.07-0.53)
Platelet (10^3/μL)	351.5 (272.5-419)
MPV (fL)	9.9 (9.4-10.5)
PCT (%)	0.3 (0.2-0.4)
PDW (%)	11.1 (9.7-12)
CRP (mg/L)	1 (0.6-4.5)
IgG (g/L)	10.8 (8-13.3)
NLR	1.4 (0.8-2)
PLR	112.5 (66.4-144.2)
Chest CT findings†	
Consolidation	11 (55)
Atelectasis	9 (45)
Mosaic perfusion	7 (35)
Ground-glass opacity	6 (30)
Bronchiectasis	4 (20)
Pleural effusion	2 (10)
Centrilobular small nodules	7 (35)
Interlobular septal thickening	5 (25)
Tree-in-bud pattern	3 (15)
Bronchoscopy results†	
Mucosal Appearance	
Normal	17 (85)
Pale	1 (5)
Pale with nodular changes	2 (10)
Secretions, yes	13 (65)
BAL analysis	
BAL co-infection†	13 (65)
Haemophilus influenzae	8 (40)
Influenza A	3 (15)
RSV	1 (5)
AGBHS	1 (5)
BAL leukocytes (mm^3)*	375 (112.5-800)
BAL PMNL (%)*	45 (10-78.7)
BAL CMV DNA (IU/mL)*	1416 (311-16874)

***: median (IQR), †: n(%), AGBHS:** group A β-hemolytic streptococcus, **BAL:** bronchoalveolar lavage, **CRP:** C-reactive protein, **CT:** computed tomography, **MPV:** mean platelet volüme, **NLR:** neutrophil-to-lymphocyte ratio, **PCT:** plateletcrit, **PDW:** platelet distribution width, **PLR:** platelet-to-lymphocyte ratio, **PMNL:** polymorphonuclear leukocytes, **RSV:** Respiratory syncytial virus*

and atelectasis (45%) (Table II). Bilateral lung involvement was present in 14 patients (70%), whereas 6 patients (30%) had unilateral involvement. Multilobar involvement was observed in 14 patients (70%), with a median of 2 lobes involved (1–5). Regarding lobar distribution, involvement was detected in the right upper lobe in 9 patients (45%), right middle lobe in 8 (40%), right lower lobe in 12 (60%), left upper lobe in 11 (55%), and left lower lobe in 12 patients (60%).

On flexible bronchoscopy, 17 patients (85%) had normal mucosal appearance, and 13 (65%) had abundant secretions. BAL cytology demonstrated neutrophilia in 16 patients (80%), with eosinophilia in one patient. Co-infections were identified in BAL samples in 13 patients (65%), including *Haemophilus influenzae* (40%), Influenza A (15%), group A β-hemolytic *streptococcus*, and Respiratory syncytial virus in each patient.

Table III: Comparative analysis of demographic, clinical, and laboratory findings according to ganciclovir treatment status

	yes	no	p
Number of patients	11	9	-
Age (months)*	6 (1-9)	6 (3.3-11.5)	0.503
Gender (male)†	8 (72.7)	3 (33.3)	0.078
Onset age (months)*	1 (0.8-4.5)	3.8 (0.9-6.8)	0.552
Symptom†			
Cough	8 (72.7)	9 (100)	0.089
Wheezing	7 (63.6)	6 (66.7)	0.888
Recurrent pneumonia	8 (72.7)	5 (55.6)	0.423
Dyspnea	5 (45.5)	3 (33.3)	0.582
Fever	2 (18.2)	0	0.178
Diarhea	1 (9.1)	0	0.353
Physical examination			
zWeight*	-0.9 (-1.5-(-0.2))	-0.4 (-0.8-0.5)	0.175
zHeight*	-0.5 (-2.8-0.2)	-0.3 (-1.3-0.7)	0.370
zBMI*	-1 (-1.7-1.1)	-0.1 (-0.8-0.4)	0.336
Rhonchi†	5 (45.5)	5 (55.6)	0.653
Rales†	5 (45.5)	3 (33.3)	0.582
Tachypnea†	5 (45.5)	2 (22.2)	0.279
Respiratory distress†	4 (36.4)	2 (22.2)	0.492
Hypoxemia†	1 (9.1)	1 (11.1)	0.881
Monocytes (10^3/μL)*	1050 (740-1600)	600 (300-730)	0.010
MPV (fL)*	10.3 (10.1-10.8)	9.4 (8.4-9.7)	0.001
Chest CT findings†			
Bilateral involvement	8 (72.7)	6 (66.7)	0.769
Multilobar involvement	8 (72.7)	6 (66.7)	0.769
Consolidation	6 (54.5)	5 (55.6)	0.964
Atelectasis	5 (45.5)	4 (44.4)	0.964
Mosaic perfusion	3 (27.3)	4 (44.4)	0.423
Ground-glass opacity	3 (27.3)	3 (33.3)	0.769
Bronchiectasis	1 (9.1)	3 (33.3)	0.178
Pleural effusion	2 (18.2)	0	0.178
Centrilobular small nodules	3 (27.3)	4 (44.4)	0.423
Interlobular septa thickening	1 (9.1)	4 (44.4)	0.069
Tree-in-bud pattern	1 (9.1)	2 (22.2)	0.413
Serum CMV positivity†	6 (54.5)	0	0.008
Serum CMV DNA (IU/mL)*	212 (0-873)	0	0.038
BAL CMV DNA (IU/mL)*	9110 (3137-24744)	330 (247-539)	0.001
BAL PMNL (%)*	45 (10-50)	70 (7.5-80)	0.710
BAL leukocytes (mm^3)*	800 (80-800)	340 (115-915)	0.656

***: median (IQR), †: n(%), BAL:** bronchoalveolar lavage, **BMI:** body mass index, **IQR:** interquartile range, **CT:** computed tomography, **MPV:** mean platelet volüme, **PMNL:** polymorphonuclear leukocytes*

The median BAL CMV load was 1416 IU/mL (311-16874). In contrast, only six patients (30%) had detectable serum CMV DNA, with a median viral load of 700 (443-2650).

Correlation analysis of laboratory findings with CMV PCR

BAL CMV DNA load showed a strong positive correlation with serum monocyte count ($r=0.861$, $p<0.001$) and MPV ($r=0.759$, $p<0.001$). Scatter plots illustrating these correlations are presented in Figure 2.

Serum CMV DNA load were not significantly correlated with serum monocyte count or MPV ($p>0.486$). Notably, no significant correlation was observed between BAL and serum CMV loads ($p>0.963$).

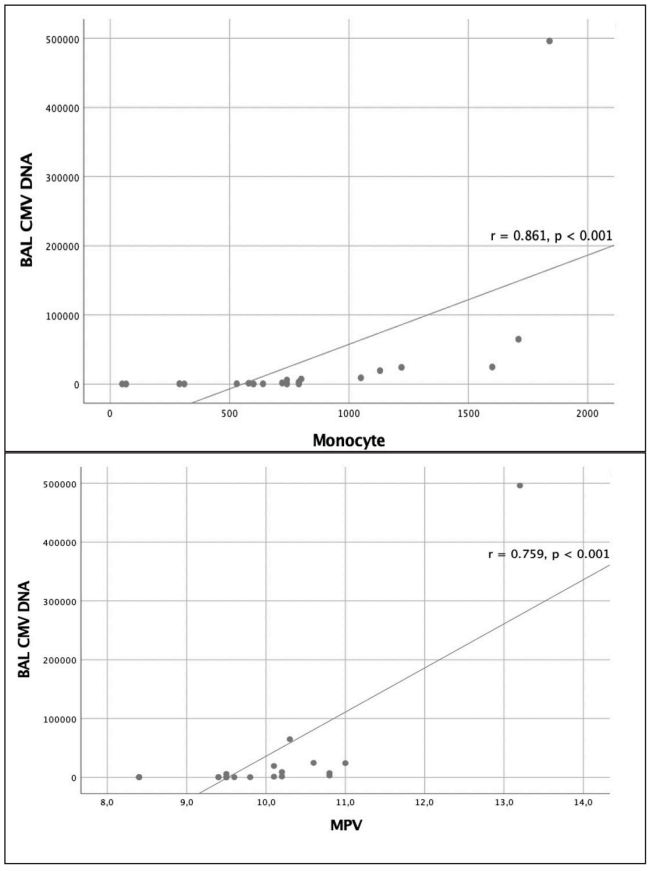

Figure 2: Scatter plot graphics and correlation between BAL CMV DNA (y-axis) and hematologic parameters (x-axis)

Comparison of patients based on treatment

All patients with positive serum CMV PCR results (n=6) received intravenous ganciclovir treatment. In addition, five patients with negative serum CMV PCR but high BAL CMV DNA load and severe clinical or radiological findings were also treated. Eleven patients (55%) received intravenous ganciclovir (5 mg/kg/per dose, twice daily) for 21 days. No clinically significant adverse effects were observed.

During a median follow-up of 1.3 years (1.2-1.5), all treated patients demonstrated both clinical and radiological resolution without complications.

Compared with the non-treatment group (n=9), the treatment group (n=11) had significantly higher serum monocyte count (1.05 vs 0.6x10^3/µL, p=0.010), MPV value (10.3 vs 9.4 fL, p =0.001), and BAL CMV DNA load (9.110 vs 330 IU/mL, p=0.001). No significant differences were observed between the groups regarding demographic characteristics, clinical presentation, anthropometric measurements, physical examination findings, other laboratory results, chest CT findings, or BAL analyses (Table III).

Follow-up chest radiographs demonstrated radiological improvement in all 11 patients who received antiviral treatment. Among the nine patients who did not receive antiviral therapy, persistent atelectasis was observed in one patient and residual hyperinflation in one patient, while the remaining patients showed radiological resolution.

Discussion

This study characterises the clinical features of immunocompetent children with CMV pneumonia and underscores the potential diagnostic value of BAL CMV PCR. Among children who underwent flexible bronchoscopy, the proportion with CMV pneumonia was 32.2%, suggesting that CMV pneumonia may not be uncommon in this selected population. Serum CMV PCR was positive in fewer than one-third of these cases, supporting BAL as a more sensitive diagnostic modality than serum testing. Higher monocyte counts and MPV were significantly associated with BAL CMV load.

The exact frequency of CMV pneumonia among children has not been clearly established. Most studies have focused on CMV pneumonia developing in patients with immunodeficiency or those who have undergone hematopoietic stem cell transplantation (5,11,16-18). In a study evaluating children with primary immunodeficiency, CMV pneumonia was detected in 6.8% (16). The incidence of CMV infection among pediatric hematopoietic stem cell transplantation patients has been reported to range from 8% to 14.5% (17,18). Population-based prevalence data for CMV pneumonia in immunocompetent children are lacking. Current knowledge derives largely from studies of flexible bronchoscopy cohorts—typically children with persistent symptoms or lower respiratory tract infections. In a study including 102 infants who underwent flexible bronchoscopy for persistent wheezing and diffuse interstitial infiltrates on radiological evaluation, CMV PCR in BAL fluid was positive in 51 patients (5). In a cohort of 49 immunocompetent children hospitalized for CMV infection, 41% were found to have CMV pneumonia (11). In our bronchoscopy-based cohort, CMV pneumonia was identified in 32.2% (20/62) of cases. This proportion is higher than previously reported, likely attributable to routine BAL CMV PCR testing in our center. These findings suggest that CMV should be considered in the differential diagnosis of recurrent or persistent lower respiratory disease, and BAL CMV PCR should be obtained when appropriate.

Previous studies suggest that direct detection of CMV in the respiratory tract is more indicative of CMV pneumonitis than detection in serum samples (19,20). Serum CMV DNA was positive in only one-third of the patients in our study, and we found no correlation between serum CMV DNA and BAL CMV DNA. A previous study reported that 33% of BAL CMV PCR-positive infants had serum CMV PCR positivity (5). They concluded that BAL CMV PCR was more effective than serum CMV PCR in diagnosing lower respiratory tract infections due to CMV in immunocompetent infants. In another study investigating infants with pertussis, BAL CMV PCR was found to be positive in 15% of those who were serum CMV-negative (9). On the other hand, the correlation between CMV viral loads in serum and BAL samples remains controversial (5,9,21). While no correlation was found in immunocompetent infants, another study evaluating serum and BAL CMV load among adult immunocompromised patients showed a strong positive correlation (5,21). Our findings suggest that the presence of CMV DNA in the lower airways may represent a localized infection independent of

systemic dissemination observed in immunocompromised individuals.

The clinical interpretation of CMV DNA detected in BAL fluid is challenging, as CMV may be present in the lower respiratory tract due to asymptomatic viral shedding, and no universally accepted viral-load threshold has been defined. In hematopoietic stem cell transplant recipients, a pragmatic BAL CMV DNA threshold of approximately 500 IU/mL has been proposed to help distinguish CMV pneumonia from asymptomatic shedding, whereas in lung transplant recipients, higher thresholds around 4500 IU/mL have been suggested for the diagnosis of CMV pneumonia (22,23). Berengua et al. (24) reported that BAL CMV load of ≥1258 IU/mL (6290 copies/mL) in immunosuppressed adults would be indicative of clinically relevant viral replication in the lung. Despite these proposed values, all major studies and consensus discussions consistently underscore that CMV DNA levels should be interpreted within the clinical and radiological context rather than relying on a fixed numeric threshold applicable to all settings. In immunocompetent children, BAL CMV PCR positivity has been mainly used as microbiological support within a compatible clinical syndrome rather than relying on a validated numeric cut-off, and BAL testing may outperform blood PCR for lower respiratory tract involvement (5). Therefore, in the present study, BAL CMV DNA positivity was interpreted as microbiological support in a compatible clinical and radiological setting rather than based on a fixed quantitative threshold.

Circulating monocytes have a short half-life (~1.6 days) and exhibit broad responsiveness to pathogens, facilitating their activation and the initiation of innate and subsequent adaptive immune responses (25). Monocytes play a pivotal role in CMV dissemination to organ tissues during primary infection and following reactivation from latency (26). Zdziarski et al. (27) demonstrated that elevated monocyte counts and percentages are positively correlated with CMV replication and may even serve as indicators of active CMV replication. Consistently, in the present study, BAL CMV DNA load was positively correlated with monocyte counts. An increase in monocyte count may occur due to prolonged survival, mobilization from the peripheral pool, or decreased uptake by tissue macrophages (27,28). We suggest that children with recurrent wheezing or pneumonia accompanied by elevated monocyte counts should be evaluated for possible CMV pneumonia.

Mean platelet volume reflects platelet size and is generally associated with platelet activation, as larger platelets are metabolically and enzymatically more active (29). MPV has been shown to correlate with disease severity, mediated by pro-inflammatory cytokines (29,30). In a recent study, Gümüş et al. (31) demonstrated that MPV levels were significantly higher in asymptomatic children infected with SARS-CoV-2. In our cohort, BAL CMV DNA load showed a strong positive correlation with MPV. This finding may reflect platelet activation in the context of CMV-related inflammation within the lower respiratory tract. Future studies are warranted to clarify the specific link between CMV pneumonia and MPV.

Ganciclovir, a guanosine analogue that selectively inhibits CMV DNA polymerase, is licensed for antiviral treatment only in severe or life-threatening CMV disease in immunocompromised patients (32,33). Indications for use in immunocompetent patients remain less clearly defined. In our study, patients with higher BAL CMV load, monocyte count, or MPV value were more likely to receive ganciclovir therapy. In prior reports of CMV pneumonia in immunocompetent children, those who received ganciclovir at 10 mg/kg/day for 14–21 days demonstrated clinical improvement with normalization of chest radiographs, and no severe ganciclovir-related toxicities were observed (5,12,32). Consistent with prior reports, in our cohort, 11 patients (55%) who received intravenous ganciclovir at 5 mg/kg/per dose twice daily for 21 days achieved clinical and radiological recovery, with no complications observed over a median follow-up of 1.3 years. These findings suggest that ganciclovir can be considered a safe therapeutic option for patients with CMV pneumonia.

Limitations

This study has several limitations that should be acknowledged. First, its retrospective design inherently limits the ability to establish causal relationships between CMV viral load and clinical or laboratory findings. Second, the relatively small sample size and single-center setting may restrict the generalizability of the results. Third, no standardized viral-load cut-off was applied, and quantitative CMV PCR results may vary across assay platforms. The presence of co-infections in a considerable proportion of patients further complicates interpretation, as detection of CMV DNA alone does not establish causality. Finally, treatment decisions were not randomized and were more frequently made in patients with higher viral loads introducing potential selection bias.

Conclusion

In conclusion, our study offers valuable insights into the diagnostic and clinical significance of BAL CMV PCR in the diagnosis of CMV pneumonia in immunocompetent children with recurrent wheezing or pneumonia. Elevated monocyte counts and MPV values were associated with higher BAL CMV DNA load, suggesting a potential link between CMV activity and hematologic inflammatory markers. Intravenous ganciclovir therapy led to favorable outcomes without complications in immunocompetent children with CMV pneumonia. We propose that BAL CMV PCR should be considered in the diagnostic workup of children with recurrent pneumonia or persistent wheezing. Larger prospective and randomized studies are required to establish standardized diagnostic and therapeutic protocols.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by İzmir City Hospital (22.01.2025, reference number: 2025/30).

Contribution of the authors

Study conception and design: EO, DY; data collection: ÜAS, GMD; analysis and interpretation of results: EO, İAH; draft manuscript preparation: EO. All authors reviewed the results and approved the final version of the article.

Presented or Pre-print or Published as an abstract or as a thesis
This study was previously presented as an oral presentation at the "Türk Toraks Derneği 28. Yıllık Kongresi, 2025" held on May 2025 in Antalya, Türkiye.

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 and molecular spectrum of RASopathies in a pediatric cohort: A single-center retrospective study

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Received : 18.01.2026, Accepted : 27.04.2026
DOI: 10.12956/TJPD.2026.1301

ABSTRACT

Objective: Noonan syndrome (NS) and related RASopathies are genetically heterogeneous disorders caused by dysregulation of the RAS/MAPK signaling pathway and are characterized by overlapping clinical features, including distinctive craniofacial appearance, growth impairment, congenital heart defects (CHD), and variable neurodevelopmental involvement. Comprehensive molecular characterization is essential for accurate diagnosis and genotype–phenotype correlation. Evaluation of well-characterized single-center pediatric cohorts may provide clinically relevant real-world insight into genotype–phenotype relationships within routine practice. The aim of this study is to delineate genotype–phenotype correlations in a well-characterized pediatric cohort.

Materials and Methods: This retrospective single-center study included pediatric patients between January 2022 and September 2025 with molecularly confirmed diagnosis of NS and related RASopathies. Clinical, laboratory, and imaging findings were reviewed. Targeted next-generation sequencing of RASopathy-associated genes was performed. Detected variants were interpreted according to American College of Medical Genetics and Genomics guidelines, and segregation analysis was conducted when available.

Results: The cohort comprised 20 pediatric patients from 19 unrelated families, with a mean age of 6.1 years. CHD was identified in 80% of patients, most commonly pulmonary valve stenosis (65%), while cardiac involvement was not universal. Short stature was observed in 65% of cases and represented the most frequent reason for referral. Disease-associated variants were identified in nine different genes, with *PTPN11* being the most frequently affected (40%), followed by *LZTR1* (15%), *NF1* (10%), and *RAF1* (10%). Most variants were classified as pathogenic or likely pathogenic, whereas a limited number were categorized as variants of uncertain significance. Integrated interpretation incorporating phenotype–genotype concordance and segregation data supported the potential clinical relevance of selected uncertain variants.

Conclusion: This pediatric cohort highlights the marked clinical and genetic heterogeneity of NS and related RASopathies. The absence of cardiac involvement in some patients underscores the limitations of phenotype-based assessment alone. Comprehensive molecular testing remains critical for accurate diagnosis, refinement of genotype–phenotype correlations, and appropriate long-term management.

Keywords: Genotype–phenotype correlation, genetic testing, MAP kinase signaling system, next-generation sequencing, noonan syndrome, rasopathies

Introduction

The Ras/mitogen activated protein kinase (MAPK) pathway plays an essential role in regulating critical cellular processes such as growth, differentiation, proliferation, aging, and apoptosis. By transducing extracellular mitogenic signals into the cell, this pathway helps coordinate cellular responses that are vital for development and maintaining homeostasis. It consists of a series of protein kinases—RAS, RAF, MEK, and ERK—which interact in a cascade to modulate various cellular functions (1).

Genetic alterations within components of the Ras/MAPK pathway can disrupt these cellular processes, leading to a range of developmental and physiological anomalies. RASopathies are a group of genetic disorders caused by pathogenic germline mutations in genes involved in the Ras/MAPK signaling pathway (2, 3). These conditions are clinically diverse and can manifest with a wide range of symptoms, complicating diagnosis and management. Common features include CHDs, craniofacial anomalies, growth delays, cognitive impairments, skin abnormalities, and cancer predisposition (4, 5).

Noonan syndrome (NS) is the most common form of RASopathies, with an estimated incidence of approximately 1 in 1,000–2,500 live births. Clinically, NS is defined by a recognizable constellation of findings such as characteristic craniofacial features, postnatal growth impairment, and CHD—most frequently pulmonary valve stenosis (PS), atrial septal defect (ASD), or hypertrophic cardiomyopathy (HCM). Additional manifestations may involve a short or webbed neck, thoracic deformities with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, bleeding diatheses due to coagulation abnormalities, lymphatic dysplasia, and ophthalmologic anomalies (6,7). Several other conditions—including Cardiofaciocutaneous syndrome (CFCS), Costello syndrome (CS), Legius syndrome (LGSS), Neurofibromatosis–Noonan syndrome (NFNS), Noonan-like syndrome with loose anagen hair (NSLH), and Noonan syndrome with multiple lentigines (NSML) formerly known as LEOPARD syndrome—share overlapping clinical and molecular characteristics with NS. Due to these shared features and their common involvement of the Ras/MAPK pathway, these disorders are collectively classified as NS-related disorders (8).

To date, pathogenic variants in numerous genes encoding components or regulators of the Ras/MAPK pathway have been implicated in the molecular etiology of NS and related disorders. These include *PTPN11, SOS1, SOS2, RAF1, RIT1, LZTR1, MAP2K1, MAP2K2, BRAF, KRAS, NRAS, HRAS, SHOC2, CBL, SPRED1, NF1, RRAS2, RASA2, PPP1CB, MAPK1*, and *MRAS* (8,9).

A defining characteristic of RASopathies is their pronounced clinical overlap and phenotypic variability, whereby comparable clinical manifestations may arise from pathogenic variants in different genes, while distinct phenotypic profiles can result from variants affecting the same gene. This observation highlights the inherent complexity of genotype–phenotype correlations across RASopathies, and underscores the limited discriminatory value of clinical findings alone. Accordingly, comprehensive molecular characterization is essential for accurate diagnosis, improved prognostic stratification, and the implementation of individualized clinical monitoring and emerging targeted therapeutic approaches (5).

The aim of this study was to retrospectively analyze the clinical, molecular, and laboratory characteristics of pediatric cases diagnosed with NS and related disorders. This analysis sought to broaden the understanding of the clinical spectrum, evaluate the relationships between genetic variants and phenotypic manifestations, and clarify genotype–phenotype correlations.

Materials and Methods

This study was designed as a retrospective cohort study conducted at Samsun Training and Research Hospital. Written informed consent for both clinical evaluation and genetic testing was obtained from the parents or legal guardians of all participants, in accordance with the Declaration of Helsinki.

Pediatric patients who were suspected of having NS and related disorders, underwent genetic testing between January 2022 and September 2025, and whose diagnoses were subsequently confirmed by molecular genetic analysis were included in the study.

Demographic and clinical data were retrospectively extracted from patient files and electronic medical records. Collected variables included: age at presentation, sex, presenting symptoms, consanguinity, family history, growth parameters (including height, weight, and head circumference percentiles), craniofacial features, cardiac anomalies, skeletal abnormalities, cutaneous findings, developmental millestones, and involvement of other organ systems. Additionally, laboratory findings, including bleeding parameters, and imaging studies performed for tumor screening were recorded when available.

Short stature was defined as height <–2 SDS, low body weight as weight <–2 SDS, and macrocephaly as head circumference > +2 SDS for age and sex. Relative macrocephaly was defined as a head circumference within the normal range but disproportionately large in relation to height and/or weight. Developmental milestones were assessed using the Denver Developmental Screening Test II (Denver II), and age-appropriate Wechsler Intelligence Scale for Children–Revised (WISC-R), when applicable.

For genetic analysis, genomic DNA was extracted from peripheral blood leukocytes using standard protocols. Targeted sequencing was performed for genes associated with RASopathies, including *BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NF1, NRAS, PTPN11, RAF1, RASA2, RIT1, SHOC2, SOS1, SOS2,* and *SPRED1*, using hybridization-based capture with the xGen™ DNA Library Prep EZ Kit and related IDT enrichment kits (Integrated DNA Technologies, USA). Genomic DNA was fragmented and enriched according to the manufacturer's instructions, and sequencing libraries were generated accordingly.

Sequencing was performed on Illumina® platforms, achieving a mean coverage depth of 70×–100×, with ≥90% of target regions covered at this depth. Variant calling and primary filtering were conducted after base calling, with low-quality variants excluded during initial filtering steps.

Bioinformatic analysis was carried out using a standardized pipeline. Quality control of raw sequencing data was performed with FastQC, followed by adapter trimming and read filtering using Cutadapt. Reads were aligned to the GRCh37/hg19 human reference genome using the BWA-MEM algorithm. Duplicate reads were marked, base quality score recalibration was applied, and variant calling was performed in accordance with GATK Best Practices. Variants with a read depth <10× were excluded from further analysis.

Variant annotation was performed using the Ensembl Variant Effect Predictor. Only variants located within protein-coding exons and flanking intronic regions (±10 base pairs) were evaluated. Variants were prioritized if they had a minor allele frequency <1% in public population databases, including gnomAD, ExAC, 1000 Genomes, dbSNP, and Kaviar. Previously reported disease-associated variants were assessed using ClinVar, HGMD® Public, Franklin, and VarSome databases.

The potential functional impact of identified variants was evaluated using multiple in silico prediction tools, including SIFT, PolyPhen-2, MutationTaster, MutationAssessor, LRT, CADD, DANN, FATHMM, FATHMM-MKL, MetaSVM, MetaLR, GERP, phyloP, phastCons, and SiPhy. Variant interpretation and classification were performed in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines, taking into account all known inheritance models.

Statistical analysis

Descriptive statistics were used to summarize the data. Continuous variables were expressed as mean and standard deviation (SD), and categorical variables were presented as frequencies and percentages.

Results

Demographic and Clinical Characteristics

A total of 20 pediatric patients from 19 unrelated families were included in the study. The cohort consisted of 11 females (55%) and 9 males (45%). The mean age at evaluation was 6.1 years, ranging from 1 month to 13.5 years.

Parental consanguinity was noted in one patient, and two patients had a parent with phenotypic features suggestive of NS. Prenatal history was unremarkable in most cases; however, polyhydramnios was reported in 2 patients (10%), and intrauterine growth restriction in 1 patient (5%).

The most common reasons for referral for genetic investigation were short stature and congenital heart disease, together accounting for 65% of cases. Short stature was present in 13 patients (65%), and low body weight was observed in seven patients (35%). None of the patients met the criteria for macrocephaly.

Neurodevelopmental milestones were within the normal range in 12 patients (60%), whereas developmental delay of varying severity was observed in 8 patients (40%). Hypotonia was documented in 1 patient (5%).

A typical facial phenotype consistent with NS was observed in 12 of 20 patients (60%). Among the most frequent dysmorphic features, hypertelorism was observed in 19 patients (95%), ptosis in 12 patients (60%), downslanting palpebral fissures in 11 patients (55%), high-arched palate in 7 patients (35%), and short neck in 5 patients (25%). Representative facial phenotypes observed in Noonan syndrome and related disorders are illustrated in Figure 1.

CHD was identified in 16 patients (80%), while 4 patients (20%) had no detectable cardiac anomalies. The most frequent cardiac abnormality was PS, observed in 13 patients (65%). Other cardiac findings included ASD in 6 patients (30%), HCM in 3 patients (15%), ventricular septal defect in 1 patient (5%), and aortic stenosis in 1 patient (5%). Some patients exhibited more than one cardiac anomaly.

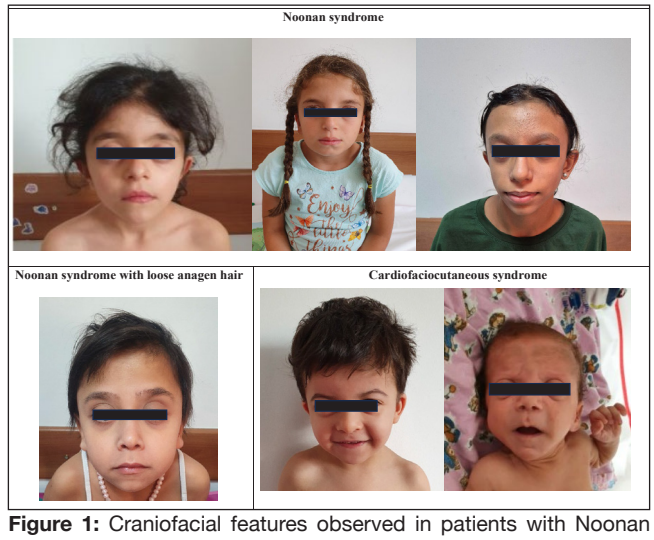

Figure 1: Craniofacial features observed in patients with Noonan syndrome, Noonan syndrome with loose anagen hair, and cardiofaciocutaneous syndrome.

Pectus deformity was identified in 7 patients (35%), including pectus excavatum in 5 patients (25%) and pectus carinatum in 2 patients (10%). Scoliosis was present in 2 patients (10%), and cubitus valgus was observed in 2 patients (10%).

Ectodermal manifestations were common, with café-au-lait macules observed in 6 patients (30%) and lentigines in 2 patients (10%). Deep palmar creases were identified in 3 patients (15%) and hair anomalies in 2 patients (10%). Additionally, a cutaneous vascular malformation was detected in 1 patient (5%).

Cryptorchidism was present in 2 patients (10%), while no other genitourinary anomalies were identified. Ophthalmologic abnormalities were limited to strabismus, observed in 2 patients (10%). Hearing loss was detected in 1 patient (5%). No lymphatic malformations were identified in any of the patients in our cohort. Initial hematologic and oncologic assessments revealed no abnormalities in any patient.

The overall clinical characteristics of the study cohort are summarized in the table I.

Molecular Genetic Findings

A definite molecular diagnosis was established in all 20 patients through integrated clinical and genetic evaluation. Overall, 9 different genes were implicated in the molecular etiology. All detected variants were heterozygous. A total of 19 distinct variants were identified, as the monozygotic twins shared the same *PTPN11* variant. A comprehensive summary of the genetic findings is provided in Table II.

The most frequently affected gene was *PTPN11*, with variants identified in 8 patients (40%). Other genes included *LZTR1* in 3 patients (15%), *NF1* in 2 patients (10%), and *RAF1* in 2 patients (10%). Single patients (5% each) harbored variants in *BRAF, SHOC2, SPRED1, RIT1*, and *MAP2K2*.

Table I: Demographic and clinical characteristics of the study cohort

No	Gender/ Age*	Presenting Symptoms	Height (SDS)	Craniofacial findings	CA	Skeletal findings	Ectodermal findings	DD/ID	Other
1	F/123	DD	-4.5	H, ptosis, high-arched palate, relative macrocephaly	-	-	CALMs, deep palmar and plantar creases, fine and sparse slow-growing hair	+	Strabismus
2	M/92	Short stature	-3.1	H, ptosis, DPF, triangular face	PS, ASD	CV	-	-	-
3	M/3	CA	-0.96	H, ptosis, DPF, short neck	PS, ASD	-	CALMs	-	Cryptorchidism
4	F/5	CA	-1.23	H, high-arched palate	PS	CV	CALMs	-	-
5	M/94	Short stature	-2.34	H, ptosis, epicanthus	HCM	-	-	-	-
6	F/124	Short stature	-3.43	H, DPF, deep philtrum, short neck, and webbed neck	-	PE, scoliosis	-	-	-
7	F/124	Lentigines	-2.09	H, depressed nasal bridge, high-arched palate	PS ASD	-	Multiple lentigines	+	-
8	F/162	Dysmorphism	-2.05	H, ptosis, DPF, triangular face	PS	Scoliosis	-	-	Strabismus
9	F/100	Short stature	-2.1	Depressed nasal bridge, high-arched palate	PS	PE	CALMs	+	-
10	M/2	CA	-0.8	H, ptosis, DPF, epicanthus, depressed nasal bridge, high-arched palate, deep philtrum, pointed chin, low-set ears	PS	PE	Sparse hair, sparse eyebrows, deep palmar creases, loose skin	-	Hearing loss, hypotonia
11	M/120	Short stature	-2.4	H, ptosis, DPF	PS	PE, scoliosis	-	-	-
12	M/1	CA	-1.57	H, ptosis, DPF, dysplastic and low-set ears, brachycephaly, short neck	VSD, ASD, HCM	-	-	-	Cryptorchidism
13	F/98	Short stature	-3.2	H, depressed nasal bridge	-	-	CALMs	-	-
14	M/18	CA	-0.42	H, ptosis, DPF, prominent and broad forehead, deep philtrum, short neck	HCM	-	-	-	-
15	F/6	Short stature	-2.05	H, DPF, epicanthus, high-arched palate	-	None	CALMs	-	-
16	F/103	Dysmorphism	-2.17	H, ptosis, DPF, proptosis	PS	PE	-	+	-
17	M/58	DD	-3.47	H, ptosis, DPF, prominent forehead, relative macrocephaly	PS	Pectus carinatum	Deep palmar creases,	+	-
18	M/24	DD	-1.12	H, ptosis, dysplastic and low-set ears, depressed nasal bridge, prominent forehead	PS	-	-	+	Cutaneous vascular malformation
19	F/124	Lentigines	-2.02	H, depressed nasal bridge, high-arched palate	PS, ASD	None	Multiple lentigines	+	-
20	F/11	CA	0.95	H, prominent forehead, deep philtrum, short neck	PS, AS, ASD	Pectus carinatum	-	-	-

***:** *months,* ***M:** *male,* ***F:** *female,* ***CA:** *Cardiac anomaly* ***DD:** *Developmental delay,* ***H:** *Hypertelorism,* ***DPF:** *Downslanting palpebral fissures,* ***CV:** *Cubitus valgus,* ***PE:** *Pectus excavatum,* ***SDS:** *standard deviation score,* ***PS:** *pulmonary stenosis,* ***ASD:** *atrial septal defect,* ***HCM:** *hypertrophic cardiomyopathy,* ***VSD:** *ventricular septal defect,* ***AS:** *aortic stenosis,* ***CALMs:** *café-au-lait macules,* ***ID:** *Intellectual disability*

Table II: Molecular genetic findings of the study cohort

No	Confirmed Diagnosis	Gene	Nucleotide Change	Aminoacid Change	Zygosity	Variant Type	Variant Classification (ACMG)	Novel/ Known	dbSNP ID	Inheritance
1	NSLH	*SHOC2*	c.4A>G	p.(Ser2Gly)	Het	Missense	P	Known	rs267607048	De novo
2	NS	*PTPN11*	c.317A>C	p.(Asp106Ala)	Het	Missense	P	Known	rs397507517	
3	NS	*PTPN11*	c.184T>G	p.(Tyr62Asp)	Het	Missense	P	Known	rs121918460	
4	NFNS	*NF1*	c.7415del	p.(Pro2472LeufsTer17)	Het	Frameshift	P	Known	rs1597859768	De novo
5	NS	*LZTR1*	c.27dup	p.(Gln10AlafsTer24)	Het	Frameshift	P	Known	rs587777613	
6	NS	*PTPN11*	c.5C>T	p.(Thr2Ile)	Het	Missense	P	Known	rs267606990	
7	NSML	*PTPN11*	c.836A>G	p.(Tyr279Cys)	Het	Missense	P	Known	rs121918456	De novo
8	NS	*LZTR1*	c.742G>A	p.(Gly248Arg)	Het	Missense	P	Known	rs869320686	De novo
9	NFNS	*NF1*	c.3461A>T	p.(Asn1154Ile)	Het	Missense	LP	Known	rs371544233	
10	CFCS	*BRAF*	c.770A>G	p.(Gln257Arg)	Het	Missense	P	Known	rs180177035	De novo
11	NS	*PTPN11*	c.188A>G	p.(Tyr63Cys)	Het	Missense	P	Known	rs121918459	
12	NS	*PTPN11*	c.417G>C	p.(Glu139Asp)	Het	Missense	P	Known	rs397507520	De novo
13	LGSS	*SPRED1*	c.304dup	p.(Thr102AsnfsTer7)	Het	Frameshift	P	Known	rs1555391053	
14	NS	*RAF1*	c.769T>C	p.(Ser257Pro)	Het	Missense	LP	Known	rs727505017	De novo
15	NS	*LZTR1*	c.1495G>A	p.(Val499Met)	Het	Missense	VUS	Known	rs773420178	De novo
16	NS	*PTPN11*	c.417G>C	p.(Glu139Asp)	Het	Missense	P	Known	rs397507520	
17	CFCS	*MAP2K2*	c.247G>A	p.(Gly83Ser)	Het	Missense	VUS	Known	rs765755554	Mat
18	NS	*RAF1*	c.761G>A	p.(Arg254Lys)	Het	Missense	VUS	Novel		De novo
19	NSML	*PTPN11*	c.836A>G	p.(Tyr279Cys)	Het	Missense	P	Known	rs121918456	De novo
20	NS	*RIT1*	c.335G>C	p.(Gly112Ala)	Het	Missense	P	Known	rs672601335	Pat

NSLH : *Noonan-like syndrome with loose anagen hair;* ***NS:*** *Noonan Syndrome;* ***NFNS:*** *Neurofibromatosis–Noonan syndrome;* ***NSML:*** *Noonan syndrome with multiple lentigines;* ***CFCS:*** *Cardiofaciocutaneous syndrome;* ***LGSS:*** *Legius syndrome;* ***Het:*** *heterozygous;* ***P:*** *pathogenic;* ***LP:*** *likely pathogenic;* ***VUS:*** *variant of uncertain significance;* ***ACMG:*** *American College of Medical Genetics and Genomics;* ***dbSNP:*** *Single Nucleotide Polymorphism Database;* ***Mat****: maternal;* ***Pat:*** *paternal*

Based on combined clinical and molecular findings, the final diagnoses were NS in 12 patients (60%), NFNS in 2 patients (10%), CFCS in 2 patients (10%), NSML in 2 patients (10%), LGSS in 1 patient (5%), and NSLH in 1 patient (5%).

Regarding variant type, 16 of the 19 variants (84.2%) were missense, while 3 variants (15.8%) were frameshift. According to ACMG classification, 14 variants (73.7%) were pathogenic, 2 (10.5%) were likely pathogenic, and 3 (15.8%) were classified as variant of uncertain significance (VUS). Only one variant was novel, whereas all remaining variants had been previously reported.

Segregation analysis was available for 12 patients; two had a affected parent with suggestive features of NS, while the remaining variants were confirmed to be de novo, and the affected parents were referred for further clinical evaluation.

The three VUS were identified in *LZTR1*, *MAP2K2*, and *RAF1*. The MAP2K2 variant was detected in a patient presenting with a phenotype consistent with CFCS, including short stature, relative macrocephaly, ptosis, hypertelorism, downslanting palpebral fissures, prominent forehead, PS, pectus deformity, and developmental delay. The same variant was also identified in the patient's mother, who exhibited a similar phenotype accompanied by mild intellectual disability. A VUS variant in the *LZTR1* was detected in a patient with typical NS facial features, short stature, and café-au-lait macules and was confirmed to be de novo. A novel VUS in *RAF1* (c.761G>A) was identified in a patient with characteristic NS facial features and PS, and was confirmed to be de novo. Based on the concordance between the clinical phenotype, molecular findings, and the available segregation data, this variant was considered potentially disease-associated.

Discussion

In this study, we evaluated the clinical and molecular characteristics of a pediatric cohort consisting of 20 patients diagnosed with NS and related disorders. In our study cohort, NS constituted the most common diagnostic category, accounting for 60% of cases. However, the clinical spectrum extended beyond classic NS and also included NFNS, CFCS, NSML, LGSS, and NSLH. The most frequently identified genetic etiology was *PTPN11* variants, accounting for 40% of cases, followed by *LZTR1* (15%), *NF1* (10%), and *RAF1* (10%). Overall, variants classified as pathogenic, likely pathogenic, and selected VUS were identified in nine different genes, highlighting the marked genetic heterogeneity of RASopathies (5).

The frequency of *PTPN11* mutations observed in our cohort (40%) is broadly consistent with published data, in which *PTPN11* variants account for approximately half of NS cases (10). In comparison with national data, our findings are closely

aligned with the 50% mutation rate reported in a recent Turkish RASopathy cohort by Alkaya et al. (11), while exceeding the lower frequency (27%) documented in an earlier Turkish series by Şimşek-Kiper et al. (12). From an international perspective, reported *PTPN11* mutation frequencies vary substantially across populations, ranging from 29% in an Indian cohort to 51% in a large Russian series (13,14). Overall, these inter-study differences likely reflect variations in patient selection, cohort size, diagnostic approaches, and population-specific genetic backgrounds.

Notably, no *SOS1* variants were identified in our cohort, despite *SOS1* accounting for approximately 10–20% of Noonan syndrome cases (15,16). Moreover, SOS1 variants have been reported in 19–27% of patients in Turkish cohorts (11,12). This absence is likely attributable to the relatively small sample size, but may also be related to the phenotypic characteristics of our cohort. In the literature, *SOS1* variants are generally associated with a milder clinical phenotype, the presence of ectodermal features (such as keratosis pilaris and curly hair), and, most importantly, a lower frequency of short stature or an association with normal height (17, 18). Therefore, patients harboring *SOS1* mutations, who often exhibit normal stature, may not have been referred for genetic evaluation, as short stature was present in 65% of patients in our cohort.

A particularly notable finding was the relatively high prevalence of *LZTR1* variants, detected in 15% of patients, which exceeds the generally reported prevalence of 4–9% in the literature (19). However, our finding is comparable to the 11.1% reported in a recent Turkish cohort, suggesting that *LZTR1* mutations may be more frequent in the Turkish population than previously estimated in broader international series (11).

In our study, a novel missense variant in *RAF1* (c.761G>A) was identified in a patient exhibiting characteristic NS facial features and PS. This variant is located within the highly conserved region 2 (CR2) domain of the *RAF1* protein, a critical regulatory region that includes the 14-3-3 binding motif. Pathogenic variants clustering in this region, particularly around the Ser257 residue, are known to interfere with the inhibitory binding of 14-3-3 proteins, thereby leading to sustained activation of the Ras/MAPK pathway and a high predisposition to HCM (20). Although the de novo occurrence and the close proximity to known pathogenic clusters strongly support its clinical significance, the variant is currently classified as a VUS. To definitively upgrade its classification according to ACMG guidelines, functional evidence is required. Until such functional evidence is obtained, the variant remains potentially disease-associated based on the strong concordance between the clinical phenotype, molecular findings, and available segregation data.

Patients in our cohort classified as having NFNS presented with café-au-lait macules, PS, and pectus deformity, while lacking classic *NF1* features such as neurofibromas or Lisch nodules. The phenotypic overlap between NS and *NF1* has been well recognized in the literature (4, 21). Given that *NF1* can give rise to distinct clinical presentations, an NFNS overlap diagnosis should be considered in patients with Noonan-like features who do not fully meet diagnostic criteria for *NF1*.

Cardiovascular involvement was observed in 80% of patients, with PS being the most common anomaly (65%). This frequency is consistent with the reported 50–60% prevalence of PS in NS (22). In terms of genotype–phenotype correlations, the strong association between *PTPN11* mutations and PS is well established (23). PS was indeed the predominant cardiac finding among *PTPN11*-positive patients in our cohort, observed in 6 of 8 patients (75%). In contrast, *RAF1* mutations have been reported to be associated with HCM in up to 80–95% of cases (24). Most pathogenic *RAF1* variants cluster within the CR2, particularly around Ser257, and are strongly linked to severe HCM (20, 24). In our cohort, two patients harbored *RAF1* variants, one presenting with HCM and the other with PS. Similarly, *RIT1* variants are known to confer a high risk of HCM (56–75%) in NS patients; however, in our cohort, the *RIT1*-positive patient presented with PS (25,26). While strong genotype–phenotype correlations have been established for certain genes, cardiac manifestations across RASopathies represent a broader and more variable cardiac spectrum. Importantly, in our cohort, four patients had no detectable cardiac abnormalities, underscoring that structural heart disease, although common, is not an obligatory feature of NS, and emphasizing that molecular diagnosis should not be excluded in the absence of cardiac findings.

Genotype–phenotype correlations have been described for growth impairment across NS and related disorders. *PTPN11*-positive individuals are frequently reported to be shorter than NS patients without *PTPN11* variants, whereas normal stature or a lower frequency of short stature has been described in specific subgroups such as *SOS1* and RIT1–related NS (26-28). In contrast, *SHOC2*-related NSLH is consistently associated with prominent ectodermal features and postnatal growth failure, and severe short stature has been repeatedly reported (29,30). Consistent with these gene-specific trends, short stature was the most common reason for referral in our cohort, being most severe in the *SHOC2*-positive patient (height SDS −4.5) and frequent among *PTPN11*-positive patients (6/8, 75%), whereas normal stature was observed in the *RIT1*-positive patient, underscoring both established correlations and the overall heterogeneity of growth outcomes in NS and NS-related disorders.

No malignancies were observed in our cohort. Nevertheless, NS patients—particularly those with *PTPN11* and *KRAS* mutations—are known to have an increased risk of juvenile myelomonocytic leukemia and other hematologic malignancies (31,32). Moreover, *LZTR1* variants have been associated with a predisposition to schwannomatosis (33). These considerations highlight the importance of long-term clinical follow-up in affected patients.

Limitations

Despite its comprehensive molecular characterization, this study has several limitations. The sample size is relatively small (n=20), which limits the ability to generalize the frequency of rare genetic variants or establish definitive genotype–phenotype correlations for less common genes. For instance, the absence of SOS1 or *HRAS* variants in our cohort may be due to the limited number of participants rather than a true absence in the local population. As a single-center retrospective study, there may be an inherent referral bias; patients with more severe or classic clinical presentations

(such as significant short stature or complex cardiac defects) might have been more likely to be referred for genetic testing, potentially excluding those with milder phenotypes. A significant limitation of this study is the absence of functional validation for the identified novel and uncertain variants. Future multi-center studies with larger, longitudinal cohorts are needed to further clarify the regional genetic landscape of RASopathies.

Conclusion

In conclusion, our single-center pediatric cohort highlights the marked clinical and genetic heterogeneity of Noonan syndrome and related RASopathies. Using a targeted multigene panel, a molecular diagnosis was established in all patients, with *PTPN11* as the most frequent cause, followed by *LZTR1*, *NF1*, and RAF1. Integrated interpretation of selected VUS, incorporating phenotype–genotype concordance and segregation data alongside ACMG criteria, proved valuable for resolving diagnostic gray zones. The observed phenotypic variability, including variable cardiac and growth involvement, underscores the limitations of clinical assessment alone. Overall, our findings support comprehensive molecular testing to refine diagnosis, guide surveillance, and enable accurate genetic counseling in NS-spectrum disorders.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Samsun University Ethics Committee (01.12.2025, reference number: GOKAEK 2025/21/4).

Contribution of the authors

A.S. and O.S. contributed to the conception and design of the study. AS, TKC, EU, ES, and OS. were responsible for data collection and clinical evaluation. AS, MBM, and OS. performed data analysis and interpretation. AS. drafted the initial version of the manuscript. TKC, EU, MBM, ES, and O.S. critically revised 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

Platelet count and serum potassium: An overlooked link in pediatric thrombocytosis

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Received : 12.02.2026, Accepted : 21.05.2026
DOI: DOI: 10.12956/TJPD.2026.1310

ABSTRACT

Objective: Thrombocytosis, particularly in children, can lead to spurious biochemical findings such as pseudohyperkalemia, which may result in unnecessary interventions if unrecognized. This study aimed to evaluate the effect of platelet count on serum potassium levels in children with thrombocytosis and to analyze the association between potassium levels and the etiological factors of thrombocytosis.

Materials and Methods: In this retrospective study, 1899 pediatric patients with platelet counts >600×10^9/L were analyzed over one year. After excluding conditions that could affect serum potassium (e.g., essential thrombocytosis, anemia, polycythemia/leukocytosis, renal or hepatic disease, and hyperbilirubinemia), 1210 cases of reactive thrombocytosis were included. Patients with available serum potassium measurements and follow-up data at 3 and 6 months were assessed.

Results: The mean age of the 1210 patients was 2.7±3.4 years, and 54.8% were male. Thrombocytosis was primarily due to infections (71.8%) and surgery, burns, or trauma (28.2%). Platelet counts ranged from 600×10^9/L to 2.193×10^9/L, and serum potassium levels from 2.47 to 9.3 mEq/L. Hyperkalemia occurred in 20.4% of patients, increasing with higher platelet counts (16.7% for 600–900×10^9/L, 29.1% for 900–1000×10^9/L, and 33.5% for >1000×10^9/L). Significant decreases in platelet and potassium levels were observed at 3- and 6-month follow-ups ($p<0.001$). A weak positive correlation was observed between platelet and potassium levels ($r=0.187$), more pronounced in infection-related cases ($r=0.218$). Potassium increased by 0.06 mEq/L for every 100×10^9/L rise in platelet count, with a significant correlation only above 1000×10^9/L ($r=0.196$, $p=0.038$).

Conclusion: Pseudohyperkalemia is a common yet overlooked phenomenon in pediatric thrombocytosis. Recognizing the quantitative platelet–potassium relationship can prevent diagnostic confusion and unnecessary treatment.

Keywords: Hyperkalemia, thrombocytosis, platelet count, pseudohyperkalemia

Introduction

Potassium is an essential electrolyte with a narrow physiological range, and both elevated and decreased levels can necessitate urgent medical attention (1,2). Obtaining accurate and reliable measurements is therefore critical (3). Several pre-analytical factors can lead to erroneous potassium results that do not accurately reflect in vivo concentrations (4,5). Such incorrect readings are often classified as pseudohyperkalemia (PHK) or pseudonormokalemia (PNK) (6–8). Hemolysis during sample collection and transport, as well as leukocytosis, can contribute to PHK or PNK (9). In addition, thrombocytosis represents another significant cause of such spurious results (10). This phenomenon, first described by Hartman in 1955, demonstrated significantly higher serum potassium levels compared to plasma levels in the absence of clinical symptoms. It was attributed to the release of potassium from platelets during aggregation and degranulation in test tube (11).

In patients with thrombocytosis, spuriously elevated serum potassium levels can lead to inappropriate administration of potassium-lowering therapies, potentially resulting in unrecognized iatrogenic hypokalemia or life-threatening cardiac arrhythmias. Similarly, in cases of PNK, where potassium levels appear within the normal range, true hypokalemia may remain

undetected (10,12,13). The most reliable method to identify PHK and PNK is to analyze the sample in a lithium-heparin tube after centrifugation.

In adult populations, previous investigations reported platelet count thresholds of 500×10^9/L and 598×10^9/L for PHK and PNK, respectively, based on serum versus plasma potassium measurements. Furthermore, these studies revealed a strong association between platelet counts and serum potassium concentrations, while plasma potassium levels were unaffected.

In this study, we investigate the impact of platelet count on serum potassium levels in children with thrombocytosis of various etiologies and examine the relationship between potassium concentrations and the underlying causes of thrombocytosis.

Materials and Methods

In this retrospective analysis, patients younger than 18 years with platelet counts greater than 600×10^9/L on complete blood count were evaluated between January 1, 2021, and January 1, 2022. Patients with thrombocytosis who had concurrent serum potassium measurements were included in the analysis. When available, platelet and potassium levels obtained at 3- and 6-month follow-up visits were also recorded. Ankara Bilkent City Hospital, Department of Pediatrics, a large tertiary pediatric center in Türkiye, identified 1899 patients with platelet counts $>600\times10^9$/L within one year. Of these patients, 1594 had simultaneous serum potassium measurements available. To minimize potential confounding factors, newborns and patients with anemia, polycythemia, primary thrombocytosis, leukocytosis, renal or hepatic disease, or hyperbilirubinemia were excluded, as these conditions could influence potassium homeostasis. The remaining patients were categorized into two etiological groups: those with reactive thrombocytosis due to infections and those with thrombocytosis related to soft tissue injury caused by surgery, burns, or trauma. After applying the exclusion criteria, a total of 1210 patients with reactive thrombocytosis were eligible and included in the final analysis. Patients were categorized based on their platelet counts as follows: moderate thrombocytosis for platelet counts between $600\text{-}900\times10^9$/L, severe thrombocytosis for counts between $900\text{-}1000\times10^9$/L, and very severe thrombocytosis for counts above 1000×10^9/L. The process of patient selection, including inclusion and exclusion criteria and final cohort composition, is summarized in Figure 1.

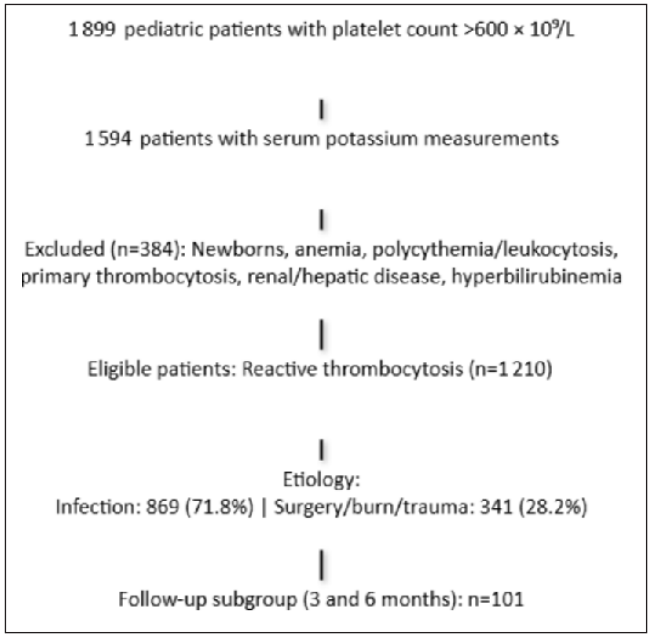

Figure 1: Flowchart of patient selection and study population

Venous blood samples for complete blood count analysis were drawn into 3 mL EDTA tubes and processed using an automated hematology analyzer (Advia 2120, Siemens, Helatneer, Germany). Venous blood samples for serum potassium concentration were collected in 5 mL serum separator tubes. The samples were centrifuged at 4000 rpm for 10 minutes and analyzed using an automated chemistry analyzer (Atellica, Siemens, Helatneer, Germany). All automated analyzers are subjected to daily internal quality control and monthly external proficiency testing to maintain analytical accuracy and consistency. In our institution, hemolyzed samples are automatically flagged by the laboratory information system as part of routine quality control and only data from non-hemolyzed samples were included in the analysis. The reference interval for serum potassium was defined as 3.5–5.5 mEq/L.

This retrospective study was conducted using anonymized data obtained from the hospital's electronic medical records. As the study did not involve direct contact with patients and no identifiable personal information was used, individual informed consent was not required.

Statistical analysis

The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and IQR where appropriate. To evaluate the change in the potassium and platelet levels obtained in the time interval (baseline, 3rd month, 6th month) Friedman Test was applied. The Bonferroni adjusted Wilcoxon signed-rank test was used for multiple comparisons of times. The relationship between serum potassium concentrations and platelet counts was evaluated using the Pearson or Spearman correlation coefficient, based on the normality of the data. Simple linear regression analyses were performed to derive equations for predicting potassium levels from platelet counts in the entire cohort and in diagnostic subgroups. The R^2 values of the regression models were calculated, and scatter plots with corresponding regression lines were produced to visually represent the associations. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA), and R software, Version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Graphical visualizations were created using the ggplot2 and cowplot packages in R.

Results

The mean age of the 1210 patients was 2.7±3.4 years, of whom 663(54.8%) were male and 547 (45.2%) were female. Demographic characteristics and diagnostic details are summarized in Table I. Etiologies of thrombocytosis were categorized, with 869 patients (71.8%) presenting with infections and 341 patients (28.2%) associated with surgery, burns, or trauma. The serum potassium concentrations of the patients ranged from 2.47 to 9.3 mEq/L, while their platelet counts ranged from 600×10^9/L to 2193×10^9/L. Among the 1210 patients, 908 (75%) had moderate thrombocytosis, 141 (11.6%) had severe thrombocytosis, and 161 (13.4%) were classified as very severe.

Of the 1210 patients with thrombocytosis, 20.4% had hyperkalemia (serum potassium >5.5 mEq/L). Hyperkalemia prevalence increased with platelet count: 16.7% in moderate, 29.1% in severe, and 33.5% in very severe thrombocytosis. Platelet and potassium values for each subgroup are summarized in Table I. A total of 101 patients had complete blood count and serum potassium measurements at both 3- and 6-month follow-ups, showing a statistically significant decrease in median platelet counts and potassium levels over time (p<0.001 for both) (Table II).

Platelet counts showed a weak positive correlation with serum potassium levels in the overall cohort (r=0.187), which was slightly stronger in patients with infections (r=0.218). Simple linear regression was used to estimate potassium from platelet counts in the total sample and diagnostic subgroups, with statistically significant equations and R^2 values presented in Table III.

The relevant scatter plots with regression lines are shown in Figure 2. For every 100×10^9/L increase in platelet count, serum potassium rose by approximately 0.06 mEq/L in the total sample, 0.05 mEq/L in the surgery-burn-trauma subgroup, and 0.08 mEq/L in the infection subgroup. When analyzed by platelet subgroups, no significant correlation was observed for counts of 600–900×10^9/L (r=0.008, p =0.819) or 900–1.000×10^9/L (r=0.030, p=0.141). A weak positive correlation emerged for platelet counts exceeding 1.000×10^9/L (r=0.196, p=0.038) (Table III).

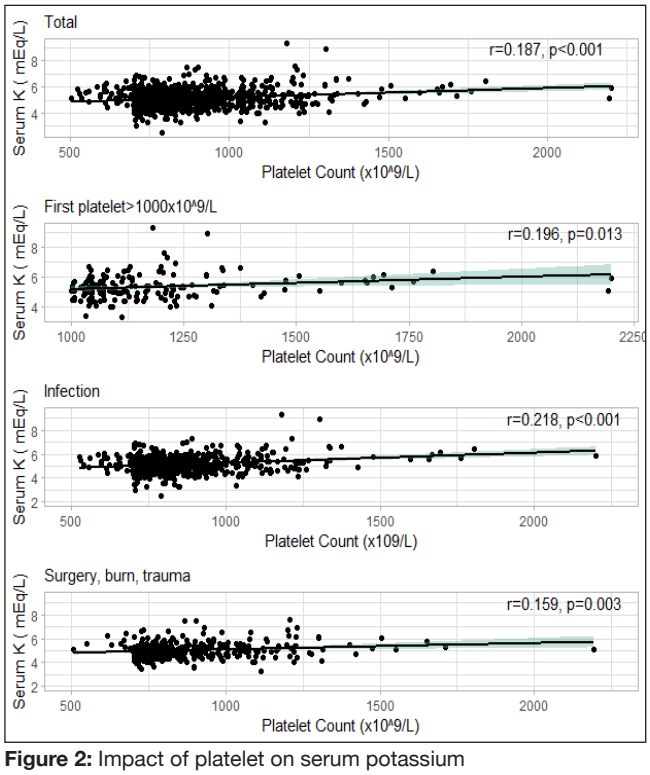

Figure 2: Impact of platelet on serum potassium

Table I: Demographical Characteristics, diagnosis, platelet count, and serum potassium concentration of patients (n=1210)

Variable	Value
Age (year)*	2.7±3.4; 1.0 (1.0–3.0)
Gender†	
Male	663 (54.8)
Female	547 (45.2)
Diagnosis†	
Infection	869 (71.8)
Surgery–burn–trauma	341 (28.2)
Platelet Count (×10^9/L)*	
Infection	830.1±160.1; 782.0 (731.0–879.5)
Surgery–burn–trauma	877.5±193.2; 814.0 (744.5–954.5)
Serum Potassium (mEq/L)*	
Infection	5.1±0.6; 5.1 (4.7–5.5)
Surgery–burn–trauma	5.0±0.7; 4.9 (4.6–5.4)

**: mean±SD;median (IQR), †: n(%)*

Discussion

Reactive thrombocytosis is common in children, particularly among hospitalized patients, and is clinically significant due to its potential impact on serum potassium levels. Elevated platelet counts can lead to PHK, which may result in misinterpretation of laboratory results and unnecessary interventions. Recognizing this phenomenon is crucial to prevent inadvertent iatrogenic hypokalemia and associated cardiac complications. Our study demonstrates that serum potassium levels increase with rising platelet counts, with the relationship influenced by the underlying cause of thrombocytosis. These findings highlight the importance of careful potassium monitoring in children with marked thrombocytosis to guide appropriate clinical management.

Delgado et al. (14) reported PHK and PNK in 0.14% of all serum potassium measurements when compared with plasma values, whereas Thurlow et al. (15) found the incidence of PHK to be as high as 16% in patients with platelet counts exceeding 500×10^9/L. In our study, hyperkalemia was observed in 20.4% of patients with moderate to severe reactive thrombocytosis, and its prevalence increased with rising platelet counts. However, the exact frequency of PHK could not be determined, as simultaneous plasma potassium measurements, the gold standard for differentiating true hyperkalemia from PHK, were not available.

Spurious hyperkalemia has been highlighted in several studies for its clinical significance and risk of misdiagnosis (16). Moderate-to-strong correlations between platelet counts and serum potassium have been reported, particularly in adults with myeloproliferative disorders (17,18). In a large retrospective study by Makale et al. (19), the correlation was

Table II: Changes in platelet count and serum potassium concentration over time

	Baseline*,†	3rd month †	6th month	p*	p†	p‡	p §
Platelet (n=101)	820.0 (768.8-966.5)	598.5 (521.0-700.8)	423.0 (364.8-488.3)	<0.001	<0.001	<0.001	<0.001
Potassium (n=101)	5.2 (4.7-5.6)	4.8 (4.4-5.3)	4.5 (4.2-4.9)	<0.001	<0.001	<0.001	<0.001

***:** *Overall p value,* **†:** *Baseline vs. 3rd month,* **‡:** *Baseline vs. 6th month,* **§:** *3rd vs. 6th month. Data are presented as median (IQR). Comparisons among the three time points were performed using the Friedman test. Post hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction.*

Table III: Linear regression analysis predicting serum potassium level from platelet count

	B	SE B	β	t	p	95% CI for B	R^2
Total sample	0.06×10^{-2}	0.01×10^{-2}	0.187	6.603	<0.001	0.04×10^{-2}-0.09×10^{-2}	0.035
Baseline platelet≥1000x10⁹/L	0.08×10^{-2}	0.03×10^{-2}	0.196	2.523	0.013	1.80×10^{-4}-1.00×10^{-3}	0.038
Diagnosis							
Infection	0.08×10^{-2}	0.01×10^{-2}	0.218	6.568	<0.001	5.98×10^{-4}–1.00×10^{-3}	0.047
Surgery, burn, trauma	0.05×10^{-2}	0.01×10^{-2}	0.159	2.973	0003	0.01×10^{-2}-0.09×10^{-2}	0.025

***B:** Unstandardized regression coefficient,* ***SE:** Standard error,* ***β:** Standardized regression coefficient,* ***CI:** Confidence interval. Platelet count was used as the independent variable, and serum potassium level was used as the dependent variable.*

0.155, likely due to limited preanalytical corrections and lack of etiological categorization. The highest correlation (r=0.82) was observed in patients with polycythemia vera (20). A study comparing different etiologies suggested higher PHK incidence and stronger correlations in primary thrombocytosis, although mild reactive cases were underrepresented (18). Primary thrombocytosis is extremely rare in children and is known to affect serum potassium levels; therefore, patients with primary thrombocytosis were excluded from our study.

In our large pediatric cohort, weak correlations were observed in both infection and surgery-burn-trauma subgroups. These correlations were lower than those reported in primary thrombocytosis, where higher and more stable platelet counts and altered platelet fragility contribute to a stronger association. No correlation was detected in our cohort for platelet counts below 1.000×10^9/L. While previous smaller studies suggested a threshold of $500–600\times10^9$/L for PHK/PNK, our findings indicate that this threshold is higher in children with reactive thrombocytosis. The stronger correlations reported in patients with essential thrombocytosis or myeloproliferative disorders suggest additional factors influencing PHK that are absent in reactive thrombocytosis.

This study has several limitations. One important factor affecting PHK in the preanalytical process is platelet elevation; however, other influencing variables could not be fully excluded and should be addressed in future prospective studies. Patients with essential thrombocytosis were not included in comparative analyses due to their limited number. Furthermore, the absence of plasma potassium measurements prevented the determination of a definitive platelet cutoff for identifying PHK. Additionally, multivariate adjustments for potential confounders such as age and sex were not performed when evaluating the correlation between platelet counts and serum potassium levels. Finally, the single-center design may limit the generalizability of our findings to broader pediatric populations and diverse healthcare settings.

Limitations

Despite its limitations, the study's key strengths lie in its large pediatric sample, the analysis of diverse causes of reactive thrombocytosis, and the generation of practical, clinically relevant findings that can help clinicians accurately recognize pseudohyperkalemia and avoid inappropriate or potentially harmful treatments.

Conclusion

Thrombocytosis-related PHK is a clinically significant in vitro phenomenon that may lead to misinterpretation of laboratory results and inappropriate treatment, especially in pediatric patients. Our study demonstrates that serum potassium levels increase proportionally with platelet counts in children with reactive thrombocytosis, particularly due to infections and surgery-burn-trauma, even in the absence of comorbidities. Clinicians should consider simultaneous platelet counts when evaluating elevated potassium results, as unrecognized PHK may mask true hypokalemia. This awareness can prevent unnecessary interventions and iatrogenic complications. While our findings support the need for cautious interpretation of potassium levels in thrombocytosis, further prospective studies are warranted to develop standardized correction approaches and broader clinical guidelines.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (18.09.2024, reference number: TABED 2-24-494).

Contribution of the authors

Concept: BD, NY; Design: BD, NY, DK; Formal analysis and investigation: BD, NY, EA; Analysis of data: SPY, BD; Literature search; BD, NY, EA; Writing – original draft preparation: BD, NY; Editing: NY; Supervision: NY

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

Psychosocial outcomes in healthy siblings of children with celiac disease: A controlled cross-sectional study

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Received : 24.02.2026, Accepted : 01.06.2026
DOI: 10.12956/TJPD.2026.1316

ABSTRACT

Objective: The aim of this study was to compare health-related quality of life (QoL) and anxiety/depressive symptoms in healthy siblings of children with celiac disease (CD) with age- and gender-similar healthy siblings of children without chronic illness.

Materials and Methods: This controlled cross-sectional study, conducted in a pediatric gastroenterology and child psychiatry setting at a tertiary-care hospital, enrolled healthy siblings aged 8–17 years into a CD-sibling group (n=70) and a control group (n=70). Sociodemographic data were collected using a standardized form, QoL was assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, and psychiatric symptoms were assessed using the Revised Child Anxiety and Depression Scale (RCADS). Between-group comparisons and Spearman rank correlations were used, and predictors of total anxiety and psychosocial QoL were examined using univariable and multivariable linear regression.

Results: Sociodemographic and familial characteristics were largely comparable between groups. Compared with controls, the CD-sibling group had higher total anxiety scores (p=0.007), whereas depressive symptoms were similar between groups (p=0.758). Psychosocial and total QoL were lower in the CD-sibling group (both p<0.001), while physical QoL did not differ between groups (p=0.201). In multivariable models within the CD-sibling group, longer time since diagnosis and maternal psychiatric disorder independently predicted higher anxiety and poorer psychosocial QoL, whereas a greater number of siblings predicted lower anxiety and better psychosocial QoL.

Conclusion: Healthy siblings of children with CD experience increased anxiety and reduced psychosocial/total QoL, underscoring the importance of family-centered monitoring that includes sibling well-being and maternal mental health.

Keywords: Anxiety, celiac disease, depression, quality of life, pediatric, siblings

Introduction

Childhood chronic illnesses impose a multidimensional burden that extends beyond the affected child and permeates the entire family system (1). Advances in medical care have markedly improved survival and long-term outcomes for many pediatric chronic conditions; consequently, the psychosocial sequelae experienced by family members have become an increasingly important focus of clinical attention (2,3). Within this context, healthy siblings represent a particularly vulnerable yet often overlooked group who may be required to navigate complex emotional and developmental challenges. As parental time, energy, and financial resources are disproportionately directed toward the ill child, parents' emotional and physical availability for other children may diminish. In parallel, greater household responsibilities and heightened exposure to family stress can adversely affect healthy siblings' emotional well-being and everyday functioning (4,5).

A growing body of research suggests that healthy siblings of children with chronic illness may report poorer health-related quality of life (QoL) and face elevated risks of internalizing symptoms such as anxiety and depressive features, as well as behavioral problems and adjustment difficulties (6–8). Nevertheless, findings across studies remain heterogeneous, indicating that the magnitude and form of sibling impact are not uniform. Reported variability appears to be influenced by

illness- and context-related factors, including disease severity and visibility, treatment burden, illness duration, family coping resources, and socioeconomic circumstances (9–12).

Celiac disease (CD) is an immune-mediated disorder with distinctive management challenges, primarily characterized by the need for lifelong, strict adherence to a gluten-free diet (13). Unlike many chronic conditions in which treatment is episodic or largely clinic-based, CD management is embedded in daily life and requires continuous vigilance. Ongoing demands may include careful food selection, prevention of cross-contamination, restructuring of household meal routines, and sustained accommodations in school and social environments, as well as planning for travel and social events (14,15). These persistent requirements can shape family routines and the broader family climate (16,17). Notably, children with CD have been reported to exhibit a higher burden of psychological symptoms (e.g., anxiety and depressive symptoms) and poorer health-related QoL than their healthy peers (18). In parallel, parents of children with CD have been reported to experience higher parenting stress and a greater burden of mental health problems than parents of healthy children (16,19). Through mechanisms such as dietary restrictions, shifts in intra-family interactions, elevated parental stress, and concerns about exclusion or social adaptation, CD may also affect the mental health and psychosocial functioning of healthy siblings (17,19,20).

Although there is substantial literature on healthy siblings in the context of various pediatric chronic diseases (e.g., cancer, neurological disorders, congenital heart disease, and diabetes), studies directly examining psychosocial outcomes among healthy siblings in families affected by pediatric CD remain limited (4,19,21–23). Therefore, in this study, we evaluated health-related QoL and levels of anxiety and depressive symptoms in healthy siblings of children with CD by comparing them with age- and gender-similar healthy siblings of children without chronic illness.

Materials and Methods

This controlled cross-sectional study was conducted between June and December 2025 at the Pediatric Gastroenterology, Hepatology, and Nutrition and the Child and Adolescent Psychiatry outpatient clinics of Gulhane Training and Research Hospital. Participants aged 8–17 years were recruited into two groups. A total of 140 participants were enrolled (70 in the CD-sibling group and 70 in the healthy-sibling group). The CD-sibling group comprised healthy siblings of children with CD who were under follow-up at the Pediatric Gastroenterology clinic; eligible siblings were invited when families attended the clinic during the study period. Healthy siblings were defined as siblings without any known chronic physical illness, including a previous diagnosis of CD. In the CD-sibling group, eligible siblings had also undergone serological screening for CD as part of routine first-degree relative screening; those with positive CD serology or diagnosed CD were not included. The diagnosis of CD in the index child was confirmed by upper gastrointestinal endoscopy and small intestinal biopsy, in accordance with the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2020 criteria (24). As standard of care, all patients were prescribed a strict gluten-free diet after diagnosis. The healthy-sibling group (controls) comprised healthy siblings of children who presented to the same outpatient clinic for routine pediatric assessment (e.g., well-child/routine check-up) and who had no history of chronic medical illness; participating siblings in the control group were also required to have no chronic medical illness. The control group was selected to be similar to the CD-sibling group in terms of age and sex distribution.

Participants were excluded if the index sibling had a chronic disease other than CD, if the participant had any chronic physical illness, or if there was a history of a severe psychiatric diagnosis or treatment (e.g., autism, intellectual disability, schizophrenia). Participants were also excluded if they had neurocognitive, language, visual, or hearing impairment that could compromise valid questionnaire completion. In addition, participants were excluded if they were currently receiving psychotropic medication or active psychiatric treatment, to minimize potential confounding of symptom ratings and questionnaire-based outcomes. Participants with an acute medical condition at the time of assessment, those who declined participation, or those who left the questionnaire set incomplete were also excluded. These exclusion criteria were assessed during recruitment through a brief child psychiatry interview with the participant and parent/legal guardian, parental report, and review of available hospital records where applicable.

Participants who met the inclusion criteria and voluntarily agreed to participate were referred to the child psychiatry outpatient clinic. All data collection instruments were administered individually to participants, and completed forms were reviewed on-site to minimize missing responses. A study-specific semi-structured sociodemographic form was used to record parent- and child-related characteristics, including parental age, educational level, employment status, and history of chronic medical illness or psychiatric disorders, as well as monthly household income, number of siblings, birth order, and the child's age and gender; in the CD-sibling group, time since diagnosis (months) was also recorded. Health-related QoL was assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales (self-report, used in this study for participants aged 8–17 years), which evaluates physical, emotional, social, and school functioning and yields physical, psychosocial, and total QoL scores. Higher scores indicate better QoL. The original scale was developed by Varni et al. (25), and the Turkish validity and reliability of the relevant age forms were established by Memik et al. (26,27). Anxiety and depressive symptoms were assessed using the Revised Child Anxiety and Depression Scale (RCADS). The RCADS yields six subscale scores (Separation anxiety, social anxiety, obsessive–compulsive disorder, panic disorder, generalized anxiety, and major depressive disorder) and the composite indices used in this study: total anxiety score and anxiety–depression total score. The instrument was originally developed by Chorpita et al., and the Turkish adaptation was validated by Görmez et al. (28,29)

Statistical analysis

An a priori sample size calculation was performed using G*Power 3.1. For comparisons between two independent

groups on continuous outcomes, assuming a moderate effect size (Cohen's d = 0.50), a two-sided α level of 0.05, and 80% power, at least 64 participants were required per group. To account for possible incomplete data, we planned to recruit at least 65 participants per group; the final sample included 70 participants in each group.

All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro–Wilk test. Continuous variables are presented as or median with interquartile range (IQR), as appropriate, and categorical variables as n (%). Between-group comparisons used the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Associations between continuous variables were evaluated using Spearman rank correlation analysis (ρ). Univariable linear regression analyses were performed to examine the association of each candidate predictor (demographic and clinical variables) with psychosocial QoL and total anxiety scores. Variables with p<0.100 in univariable analyses were considered for multivariable modeling, and age and sex were included a priori. Multivariable linear regression models were then fitted using the enter method. Model assumptions were checked, including linearity, homoscedasticity, multicollinearity, and normality of residuals. Unstandardized coefficients (B) with 95% confidence intervals (CI), standardized coefficients (β), p values, and coefficients of determination (R^2) were reported. Two-sided p values <0.050 were considered statistically significant.

Results

A total of 140 participants were enrolled, with 70 individuals in the CD-sibling group and 70 in the healthy-sibling group. Sociodemographic and familial characteristics were largely comparable between groups (Table I). Child age, duration of breastfeeding, maternal age, and paternal age were similar across groups (Table II). Maternal psychiatric disorder was more frequent in the CD-sibling group than in the healthy-sibling group (20.0% vs 8.6%); however, this difference did not reach statistical significance (p=0.053) (Table I).

RCADS anxiety-related symptom scores were higher in the CD-sibling group than in the healthy-sibling group (Table II). The CD-sibling group had significantly higher scores for separation anxiety (p=0.005), generalized anxiety (p=0.014), panic disorder (p=0.006), and social anxiety (p=0.009). Obsessive–compulsive symptoms did not differ significantly between the groups (p=0.064). Depressive symptom scores did not differ between the groups (p=0.758). Total anxiety (p=0.007) and the total anxiety–depression score (p=0.018) were higher in the CD-sibling group.

PedsQL-assessed QoL outcomes differed between groups (Table II). Psychosocial QoL scores were significantly lower in the CD-sibling group (p<0.001), and total QoL scores were also lower in this group (p<0.001). Physical QoL scores did not differ between the groups (p=0.201).

In the CD-sibling group (n=70), time since diagnosis (months) had a median of 7.0 (IQR: 2.0–18.0; range: 0–36). Spearman rank correlation analyses indicated that time since diagnosis

Table I: Comparison of categorical sociodemographic and familial characteristics between the CD-sibling and healthy-sibling groups

	CD-sibling	Healthy-sibling	p
Total number of patient	70	70	-
Child gender (Male/Female)*	38 (54.3) / 32 (45.7)	35 (50.0) / 35 (50.0)	0.612
Number of siblings*			
1	28 (40.0)	23 (32.9)	0.668
2	32 (45.7)	35 (50.0)	
3	10 (14.3)	12 (17.1)	
Birth order*			
First	26 (37.1)	28 (40.0)	
Second	34 (48.6)	34 (48.6)	0.659
Third	10 (14.3)	7 (10.0)	
Fourth	0 (0)	1 (1.4)	
Pregnancy complications, yes*	4 (5.7)	3 (4.3)	1.000
Maternal education level*			
Primary	20 (28.6)	25 (35.7)	0.623
High school	35 (50.0)	33 (47.1)	
University	15 (21.4)	12 (17.1)	
Maternal employment status* (Not working)	46 (65.7)	48 (68.6)	0.719
Maternal chronic physical illness, yes*	14 (20.0)	8 (11.4)	0.164
Maternal psychiatric disorder, yes*	14 (20.0)	6 (8.6)	0.053
Paternal education level*			
Primary	14 (20.0)	16 (22.9)	0.744
High school	34 (48.6)	36 (51.4)	
University	22 (31.4)	18 (25.7)	
Paternal employment status* (Not working)	4 (5.7)	3 (4.3)	1.000
Paternal chronic physical illness, yes*	6 (8.6)	5 (7.1)	0.753
Paternal psychiatric disorder, yes*	10 (14.3)	5 (7.1)	0.172
Monthly household income*			
Minimum wage	6 (8.6)	9 (12.9)	0.714
1–2 × minimum wage	38 (54.3)	36 (51.4)	
>2 × minimum wage	26 (37.1)	25 (35.7)	

***:** *n (%) (Pearson chi-square test/ Fisher's exact test),* ***CD:** *celiac disease*

was negatively correlated with total QoL (ρ=–0.383, p=0.001) and psychosocial QoL (ρ=–0.374, p=0.001), and positively correlated with total anxiety (ρ=0.309, p=0.009) and total anxiety–depression scores (ρ=0.311, p=0.009). Psychosocial and total QoL were negatively correlated with both total anxiety and total anxiety–depression scores (all p<0.001) (Figure 1). Additionally, the number of siblings was negatively correlated with total anxiety (ρ=–0.645) and total anxiety–depression scores (ρ=–0.632), and positively correlated with psychosocial QoL (ρ=0.667) and total QoL (ρ=0.685) (all p<0.001). Other examined variables (child age, maternal age, paternal age, and breastfeeding duration) were not significantly correlated with these outcomes.

In multivariable linear regression models predicting total anxiety (adjusted R^2=0.477) and psychosocial QoL (adjusted R^2=0.620), number of siblings, time since diagnosis, and maternal psychiatric disorder remained independently associated with both outcomes (Table III). In the total anxiety model, a greater number of siblings was associated with lower anxiety scores

Table II: Comparison of continuous sociodemographic and clinical variables between the CD-sibling and healthy-sibling groups

	CD-sibling*	Healthy-sibling*	p
Total number of patients	70	70	-
Child age (years)	12.00 (9.00–14.00)	11.00 (9.25–13.00)	0.387
Duration of breastfeeding (months)	12.00 (6.25–18.00)	12.00 (9.00–18.00)	0.935
Maternal age (years)	40.00 (36.00–42.75)	39.50 (36.25–41.00)	0.378
Paternal age (years)	41.00 (38.25–44.00)	42.00 (39.25–44.00)	0.465
Separation anxiety disorder score	3.00 (1.00–7.00)	2.00 (1.00–2.75)	0.005
Generalized anxiety disorder score	6.50 (2.00–12.00)	4.00 (2.00–7.00)	0.014
Panic disorder score	4.00 (1.25–11.00)	2.00 (1.00–4.75)	0.006
Social anxiety score	6.00 (2.00–11.75)	3.00 (2.00–5.75)	0.009
Obsessive–compulsive disorder score	3.50 (1.00–9.00)	2.00 (1.00–5.75)	0.064
Depression score	5.00 (2.00–8.75)	5.00 (2.00–7.75)	0.758
Total anxiety score	26.00 (8.00–53.00)	13.00 (8.00–24.75)	0.007
Anxiety–depression total score	32.50 (11.00–62.00)	18.00 (12.00–31.00)	0.018
Psychosocial QoL score	67.50 (46.67–89.58)	85.83 (73.33–91.67)	<0.001
Physical QoL score	85.94 (75.00–93.75)	87.50 (81.25–93.75)	0.201
Total QoL score	70.65 (58.70–86.68)	85.87 (76.36–93.48)	<0.001

***:** *median (IQR) (Mann–Whitney U test),* ***CD:** *celiac disease,* ***QoL:** *quality of life*

Table III: Multivariable linear regression analyses of predictors of psychosocial QoL and total anxiety scores in the CD-sibling group

Variable	B	95% CI	β	p
Psychosocial QoL score				
Time since diagnosis	-0.68	[-1.07, -0.29]	-0.29	0.001
Number of siblings	15.85	[10.26, 21.43]	0.51	<0.001
Birth order	0.98	[-5.22, 7.18]	0.03	0.754
Maternal chronic physical illness*	-7.25	[-16.33, 1.83]	-0.13	0.115
Maternal psychiatric disorder*	-17.74	[-27.40, -8.08]	-0.33	<0.001
Paternal psychiatric disorder*	2.55	[-8.74, 13.84]	0.04	0.653
Child age	-0.13	[-1.73, 1.47]	-0.02	0.870
Child gender (female)	1.10	[-6.24, 8.44]	0.03	0.765
Total anxiety score				
Time since diagnosis	0.53	[0.06, 1.01]	0.21	0.027
Number of siblings	-17.97	[-24.63, -11.30]	-0.55	<0.001
Maternal psychiatric disorder*	13.84	[2.40, 25.27]	0.24	0.019
Paternal psychiatric disorder*	-3.70	[-16.88, 9.48]	-0.06	0.577
Child age	-0.58	[-2.28, 1.12]	-0.07	0.497
Child gender (female)	2.05	[-6.55, 10.66]	0.05	0.635

***:** *Yes*

(p<0.001), whereas longer time since diagnosis (p=0.027) and maternal psychiatric disorder (p=0.019) were associated with higher anxiety scores. In the psychosocial QoL model, a greater number of siblings was associated with higher psychosocial QoL (p<0.001), while longer time since diagnosis (p=0.001) and maternal psychiatric disorder (p<0.001) were associated with lower psychosocial QoL. Child age, gender, paternal psychiatric disorder, maternal chronic physical illness, and birth order were not significantly associated with either outcome (Table III).

Discussion

In this study, healthy siblings of children with CD exhibited a marked psychosocial burden compared with an age- and gender-similar control group. The CD-sibling group reported higher anxiety symptoms; in parallel, psychosocial and total health-related QoL scores were significantly lower. In contrast, depressive symptom levels did not differ between groups. Within the CD-sibling group, longer time since diagnosis was associated with higher anxiety and lower psychosocial/total QoL. Moreover, the strong inverse correlations between QoL scores and both total anxiety and the anxiety–depression composite further support a close link between emotional symptom burden and children's perceived well-being. These findings are consistent with the broader literature indicating that healthy siblings of children with chronic illness may experience poorer QoL and an elevated risk of internalizing symptoms (4,6,7). Notably, our study adds to this evidence base by characterizing psychosocial symptom burden in healthy siblings specifically within the context of pediatric CD.

Celiac disease represents a distinctive model among chronic pediatric conditions because its management relies less on a pharmacologic regimen than on a sustained lifestyle intervention that necessitates reorganization at the household level (13). Maintaining a lifelong gluten-free diet creates a continuous need for risk management that permeates everyday domains, including food purchasing, meal preparation, prevention of cross-contamination, coordination with schools/other institutions, and eating outside the home (14,15,30). This process is often experienced as a multidimensional burden, in which responsibility for diet management concentrates on

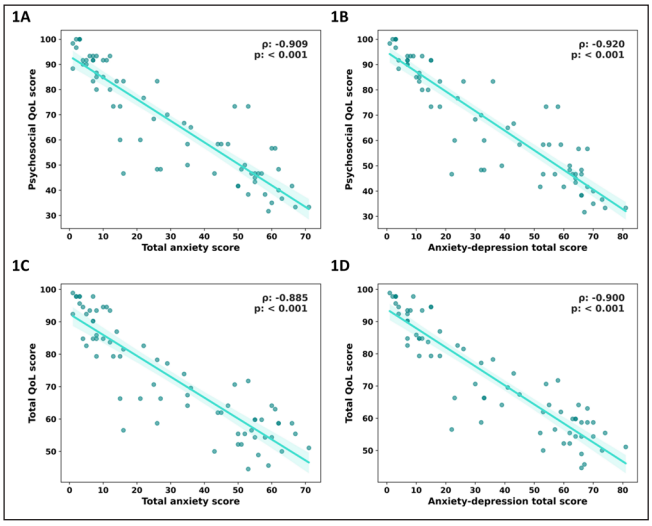

Figure 1: Associations between psychiatric symptom scores and QoL scores in the CD sibling group. Scatterplots illustrate the relationships between total anxiety score (1A) and anxiety–depression total score (1B) with psychosocial QoL score, as well as their associations with total QoL score (1C and 1D).

caregivers and co-occurs with restrictions in social activities, increased food-related costs, and heightened worries about the child's future (16,17,19,31). Re-defining household routines (e.g., mealtime practices, kitchen rules, and food sharing) may reduce healthy siblings' day-to-day autonomy and social spontaneity, while caregiver anxiety and sustained hypervigilance can become embedded in the family climate, strengthening perceptions of uncertainty or threat and, in turn, amplifying anxiety symptoms in healthy siblings (17–19,30,31). In family interviews conducted by Russo and colleagues, mothers reported carrying the primary responsibility for gluten-free diet management, whereas healthy siblings described dissatisfaction with limited food options at home and in restaurants and identified receiving less attention due to the family's focus on the affected child as salient areas of negative impact (19). Taken together, this framework suggests that the higher anxiety symptom levels across multiple domains and the lower psychosocial QoL observed in our CD-sibling group may be interpreted in the context of an enduring, vigilance-intensive management burden that becomes woven into daily family life.

In the regression analyses, a maternal history of psychiatric disorder emerged as one of the strongest and most consistent independent predictors of both total anxiety levels and psychosocial QoL. This finding aligns with theoretical frameworks suggesting that parental mental health can shape children's psychosocial adjustment through pathways such as caregivers' emotional availability, the broader family emotional climate, communication patterns, and coping processes (30,32–35). Although paternal psychiatric history was associated with children's anxiety symptoms and QoL scores in univariable analyses, the maternal variable remained more prominent in multivariable models, which may relate to mothers' often more central role in the day-to-day management of the gluten-free diet and in coordinating school and social planning in pediatric CD (16,18,19,30,36).

Within the CD-sibling group, longer time since diagnosis was associated with higher total anxiety levels and lower QoL. Given the enduring nature of CD management, it is plausible that the family-level management burden accumulates over time and that dietary and social adaptation demands become increasingly salient, potentially exerting a cumulative influence on the family climate and siblings' anxiety (16,19,20). Nevertheless, because of the cross-sectional design, this finding should not be interpreted as evidence of causality or within-person change over time (trajectory), but rather as an association between variables.

The finding that a lower number of siblings was associated with higher anxiety and poorer psychosocial QoL may reflect several family-level mechanisms, including reduced emotional buffering within the household, fewer opportunities for shared coping, and a greater concentration of responsibilities and parental attention across a smaller number of children (37–39). Notably, in a case–control study of healthy siblings of children with chronic illness, the number of family members was identified as an independent determinant of QoL, with higher family size (and, in most cases, a greater number of siblings) associated with higher sibling QoL scores (38). This pattern is also consistent with prior work emphasizing that within-family support networks and coping resources may play a protective role in siblings' adjustment (10,12).

Our findings highlight the need for a family-centered approach in pediatric CD care that explicitly includes healthy siblings. In routine follow-up, brief screening for anxiety symptoms and early identification of families with maternal mental health vulnerabilities may be clinically useful. Integrated, collaborative care between pediatric gastroenterology and child and adolescent mental health services may facilitate sibling-focused psychoeducation, supportive counseling, and interventions that strengthen coping skills (e.g., emotion regulation, stress management, and family communication) (8,37,40). In addition, support programs may target practical challenges such as managing eating-related situations in school and social settings, balancing household routines, and addressing siblings' concerns about exclusion and social adjustment (17,19,20).

Limitations

Despite these clinical implications, several limitations warrant consideration. The cross-sectional design limits causal inference, and the sample from a single tertiary-care center may reduce generalizability. Psychiatric symptoms were assessed using self-report measures; therefore, the findings reflect symptom levels rather than clinical diagnoses. The exclusion of participants receiving psychotropic medication or ongoing psychiatric care was intended to minimize potential confounding effects on questionnaire-based symptom scores; however, this criterion may have excluded the most severely affected siblings, potentially leading to selection bias and an underestimation of the true psychosocial burden in this population. In addition, unmeasured factors (e.g., family functioning, disease severity, challenges with gluten-free diet adherence, and stigma) may have influenced between-group differences. Accordingly, longitudinal and interventional studies examining underlying psychosocial mechanisms are warranted.

Conclusion

In conclusion, this study demonstrates that healthy siblings of children with CD experience a clinically meaningful psychosocial burden, characterized by higher anxiety symptoms and lower psychosocial and total health-related QoL compared with controls. Our findings further suggest that a lower number of siblings and a maternal history of psychiatric disorder may be associated with this burden, underscoring the need for family-centered psychosocial screening and supportive care that extends beyond the affected child to include healthy siblings and caregivers. Given the limited number of studies directly examining psychosocial outcomes in healthy siblings in the context of pediatric CD, our work adds novel evidence to the field and provides a clinically relevant foundation for future multicenter, longitudinal, and interventional research.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Gülhane Training and Research Hospital (12.06.2025, reference number: 2025/114).

Contribution of the authors

Study conception and design: HT, HTM, ST, YME, BIA, MAC, NB; data collection: HT, HTM, ST, YME, BIA; analysis and interpretation of results: HT, ST; draft manuscript preparation: HT. 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 fetuin-A in adolescent obesity: Association with anthropometric and metabolic parameters

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Received : 02.03.2026, Accepted : 15.06.2026 DOI: 10.12956/TJPD.2026.1322

ABSTRACT

Objective: Childhood obesity is a growing global health problem linked to chronic inflammation and metabolic complications, including dyslipidemia, insulin resistance, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and hypertension. Fetuin-A, a hepatokine involved in insulin signaling and inflammation, has been studied in adults, but its role in pediatric obesity is unclear. This study evaluated fetuin-A levels in obese adolescents and their association with anthropometric and metabolic parameters.

Materials and Methods: This cross-sectional study included 40 obese adolescents (BMI > 95th percentile) and 30 healthy controls (BMI between the 15th and 85th percentiles) who had no additional systemic diseases and were not receiving any medication. Anthropometric measurements and fasting glucose, insulin, high-sensitivity C-reactive protein, and fetuin-A were assessed. The presence of dyslipidemia, hepatic steatosis, and hypertension was evaluated.

Results: Hs-CRP levels were significantly higher in obese patients than in controls (p=0.015) However, fetuin-A levels did not differ significantly between the groups. Fetuin-A showed no correlation with insulin resistance, lipid parameters, hepatic steatosis, or hypertension.

Conclusion: Obesity-related complications (insulin resistance, dyslipidemia, fatty liver, and hypertension) were observed in more than half of our group. Although hs-CRP levels of obese cases were high, fetuin-A concentrations were observed to be similar in all cases and in subgroup analyzes. It may be due to factors affecting fetuin-A levels or its posttranslational modification. Further large-scale longitudinal studies are required to elucidate its contribution to metabolic inflammation in children.

Keywords: Adolescent, children, α2- Heremans-Schmid glycoprotein, obesity

Introduction

Childhood obesity is rising daily due to contemporary lifestyles globally. This condition is associated with several metabolic and cardiovascular consequences, including dyslipidemia, insulin resistance, type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), and hypertension. Obesity is thought to initiate systemic inflammatory pathways, and obesity-induced endotoxemia may exacerbate associated comorbidities. Chronic inflammation is proposed to contribute to the etiopathogenesis of insulin resistance (1, 2).

Fetuin-A, also known as α2 -Heremans-Schmid glycoprotein, is a glycoprotein that inhibits the endogenous insulin receptor tyrosine kinase and is mostly produced in the liver (3). This hepatokin possesses various roles owing to its intricate structure and its interaction with distinct toll-like receptors (TLR) across diverse tissues (4). Numerous studies have shown that TLR4 is involved in obesity-related inflammation and insulin resistance, with fetuin-A serving as the endogenous ligand of TLR4 (4,5). Furthermore, it disrupts insulin signaling in skeletal muscle and adipose tissue by inhibiting the autophosphorylation of the insulin receptor (3,4). Another potential mechanism is the elevation of inflammatory cytokines and suppression of adiponectin (4,6). Fetuin-A is recognized as a mediator of inflammation. In adult research, fetuin-A is linked to various diseases, including infections, renal and cardiovascular disorders, cirrhosis, cancer, insulin resistance and metabolic syndrome (3,7,8,9). There exists a finite quantity of studies concerning children (5, 6, 10-15).

Investigating fetuin-A, a multifunctional protein, across several disease cohorts will enhance our comprehension of

its pathogenesis. This study aimed to assess fetuin-A levels in obese adolescents and their correlation with anthropometric measurements, insulin levels, and high-sensitive C-reactive protein (hsCRP).

Materials and Methods

The research was performed at the pediatric endocrinology outpatient clinic of Dr. Sami Ulus Training and Research Hospital between January and December 2017. Informed consent was acquired from the parents of all participants.

The study comprised 40 obese adolescents (BMI>95th percentile) and 30 healthy controls (BMI between the 15th and 85th percentiles) all of whom had no other systemic diseases and were not undergoing any pharmacological treatment. The study included cases aged 10 to 19 who were undergoing puberty. Anthropometric measures, fasting glucose, insulin, hsCRP, and fetuin-A levels were assessed in both groups. Information concerning obesity-related comorbidities, such as dyslipidaemia and hepatosteatosis, was obtained from hospital records. In the healthy control group, dyslipidemia, hypertension, and steatosis were not assessed. A SECA scale (SECA, Hamburg, Germany) was utilised to measure weight, while a Harpenden stadiometer (Holtain Ltd., Crymych, UK) was employed to assess height. Anthropometric reference data for the Turkish population, encompassing height, weight, and body mass index (BMI), were sourced from an internet database (www.ceddcozum.com) (16). Venous blood samples were obtained from both the patient and control groups prior to 9:00 AM following an overnight fast. Serum glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were assessed using the Architect C16000 auto-analyzer system, whereas insulin concentrations were measured via the chemiluminescence method (Advia Centaur XP). Hs-CRP levels were quantified by a cassette-based assay with Getein 1600 immunofluorescence quantitative analyser (Getein Biotech, Nanjing, China). Serum fetuin-A levels were measured using a commercially available sandwich enzyme-linked immunosorbent test (ELISA) kit from Elabscience Biotechnology Inc., Houston, TX, USA.

Insulin resistance was assessed using the homeostatic model assessment (HOMA-IR), calculated as follows: HOMA-IR= [fasting insulin (μU/ml) × fasting glucose (mg/dl)]/405 (the cut-off was taken as 3.82 for pubertal girls and 5.22 for pubertal males) (17). Dyslipidemia was defined based on the American Academy of Pediatrics criteria, including total cholesterol ≥ 200 mg/dl, LDL cholesterol ≥ 130 mg/dl, triglycerides ≥ 130 mg/dl, HDL cholesterol < 40 mg/dl (18). Ambulatory blood pressure monitoring (ABPM) was applied to cases with three high blood pressure (BP) readings measured after at least 10 minutes of rest. An oscillometric monitor (Mobil-OGraph®NG, v.20.0, Stolber, Germany) and a correctly sized cuff were utilized on the non-dominant arm for ABPM. The monitor recorded BP measurements every 20 minutes from 08:00 to 20:00, then every 30 minutes from 20:00 to 08:00. Parameters for daytime, nocturnal, and 24-hour ABPM were documented. ABPM was deemed dependable if above 70% of the measurements were valid. The diagnosis of hypertension with ABPM was predicated on a mean systolic and/or diastolic BP exceeding the 95th percentile or a BP load beyond 25% (19).

Statistics analysis:

The Shapiro-Wilk test was used to assess the normality of data distribution. Continuous variables were expressed as mean and standard deviation or median (minimum-maximum), as appropriate. For variables adhering to a normal distribution, group comparisons were conducted using the Student t-test; otherwise, the Mann-Whitney U test was utilised. Group comparisons were performed using Chi-square or Fisher's exact test for categorical variables. Correlations between variables were analyzed using Spearman's rank correlation coefficient, as the data did not meet the assumption of normal distribution. Simple linear regression analysis was performed to evaluate the independent effects of metabolic parameters on serum fetuin-A levels. A p-value of less than 0.050 was deemed statistically significant. All analyses were conducted using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA).

Results

Forty pubertal obese and 30 healthy adolescents were included in the study. Anthropometric and biochemical measurements are displayed in Table I, while the results of the subgroup analysis are shown in Table II. In our study, insulin resistance was observed in 65%, dyslipidaemia 77.5%, fatty liver 84%, and hypertension 35.9% of obese patients.

There was no difference in fetuin-A levels between obese and healthy cases in the whole group; however, obese patients had significantly higher hs-CRP levels than healthy individuals (p=0.015). Fetuin-A concentrations were comparable across boys and girls in the obese cohort. Although the fasting glucose levels of the patients were similar, the insulin and HOMA-IR levels in obese patients were considerably elevated compared to those in healthy individuals (p=0.127; p=0.000; p=0.000, respectively). No significant variations in fetuin-A and hs-CRP levels were identified between the insulin resistant and insulin non-resistant groups classified by HOMA-IR. Oral glucose tolerance test (OGTT) was conducted on 32 patients with additional risk factors within the obese cohort. In OGTT, the plasma glucose concentration at 0 minutes was 88.2±7.7 (72-106) mg/dl, and at 120 minutes, it was 116.7±25.6

Table I: Comparison of antropometric and laboratory findings between obese and control groups

	Obese	Normal-weight	p
Total number of patients	40	30	-
Gender (Female)*	65%	73.3%	0.463
Age (years)†	15.3±2.1	14.3±2.1	0.063
Height SDS†	0.33±1.4	0.145±0.7	0.073
BMI (kg/m^2)†	33.1±4.2	21.5± 2.2	0.001
BMI SDS†	2.8±0.55	0.4±0.7	0.001
Fasting glucose (mg/dl)†	95.1±8.8	91.4±8	0.127
Fasting insulin (μIU/ml)‡	21.4 (8.7-56.9)	11.4 (4.6-30.8)	0.001
HOMA-IR‡	5.01 (1.7-14.7)	2.5 (1.0-7.2)	0.001
Fetuin-A (ng/ml)‡	418.2 (255.9-638.6)	448.8 (232.9-694.2)	0.151
HSCRP (mg/dl)‡	0.23 (0-0.5)	0.11 (0-0.5)	0.015

**: n(%) (Chi-square test), †: mean±SD (Independent samples t-test), ‡: median (min-max) (Mann-Whitney U test)*

Table II: Comparison of laboratory findings according to insulin resistance, dyslipidemia, hepatic steatosis, and hypertension

	Insulin Resistance			Dyslipidemia			Steatosis			Hypertension		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Total number of patients	26 (65%)	14 (35%)	-	31 (77.5%)	9 (22.5)	-	32 (84%)	6 (15.7%)	-	14 (35.9%)	25 (64.1%)	-
Gender(F)*	69.3%	57.2%	0.295	64.5%	66.7%	1.000	68.8%	33.3%	0.321	50%	72%	0.163
BMI (kg/m^2)†	34.1±4.2	31.7±4.2	0.386	33.6±4.4	31.5±3.6	0.103	33.9±4.3	29.8±3.3	0.049	36.2±4.7	31.6±3.1	<0.001
BMI SDS†	2.9±0.5	2.6±0.6	0.017	2.9±0.5	2.6±0.6	0.055	2.9±0.5	2.5±0.6	0.108	3.0±0.7	2.8±0.5	0.222
Fasting glucose (mg/dl)†	95±7.2	95.4±11.2	0.864	95.3±8.2	94.7±11.3	0.854	94.3±8.6	100.8±8.3	0.125	96.4±9.5	94.0±8.5	0.442
Fasting insulin (µIU/ml)‡	33.4 18.1-81.5	11.6 8.7-23.8	0.001	24. 8.7-56.9	12.8 9.3-23.8	0.002	21.2 8.7-42.9	12.1 11.4-12.8	0.985	22.6 9.9-81.5	27.2 8.7-51.3	0.917
HOMA-IR ‡	7.4 4.1-17.5	2.7 1.7-5.3	0.001	5.7 1.8-14.7	3.5 1.7-5.5	0.004	4.6 1.7-9.6	3.2 2.8-3.6	0.955	5.15 2.6-17.5	6.2 1.75-13.68	0.964
Fetuin-A (ng/ml) ‡	403.4 256-655.7	403 256.8-634.8	0.231	410.8 256-655.7	341 256.9-634.8	0.296	395.6 256-655.7	436.4 313.6-559	0.967	418.2 256.8-655.7	313.6 255.9-634.8	0.731
HSCRP (mg/dl) ‡	0.28 0.0-0.5	0.23 0.03-0.5	0.910	0.2 0.0-0.5	0.5 0.2-0.5	0.019	0.26 0.0-0.5	0.34 0.18-0.5	0.733	0.5 0.0-0.5	0.23 0.0-0.5	0.424

**: n(%) (Chi-square test), †: mean±SD (Independent samples t-test), ‡: median (min-max) (Mann-Whitney U test). Missing data: Insulin resistance group (n=38) and hypertension group (n=39); other groups included 40 patients. Analyses were performed using available data.*

(75-205) mg/dl. Glucose intolerance was identified in four cases and diabetes mellitus in one case. No significant association was seen between plasma glucose levels during the OGTT at 0,30,60,90 and 120 minutes and fetuin-A levels (correlation coefficients: r=-0.02; p=0.880; r=0.16, p=0.360; r=0.15, p =0.390; r=0.19, p=0.280; r=-0.06, p=0.710).

Eight of the obese patients exhibited elevated cholesterol levels, 15 presented with excessive triglycerides, eight had increased LDL, and 20 demonstrated low HDL. There was no significant difference in fetuin-A levels between dyslipidemic and non-dyslipidemic groups (p=0.296), however hs-CRP levels were considerably elevated in the non-dyslipidemic group (p=0.019). No association existed between lipid metrics and fetuin-A levels.

In simple linear regression analysis, no significant association was found between serum fetuin-A levels and lipid parameters in the obese group. Total cholesterol showed borderline but non-significant positive relationship with fetuin-A (B=1.397, p=0.086, R2=0.078), while LDL cholesterol (B=0.606, p=0.503), HDL cholesterol (B=2.288, p=0.318), and triglycerides (B=0.315, p=0.300) were not significant predictors of fetuin-A levels.

Thirty-two obese cases had fatty liver (Grade 1; 10 cases, Grade 2; 13 cases, Grade 3; 9 cases), with two cases showing elevated SGOT-SGPT levels. No significant difference was observed in fetuin-A and hs-CRP levels between cases with and without fatty liver (p=0.967, p=0.733, respectively). Hypertension was identified in 14 obese patients with 24-hour blood pressure monitoring. The fetuin-A levels in hypertension patients were 418.2 (256.8-655.7) ng/ml, compared to 313.6 (255.9-634.8) ng / ml in normotensive individuals, with no statistically significant difference (p = 0.731). Furthermore, there was no significant difference between the two groups regarding hs-CRP (p=0.424).

Discussion

The present study investigated the association between serum fetuin-A levels and anthropometric and metabolic parameters in obese adolescents. Our principal finding was that fetuin-A concentrations did not differ significantly between obese and healthy-weight pubertal adolescents, despite the presence of substantially elevated hs-CRP levels (p= 0.015) and a high prevalence of obesity-related metabolic complications, including insulin resistance (65%), dyslipidemia (77.5%), hepatic stetosis (84%), and hypertension (35.8%) in the obese group. Furthermore, fetuin-A showed no significant correlation with insulin resistance, OGTT glucose values at any time point, lipid parameters, hepatic steatosis grade, or hypertension status in subgroup analyses.

The absence of fetuin-A elevation in our obese adolescent cohort stands in marked contrast to the well- established association between fetuin-A and obesity in adult populations. In a large study of 345 adults with type 2 diabetes and 300 normoglycemic controls stratified by BMI (cut off 25 kg/m^2), demonstrated that obese individuals with type 2 diabetes had the highest fetuin-A concentrations, and that independent associations of fetuin-A with free fatty acids, HOMA-IR, CRP, and adiponectin were exclusively observed in the obese subgroups. The odds ratio for obesity increased progressively with fetuin-A quartiles (p for trend <0.001), leading the authors to conclude that fetuin-A functions as a molecular bridge connecting obesity and type 2 diabetes (3). In the context of MASLD, Elhoseeny et al.(8) reported that fetuin-A was markedly elevated in adult MASLD patients compared to controls, with a diagnostic cut off of 702.5 ng/mL yielding 82% sensitivity and 90% specificity. In another study, however, it has been showed that fetuin-A concentrations in type 2 diabetic adults were significantly influenced by total and LDL cholesterol levels, though no direct correlation with hepatic steatosis was observed. These adult findings collectively support a role for fetuin-A in mediating obesity-related metabolic dysfunction (9).

However, pediatric literature reveals a considerably more heterogeneous picture, with several studies reporting findings consistent with our results. Notably, in a pediatric study, evaluated fetuin-A in 81 obese children with biopsy-proven MASLD, 79 obese children with ultrasonographically detected MASLD, and 23 lean controls (10). They found virtually identical fetuin-A concentrations between obese and lean children (694.6±221.9

vs. 695.0±220.9 ng/mL, p=0.996). Although fetuin-A was higher in the ultrasound-detected MASLD group than in those without steatosis. There was no significant difference in fetuin-A between children biopsy-confirmed MASLD and those with simple steatosis, nor did fetuin-A differ across histological grades of steatosis, inflammation, ballooning, or fibrosis. The authors concluded that fetuin-A is not a reliable marker of liver damage severity in obese children. Conversely, other pediatric studies have reported elevated fetuin-A in association with obesity. In a study, evaluating 45 obese and 30 healthy children, they found significantly higher fetuin-A in obese children compared to controls (11). The MASLD subgroup (n=19) had the highest fetuin-A, though no significant difference existed between obese children with and without MASLD, and fetuin-A did not correlate with HOMA-IR, lipid parameters, or intima-media thickness (11). In a different study, significant correlations has been found between serum fetuin-A and BMI, waist and hip circumferences, subcutaneous fat thickness, and HOMA-IR in the 42 obese Turkish children compared to 40 controls (12). In a prepubertal cohort, Selvaraju et al. (14) demonstrated that salivary fetuin-A was markedly elevated in overweight and obese children aged 6-10 years compared to normal-weight peers, with strong positive correlations between fetuin-A and BMI z-score (r= 0.538), fetuin-A and insulin (r= 0.875), and negative correlation with adiponectin (r= 0.467). The authors have suggested that salivary fetuin-A could be valuable as a non-invasive marker. These conflicting findings across pediatric studies underscore the complexity of fetuin-A biology in the growing child.

Several mechanistic and methodological factors may explain the discordance in fetuin-A findings across pediatric studies. First, the developmental biology of fetuin-A must be considered. Fetuin-A is a multifunctional protein with significant biological variation across the lifespan (20). Serum concentrations are highest in neonates, gradually declining through childhood and stabilizing by late adolescence. On the other hand, posttranslational modifications of fetuin-A may play a critical role. Fetuin-A exists in two distinct compartments in the circulation: as a soluble plasma protein and within colloidal calciprotein particles, each with different functional implications (7). Most commercial ELISA kits, including the one used in our study, measure total fetuin-A without distinguishing between phosphorylated and non-phosphorylated forms. This methodological limitation could account for the apparent discrepancy between elevated hs-CRP and unchanged total fetuin-A levels in our obese cohort. Indeed, as Trepanowski et al. (4) emphasized, future studies must measure phosphorylated fetuin-A specifically to accurately assess its metabolic impact.

The complex organokine crosstalk network may differentially regulate fetuin-A across age groups and metabolic states. As a hepatokine, fetuin-A is primarily produced by the liver, but emerging evidence indicates that it also functions as an adipokine, being secreted from adipose tissue (4,7). Its expression is therefore influenced by adipose tissue inflammation, skeletal muscle metabolism, and systemic factors (21,22). Recent studies have highlighted the multifaceted endocrine role of hepatokines, including fetuin-A, noting that their clinical effects involve complex regulatory feedback loops (23). Kim et al. (22) examined the progression of metabolic syndrome, noting that it involves temporal activation of various adipokines and hepatokines, with the pattern of their dysregulation potentially differing between children and adults. These data suggests the organokine environment in adolescent obesity may fundamentally different from that in adult obesity, which could explain why fetuin-A does not behave as expected in our cohort.

Furthermore, differences in study populations-including age, pubertal status, ethnicity, degree and duration of obesity, genetic background, dietary habits, and physical activity levels-may all influence fetuin-A concentrations (20,24). A meta-analysis has been shown that exercise significantly modulates hepatokine levels in obese adults, with different exercise modalities (aerobic, resistance, and high-intensity interval training) producing varying effects on fetuin-A (24). Robinson et al. (20) reported that just seven days of aerobic exercise reduced fetuin-A 11% in adults. These observations suggest that even habitual physical activity levels in our adolescent cohort could have influenced the results, a variable we did not assess. The significantly elevated hs-CRP levels in our obese cohort (p=0.015) confirm the presence of systemic low-grade inflammation, validating our study's ability to detect obesity-related inflammatory changes. The dissociation between hs-CRP elevation and unchanged fetuin-A levels is particularly noteworthy. This pattern may reflect the activation of different inflammatory pathways at different stages of obesity progression. While CRP is an acute-phase reactant produced in response to IL-6 and IL-1b, fetuin-A's role in inflammation operates through a distinct mechanism involving TLR4 activation and the formation of the fetuin-A-free fatty acid complex (4).

Limitations

This study has several limitations. First, the relatively small sample size may have resulted in limited statistical power for fetuin-A comparison, which could explain the lack of statistically significant differences between groups despite a clinically relevant trend. Larger prospective studies are needed to confirm these findings. In addition, physical activity levels were not assessed. Given that exercise may influence circulating fetuin-A concentrations, the lack of adjustment for physical activity may have confounded the observed results.

Conclusion

In conclusion, although obese adolescents demonstrated significant metabolic and inflammatory alterations, fetuin-A levels were comparable to those of normal-weight peers and showed no association with metabolic risk parameters. This may indicate that fetuin-A has limited utility as a biomarker of early metabolic dysfunction in pediatric obesity. Longitudinal studies are needed to determine whether its clinical significance emerges only in more advanced stages of disease.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Numune Training and Research Hospital (25.01.2017, reference number: E-16–1134).

Contribution of the authors

Study conception and design: GKK, SÇ, ZA; data collection: GKK, SÇ, EK, EB, ŞÖ; analysis and interpretation of results: GKK, SÇ, GD, HSÖ; draft manuscript preparation GKK, SÇ, ŞSE, ZA. 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

Case Report

MSUD presenting with phenylalanine elevation on neonatal screening

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Received : 07.01.2026, Accepted : 21.04.2026 DOI: 10.12956/TJPD.2026.1298

ABSTRACT

Maple syrup urine disease (MSUD) is an inborn error of metabolism characterized by an increase in branched-chain amino acids (BCAAs), resulting from a deficiency in the branched-chain α-ketoacid dehydrogenase (BCKD) enzyme. A 22-day-old asymptomatic male infant was referred to our center following the detection of elevated phenylalanine (PHE) levels in the newborn screening program and was hospitalized with suspected Phenylketonuria (PKU). Blood amino acid analysis revealed a normal PHE level (48.9 nmol/mL), while BCAA levels were markedly elevated: Leucine 824.4 nmol/mL (normal: 48-175), isoleucine 413.1 nmol/mL (normal: 31-105), and valine 683.1 nmol/mL (normal: 83-300). Results confirmed false positive result for PKU diagnosis however, laboratory findings were consistent with MSUD. Phenylketonuria, a preliminary diagnosis made due to high PHE levels in newborn screening, has masked the underlying MSUD diagnosis, and is presented here as an extremely rare phenomenon. This case is reported to underscore a critical gap in our country's newborn screening program, which does not currently include MSUD. Considering the acute and potentially fatal neonatal presentation of MSUD, our findings underline the need to expand the national newborn screening program to include MSUD.

Keywords: Branched-chain amino acids, leucine, maple syrup urine disease, phenylalanine, phenylketonuria

Introduction

Maple syrup urine disease (MSUD, OMIM #24860) is an inborn error of metabolism caused by a deficiency of the branched-chain α-ketoacid dehydrogenase (BCKD) enzyme, resulting in the accumulation of branched-chain amino acids (BCAA), leucine (LEU), isoleucine (ILE) and valine (VAL). The BCKD enzyme is a multi-enzyme complex consisting of three catalytic components. It consists of the E1 subunit, a decarboxylase composed of subunits 1a and 1b, the E2 subunit, a transacylase, and the E3 subunit, a dehydrogenase, and is regulated by two regulatory enzymes, a kinase and a phosphatase. The catalytic components require five cofactors for optimal enzyme function: thiamine pyrophosphate (TPP), flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD), coenzyme Q10, and a lipoamide prosthetic group (1). It is diagnosed by autosomal recessively inherited mutations in any of the genes encoding the catalytic subunits of the BCKD complex: BCKDHA (E1a), BCKDHB (E1b), DBT (E2) or DLD (E3) (2). The E3 subunit encoded by the DLD gene is also a component of the pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase enzyme complexes; therefore, its deficiency is accompanied by various findings (2). The incidence is extremely rare, approximately one in 150.000 live births (3). Clinical symptoms result from an increase in branched-chain amino acids (BCAAs), which have neurotoxic effects. Leucine is the mainly responsible amino acid for the clinical signs (4). MSUD is classified into classic, intermediate and intermittent subtypes based on clinical manifestations and age of onset. Classic MSUD have clinical signs within the first weeks after birth, including maple syrup odor, feeding problems, seizures, coma and possibly death (5). It can be screened by detecting elevated leucine levels from the neonatal period (6). Phenylketonuria (PKU) is an autosomal recessive disorder of aromatic amino acid metabolism. In PKU, phenylalanine (PHE) cannot be converted to tyrosine due to a deficiency in the PHE-hydroxylase enzyme, and PHE levels increase (7). Here, we report a patient who had elevated PHE level detected in newborn screening and was initially suspected of having PKU, had elevated blood leucine levels, and was incidentally diagnosed with MSUD

in the absence of any clinical findings. We present this case, which is extremely rare in the literature.

Case Report

Blood samples for the newborn screening program were collected on the seventh day of life, which revealed elevated PHE levels. Subsequently, the patient was referred and admitted to our center at 22 days of age for further evaluation. He had no additional clinical complaints. Physical examination revealed normal vital signs appropriate for age and gender, and normal organ system assessment. Laboratory tests mainly included serum glucose, blood gas analysis, liver and kidney function tests and plasma-amino acid analysis. The serum glucose was 99 mg/dL, PH 7.42, base excess -2.9 mmol/L, lactic acid 3.8 mmol/L, white blood cell count 8.70×10^3/uL, neutrophil percentage (N%) 24.4%, hemoglobin 14.5 g/dL, platelet 377×10^9/L, serum total protein 5.4 g/dL, serum albumin 3.9 g/dL, uric acid 3.2 mg/dL. Plasma-amino acid analysis demonstrated PHE 48.9 nmol/mL (28-80), isoleucine 413.1 nmol/mL (31-105), leucine 824.4 nmol/mL (48-175) and valine 683.1 nmol/mL (83-300) (Table I). Whole exome sequencing (WES) analysis, performed to confirm the diagnosis of MSUD, revealed compound heterozygous mutations in the BCKDHA gene (NM_000709.4); c.745 G>A (p.G249S) likely pathogenic (paternal) and c.1312 T>A (p.Y438N) pathogenic (maternal). No mutation was reported in the PAH gene (NM_000277.3).

Laboratory test results were compatible with MSUD. The diagnosis was confirmed by genetic analysis and treatment was started. Protein and leucine restricted diet was introduced. His diet included 3 g/kg/D protein and 25 mg/kg/D leucine. Control BCAA values decreased after the diet began. Thiamine vitamin was added. He benefited significantly from thiamine. During the follow-up, he did not experience a metabolic attack, and neurological and developmental assessments showed a normal course. Plasma leucine levels consistently remained below 400 nmol/mL. Adding thiamine to his treatment made the decrease in leucine levels even more pronounced. During follow-up, the protein-restricted diet was gradually reduced, and the patient benefited from thiamine therapy (Figure 1). Written informed consent was obtained from the patient's parents for the publication of this case report. Patient data confidentiality was strictly maintained throughout the process.

Table I: Laboratory findings across different clinical stages

Metabolic Parameters	Reference Values	22. Days	120. Days	240. Days
Glucose (mg/dL)	51- 99	50	82	79
pH	7.35- 7.45	7.39	7.38	7.40
HCO3 (mEq/L)	22- 26	21.2	21.3	19.5
Lactate (mmol/L)	<2.5	3.8	3.3	4.7
Ammonia (µmol/L)	<90	90.2	48.4	38
AST (U/L)	<40	68	42	59
ALT (U/L)	<40	33	27	32
Leucine (nmol/mL)	48- 175	824.4	57.6	130.2
Isoleucine (nmol/mL)	31- 105	413.1	164.6	126.4
Valine (nmol/mL)	83- 300	683.1	354.2	150.3
Phenylalanine (nmol/mL)	28- 80	48.9	39.9	61.6

Day 22 represents the pre-treatment admission, Day 120 represents the period strictly on a leucine-restricted diet, and Day 240 represents the follow-up period after the addition of thiamine.

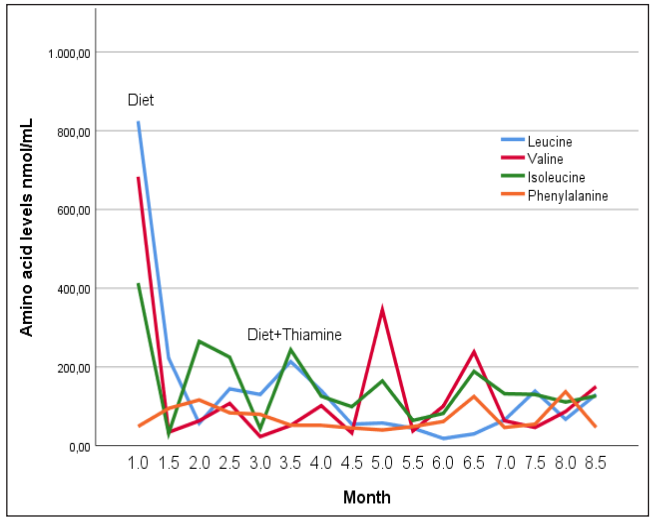

Figure 1: Amino acid levels and response to treatment over time. The graph indicates the initial phase treated only with a restricted diet (Months 1.0 to 3.0) and the subsequent phase where thiamine was added to the diet therapy (Months 3.5 onwards).

Discussion

Classic MSUD is a devastating metabolic disorder that presents in the neonatal period with feeding difficulties, vomiting and restlessness, progressing to lethargy and coma within 48-72 hours after birth. If undetected, a complete neurologic syndrome with seizures, opisthotonus and progressive encephalopathy occurs within the first week and a fatal outcome can occur shortly thereafter due to respiratory failure. In many patients, severe and permanent brain damage can occur even if symptoms are controlled (8). Patients with elevated blood LEU concentrations are presumed to have MSUD until proven otherwise. Protein catabolism, infection, presence of other metabolic disorders, liver disorders, steroid use and parenteral nutrition may cause LEU elevations in newborns. The traditional treatment in the acute phase is hemodialysis. In the chronic phase, strict leucine-restricted diet therapy is required. The treatment plan is to feed a formula that does not contain BCAA. The aim is to maintain plasma BCAA levels within the non-neurotoxic range and to meet adequate nutritional needs. Vitamin B1 and L-carnitine therapies have also been reported to be beneficial in long-term treatment (9). In many countries, MSUD is included in newborn screening programs. In cases of LEU elevation, detailed investigations are performed for the diagnosis of MSUD. Similarly, PKU is also screened in many countries and PHE levels are measured. In the literature, cases with elevated PHE in newborn screening and subsequently diagnosed as MSUD are very rare. In a study by Capistrano-Estrada et al. (10) 15 patients were diagnosed with MSUD among approximately one million patients with elevated Phe. The biochemical basis for elevated PHE in MSUD patients on

neonatal screening involves the complex interplay of neutral amino acids sharing the same transport systems. Elevated BCAAs, particularly leucine, compete for the Large Neutral Amino Acid Transporter (LAT1). While this typically leads to decreased cerebral PHE levels, systemic elevations of PHE in the neonatal period of MSUD patients may be attributed to intense catabolism and protein degradation during metabolic crisis, or interference in the analytical methods used during initial screening (11). Similar to the literature, our patient lacked classic MSUD symptoms such as feeding difficulties or encephalopathy during the neonatal period, and the underlying MSUD diagnosis was incidentally unmasked due to the false-positive PHE elevation. The primary limitation of this case report is that it is based on a single patient's experience. Additionally, long-term neurodevelopmental follow-up data beyond the current observation period are not yet available.

Conclusion

This rare case underscores a critical gap in our country's newborn screening program, which does not currently test for MSUD. Considering the acute and often fatal neonatal presentation of the disease, we recommend the inclusion of MSUD in the screening panel. This report contributes to the literature by providing further evidence of the benefits of early screening.

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Turkish Journal of Pediatric Disease

Case Report

Atypical presentation of Hodgkin lymphoma with predominant osseous involvement in a 10-year-old child

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Received : 09.02.2026, Accepted : 21.05.2026

DOI: 10.12956/TJPD.2026.1286

ABSTRACT

Hodgkin lymphoma (HL) in pediatric patients typically presents with mediastinal and supradiaphragmatic lymphadenopathy. Predominant skeletal involvement at diagnosis is exceptionally rare and represents a significant diagnostic challenge. We present the case of a 10-year-old child with a 6-month history of progressive weight loss, right hip pain, and gait disturbance. Initial imaging suggested non-malignant orthopedic conditions, but further studies revealed multifocal osteolytic bone lesions. A bone biopsy ultimately confirmed classical Hodgkin lymphoma. A Positron Emission Tomography/Computed Tomography (PET/CT) scan demonstrated intensely hypermetabolic osseous lesions with only minimal, disproportionately mild, nodal disease. Based on the Lugano classification, the patient was classified as Ann Arbor stage IV. The patient exhibited rapid clinical improvement following the initiation of OEPA (Vincristine, Doxorubicin, Etoposide, Prednisone) induction chemotherapy. This case underscores the importance of including lymphoproliferative disorders in the differential diagnosis of unexplained multifocal osteolytic lesions in children and highlights the critical role of timely tissue biopsy.

Keywords: Bone, chemotherapy, child, extralymphatic, Hodgkin lymphoma

Introduction

Hodgkin lymphoma (HL) is the most common hematologic malignancy in adolescents and young adults, accounting for approximately 3-5% of all pediatric cancers (1). The disease typically presents supradiaphragmatic lymphadenopathy, with mediastinal involvement observed in 60-90% of cases at diagnosis (1,2). Extranodal involvement, affecting sites such as the liver, spleen, or lungs, occurs in 10-15% of advanced cases (3).

While bone marrow infiltration can be seen in 2-5% of patients, the skeletal involvement at presentation accounts for only 0.1–15% of cases, Such an atypical presentation poses substantial diagnostic challenges, as initial radiological findings often mimic other conditions like metastatic bone disease, osteomyelitis, or Langerhans cell histiocytosis (LCH) (4,5). Definitive diagnosis invariably requires histopathological confirmation of CD30+ Hodgkin and Reed-Sternberg cells (1).

We present an atypical case of pediatric Hodgkin lymphoma characterized by predominant multifocal skeletal involvement and minimal nodal disease, emphasizing the necessity of a broad differential diagnosis and early bone biopsy in children presenting with multifocal osteolytic lesions.

Case Report

A 10-year-old male presented with a six-month history of progressive constitutional symptoms and right hip pain. The clinical course was characterized by an estimated weight loss of 10 kg, nocturnal diaphoresis, and a functional gait disturbance. His past medical history was unremarkable. On physical examination, the child showed signs of malnutrition and generalized asthenia. The musculoskeletal exam revealed restricted mobility of the right hip and an antalgic gait. Small, non-tender submandibular lymph nodes (approximately 1.0–1.5 cm) were palpable bilaterally; however, no other significant lymphadenopathy was noted.

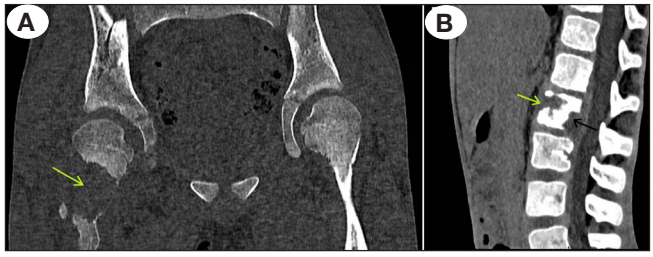

Figure 1: CT of the right hip demonstrating an anterior para-osseous osteolytic mass at the upper extremity of the right femur, associated with other mixed osteolytic and osteocondensing vertebral lesions at L1 and L2.

Figure 2: Technetium-99m bone scintigraphy (Anterior and Posterior views) showing multiple sites of pathological hyperfixation in the axial and peripheral skeleton.

Laboratory investigations showed a mild normocytic anemia (Hemoglobin: 10.4 g/dL) and an elevated erythrocyte sedimentation rate (40 mm/h). Biochemical analysis revealed reduced serum iron (15.23 µg/dL) and hypoalbuminemia (24.5 g/L). Lactate dehydrogenase (LDH) and calcium levels were within normal limits.

The diagnostic workup began with imaging of the right hip. Ultrasound and plain radiography were initially interpreted as a slipped capital femoral epiphysis (SCFE) with a grade 1 slip and an avulsion of the lesser trochanter. However, given the systemic symptoms, further investigation was pursued. A computed tomography (CT) scan of the hip revealed an anterior para-osseous osteolytic mass at the upper extremity of the right femur, along with mixed osteolytic and sclerotic lesions in the L1 and L2 vertebrae (Figure 1). Subsequently, a Technetium-99m bone scintigraphy confirmed multiple sites of pathological hyperfixation in the bilateral femoral heads, lumbar vertebrae, and anterior costal arches (Figure 2).

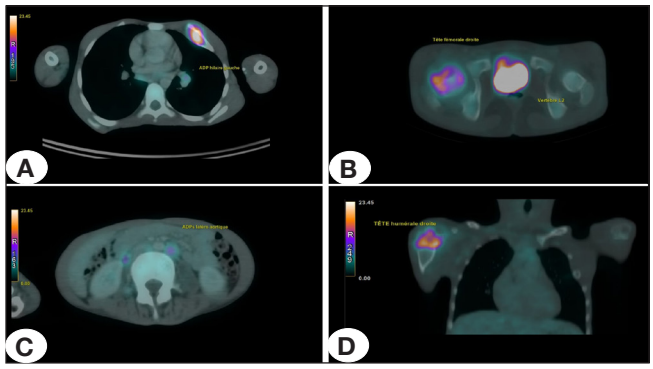

Figure 3: PET/CT images (Coronal and Transaxial) displaying intensely hypermetabolic osteolytic lesions in the right femoral head and L1 vertebral body.

For definitive staging, an 18F-FDG Positron Emission Tomography (PET/CT) scan was performed. This confirmed disseminated disease, demonstrating intensely hypermetabolic osteolytic lesions in the right humeral head, right femoral epiphysis, L1 vertebral body, and left third rib (Figure 3). The scan revealed only minimal mediastinal and retroperitoneal lymphadenopathy (largest node 15 mm), which was disproportionately mild compared to the extensive skeletal burden. No hepatic or splenic involvement was detected. A subsequent bone marrow biopsy was performed and showed no evidence of lymphoma involvement. According to the Lugano classification, the findings corresponded to Ann Arbor Stage IV disease (8,9).

An ultrasound-guided core biopsy of the right femoral neck lesion was performed. Histopathological examination revealed a cellular infiltrate containing small lymphocytes, histiocytes, and scattered multinucleated giant cells (Figure 4A). Immunohistochemical analysis identified large neoplastic cells with a CD30+ (Figure 4B), CD15- (Figure 4D), CD20-, CD3-, and weak PAX5+ (Figure 4C) immunophenotype.The available tissue was consumed for these initial diagnostic panels; consequently, additional markers, including EBER in situ hybridization and CD45 immunohistochemistry, were not performed.

The patient was treated according to the EuroNet-PHL-C1 protocol for Stage IV disease. He received two cycles of OEPA induction chemotherapy (Vincristine, Doxorubicin, Etoposide, Prednisone). One month following treatment initiation, the patient showed significant clinical improvement, including pain reduction, improved ambulation, and weight gain.

Follow-up and Outcome

An interim PET/CT scan was performed after the two OEPA cycles to assess treatment response. The scan demonstrated a robust morpho-metabolic response. However, the response was classified as incomplete due to residual bone lesions exhibiting FDG uptake levels marginally above the liver background (Deauville Score of 4), the patient proceeded with consolidation therapy consisting of 4 cycles of COPDAC (Cyclophosphamide, Prednisone, Vincristine, Doxorubicin, Dacarbazine) (Figure 5).

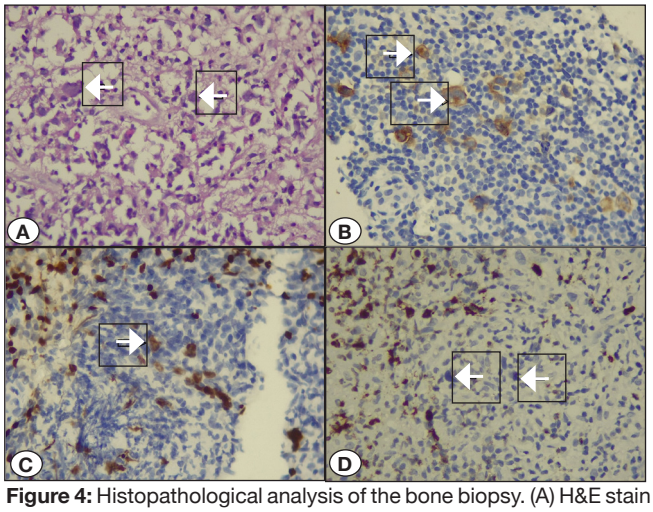

Figure 4: Histopathological analysis of the bone biopsy. (A) H&E stain (400x) showing classic Reed-Sternberg cells within an inflammatory milieu. Immunohistochemistry demonstrates that the neoplastic cells are strongly positive for (B) CD30, weakly positive for (C) PAX5, and negative for (D) CD15, confirming classical Hodgkin lymphoma.

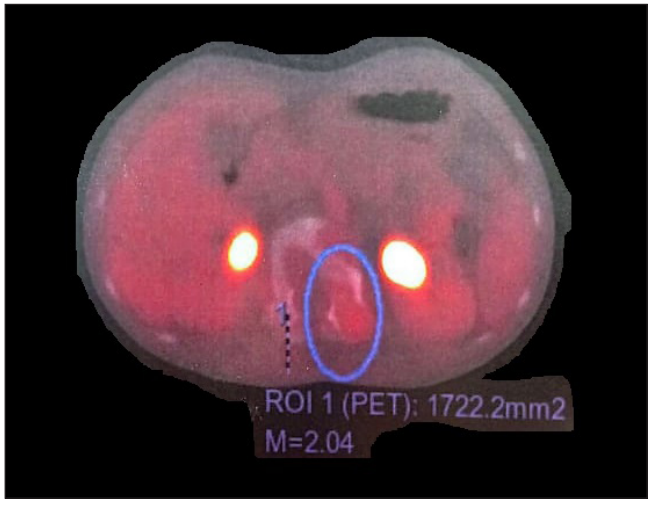

Figure 5: Evaluation revealed a robust morpho-metabolic response. However, the response was classified as incomplete due to residual bone lesions exhibiting FDG uptake levels marginally above the liver background (consistent with a Deauville Score of 4).

Discussion

This case illustrates a highly atypical presentation of pediatric Hodgkin lymphoma, defined by predominant destructive skeletal involvement with minimal nodal disease. This presentation contrasts sharply with the typical pattern of bulky lymphadenopathy. The discordance between the minimal nodal disease and extensive osseous destruction is a salient feature of this case, distinguishing it from typical advanced-stage HL. Due to the overwhelming discordance between the extensive, destructive cortical bone lesions and the minimal nodal burden detected only on PET/CT, this case is best classified as Primary Osseous Hodgkin Lymphoma (POHL). While primary nodal HL with secondary skeletal dissemination is more common, the presentation of multifocal destructive bone lesions as the herald symptom with disproportionately mild lymphadenopathy justifies the POHL designation.

The differential diagnosis for multifocal osteolytic lesions in this age group is broad, including metastatic neuroblastoma, Ewing sarcoma, osteomyelitis, and Langerhans cell histiocytosis (LCH) (4,5). The immunophenotype (CD30+, CD15-, PAX5+) and negative staining for CD1a, S100 expression on biopsy definitively excluded this diagnosis. The exact mechanism of primary osseous involvement in HL remains unclear but may involve retrograde lymphatic spread or hematogenous dissemination.

The diagnosis of classical HL in bone biopsies is often challenging due to sample size constraints and decalcification artifacts. While CD45 and EBER were not assessed in this case due to tissue exhaustion, the diagnosis was supported by pathognomonic Reed-Sternberg cell morphology in a typical inflammatory milieu, combined with a CD30+/weak PAX5+/CD20-/CD3- profile. Although CD15 was negative, this is observed in approximately 15% of classical HL cases and does not preclude the diagnosis when other markers are consistent (9).

Furthermore, while EBER is a valuable tool for identifying EBV-associated HL, particularly common in the pediatric population, the diagnosis of HL remains primarily a morphologic and immunophenotypic one. In the context of POHL, where tissue is scarce, the exclusion of more common mimics through the available panel was prioritized (10).

Prognostically, Stage IV HL has historically carried a guarded prognosis. However, modern risk-adapted protocols like EuroNet-PHL-C1, which use interim PET/CT to guide therapy intensity, have significantly improved outcomes (6, 7). Our patient's rapid clinical and metabolic response to induction chemotherapy is encouraging and aligns with reported outcomes from this regimen.

Conclusion

In conclusion, this case reinforces that Hodgkin lymphoma must be considered in the differential diagnosis of pediatric bone lesions, even in the absence of significant lymphadenopathy. A thorough, multidisciplinary diagnostic approach, centered on timely tissue biopsy, is essential for accurate diagnosis and effective management.

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Turkish Journal of Pediatric Disease

Review Article

Pediatric perioperative management: An integrated review of preoperative evaluation, fasting protocols, postoperative nausea and vomiting, and postoperative pain in light of current guidelines

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Received : 28.02.2026, Accepted : 30.06.2026 DOI: 10.12956/TJPD.2026.1356

ABSTRACT

The aim of this review is to present an integrated overview of pediatric perioperative anesthesia care by focusing on its fundamental components—preoperative evaluation, fasting management, prevention of postoperative nausea and vomiting (PONV), and postoperative pain control—based on current guidelines and evidence. The aim is to emphasize the need for individualized, risk-based approaches in pediatric patients.

This study is designed as a narrative review based on current international guidelines and relevant literature on pediatric perioperative anesthesia. Key domains including preoperative assessment, fasting protocols, PONV prophylaxis, and postoperative pain management were evaluated within a comprehensive and integrated clinical framework. Emphasis was placed on risk stratification strategies, avoidance of unnecessary routine investigations, and the implementation of multimodal and age-appropriate approaches.

Current evidence indicates that pediatric perioperative care differs significantly from adult practice due to limited physiological reserves, developmental variability, and age-related pharmacokinetic and pharmacodynamic differences. Risk-adapted strategies improve patient safety and outcomes. Specifically, shortened and evidence-based fasting protocols reduce metabolic stress; opioid-sparing multimodal analgesia minimizes adverse effects; risk-based antiemetic prophylaxis decreases the incidence of PONV; and age-appropriate pain assessment tools enhance postoperative pain management. Avoiding unnecessary routine tests further contributes to efficient and patient-centered care.

Pediatric perioperative anesthesia care should be based on an integrated, individualized, and risk-oriented approach. The effective combination of optimized preoperative evaluation, evidence-based fasting strategies, tailored PONV prevention, and multimodal pain management improves safety and clinical outcomes. Current evidence strongly supports a shift from routine, standardized practices toward patient-specific, guideline-driven perioperative management in children.

Keywords: Pediatric anesthesia, postoperative nausea and vomiting, postoperative pain

Introduction

Pediatric perioperative care is fundamentally aimed not only at ensuring the safe completion of the surgical procedure, but also at maintaining perioperative physiological homeostasis, minimizing complications, and enabling the child to transition into the recovery phase with the least possible stress (1). In this context, although preoperative evaluation, fasting management, PONV prophylaxis, and postoperative pain treatment may appear as separate domains, in clinical practice they are directly interrelated and mutually influential processes. For example, inadequate preoperative evaluation may lead to overlooked respiratory or cardiac risks; unnecessarily prolonged fasting may result in metabolic instability and irritability; poorly planned analgesia may increase opioid requirements; and this, in turn, may lead to a higher risk of PONV and respiratory depression. Therefore, contemporary pediatric anesthesia practice supports not a fragmented but a comprehensive and integrated perioperative care model.

Preoperative evaluation: Identification of risk and individualized planning

Pediatric preoperative evaluation is not merely a simple checklist performed before surgery; rather, it is a structured clinical process aimed at identifying the patient's physiological resilience, comorbidity burden, airway characteristics, current medications, family history, and specific conditions predisposing to perioperative complications. Although a large proportion of children undergoing surgery are otherwise healthy, it has been emphasized that serious perioperative events are not limited to high-risk patients, and that respiratory complications may also occur in children considered healthy. Therefore, systematic evaluation is required even in apparently healthy children (2-3).

The medical history should comprehensively include birth history, prematurity, neonatal complications, growth and developmental characteristics, genetic syndromes, craniofacial anomalies, cardiac and pulmonary diseases, neuromuscular disorders, endocrine conditions, and current medications. The perioperative management of medications used in pediatric patients requires careful consideration. Discontinuation of antiepileptic drugs increases the risk of seizures, whereas continuation of asthma control medications is recommended. In patients receiving chronic steroid therapy, the need for stress-dose steroids should be evaluated due to the risk of adrenal suppression. A history of prematurity, bronchopulmonary dysplasia, and postmenstrual age are particularly important predictors of postoperative apnea and bradycardia risk. Family history should include malignant hyperthermia, pseudocholinesterase deficiency, bleeding diathesis, congenital myopathies, and severe drug reactions, as these may directly influence anesthetic planning. Behavioral and social history is also relevant in children and adolescents; substance use, psychosocial stress, and concealed health issues in adolescents may impact perioperative safety (2,4).

The physical examination should primarily focus on airway, cardiovascular, respiratory, neurological status, and hydration. Mallampati classification, mouth opening, neck mobility, dentition, and craniofacial anomalies are important predictors of difficult airway. Conditions such as trisomy 21, mucopolysaccharidoses, syndromes associated with cervical anomalies, and head and neck masses may complicate airway management. The ASA physical status (PS) classification provides a useful general framework for risk assessment in pediatric patients; however, it is not sufficient on its own (Table I) (5). Younger age, urgency of surgery, coexisting airway disease, and type of surgery may be equally or more decisive in clinical practice.

Current recommendations do not support routine laboratory testing in healthy children undergoing low-risk procedures. Instead, a targeted approach based on findings from history and physical examination is recommended. For instance, electrocardiography and, if necessary, echocardiography may be considered in cases of unexplained murmur, exercise intolerance, growth retardation, severe scoliosis, bronchopulmonary dysplasia, or neuromuscular disease (6). Similarly, routine chest radiography is not recommended in children with normal oxygen saturation and no clinical findings; however, it may be indicated in severe asthma, bronchopulmonary dysplasia, suspected mediastinal mass, or active pulmonary disease. This selective strategy reduces unnecessary interventions while focusing on clinically meaningful findings (2).

In children with upper respiratory tract infection, perioperative respiratory complications may increase by 2–7

Table I: ASA PS Classification (5)

ASA PS Classification	Definition	Pediatric Examples, Including but not Limited to:
ASA I	A normal healthy patient	Healthy (no acute or chronic disease), normal BMI percentile for age
ASA II	A patient with mild systemic disease	Asymptomatic non cyanotic congenital cardiac disease, well controlled dysrhythmias, asthma without exacerbation, well controlled epilepsy, non-insulin dependent DM, abnormal BMI percentile for age, mild/ moderate OSa, oncologic state in remission, autism with mild limitations, malignant hyperthermia risk (family history or patient with history)
ASA III	A patient with severe systemic disease	Uncorrected stable congenital cardiac abnormality, asthma with exacerbation, poorly controlled epilepsy, insulin dependent diabetes mellitus, morbid obesity, malnutrition, severe OSa, oncologic state, renal failure, muscular dystrophy, cystic fibrosis, history of organ transplantation, brain/ spinal cord malformation, symptomatic hydrocephalus, premature infant PCa
ASA IV	A patient with severe systemic disease that is a constant threat to life	Symptomatic congenital cardiac abnormality, congestive heart failure, active sequelae of prematurity, acute hypoxic-ischemic encephalopathy, shock, sepsis, disseminated intravascular coagulation, automatic implantable cardioverter-defibrillator, ventilator dependence, endocrinopathy, severe trauma, severe respiratory distress, advanced oncologic state.
ASA V	A moribund patient who is not expected to survive without the operation	Massive trauma, intracranial hemorrhage with mass effect, patient requiring ECMO, respiratory failure or arrest, malignant hypertension with hypertensive crisis, decompensated congestive heart failure, hepatic encephalopathy, ischemic bowel or multiple organ/ system dysfunction.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

fold. Elective surgery should be postponed for at least two weeks in the presence of severe symptoms such as fever, purulent secretions, wheezing, lethargy, or oxygen requirement. In patients with mild symptoms, decision-making should be individualized based on age, comorbidities, need for airway surgery, planned intubation, institutional experience, and parental compliance. Intravenous induction with propofol, avoidance of desflurane, use of less invasive airway devices, and management by experienced pediatric anesthesia teams are recommended (7,8). The COLDS score may be helpful but is not sufficient alone (9).

In asthmatic children, recent exacerbations, emergency visits, hospitalizations, prior intubations, use of short-acting beta agonists, and steroid therapy should be assessed. Maintenance therapy should be continued, preoperative bronchodilator administration may be considered, and elective procedures should be postponed in the presence of active wheezing. In obese children and those with obstructive sleep apnea, risks of difficult ventilation, difficult intubation, excessive sedation, postoperative respiratory complications, and PONV are increased. Use of CPAP devices, review of polysomnography findings, and cautious opioid administration are recommended (2).

Premature infants represent a special risk group. Patients with postmenstrual age between 50–60 weeks require monitoring for postoperative apnea. Hematocrit levels below 30% may increase this risk. Bronchopulmonary dysplasia, hypothermia, pain, and acidosis-related pulmonary vasoconstriction are also relevant. Optimization of respiratory and nutritional status prior to elective surgery is essential; in selected cases, spinal anesthesia or perioperative caffeine administration may be considered (10). In children with neuromuscular disorders, both respiratory and cardiac insufficiency, as well as risks of rhabdomyolysis and malignant hyperthermia-like reactions, are increased; avoidance of triggering agents and careful postoperative monitoring are required (11).

Pediatric preoperative fasting: A metabolic and comfort-oriented approach beyond aspiration

The traditional aim of preoperative fasting is to reduce the risk of pulmonary aspiration during anesthesia. However, current literature indicates that aspiration of clear fluids in children is rare and, in most cases, not associated with serious sequelae; in contrast, prolonged fasting may lead to more frequent and clinically significant complications such as hypoglycemia, dehydration, irritability, ketosis, and hypotension. Therefore, the modern approach is based on the principle of "the shortest safe fasting duration" rather than "absolute prolonged fasting" (12,13).

According to current pediatric fasting guidelines, a duration of 6 hours for solid foods, 4 hours for formula and non-breast milk, 3 hours for breast milk, and 1 hour for clear fluids is recommended. This approach is consistent with the ESAIC 2022 recommendations (2,14). However, it should be noted that the ASA 2023 guideline adopts a more conservative stance and maintains a 2-hour fasting period for clear fluids. Therefore, while the 1-hour approach for clear fluids is an increasingly supported trend, there is no absolute consensus among all guidelines (15). This point should be emphasized transparently (Table II).

Table II: Preoperative fasting

6-4-3-1 Regimen & Basic Rules	Current Guidelines (ESAIC & ASA)	Contraindications for 1-Hour Fasting
• Solids: 6 hours • Formula milk: 4 hours • Other milks except breast milk: 4 hours • Breast milk: 3 hours • Clear liquids: 1 hour (TARD 2025)	• **ESAIC 2022:** 1 hour for clear liquids (max. 3 mL/kg). • **ASA 2023:** No difference between 1 hour and 2 hours, but 2 hours is recommended. • Solid food 8 hours, light solid food 6 hours. • A fasting period of 6 hours for infant formula and 4 hours for breast milk is recommended.	• Obesity • Gastroesophageal reflux • Renal failure • Some enteropathies • Esophageal strictures • Achalasia • Gastroparesis and/or Diabetes Mellitus • Surgical contraindications

Clear fluids exhibit rapid gastric emptying. According to the data summarized in the guideline, the gastric half-emptying time of clear fluids is very short, and no increase in pulmonary aspiration risk has been demonstrated with a 1-hour fasting period for clear fluids (16). Multicenter data indicate that a 1-hour clear fluid fasting protocol does not increase adverse respiratory events. Furthermore, shorter fasting durations are advantageous in reducing thirst, hunger, anxiety, and metabolic stress (17). However, in conditions such as obesity, gastroesophageal reflux, gastroparesis, achalasia, esophageal stricture, renal failure, and certain enteropathies, the 1-hour clear fluid approach is considered relatively contraindicated.

The guideline emphasizes that prolonged fasting leads to more pronounced metabolic disturbances, particularly in young children and those under 36 months of age. These include hypoglycemia, dehydration, electrolyte imbalance, increased ketone body production, irritability, and hemodynamic instability. These risks become even more significant when fasting durations exceed twelve hours. Therefore, it is important to schedule surgical lists early, prevent unnecessary delays, and encourage the intake of clear fluids safely up to the latest permissible time (13).

Carbohydrate-containing clear fluids appear to be beneficial in reducing physiological stress and maintaining insulin sensitivity. However, the available evidence is not uniformly strong enough across all contexts to conclude that they are superior to plain clear fluids in every situation. Perioperative glucose management requires special attention in children with diabetes; blood glucose levels should be maintained within the range of 90–180 mg/dL, measurements should be performed at least hourly, and more frequently in cases of rapid fluctuations. It has also been noted that gastric emptying may be delayed in diabetic patients even when standard fasting durations are followed. In such cases, or when fasting history is uncertain, gastric ultrasonography may assist in clinical decision-making (18-20).

Postoperative nausea and vomiting: risk-adapted yet increasingly liberal multimodal prophylaxis

Postoperative nausea and vomiting (PONV) is a significant perioperative problem, particularly in ambulatory surgery, as it delays discharge, impairs oral intake, complicates pain

management, and reduces family satisfaction. The current 5th consensus guideline emphasizes the importance of an algorithm-based and multimodal approach in both adults and children (21). However, the evidence base in children is more limited compared to adults, and therefore the strength of some recommendations does not reach the level observed in adult populations. It is important to preserve this distinction.

In children, the concept of postoperative vomiting (POV) is often emphasized rather than PONV, as the verbal expression of nausea may be difficult in younger patients. Validated scoring systems such as VPOP (Vomiting in the Postoperative Period) and POVOC (Postoperative Vomiting in Children) are used in this population. High-risk surgical procedures include strabismus surgery, tonsillectomy/adenoidectomy, and tympanoplasty. The use of volatile anesthetic agents, opioids, anticholinesterases, and female sex after puberty may confer additional risk. However, the guideline emphasizes that a mechanistic strategy of increasing pharmacological agents solely based on the cumulative number of risk factors does not always yield consistent benefit; particularly in high-risk groups, risk-reduction strategies are at least as important as pharmacological interventions (21).

Propofol-based total intravenous anesthesia (TIVA) reduces the incidence of PONV/POV in both adults and children. Adequate hydration, opioid-sparing analgesia, the use of local and regional techniques, and in certain cases dexmedetomidine may reduce the risk of PONV (22,23). Avoidance of nitrous oxide may be considered, particularly in high-risk pediatric patients. The guideline also notes that evidence is limited regarding the routine addition of more than three pharmacological prophylactic agents in children; therefore, in high-risk patients, non-pharmacological and anesthetic risk-reduction strategies should be maximized (24).

Ondansetron and dexamethasone are the most extensively studied agents in children. The combination of dexamethasone and ondansetron is more effective than monotherapy (25). However, evidence supporting the benefit of adding a third agent in high-risk groups is limited; although some retrospective data suggest the addition of scopolamine or diphenhydramine, these findings should be interpreted with caution. If PONV develops despite prophylaxis, rescue therapy with an agent of a different mechanism of action is recommended rather than repeating a dose from the same drug class. The overarching message of the guideline is that applying a better algorithm is more important than simply administering more medications (Table III).

PONV is not solely a matter of antiemetic selection. Prolonged fasting, increased opioid use, and inadequate hydration may exacerbate PONV. Conversely, early oral fluid intake has been shown in some studies to reduce both opioid requirements and vomiting. This finding highlights why fasting, pain, and PONV management should not be considered as separate entities, but rather as components of a unified recovery strategy within the perioperative process (21).

Pediatric postoperative pain: Assessment and multimodal management

The management of postoperative pain in pediatric patients is an integral component of successful surgical care. The guideline emphasizes that pain control not only provides comfort but also reduces the stress response, supports functional recovery, facilitates early mobilization, and may decrease the risk of chronic pain development. Furthermore, it is also critical in preventing negative pain memory in the child, maintaining the child–healthcare provider relationship, and ensuring family satisfaction (26,27).

Table III: Prophylaxis in PONV

Drug	Dose
Ondansetron	0.1 mg/kg up to 4 mg
Dolasetron	0.35 mg/kg up to 12.5 mg
Granisetron	0.04 mg/kg up to 0.6 mg
Palonosetron	0.5-1.5 mcg/kg
Tropisetron	0.1 mg/kg up to 2 mg
Droperidol	10-15 mcg/kg up to 1.25 mg
Dimenhydrinate	0.5 mg/kg up to 25 mg
Dexamethasone	0.15 mg/kg up to 4 mg
Aprepitant	3 mg/kg up to 125 mg

Nociceptive receptors and thalamocortical pain pathways become functionally active during the later stages of fetal development. Therefore, the notion that neonates and infants do not "perceive" pain is not scientifically valid. Moreover, due to the immaturity of inhibitory neurotransmitter systems, pain modulation may be insufficient, and the pain response may be more pronounced (28). This biological reality indicates that pediatric pain treatment should not be delayed and that the "we can address it later if necessary" approach should be abandoned.

A single pain assessment scale is not suitable for all pediatric age groups. In children capable of communication, self-report is considered the gold standard. Visual Analog Scale (VAS), Numeric Rating Scale (NRS), and Wong-Baker FACES are commonly used in this group. In neonates and younger children, behavioral and physiological scales are required; FLACC, revised FLACC, PIPP, the COMFORT Scale, and CRIES are among the most prominent examples. One of the key points emphasized in the guideline is that pain should be assessed both at rest and during movement, and unexpected increases in pain scores should also be interpreted as potential indicators of surgical complications (26,27,29) (Table IV-V).

The guideline presents the use of multimodal analgesia in both children and adults as a strong recommendation supported by high-quality evidence. This approach may include appropriate combinations of paracetamol, NSAIDs, opioids when necessary, ketamine, gabapentinoids, intravenous lidocaine, regional blocks, and neuraxial techniques. The aim is not to administer more medications, but to achieve more effective analgesia with reduced opioid requirements by targeting different mechanisms (29,30).

Paracetamol is the primary agent for mild to moderate pain and is available in oral, rectal, and intravenous forms. In neonates and young infants, dosing should be carefully adjusted due to differences in volume of distribution and elimination. The total daily dose should not be exceeded due to the risk of toxicity. NSAIDs reduce opioid requirements; however, they should be used with caution due to

Table IV: Pain intensity rating scales in children (29)	
Scales based on self-report	
FACES Scale (Wong Baker)	Aged 3 to 18 years (the scale consists of 6 drawings of facial expressions; each face is scored 0-5 or 0-10)
Faces Pain Scale	Revised- for those aged 4 to 12 years (the scale consists of 6 drawings of face expressions; an examiner gives 0,2,4,6,8 or 10 points to faces indicated by the child (counting from left to right)
VAS Scale (Visual Analogue Scale)	Aged 3 to 18 years (the VAS scale is a 10 cm line with 0 meaning total absence of pain, and 10 meaning the worst pain imaginable
NRS Scale (Numeric Rating Scale)	Aged 3 to 18 years (scale from 0 to 10, where 0 means I'm not feeling any pain, and 10 means the worst pain imaginable)
Pieces of Hurt Tool Scale	Aged 3 to 18 years
Scales based on child's behaviour or behaviour and physiological parameters	
Children and adolescents without cognitive impairment	
FLACC Scale (Face, Legs, Activity, Cry, and Consolability)	Aged 1 to 18 years
PPPM Scale	Parent's Postoperative Pain Measure
COMFORT scale	Behavioural and physiological parameters
Children and adolescents with cognitive impairment	
NCCPC-PV Scale (Non-Communicating Children's Pain Checklist-Postoperative Version)	Aged 3 to 18 years
PPP Scale(Paediatric Pain Profile)	Aged 1 to 18 years
FLACC Scale-Revised (Face, Legs, Activity, Cry, and Consolability)	Aged 4 to 18 years
INRS (Individualized Numeric Rating Scale)	Aged 3 to 18 years

Table V: Pain intensity rating scales in children (29)			
Scale	**Parameter**	**Outcome**	**Application**
Premature infant pain profile (PIPP)	Age from conception, behaviour, pulse, haemoglobin oxygen saturation, raising eyebrows, tightening of eyelids, nasolabial sulcus	Number of points to score: 0-21 Each parameter scored 0-3 points Minimal pain ≤6, moderate-to severe pain >12	Procedural and postoperative pain
FLACC (Face, legs, activity, cry, and Consolability)	Facial expression, leg position activity, cry, possibility of consoling	Number of points to score: 0-10 Each parameter scored 0-2 points Moderate pain>4, severe pain >7	Procedural and postoperative pain
COMFORT scale (behavioural and physiological parameters)	Wakefulness, mood, reaction to ventilator breathing, ambulation, muscle tone, fasial expressions, MAP, HR	Number of points to score: 8-40 Each parameter scored 1-5 points Sufficient sedation 17-26, insufficient sedation/analgesia >27	Pain and sedation in neonatal intensive care unit
CRIES (Crying, requirement, for O2, increased heart rate, expression, sleeplessness)	Cry, demand for additional oxygen supply for saturation >95%, vital signs, facial expressions, sleep patterns	Number of points to score: 0-10 Each parameter scored 0-2 points Moderate pain>4, severe pain >7	Postoperative pain in neonatal intensive care unit

gastrointestinal, renal, and bleeding-related adverse effects, as well as potential effects on anastomotic healing in certain surgical procedures. Opioids remain necessary for moderate to severe pain; however, close monitoring is essential due to risks such as sedation, respiratory depression, and PONV. Patient-controlled analgesia (PCA) is an effective strategy in appropriately selected patients, although routine basal infusion is not recommended in opioid-naïve individuals. Ketamine and gabapentinoids may provide opioid-sparing effects, but sedation and neuropsychiatric side effects should be considered. Intravenous lidocaine may be considered in selected patients, particularly in abdominal surgery; however, safe administration requires an experienced team (26,29,31,32).

Techniques such as peripheral nerve blocks, epidural analgesia, and local infiltration can reduce opioid requirements and positively influence both analgesia and PONV control, particularly in major surgical procedures. Continuous peripheral blocks and epidural techniques are beneficial when appropriate organizational and monitoring conditions are ensured (33). Non-pharmacological approaches should not be underestimated; transcutaneous electrical nerve stimulation (TENS), cognitive therapy, relaxation techniques, music therapy, and play-based distraction methods may contribute to pain modulation, particularly in anxiety-related pain perception. These methods should be considered not as replacements for pharmacological treatment, but as complementary components (34).

Discussion

Four key messages emerge for pediatric perioperative care. First, the more thoroughly the preoperative evaluation is performed, the greater the likelihood of anticipating and preventing perioperative complications; in particular,

conditions such as upper respiratory tract infection, asthma, obstructive sleep apnea, prematurity, and neuromuscular disorders cannot be managed using a standard "healthy child" approach. Second, the traditional concept of "the longer the fasting, the safer it is" is no longer sustainable; shorter, physiology-based fasting is both safer and more comfortable for the child, although there are still nuances among guidelines regarding the 1-hour clear fluid approach, and these nuances should be acknowledged transparently. Third, in the management of PONV, the focus should not be solely on administering more antiemetics, but rather on accurately identifying risk and implementing fundamental risk-reduction strategies such as total intravenous anesthesia (TIVA), adequate hydration, and opioid-sparing approaches. Fourth, postoperative pain management in children is not a secondary concern but a central component of perioperative care; delayed recognition of pain adversely affects not only the child's comfort but also other outcomes such as respiration, mobilization, nutrition, and PONV. When these four domains are considered together, the true objective should not merely be "to successfully complete the surgery," but rather "to guide the child safely and in a physiologically balanced manner into the recovery process."

Conclusion

Pediatric perioperative care should be based on the systematic identification of preoperative risks, optimization of fasting durations according to physiological evidence, implementation of risk-adapted multimodal prophylaxis for PONV, and the monitoring and treatment of postoperative pain using age-appropriate scales and multimodal strategies. These four domains should not be viewed as independent components, but rather as interrelated elements of the same clinical trajectory. Successful perioperative management in pediatric patients depends not on performing more tests, prolonging fasting, or administering more medications, but on selecting the appropriate intervention at the right time and with the appropriate intensity for the right patient. The common message of current evidence is clear: quality in pediatric anesthesia lies in achieving a balance between standardization and individualization.

Contribution of the authors

VE: draft manuscript preparation. All authors **VE, EH** reviewed the results and approved the final version of the manuscript.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Clinical and laboratory characteristics of nephropathic cystinosis in a resource-limited region": Linear growth retardation as a clinically important signal

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Received : 11.06.2026, Accepted : 30.06.2026 DOI: 10.12956/TJPD.2026.1387

Introduction

I read with great interest the article by Köksoy and Görükmez (1). Longitudinal data on nephropathic cystinosis from regions of high consanguinity, with constrained access to leukocyte cystine monitoring and uninterrupted cysteamine supply, are scarce, and the authors provide a valuable real-world account of presentation, tubular phenotype, genetics, and renal trajectory. The cohort is especially informative because the recurrent CTNS variant c.681G>A was observed in homozygous form in most genotyped patients.

A particular strength of this cohort is the early age at diagnosis, at a median of around 11 months, which the authors note compares favorably with other series from developing settings and likely reflects heightened regional awareness of consanguinity-related disease (1). This makes the outcomes all the more thought-provoking: despite early diagnosis, estimated glomerular filtration rate (eGFR) declined significantly (116.66 to 77.40 mL/min/1.73 m², p=0.007) and height SDS fell further over follow-up, from −2.8 to −3.9 (p=0.034), while weight SDS did not change significantly and body bass index (BMI) SDS remained around −2.0 (1). This gap between early diagnosis and subsequent growth and renal outcome suggests that what determines outcome is not only how early cystinosis is recognized, but what is done after diagnosis to protect growth and bone. Growth retardation was in fact the leading presenting complaint in this cohort, and I would like to use this growth signal to draw attention to three areas that the study, by its scope, could not detail but that are central to that question.

Before doing so, one nuance on the data should be addressed. The authors appropriately frame the height decline as multifactorial, citing chronic hypokalemia, persistent acidosis, phosphate loss with defective bone mineralization, reduced caloric intake, and hormonal factors (1). I read the magnitude cautiously given the small sample and heterogeneous follow-up, but the direction is informative: weight did not decline and rose numerically, BMI was stable, and only height fell further behind. To the extent that reduced caloric intake is invoked, this dissociation suggests that it is unlikely to be the principal driver of the linear growth deficit, although the absence of detailed nutritional data in a retrospective cohort precludes a firm conclusion. Either way, linear growth deserves attention as an outcome in its own right.

First, the bone-mineral observations may be usefully unified under a single framework. The authors discuss rickets in four patients, nephrocalcinosis in six, and the delicate balance between correcting mineral depletion and overtreatment with active vitamin D, calcium, and phosphate (1). These are facets of what is increasingly recognized, though not yet widely familiar in general practice, as a distinct entity: cystinosis-associated metabolic bone disease (CMBD), which differs from conventional chronic kidney disease (CKD)-mineral and bone disorder (2). Mechanistically, tubular phosphate wasting, reduced 1.25-dihydroxyvitamin D, and chronic metabolic acidosis impair growth-plate mineralization and induce relative resistance to the growth hormone and insulin like growth factor-1 (IGF-1) axis (3). The entity also carries a disease-specific mineral signature with a direct monitoring implication: because persistent tubular phosphate leak keeps serum phosphate low, fibroblast growth factor-23 (FGF-23) remains paradoxically low rather than rising as it does early in typical CKD, so secondary hyperparathyroidism tends to appear late and can be missed if sought only on the usual CKD timeline (4). Bone turnover is additionally altered across CKD stages and deteriorates with age (5). Much of this evidence derives from overlapping European cohorts,

so independent confirmation in populations such as the one studied here would be genuinely valuable.

Second, the growth hormone axis deserves explicit emphasis. The authors note, appropriately, that effects within this axis may become more evident as chronic kidney disease progresses, consistent with the three patients who reached stage 3 CKD and the three requiring replacement therapy (1). I would add that recombinant human growth hormone (rhGH) may be an actionable option in selected patients before advanced CKD develops. International consensus recommends considering rhGH when adequate cysteamine therapy, nutrition, and symptomatic treatment fail to prevent growth retardation, including in selected patients without advanced renal failure; CKD-specific recommendations support its use once treatable risk factors are corrected and growth potential remains (2,6). In nephropathic cystinosis specifically, long-term rhGH has been reported to roughly double height velocity and to raise height SDS by about 1.6 over three years in prepubertal children on conservative treatment (7). Documenting whether eligible children with persistent growth failure were assessed for rhGH, after optimization of Fanconi replacement, nutrition, cysteamine, and thyroid status, would meaningfully enrich the interpretation of growth outcomes in future cohorts. This last point connects to a feature of the cohort worth underlining: the authors themselves link the relatively high incidence of renal failure to adherence shaped by socioeconomic conditions, and report poorer adherence among those who progressed to advanced CKD (1). Extending their reasoning, I would suggest the same treatment and monitoring gap may also bear on linear growth, since initiation of cysteamine is not equivalent to adequate, adherent, cystine-guided treatment: early initiation and lower leukocyte cystine levels are associated with better linear growth, and outcome depends more on early, presymptomatic intervention than on genotype (8,9). As the authors candidly acknowledge that adherence was assessed subjectively and leukocyte cystine could not be measured locally, this is best read as an association rather than established causation, and likely a bidirectional one; even so, it identifies a modifiable target and reframes early diagnosis as a window of opportunity rather than an endpoint (1).

Third, standing height alone may underestimate the burden, because growth in this disease is disproportionate. Compared with other pediatric CKD entities, children with nephropathic cystinosis show disproportionate linear growth and reduced upper-arm fat area, pointing to cystinosis-specific contributors beyond reduced glomerular filtration rate (10). In practice, sitting height and the sitting-height-to-total-height ratio, subischial leg length, the upper-to-lower segment ratio, and upper-arm fat area, together with height velocity, bone age, and pubertal staging, would characterize the deficit far better than standing height SDS alone, and would help distinguish disproportionate, rickets-driven leg shortening from the more harmonious growth deficit of other CKD.

These observations are intended to complement rather than detract from the authors' valuable real-world data. Their findings carry a clear message for pediatricians, pediatric nephrologists, endocrinologists, and dietitians: in nephropathic cystinosis, preserving kidney function and preserving growth potential are parallel therapeutic goals, and early diagnosis delivers its benefit only when followed by adherent, cystine-guided treatment and active protection of growth and bone. I would suggest that future cohorts adopt a standardized growth and bone-mineral module, organized under CMBD, capturing standing and sitting height with segmental measurements, height velocity, mineral-bone biochemistry including FGF-23 and parathyroid hormone where feasible, treatment adherence, leukocyte cystine where available, and growth hormone eligibility. Such a framework would help separate the renal, skeletal, endocrine, and nutritional contributors to growth failure and prompt earlier multidisciplinary intervention during the narrow window before loss of height potential becomes difficult to reverse.

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Turkish Journal of Pediatric Disease

Letter to the Editor

Comment on "Clinical and laboratory characteristics of nephropathic cystinosis in a resource-limited region"

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Received : 10.06.2026, Accepted : 30.06.2026 DOI: 10.12956/TJPD.2026.1384

Introduction

In the latest issue of the Turkish Journal of Pediatric Disease, Köksoy et al. (1) found that growth faltering and progression to renal failure were notable challenges for Turkish patients with cystinosis. We herein address a worthy notice. The CTNS gene mutations encoding a protein named cystinosine, which is a lysosomal cystine transporter, are the primary cause of cystinosis and there are approximately over 140 distinct CTNS mutations. The clinical phenotypes of cystinosis are controlled by the functional effects of the various CTNS mutations (2). Accordingly, sequencing the CTNS gene coding exons has been developed in numerous populations for the early cystinosis identification and characterization of the disease spectrum employing molecular diagnostic tests (3-4). Studies on the genetic landscape of cystinosis in Türkiye are scarce in the literature and they primarily involved small size series in localized settings (5-7). The available study that targeted CTNS mutations at national level based on a Turkish pediatric cystinosis registry was released by Topaloglu et al in 2017 (8). The 57-kb deletion, which is most common among Caucasian cystinosis patients, was not identified in any of the patients. However, seven novel mutations were detected. The most common CTNS mutations were c.681G.A (p.Glu227Glu), c.1015G.A (p.Gly339Arg), and c.18_21 del (p.Thr7Phefs*7) identified in 31%, 22%, and 14% of the patients respectively. Compared to other mutations, the above-mentioned three mutations were importantly correlated with the disease's earlier onset age and patients with severe CTNS mutations tended to develop worse renal outcomes (8). Notably, the identified genetic CTNS variants in Köksoy et al's study (1), namely c.681G>A (p.Glu227Glu), c.18_21delGACT (p.Thr7Phefs*7), and c.1015G>A (p.Gly339Arg), contribute to those previously addressed by Topaloglu et al (8). Updating national data on the CTNS mutational spectrum among cystinosis patients and genetic counseling where the families in Türkiye tend to be particularly large and display a high consanguinity rate (18.5%, with first cousin marriages accounting for 57.8%) (9) are deemed critical. These interventions together that recommended by by Köksoy et al (1), namely the initiation of cysteamine therapy, supporting access to the specialized healthcare facilities, and regular monitoring, are solicited to deter further breeding of cystinosis cases in Türkiye on one hand and improve patients' outcomes and quality of life on the other.

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