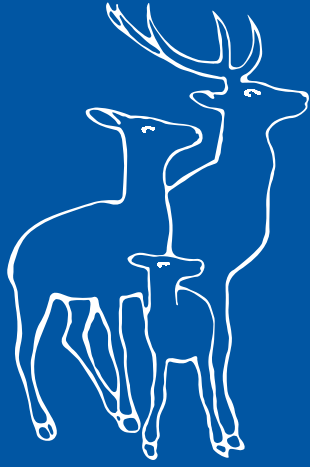




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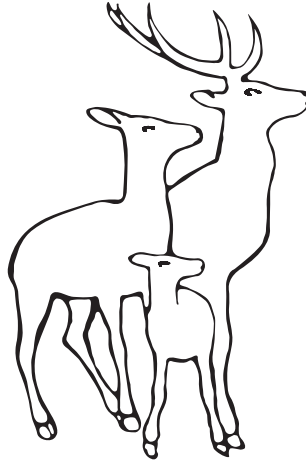
REVIEW ARTICLES

- 725 **The use of artificial intelligence in patent ductus arteriosus diagnosis and treatment: a systematic scoping review**
Chu Thi Ha, Thi Hai Yen Tran, Minh Nguyet Pham, Phuong Linh Dang, Duy Quan Vo
- 741 **Remember what you forgot: mega dose methylprednisolone in the treatment of immune thrombocytopenia - a systematic review and meta-analysis**
Dilek Kaçar, Lale Olcay, Mehtap Akçil Ok

ORIGINAL ARTICLES

- 753 **Investigating the clinical significance and predictive value of miR-146a rs2910164 polymorphism in retinopathy of prematurity: a case-control study**
Wenwen Cui, Chang Zhan, Tao Wu, Qiong Gan, Weihua Tang
- 765 **Structural vulnerabilities and adolescent pregnancy outcomes: a cross-sectional study from a tribal community in Jharkhand, India**
Indrani Dutta, Anand Kishore, Tania Pan
- 776 **Menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescents: a cross-sectional study**
Merve Tuncer, Elifnur Güneş, Özlem Şensoy
- 790 **Trends in adolescent suicide attempts requiring pediatric intensive care across pre-COVID, COVID, and post-COVID periods**
Banu Katlan, Müslüm Kul, İsmail Kızıldağ, Mesut Topdemir, Özlem Kahraman Çayan, Salim Ekici, Feyza Hatice Ekici
- 804 **A comparative analysis of Phoenix, PELOD-2, and pSOFA scores to predict mortality in children with clinical sepsis**
Ronald Chandra, Irene Yuniar, Ririe Fachrina Malisie
- 813 **Quality of life of children with cerebral palsy: an analytical cross-sectional study**
M. Gitanjali Sathiadas, Vijitha Manitheepan, Yadhury Senthana, Kinthuja Nagarasa
- 823 **Flexible bronchoscopy in pediatric atelectasis: bronchoscopic findings, management changes, and factors associated with radiographic resolution**
Ömer Faruk İpek, Ebru Yalçın, Özge Özen, Birce Sunman, Nagehan Emiralioğlu Ordukaya, Deniz Doğru, Uğur Özçelik, Nural Kiper
- 835 **Primary hypoparathyroidism in childhood: clinical and etiological spectrum in a tertiary referral center from southeastern Türkiye**
Hayrullah Manyas, Betül Kesriklioğlu, Pınar Atla
- 845 **Exploratory epigenetic analysis of host gene-dependent regulation of miR-197-3p in familial Mediterranean fever**
Yeliz Z. Akkaya Ullum, Emre Nalbant, Yağmur Bayındır, Betül Bölüköğlu, Tayfun Hilmi Akbaba, Seza Özen, Banu Balcı Peynircioğlu

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CONTENTS

VOLUME: 68

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SEPTEMBER-OCTOBER 2026

REVIEW ARTICLES

- The use of artificial intelligence in patent ductus arteriosus diagnosis and treatment: a systematic scoping review** 725
Chu Thi Ha, Thi Hai Yen Tran, Minh Nguyet Pham, Phuong Linh Dang, Duy Quan Vo
- Remember what you forgot: mega dose methylprednisolone in the treatment of immune thrombocytopenia - a systematic review and meta-analysis** 741
Dilek Kaçar, Lale Olcay, Mehtap Akçil Ok

ORIGINAL ARTICLES

- Investigating the clinical significance and predictive value of miR-146a rs2910164 polymorphism in retinopathy of prematurity: a case-control study** 753
Wenwen Cui, Chang Zhan, Tao Wu, Qiong Gan, Weihua Tang
- Structural vulnerabilities and adolescent pregnancy outcomes: a cross-sectional study from a tribal community in Jharkhand, India** 765
Indrani Dutta, Anand Kishore, Tania Pan
- Menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescents: a cross-sectional study** 776
Merve Tuncer, Elifnur Güneş, Özlem Şensoy
- Trends in adolescent suicide attempts requiring pediatric intensive care across pre-COVID, COVID, and post-COVID periods** 790
Banu Katlan, Müslüm Kul, İsmail Kızıldağ, Mesut Topdemir, Özlem Kahraman Çayan, Salim Ekici, Feyza Hatice Ekici
- A comparative analysis of Phoenix, PELOD-2, and pSOFA scores to predict mortality in children with clinical sepsis** 804
Ronald Chandra, Irene Yuniar, Ririe Fachrina Malisie
- Quality of life of children with cerebral palsy: an analytical cross-sectional study** 813
M. Gitanjali Sathiadas, Vijitha Manitheepan, Yadhury Senthana, Kinthuja Nagarasa
- Flexible bronchoscopy in pediatric atelectasis: bronchoscopic findings, management changes, and factors associated with radiographic resolution** 823
Ömer Faruk İpek, Ebru Yalçın, Özge Özen, Birce Sunman, Nagehan Emiralioğlu Ordukaya, Deniz Doğru, Uğur Özçelik, Nural Kiper
- Primary hypoparathyroidism in childhood: clinical and etiological spectrum in a tertiary referral center from southeastern Türkiye** 835
Hayrullah Manyas, Betül Kesriklioğlu, Pınar Atla
- Exploratory epigenetic analysis of host gene-dependent regulation of miR-197-3p in familial Mediterranean fever** 845
Yeliz Z. Akkaya Ulum, Emre Nalbant, Yağmur Bayındır, Betül Bölükoğlu, Tayfun Hilmi Akbaba, Seza Özen, Banu Balcı Peynircioğlu

CONTENTS

VOLUME: 68

ISSUE: 5

SEPTEMBER-OCTOBER 2026

CASE REPORTS

- A rare congenital malformation of the external iliac artery in a term neonate..... 855**
Ana Sučić, Gabriela Živković, Edi Paleka Bosak, Vinko Vrdoljak, Alen Švigir, Katarina Bojanić
- Megalopapilla in oculodentodigital dysplasia: a novel ocular finding in a rare genetic disorder 860**
Figen Bezci Aygun, Gunes Deniz Ulas, Izlem Ozturan, Sibel Kadayifcilar
- Beyond the usual: coronary artery abnormalities in Noonan syndrome 869**
Bilgehan Betül Biçer, Hayrettin Hakan Aykan, Ercan Tutar
- Colonic arteriovenous malformations in children: a missed cause of lower gastrointestinal bleeding 874**
Rohan Luthra, Natasha Gupta, Parveen Kumar
- Perineal dysmorphism and patellar luxation in SLC35A2-CDG: a new piece in the glycosylation puzzle 882**
Anıl Gök, Tolgahan Özer, Özlem Akgün Doğan, Mehmet Cihan Balci, Filiz Çizmecioğlu Jones, Bülent Kara, Yasemin Alanay
- Precocious puberty as the first clue: mediastinal germ cell tumor revealing previously undiagnosed Klinefelter syndrome..... 889**
Ahmet Fatih Yılmaz, Muammer Büyükinan, Buket Kara, Hıdır Esme

The use of artificial intelligence in patent ductus arteriosus diagnosis and treatment: a systematic scoping review

Chu Thi Ha¹, Thi Hai Yen Tran¹, Minh Nguyet Pham², Phuong Linh Dang³,
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ABSTRACT

Background. Background and objectives: Patent ductus arteriosus (PDA) is a common congenital cardiac condition, especially in premature infants, and is associated with significant morbidity and mortality. Artificial intelligence (AI) has emerged as a promising tool to aid clinicians in diagnosing PDA and guiding treatment decisions amidst this uncertainty.

Methods. A literature search (up to December 2025) was conducted in PubMed, Scopus, and Web of Science for peer-reviewed studies on AI (including machine learning, deep learning, computer vision, and predictive analytics) applied to PDA.

Results. Seventeen studies were included, predominantly involving preterm neonates. AI applications mainly targeted PDA diagnosis and outcome prediction using clinical and echocardiographic data. Imaging-based deep learning models generally outperformed tabular data approaches (with area under the curve often >0.80). Overall study quality was moderate, with limited external validation and data transparency.

Conclusions. AI has the potential to transform patent ductus arteriosus management by enabling earlier detection, more consistent decision-making, and individualized treatment planning. Integration of AI into PDA care may reduce practice variability, improve clinical outcomes, and serve as a model for the broader application of artificial intelligence in medicine.

Key words: artificial intelligence, patent ductus arteriosus, machine learning, clinical decision support, echocardiography.

Patent ductus arteriosus (PDA) is a congenital cardiovascular condition defined by the failure of the fetal ductus arteriosus to close after birth, resulting in a persistent left-to-right shunt between the aorta and pulmonary artery.¹ PDA is particularly common in preterm infants, with incidence inversely related to gestational age. In very low birth weight neonates, PDA is associated with substantial morbidity,

including chronic lung disease, necrotizing enterocolitis, renal dysfunction, intraventricular hemorrhage, and increased mortality. In term infants and older children, persistent PDA may lead to chronic cardiac volume overload, while in adults, although uncommon, untreated large PDA can result in heart failure or infective endarteritis.²⁻⁴ Conversely, in certain congenital heart diseases, the PDA may be life-sustaining;

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for ductal-dependent lesions, maintaining ductal patency is critical, and procedures such as PDA stenting may be performed to ensure adequate pulmonary or systemic blood flow.^{5,6} Thus, PDA management spans a spectrum from intentional closure to intentional maintenance of patency, depending on the clinical context.

Despite its clinical importance, optimal PDA management remains highly controversial, particularly in preterm infants.^{7,8} No universal consensus exists regarding the treatment of hemodynamically significant PDA in this population. Therapeutic strategies range from conservative management (watchful waiting and supportive care), to pharmacological closure with nonsteroidal anti-inflammatory drugs (NSAIDs, such as indomethacin or ibuprofen, or acetaminophen), and surgical ligation or catheter-based closure.^{9,10} This lack of agreement is due in part to conflicting evidence on long-term benefits of PDA closure and the difficulty of determining which PDA is truly “pathological” (hemodynamically significant) versus benign.¹¹⁻¹³ In older infants and children with PDA, treatment decisions (typically transcatheter device closure or surgery) are more straightforward once a PDA is identified, but selecting the optimal timing and device can still benefit from advanced planning tools.^{14,15} In ductal-dependent congenital heart disease, PDA stenting has emerged as a less invasive alternative to surgical shunts, but it is a technically complex procedure requiring careful planning due to highly variable ductal anatomy.^{6,16}

Within this context of diagnostic and therapeutic uncertainty, artificial intelligence (AI) and machine learning (ML) have emerged as promising tools to support clinical decision-making in PDA. AI techniques can integrate large-scale clinical, imaging, and physiological data to identify subtle patterns, improve diagnostic accuracy, and generate individualized risk predictions.^{17,18} Potential applications include predicting spontaneous ductal closure, identifying PDAs likely to cause adverse outcomes, automated PDA

detection using imaging or signal-based data, and procedural planning for interventions such as PDA stenting through anatomy-aware visualization and simulation.¹⁹⁻²¹ These applications align with broader trends toward data-driven decision support in high-acuity settings such as the neonatal intensive care unit.

Although an increasing number of studies have explored AI-based approaches for PDA diagnosis and management, a comprehensive synthesis of this evidence is currently lacking. This scoping review aims to systematically examine the application of AI in PDA across the full clinical spectrum, from diagnosis to therapeutic decision support and interventional planning, across all age groups and geographic regions. By summarizing current evidence, this review aims to clarify the evolving role of AI in improving PDA care and facilitating its integration into clinical practice.

Materials and Methods

This scoping review was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews.²²

Search strategy

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science, with supplementary searches in Google Scholar to identify additional relevant studies. The initial search was conducted in October 2025 and updated in December 2025 to capture the most recent publications. Search terms combined concepts related to patent ductus arteriosus (“patent ductus arteriosus,” “ductus arteriosus,” “PDA”) with artificial intelligence-related keywords, including “artificial intelligence,” “machine learning,” “deep learning,” “neural network,” “computer vision,” “predictive model,” “decision support,” and “automation.” Search strategies were adapted to each database. Only peer-reviewed journal articles were considered, and non-

scholarly content was excluded. No restrictions on publication date, country, or language were applied at the search stage; however, all included studies were published in English.

Eligibility criteria

A scoping review approach was adopted to capture the breadth of AI applications in PDA care. Studies were eligible if they met the following criteria: (1) involved patients with PDA of any age, including isolated PDA or PDA associated with other congenital heart diseases; (2) applied AI techniques to PDA-related diagnosis, outcome prediction, decision support, or interventional planning; (3) reported relevant outcomes such as diagnostic performance metrics, predictive accuracy, or clinical utility; and (4) were original research articles, including retrospective or prospective studies, model development, validation, or technical feasibility studies. Review articles, conference abstracts without full texts, and non-peer-reviewed reports were excluded.

Study selection and data extraction

Titles and abstracts were independently screened by two reviewers, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved by consensus. Studies that met the inclusion criteria and were included in the final analysis. From each study, data were extracted on publication year, country, patient population, AI methodology, application domain, and principal findings, including performance metrics where available.

Quality assessment

Included studies were grouped into thematic categories addressing AI applications in PDA diagnosis and AI-based treatment planning or clinical decision support. Given the scoping nature of the review, a formal risk-of-bias assessment was not performed. Instead, all included studies were evaluated for adherence to best practices in AI research in accordance with the DOME guidelines.²³

Results

Search results

A total of 312 records were initially identified through searches of three electronic databases. After removal of 16 duplicate records, 296 articles remained for title and abstract screening according to the predefined inclusion criteria. Of these, 20 studies were retrieved for full-text assessment. Following detailed evaluation, 3 articles were excluded, and 17 studies were ultimately included in the review (Fig. 1).

Characteristics of included studies

The included studies showed wide geographic representation across nine countries, with China contributing the largest number (five studies), followed by the United States and South Korea (with three studies each).

Preterm neonates were the primary population in ten studies, reflecting the clinical significance of PDA in premature and very low birth-weight infants, while other studies involved term neonates or broader pediatric cohorts.

PDA diagnosis or screening and outcome prediction were each addressed in thirteen studies, whereas treatment planning or management was examined in four, with some overlap in objectives. Clinical and laboratory tabular data were the most frequently used inputs (11 studies), followed by echocardiographic images or video (five studies), while other modalities were rarely applied (Supplementary Table S1).

Applications of AI in PDA diagnosis

Seven studies evaluated AI for PDA diagnosis or screening. CNN-based models applied to echocardiographic images and video clips achieved expert level or superior diagnostic accuracy, including advanced architectures such as ResNet 50 and CHDNet for both grayscale and color Doppler imaging.^{20,24,25} Non-imaging approaches using heart sound signals, based on recurrent neural networks, residual

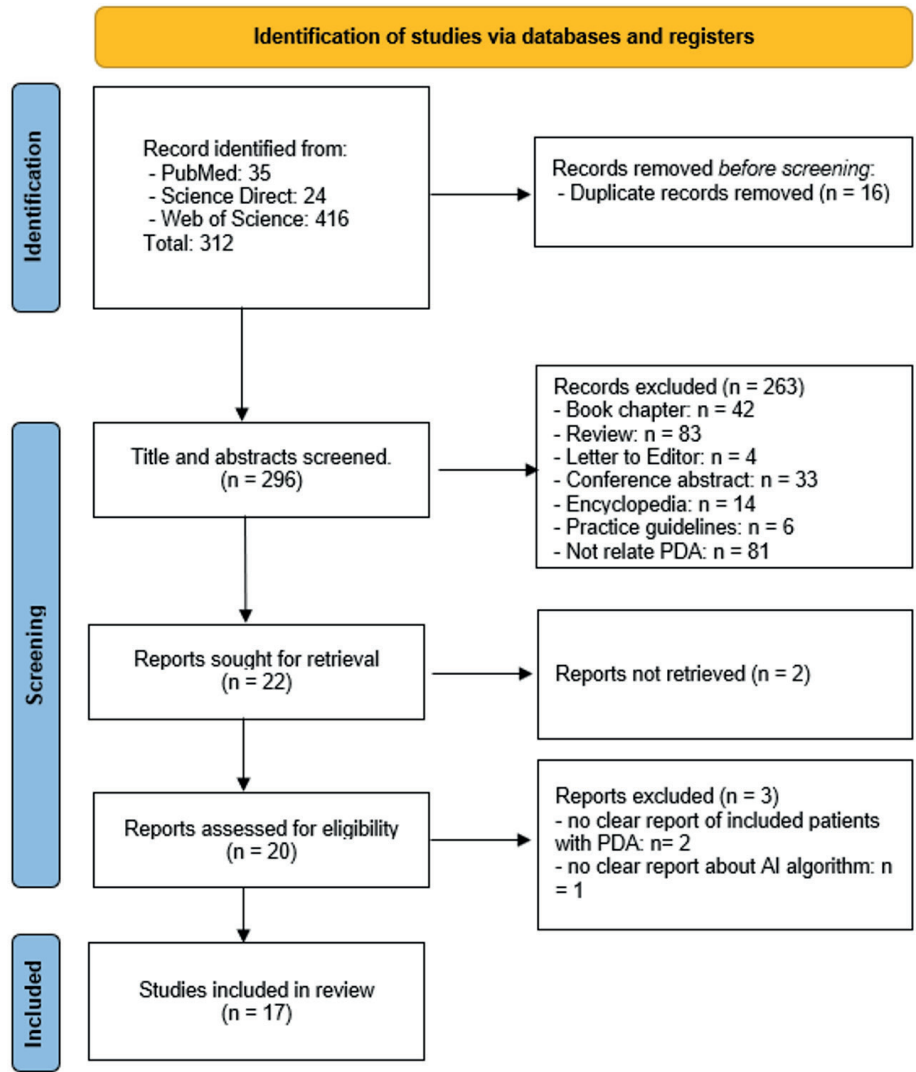


Fig. 1. Study flow-chart.

convolution recurrent neural networks, and gradient boosting, consistently outperformed clinician auscultation, supporting their role as low cost and scalable screening tools.²⁶⁻²⁸ Models using routine clinical data, particularly random forest and extreme gradient boosting, enabled early prediction of PDA risk in preterm neonates.¹⁹

Six studies focused on PDA classification and severity assessment. Supervised machine learning models including random forest, light gradient boosting machine, multilayer perceptron, and logistic regression accurately

predicted symptomatic and hemodynamically significant PDA earlier than standard clinical recognition.²⁹⁻³² Unsupervised learning identified distinct hemodynamically significant PDA (hsPDA) subphenotypes with inflammatory or respiratory acidosis dominant profiles.³³ Multimodal models combining chest X-ray imaging and clinical data improved severe PDA detection, while explainable AI approaches enhanced interpretability.³⁴ Notably, simpler linear and multilayer perceptron models also demonstrated clinically meaningful performance for early hsPDA risk prediction in extremely preterm infants (Table I).

Table I. AI applications in PDA diagnosis.

First author (Year)	Target population	Diagnostic objective	Primary input modality	AI technique / model	Key diagnostic outcome
PDA diagnosis					
Howard Lei (2021) ²⁰	Preterm neonates	PDA diagnosis	Echocardiogram video clip	Convolutional Neural Network (CNN)	Enhanced PDA detection from neonatal echocardiograms
Sergi Gómez-Quintana (2021) ²⁶	Term and late-preterm neonates	PDA symptoms detection	Heart sounds signal	Extreme Gradient Boosting (XGBoost)	Strong potential for low-cost, scalable PDA screening
Jia Liu (2022) ²⁷	Infants	PDA diagnosis	Heart sound signals	Residual Convolution Recurrent Neural Network (RCRnet)	Outperformed expert auscultation in PDA screening
Hongbo Yang (2023) ²⁸	Infants / children and adolescents	PDA diagnosis	Heart sounds signal	Recurrent Neural Network (RNN)	Improved detection accuracy for PDA and VSD
Jason Erno (2023) ²⁴	Preterm neonates	PDA diagnosis	Echocardiogram video clip	ResNet-50 CNN	Accurate detection of PDA using color Doppler echocardiography
Weimin Tan (2023) ²⁵	Infants / children	PDA diagnosis	Echocardiography images	CHDNet	Expert-level PDA diagnosis on internal datasets
Ana Maria Cristina Jura (2025) ¹⁹	Preterm neonates	PDA diagnosis	Clinical data	Random Forest (RF) and XGBoost	AI-based risk prediction may support early identification of high-risk neonates for PDA
PDA classification					
Jae Yoon Na (2021) ²⁹	Preterm neonates	predict symptomatic PDA	Clinical data	RF, Light Gradient Boosting Machine (L-GBM), Multilayer Perceptron (MLP), Support Vector Machine (SVM), k-Nearest Neighbors (k-NN)	Predicting symptomatic PDA occurrence and whether sPDA would be treated
Felipe Yu Matsushita (2023) ³³	Preterm neonates	hsPDA Subphenotyping	Clinical data	Unsupervised learning	Identify two distinct hsPDA subphenotypes: "Inflamed" vs "Respiratory acidosis"
Phillip Chang (2024) ³⁴	Preterm neonates	Severe PDA diagnosis	Chest X-ray images, clinical data	XGBoost, ConvNeXt-based CNN, Grad-CAM++ SHAP	AI models achieve high specificity to identify explainable radiographic markers of severe PDA

AI: artificial intelligence, CNN: Convolutional Neural Network, hsPDA: hemodynamically significant PDA, PDA: patent ductus arteriosus RF: Random Forest, VSD: ventricular septal defect, XGBoost: Extreme Gradient Boosting.

Table I. Continued.

First author (Year)	Target population	Diagnostic objective	Primary input modality	AI technique / model	Key diagnostic outcome
PDA classification					
Seoyeon Park (2024) ³⁰	Preterm neonates	Severe PDA diagnosis	Clinical data	RF	Detect PDA symptoms earlier than routine clinical recognition Improve diagnostic accuracy of medical professionals
Erik Küng (2025) ³¹	Extremely preterm neonates	hemodynamically significant (hs) PDA prediction	Clinical data	Linear perceptron, Multilayer perceptron, Logistic regression	Early identification of neonates at high risk for hsPDA
Oguzhan Ay (2025) ³²	Preterm neonates	hsPDA prediction	Clinical data	RF	Acurately predicts hPDA risk using non- imaging data

AI: artificial intelligence, CNN: Convolutional Neural Network, hsPDA: hemodynamically significant PDA, PDA: patent ductus arteriosusi RF: Random Forest, VSD: ventricular septal defect, XGBoost:Extreme Gradient Boosting.

Applications of AI in PDA outcome prediction and clinical decision support

Four studies investigated the application of AI to support PDA management, focusing on pharmacologic treatment optimization and outcome prediction. Overall, AI models demonstrated meaningful clinical utility in guiding therapy and anticipating treatment response or complications.

One early study showed that regression-based AI models using clinical and laboratory data could accurately predict continuous serum digoxin concentrations in neonates, supporting individualized dosing in PDA-related pharmacotherapy.³⁵ Subsequent studies shifted toward predicting treatment response in hemodynamically significant PDA. Machine learning models, particularly random forest, integrating clinical, laboratory, and echocardiographic parameters achieved good predictive performance for closure after first line NSAID therapy, enabling early identification of likely responders and non-responders.³⁶

Deep learning approaches further extended this capability. A convolutional neural network (CNN) model combining echocardiographic video sequences with clinical data successfully

predicted pharmacologic PDA closure outcomes in preterm neonates, highlighting the added value of dynamic imaging features for treatment planning.²¹ In older infants and children, ensemble machine learning models applied to clinical data identified patients at risk of post-intervention thrombocytopenia, providing actionable information for peri-intervention monitoring and risk stratification (Table II).³⁷

Main AI algorithms employed in PDA research and model accuracy

A broad spectrum of AI algorithms was employed across studies, reflecting heterogeneity in data modalities and clinical objectives. Tree-based machine-learning methods, including random forest and gradient-boosting models, were most frequently applied to structured clinical and laboratory data. Convolutional neural networks were predominantly used for echocardiographic image or video analysis and consistently demonstrated strong diagnostic performance. Artificial neural networks or multilayer perceptrons were mainly utilized for outcome prediction using tabular datasets, whereas linear models and recurrent or hybrid architectures were less commonly applied,

Table II. AI applications in PDA outcome prediction clinical decision support.

First author (Year)	Target population	Management objective	Primary input modality	AI technique/ model	Key significance
Shu-Hui Yao (2019) ³⁵	Neonates	Prediction of continuous serum digoxin concentration	Clinical data/ laboratory measurements	Regression	AI-assisted dosing support in PDA-related pharmacotherapy
Tai-Xiang Liu (2023) ³⁶	Preterm neonates	Prediction of hsPDA closure after first-line NSAID therapy	Clinical data, laboratory data, echocardiographic measurements	RF	Good predictive ability for NSAID treatment response in hsPDA
Puneet Sharma (2025) ²¹	Preterm neonates	Prediction pharmacologic PDA closure outcomes	Echocardiogram video sequence and clinical data	CNN	Predicting response to PDA pharmacotherapy
Song-Yue Zhang (2025) ³⁷	Infants / children	Outcome prediction/ Treatment planning	Clinical data	RF, XG, Adaptive Boosting (ADA), Logistic Regression	Identified children at risk of post- intervention thrombocytopenia

AI: artificial intelligence, CNN: Convolutional Neural Network, hsPDA: hemodynamically significant PDA, NSAID: non-steroid anti-inflammatory drugs, PDA: patent ductus arteriosus, RF: Random Forest, XG: Extreme Gradient.

particularly for sequential data, and generally achieved moderate performance. One study adopted unsupervised clustering to identify PDA subphenotypes; although standard accuracy metrics were not applicable, clinically meaningful subgroup differentiation was reported.

Across studies, model performance showed consistent trends related to input data modality and task complexity. Imaging-based models trained on echocardiographic images or video sequences, largely using convolutional neural networks, tended to achieve higher discriminative performance than models relying solely on clinical or laboratory variables, frequently reporting area-under-the-curve values above 0.80 for PDA detection and classification of hemodynamically significant PDA. In contrast, models based on tabular clinical and laboratory data, most often implemented using tree-based algorithms, demonstrated moderate to high performance, with area under the curve (AUC) values typically ranging from approximately 0.75 to 0.85. Although performance was generally

lower than that of imaging-based approaches, these models offered greater feasibility and scalability, particularly in resource-limited settings. Variability in reported accuracy across studies was partly attributable to differences in outcome definitions, feature selection, and validation strategies, underscoring that model performance was influenced more by data quality and modality than by algorithmic complexity alone.

Detailed characteristics of the included studies are provided in Supplementary Table S1.

Quality of included studies

Overall, the methodological quality of the included studies was moderate, with substantial variation across reporting and validation domains. A clear description of the AI methodology was provided in 94.4% of studies, and model interpretability or explanatory elements were reported in a similarly high proportion (94.4%). Most studies also reported appropriate data splitting strategies for model development and evaluation (88.9%) and

included standard performance measures such as accuracy or area under the curve (88.9%).

In contrast, transparency and reproducibility were more limited. Only 11.1% of studies made data or code publicly available, restricting independent validation. Reporting of hyperparameter tuning procedures was inconsistent and documented in just 33.3% of studies, raising concerns regarding optimization transparency. Notably, none of the included studies adhered to a recognized best-practice reporting framework for AI research.

The quality assessment of the included studies is presented in Supplementary Table S2.

Discussion

Improved diagnosis and early detection

Artificial intelligence is based on data-driven computational models that learn complex patterns directly from data rather than relying on predefined rules.³⁸ Unlike traditional statistical methods, AI algorithms can process high-dimensional, nonlinear, and multimodal inputs simultaneously, making them particularly well suited to neonatal physiology, where clinical signals are dynamic, interdependent, and often subtle.^{39,40} This capacity for representation learning allows AI-based systems to identify latent physiological signatures that are not readily apparent through standard threshold-based clinical assessment.^{41,42}

In the context of PDA, AI contributes by integrating heterogeneous data sources including demographic variables, continuous vital signs, ventilatory parameters, imaging data, and biosignals into unified predictive frameworks. Machine learning models capture complex interactions among these variables, enabling earlier recognition of hemodynamically significant ductal patency before overt clinical instability occurs. Deep learning architectures further enhance this capability by automatically extracting hierarchical features from echocardiographic images, Doppler

waveforms, and heart sounds, thereby reducing reliance on operator-defined measurements and subjective interpretation.^{24,26,27} Moreover, deep learning (DL)-based analysis of neonatal echocardiograms enables near real time detection and can be deployed on low-resource devices, supporting clinical application in settings with limited access to specialist expertise.²⁰

Comparative evaluations indicate that AI-based systems are most effective when used as clinical decision-support tools rather than substitutes for clinician judgment. Studies by Ay et al. and Küng et al. showed that AI-based interpretation achieves diagnostic performance comparable to expert assessment, facilitating early identification of neonates at high risk for hemodynamically significant PDA.^{31,32} This early risk stratification can inform surveillance intensity, enable individualized treatment decisions, reduce overtreatment, and optimize resource utilization. Such consistency and accessibility are particularly valuable in neonatal intensive care units with limited access to experienced neonatologists or pediatric cardiologists.

Personalization of treatment decisions

Artificial intelligence facilitates personalized management of PDA by addressing the challenge of identifying ductus arteriosus that require treatment and selecting optimal therapeutic strategies. Sharma et al. demonstrated high discriminative performance in predicting response to pharmacologic closure, with the potential to reduce delays in definitive treatment, enable earlier referral for procedural intervention, and support individualized care in neonatal intensive care units.²¹ Accurate prediction of treatment response is clinically valuable, as early identification of likely non-responders may prevent ineffective drug exposure and related adverse effects, while recognition of likely responders can reduce unnecessary escalation to invasive intervention.³⁶

In addition, Yao et al. reported that artificial neural network models outperformed traditional regression methods in predicting digoxin levels in neonates with patent ductus arteriosus, highlighting the feasibility of AI-assisted dosing support, particularly in settings where blood sampling is limited.³⁵ These predictive tools may also reduce variability in clinical practice by providing individualized, evidence-based risk estimates that complement clinician judgment and inform the timing and intensity of intervention.^{19,30} However, these models function as clinical decision-support systems rather than autonomous decision-makers and must be interpreted within the broader clinical context, including hemodynamic status, comorbidities, and family preferences⁴³⁻⁴⁵

Enhancement of technical interventions

In contrast to the growing body of work on diagnostic and prognostic applications, AI-related innovations targeting technical and interventional aspects of PDA management remain at an early developmental stage. In this context, Zhang et al. demonstrated that an RF model could successfully identify children at increased risk of post-intervention thrombocytopenia following PDA closure.³⁷ This approach highlights the potential role of AI in supporting procedural risk stratification, enhancing clinical trust, and facilitating anticipatory management and early intervention planning in interventional settings.

Building on recent progress in AI algorithms and interventional support systems, advanced image processing and three-dimensional reconstruction approaches are being developed to improve procedural guidance. These methods allow detailed depiction of cardiac anatomy, supporting thorough pre-procedural evaluation and informed selection of closure devices and interventional strategies.^{46,47} Computational modeling and simulation further enable patient-specific assessment of flow dynamics and device-tissue interactions, encouraging

multidisciplinary collaboration and shared decision-making while reducing dependence on individual operator experience.⁴⁸⁻⁵⁰ Over time, incorporation of these technologies may expand access to transcatheter PDA closure by shortening the learning curve in centers with limited expertise.

The clinical role of artificial intelligence in PDA management

Although artificial intelligence has demonstrated strong performance in the detection of PDA and in outcome prediction, its clinical utility must be interpreted within the evolving framework of PDA management. In current neonatal practice, there is a growing preference for conservative management, particularly in preterm infants, driven by the high likelihood of spontaneous ductal closure and the absence of consistent long-term benefits from pharmacological or interventional therapies.⁵¹⁻⁵³ Furthermore, the presence of PDA alone, including cases classified as hemodynamically significant, does not inherently justify treatment. Clinical decision-making is multifactorial and requires careful consideration of hemodynamic impact, associated comorbidities, timing of intervention, and interindividual variability in treatment response.⁸

A fundamental implication of this paradigm shift is that diagnostic accuracy alone does not directly translate into improved clinical outcomes. The central challenge in PDA management is not simply identifying the presence of a ductus, but determining which patients require intervention, when treatment should be initiated, and which patients are most likely to respond to therapy. In this context, traditional definitions of hemodynamically significant PDA based primarily on echocardiographic parameters are increasingly recognized as insufficient when used in isolation. Hemodynamic significance is dynamic and cannot be fully captured by anatomical and flow-based measurements alone.^{54,55}

Within this framework, the clinical value of artificial intelligence lies not primarily in improving PDA detection, but in its ability to integrate multidimensional data and support individualized decision-making. AI-based systems should therefore be viewed as adjunctive tools that enhance risk stratification and clinical judgment rather than autonomous decision-makers.

Alignment between current AI research and clinical needs

Against this background, the current landscape of artificial intelligence research in PDA reveals a notable mismatch between technological development and clinical priorities. As demonstrated in this review, most studies have focused on diagnostic classification or identification of hemodynamically significant PDA. While these models often achieve high performance, their direct clinical impact remains limited if they do not address treatment decision-making.

In line with this observation, only a minority of studies have explored clinically relevant applications such as prediction of pharmacologic response^{21,36}, risk stratification for adverse outcomes³⁵, or individualized treatment planning³⁷. These areas are more closely aligned with real-world clinical uncertainty, where the primary question is not whether PDA exists, but whether intervention will improve patient outcomes. This gap between current research focus and clinical needs highlights the importance of shifting future AI development toward clinically meaningful endpoints. Models that incorporate longitudinal physiological data, treatment exposure, and patient-specific characteristics may provide more actionable insights and better support bedside decision-making in neonatal intensive care settings.

Beyond methodological focus, the overwhelming majority of studies focused on preterm neonates, reflecting the population in which PDA carries the greatest clinical burden. However, this narrow focus limits insights into

the potential role of AI in older pediatric and adult populations, where disease characteristics and management strategies differ. Similarly, although the included studies spanned multiple countries, representation from low- and middle-income regions was limited. This lack of geographic diversity is clinically relevant, as AI-based diagnostic tools may offer substantial benefits in resource-constrained settings where access to echocardiography and specialist expertise is limited. Non-imaging approaches, such as heart sound analysis²⁸ or clinical data-driven models^{29,30}, are particularly promising in such environments, and prospective evaluation across diverse healthcare systems is therefore warranted.

In addition to these gaps, the current evidence base is constrained by study design limitations. Most studies were retrospective and focused on model development with internal validation, with few addressing real-time clinical implementation. As a result, the impact of AI-guided strategies on clinically meaningful outcomes remains uncertain. Randomized or pragmatic studies comparing AI-assisted management with standard care are needed to determine whether these tools can improve outcomes such as survival, bronchopulmonary dysplasia, or duration of respiratory support.

Furthermore, PDA physiology is inherently dynamic⁵⁶, yet most existing models rely on static snapshots of clinical, laboratory, or imaging data. In practice, the hemodynamic significance of PDA evolves over time in response to changing physiological conditions and therapeutic interventions. Future AI systems should therefore incorporate longitudinal data and time series modeling to provide continuously updated risk assessments and better capture disease trajectories.

Taken together, these limitations and gaps emphasize the need to reorient artificial intelligence research toward clinically meaningful applications. Future studies should prioritize decision support tools that integrate multidimensional and dynamic data to guide

treatment selection, predict therapeutic response, and align with the current shift toward individualized and conservative management strategies.

Ethical and practical considerations

The integration of artificial intelligence into PDA management raises important ethical and practical considerations. Algorithmic bias may arise if training datasets are not representative of diverse populations or healthcare settings, potentially limiting model performance in underrepresented groups. Clear guidance will be required to define clinician responsibility when AI recommendations are incorporated into care decisions.⁵⁷ Although AI tools function as supportive aids rather than decision-makers, accountability ultimately remains with the clinician.

Regulatory oversight will play a crucial role in ensuring the safety and efficacy of AI-based clinical tools. For high-stakes applications such as PDA diagnosis and treatment planning, rigorous validation and adherence to emerging regulatory frameworks will be necessary before routine clinical implementation.

Future directions

Future applications of artificial intelligence in PDA care are expected to move beyond isolated diagnostic tasks toward integrated, clinically meaningful decision support systems. In particular, multimodal AI platforms that combine physiologic monitoring, echocardiographic analysis, and treatment response prediction may enable a more comprehensive and individualized assessment of PDA at the bedside. Such systems have the potential to support earlier, more consistent, and context-aware clinical decision-making in neonatal intensive care settings.⁵⁸

Real-time data integration represents another important direction. AI algorithms capable of continuously analyzing longitudinal physiological signals, including vital signs

and respiratory parameters, may detect early hemodynamic changes associated with evolving PDA significance. This dynamic approach aligns more closely with the fluctuating nature of neonatal physiology and may allow earlier identification of clinically relevant deterioration, thereby facilitating timely intervention.^{59,60}

Beyond short-term management, AI may also contribute to predicting longer-term outcomes associated with PDA and its treatment, including chronic lung disease and neurodevelopmental impairment. Such predictive models could help refine treatment thresholds by balancing immediate therapeutic benefits against potential long term risks, thereby supporting more individualized and evidence-informed care strategies.⁶¹ In addition, AI-assisted procedural planning and intraprocedural guidance are emerging areas of interest, particularly in transcatheter PDA closure, where anatomical variability and procedural complexity remain significant challenges.⁶²

Importantly, the future application of AI-assisted evaluation of patient data must also be considered in the context of data quality and clinical expertise.⁶³ The performance, reliability, and generalizability of AI models are fundamentally dependent on the quality, completeness, and representativeness of the underlying data used for training and validation. Inaccurate, biased, or heterogeneous datasets may lead to unreliable predictions and limit clinical applicability, particularly across different healthcare settings.⁶⁴

In this context, specialist expertise remains essential for the appropriate interpretation of AI-generated outputs. AI systems are designed to support, rather than replace, clinical decision-making, and their outputs must be integrated with expert clinical judgment, particularly in complex conditions such as PDA where management decisions are highly individualized.^{65,66} The effective implementation of AI in clinical practice therefore requires not only robust data infrastructure but also close collaboration between data scientists and

experienced clinicians to ensure safe, accurate, and clinically meaningful application.

Perspective for low- and middle-income countries

The potential clinical value of artificial intelligence in the management of patent ductus arteriosus is likely to be particularly significant in low- and middle-income countries, where access to advanced imaging technologies, continuous physiological monitoring, and specialized pediatric cardiology expertise remains limited.^{67,68} In these settings, delayed diagnosis and substantial variability in clinical decision-making frequently contribute to poorer outcomes. Artificial intelligence-based approaches, especially those utilizing non-imaging data such as clinical variables, heart sound analysis²⁸, or simplified echocardiographic inputs^{24,25}, represent scalable and cost-effective solutions to address these challenges. Machine learning models capable of integrating heterogeneous data sources may facilitate earlier identification of hemodynamically significant PDA and enable more consistent risk stratification, even in resource-constrained environments.^{33,34} Furthermore, deep learning-driven automation of image interpretation has the potential to reduce dependence on highly trained specialists, thereby enhancing diagnostic consistency across healthcare facilities.^{21,24} These characteristics are particularly well aligned with healthcare delivery models in low-resource settings, where tertiary centers are frequently overcrowded and the distribution of expertise is uneven. In this regard, AI has the potential to decentralize care, support task shifting, and optimize the use of limited clinical resources.⁶⁹ Therefore, beyond its diagnostic and predictive capabilities, AI represents a feasible and transformative strategy to strengthen healthcare systems, improve equity in access to care, and ultimately enhance clinical outcomes in these regions.

Study limitations

This scoping review has several limitations that should be considered when interpreting the findings. As discussed above, the current body of evidence is limited by heterogeneity in study design, patient populations, and methodological approaches, reflecting the early stage of artificial intelligence research in patent ductus arteriosus.

In addition, most included studies were retrospective and primarily focused on model development with internal validation, with relatively few addressing external validation or prospective clinical implementation. This limits the ability to assess the real-world applicability and generalizability of the reported models.

Furthermore, issues related to transparency and reproducibility remain, as only a minority of studies provided access to underlying data or code, and reporting of model development and optimization was often incomplete. These limitations may hinder independent validation and broader clinical adoption.

Finally, as a scoping review, no formal risk-of-bias assessment or quantitative meta-analysis was performed. The findings should therefore be interpreted as a qualitative synthesis of the current literature. Overall, while artificial intelligence shows promise, its impact on clinically meaningful outcomes has not yet been established and requires further validation through well-designed prospective and outcome-oriented studies.

Conclusion

In conclusion, AI has the capacity to transform how we approach PDA – turning what has historically been a contentious and variable practice into a more data-driven, consistent, and optimized process. By leveraging AI for earlier detection, smarter decision-making, and meticulous intervention planning, we can improve the care of infants and patients with PDA, reducing morbidity and tailoring treatments to individual needs. As technology

and medicine continue to intersect, the management of PDA can serve as a model for integrating artificial intelligence into the care of complex medical conditions, ultimately enhancing outcomes and saving lives.

Supplementary materials

Supplementary materials for this article are available online at <https://doi.org/10.24953/turkjpediatr.2026.8122>

Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: VDQ; literature review: CTH, TTHY; draft manuscript preparation: PMN, DPL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Generative AI statement

During the preparation of this manuscript, ChatGPT (OpenAI, 2026) was used solely for language editing and proofreading to improve the grammar, clarity, and readability of the manuscript. The tool was not used for literature searching, data analysis, content generation, interpretation of results, or scientific writing. All content was reviewed and edited by the authors, who take full responsibility for the accuracy, integrity, and final content of the publication.

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Remember what you forgot: mega dose methylprednisolone in the treatment of immune thrombocytopenia - a systematic review and meta-analysis

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ABSTRACT

Immune thrombocytopenia (ITP) is an acquired bleeding disorder in children, and the severity of the bleeding primarily guides treatment decisions. In Türkiye, the intensive seven-day mega-dose methylprednisolone (MDMP) protocol—administered as 30 mg/kg for 3 days, then 20 mg/kg for 4 days—has been used effectively for a long time. This systematic review and meta-analysis aimed to examine the efficacy of this MDMP protocol and compare it with intravenous immunoglobulin (IVIG). Researchers searched MEDLINE, Web of Science, Cochrane, and TR Dizin databases (1970–2022) and identified 11 records from Türkiye, including 6 randomized trials involving 717 patients, following PRISMA guidelines. The primary endpoint was the response rate, defined as a platelet count greater than $20 \times 10^9/L$. The overall response rate to MDMP across these studies was 96.1%, with 81.9% achieving a complete response. In the seven studies comparing treatments, MDMP showed a response rate of 93.6% versus 93.2% for IVIG. The meta-analysis of the six randomized studies revealed no significant difference in efficacy between the two treatments (risk ratio: 0.98; $Z = -0.45$; $p = 0.65$). While side effects were more frequent with MDMP (0.83 per patient) than with IVIG (0.41 per patient), these effects were predominantly transient (mainly weight gain in 45.3% of patients); conversely, IVIG led to acute reactions and two hospitalizations for aseptic meningitis, and no cases of thrombosis were observed with either treatment. The conclusion highlights that MDMP represents a reliable, intensive, non-biological first-line treatment for pediatric ITP, offering a practical alternative to IVIG, particularly where cost and ease of administration (oral route) are important considerations. MDMP's efficacy in achieving a rapid platelet increase is deemed similar to that of IVIG. High-quality studies are needed to confirm MDMP's long-term safety profile and definitively establish its role in managing high-grade bleeding.

Key words: immune thrombocytopenia (ITP), intravenous immunoglobulin (IVIG), mega dose methylprednisolone (MDMP), pediatric ITP.

Immune thrombocytopenia (ITP) is an acquired bleeding disorder with an incidence of 1-6.4 per 100,000/year in childhood.¹ The majority of patients recover within six months with or without treatment, and nearly 10-20% develop chronic ITP.^{2,3} In ITP, platelet count does not fully correlate with bleeding risk and is influenced by other factors.^{4,5} The goal of ITP

therapy is to achieve a platelet count adequate to stop bleeding, rather than a normal count, and to reduce the risk of severe bleeding, especially intracranial hemorrhage (ICH).⁶

The current consensus on treatment for patients with newly diagnosed ITP depends on the risk of significant hemorrhage, which is estimated

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through “bleeding scores” in addition to the patient’s quality of life, accompanying factors like comorbidities, medications, and the burden to the family.^{4,5} The bleeding score of Provan et al.⁵ and “Modified Buchanan and Adix Bleeding Score”⁷ are the most popular scores that grade the bleeding manifestations.

Medical therapy is suggested for patients who have developed grade 3b, 4, 5 (moderate-high risk; severe; life-threatening-fatal) bleeding according to the latter score.⁷ Those with grade 0, 1, 2, 3a (no, minor, mild, moderate-low risk) bleeding are suggested medical therapy if they have risk factors like planned surgery or procedure likely to induce blood loss, or platelet count below $30 \times 10^9/L$ and one or more of the following: use of antiplatelet or anticoagulant medications / concomitant bleeding disorder/ very active lifestyle with frequent trauma, head trauma without any symptom or severe/unexplained headache.^{3,5} Otherwise, “watchful waiting,” consisting of regular clinical assessments and platelet count measurements, is suggested.³

In patients without severe bleeding who require a rapid increase in platelet counts due to urgent surgery, head trauma, or severe, unexplained headache, treatment with intravenous immunoglobulin (IVIG), anti-D, or oral glucocorticoids is recommended.^{3,5} In severe bleeding, depending on the bleeding grade, IVIG or anti-D is suggested to be administered alone or in combination with other therapies such as intravenous (IV) methylprednisolone [30 mg/kg/day (max 1 gram) for 2-3 days] and platelet transfusion.³

On the other hand, studies from Türkiye have shown that a different dose schedule and duration of methylprednisolone (30 mg/kg/day for 3 days and 20 mg/kg/day for the subsequent 4 days), named mega-dose methylprednisolone (MDMP), is as efficacious and quick-acting as IVIG when administered alone.⁸⁻¹⁰ However, the included case numbers in these studies are limited. To address the limitations of small-scale studies and thoroughly determine the

role of this specific regimen, we conducted a systematic review and meta-analysis. Our main goal was to compile and analyze the overall efficacy and safety outcomes of all available MDMP studies in treating ITP. Additionally, we aimed to specifically compare the effectiveness of MDMP with that of IVIG, the commonly used first-line therapy, across shared study populations.

Materials and methods

Data sources

We systematically reviewed the literature for pediatric ITP cases treated with MDMP. We searched electronic databases, including MEDLINE (Medical Literature Analysis and Retrieval System Online), Web of Science (WOS), the Cochrane Library, and the Turkish academic index TR Dizin. The search covered articles published from January 1, 1970, to December 31, 2022. The following search terms were used: “mega dose methylprednisolone” OR “corticosteroid” OR “high dose steroid” OR “prednisone” OR “first-line therapy” AND “idiopathic thrombocytopenic purpura” OR “immune thrombocytopenic purpura” OR “ITP” OR “thrombocytopenia”.

Study selection

The study selection process strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ We included randomized trials or cohort studies involving only pediatric patients (<18 years) with either acute or chronic ITP. Studies were included if their primary or secondary aim was to evaluate the MDMP response and if they reported a clear platelet increment ratio or MDMP response ratio. Studies comparing MDMP responses to IVIG were also included. We excluded articles written in any language other than English or Turkish, articles that did not report a clear response rate, case reports, review articles, letters to the editor, and studies detailing high-dose methylprednisolone

protocols that did not comply with the specific MDMP protocol. The MDMP protocol was oral or IV methylprednisolone (MP) at 30 mg/kg for 3 days, followed by 20 mg/kg for the subsequent 4 days, with or without a maximum dose (1 g/day). Administration of 30 mg/kg/day MP for 7 days was also considered consistent with the MDMP protocol. Studies on IVIG therapy used standard doses of 0.8 to 2.0 g/kg, either in a single dose or over 5 days. Higher doses (>2.0 g/kg) and non-standard schedules were excluded to avoid heterogeneity. Disease duration under 12 months was considered "acute", and over 12 months was classified as "chronic ITP".⁶ Treatment response was primarily assessed by the platelet count achieved 2-14 days post-initiation of therapy, where a partial response (PR) was defined as a platelet count $> 20 \times 10^9/L$ and $\leq 100 \times 10^9/L$, and a complete response (CR) as a count $> 100 \times 10^9/L$.

Data extraction

Two authors (DK, LO) independently screened the identified articles, first by title and abstract, and subsequently by evaluating the full texts of eligible studies. Any disagreements between the authors were resolved by discussion. The extracted data were organized into a structured form. Study characteristics, patient demographics, duration of ITP (acute vs chronic), pre-treatment platelet counts, specific MDMP and IVIG doses used, response definitions, reported response rates to both MDMP and IVIG, development of chronicity in acute ITP, and adverse effects were noted. The primary endpoint was the overall response rate (CR + PR) to MDMP therapy, while secondary endpoints included comparisons of MDMP effectiveness and safety with IVIG, assessment of the adverse effect profile, and evaluation of the rate of chronicity.

Statistics

For the descriptive analysis of qualitative variables, data were reported as counts and percentages. The quantitative synthesis (meta-

analysis) was performed using the Meta-Essentials software (version 1.5). For the comparison of platelet count increment rates between the MDMP and IVIG groups, the risk ratio (RR) was calculated as the measure of effect. While response criteria varied across studies (ranging from $>20 \times 10^9/L$ to $>150 \times 10^9/L$), we performed the meta-analysis using the lowest threshold reported in each study. Heterogeneity among the included studies was assessed using the I^2 statistic and the corresponding p-value. Given the absence of significant heterogeneity ($I^2 = 0.0\%$), a fixed-effects model was employed to combine the study results. Publication bias was assessed visually using a funnel plot and statistically via Kendall's rank correlation test (τ statistic).

Results

Study and patient characteristics

A total of 10,477 records were identified through database searches after duplicates were removed; 10,419 were excluded based on title and/or abstract, leaving 58 records for screening. After abstract and full-text screening, we identified 11 records relevant to this study's objective, which were then subjected to standardized data extraction and analysis (Fig. 1).

All the studies were from Türkiye and were published between 1993 and 2018. Seven of the 11 records¹²⁻¹⁸ (63.6%) compared MDMP to IVIG; five were randomized, prospective studies^{12,13,16-18} conducted with acute ITP patients, and two were retrospective observational studies, one of which included acute and the other included both acute and chronic ITP patients. Four of the 11 records (36.4%) discussed the effect of MDMP, all of which were prospective cohort studies.¹⁹⁻²² Two studies^{19,20} assessed the impact of MDMP on acute ITP patients as a secondary endpoint, whereas one²¹ examined its effects in refractory ITP patients, and the last study²² evaluated divided doses of MDMP in acute ITP patients.

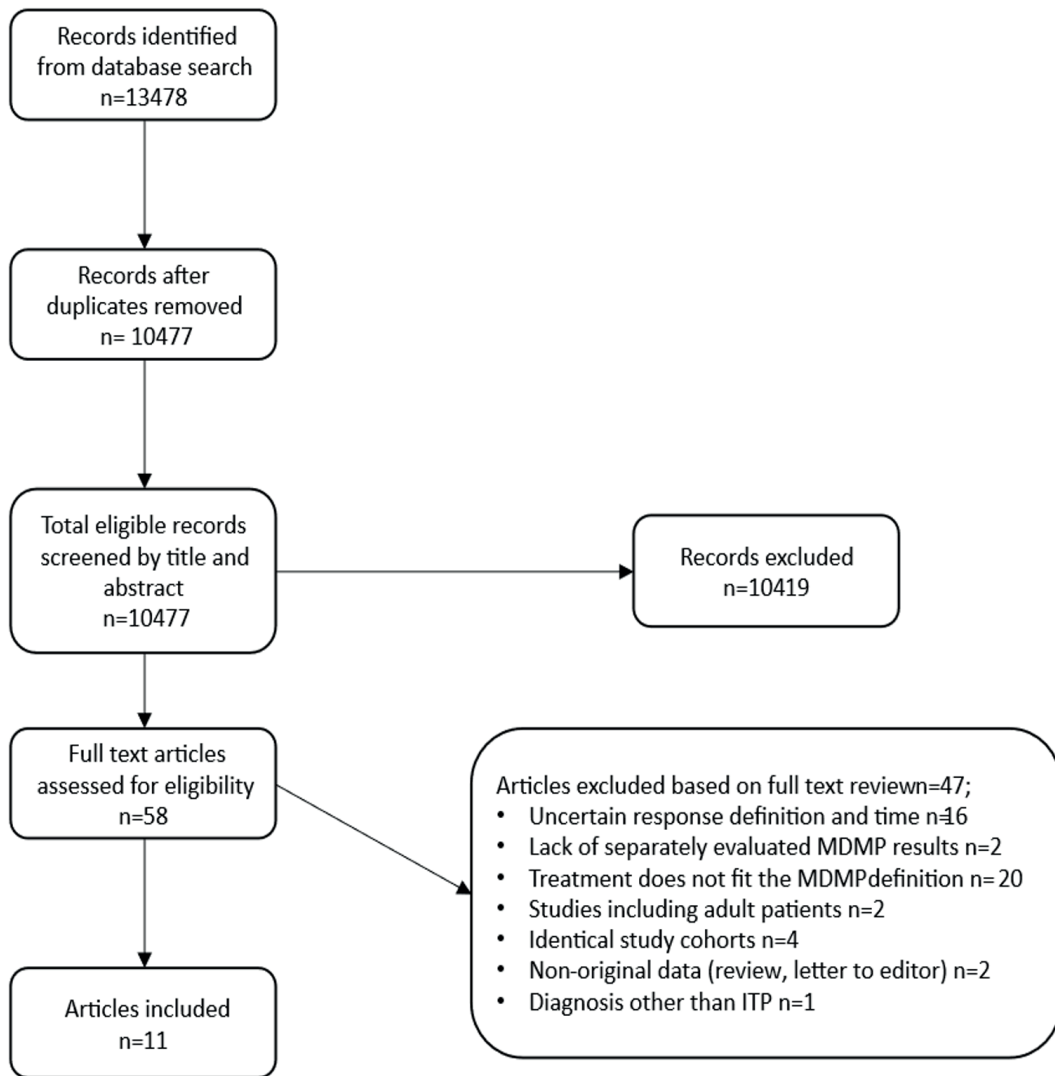


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) study flow selection.

A total of 717 patients, of whom 362 received MDMP, 219 received IVIG, and 136 received other various therapies or remained without therapy, were enrolled. The patients' ages ranged from 0 to 17 years, and the male-to-female ratio was 0.92. The highest initial platelet count was below $50 \times 10^9/L$ and was accompanied by bleeding.

A meta-analysis of platelet increments in six studies comparing MDMP to IVIG was performed (Table I).

Severity of bleeding and treatment decision

At initial presentation, bleeding presence or severity was not reported in six of the 11 studies.^{13,16-20} Only mild bleeding was reported in four of the 11 studies.^{12,14,21,22} Koçak et al.¹⁵ reported major bleeding in 9.8% of the study population in addition to minor bleeding. They also reported that one patient (1/143) experienced ICH during follow-up. Albayrak et al.¹⁸ also reported that one patient (1/57), who was refractory to treatment, developed ICH.

Table I. Characteristics and outcomes of studies included in the systematic review and meta-analysis.

References, Year	Study Design	ITP classif.	MDMP (n)	IVIG (n)	Other treatment/s or control (n)	Gender (M/F)	Age	Platelet count ($\times 10^9/L$)	MDMP response (%) Definition	IVIG response (%) Definition	Chronicity MDMP (%) Definition	Chronicity IVIG (%) Definition	MDMP side effects (n)	IVIG side effects (n)
Studies included in the meta-analysis														
Duru et al. ¹² 2002	RP	Acute	12	12	26	26/24	0-15 (range)	2-16 (range)	9 (75%) >50 $\times 10^9/L$ >150 $\times 10^9/L$	10 (83%) >50 $\times 10^9/L$ >150 $\times 10^9/L$	3 (25%) Over 12 months	2 (17%) Over 12 months	Weight gain, 12 Gastric discomfort, 7 Hyperglycemia, 1 Hypertension, 1	Headache, 4 Vomiting, 2 Fever, 1 Chills, 1
Erduran et al. ¹³ 2003	RP	Acute	20	22	-	18/24	1-13 (range)	1-20 (range)	19 (95%) >50 $\times 10^9/L$ 18 (90%) >100 $\times 10^9/L$	21 (95%) >50 $\times 10^9/L$ 19 (86%) >100 $\times 10^9/L$	5 (25%) Over 6 months	4 (18%) Over 6 months	Gastric discomfort, 2 Hyperglycemia, 2 Behavior change, 3	Fever, 5 Headache, 5 Vomiting, 5 Chills, 1
Güngör et al. ¹⁴ 2019	RO	Acute and Chronic	66	116	29	104/107	5.4 $\pm$ 4.1 (mean)	<20	61 (92%) >20 $\times 10^9/L$ 44 (67%) >100 $\times 10^9/L$	112 (97%) >20 $\times 10^9/L$ 70 (60%) >100 $\times 10^9/L$	Unspecified	Unspecified	Unspecified	Unspecified
Koçak et al. ¹⁵ 2007	RO	Acute	82	29	32	74/69	6.4 $\pm$ 3.8 (mean)	<20 or <50 with bleeding	80 (97%) >20 $\times 10^9/L$ 59 (72%) >150 $\times 10^9/L$	26 (89%) >20 $\times 10^9/L$ 15 (52%) >150 $\times 10^9/L$	14 (17%) Over 6 months	5 (17%) Over 6 months	Weight gain, 82 Hypertension, 3 Hyperglycemia, 2	Allergic reaction, 2 Aseptic meningitis, 1
Özsoylu et al. ¹⁶ 1993	RP	Acute	10	10	-	11/9	0-11 (range)	<50	8 (80%) >150 $\times 10^9/L$	9 (90%) >150 $\times 10^9/L$	Unspecified	Unspecified	No side effects	Fever, 3 Chills, 3
Balkan et al. ¹⁷ 2009	RP	Acute	10	11	-	8/13	2-16 (range)	<30	10 (100%) >150 $\times 10^9/L$	11 (100%) >150 $\times 10^9/L$	Unspecified	Unspecified	Unspecified	Unspecified

F, female; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; M, male; MDMP, mega dose methylprednisolone; RP, randomized prospective, RO, retrospective observational; PC, Prospective cohort.

Table I. Continued.

References, Year	Study Design	ITP classif.	MDMP (n)	IVIG (n)	Other treatment/s or control (n)	Gender (M/F)	Age (range)	Platelet count ($\times 10^9/L$)	MDMP response (%) Definition	IVIG response (%) Definition	Chronicity MDMP (%) Definition	Chronicity IVIG (%) Definition	MDMP side effects (n)	IVIG side effects (n)
Other studies														
Albayrak et al. ¹⁶ 1994	RP	Acute	19	19	19	31/26	0-17 (range)	<25	18 (95%) >50 $\times 10^9/L$	15 (79%) >100 $\times 10^9/L$	None Over 12 months	1 (5%) Over 12 months	Hypertension, 1 Gastric discomfort, 2	Aseptic meningitis 1 Headache, 2 Vomiting, 2
Akin et al. ¹⁹ 2011	PC	Acute	31	-	-	14 /17	2-16 (range)	<20	31 (100%) >50 $\times 10^9/L$	-	14 (45%) Over 12 months	-	Unspecified	-
Cura et al. ²⁰ 2016	PC	Acute	30	-	30	22/38	1-10 (range)	5-14 (range)	30 (97%) >100 $\times 10^9/L$	-	Unspecified	-	Unspecified	-
Özer et al. ²¹ 2000	PC	Chronic	22	-	-	8/14	2-13	<20	22 (100%) >150 $\times 10^9/L$	-	22 (100%) Over 6 months	-	Weight gain, 8 Behavior change, 2	-
Turhan et al. ²² 2018	PC	Acute	60	-	-	28/32	3-11.3 (range)	<20	60 (100%) >100 $\times 10^9/L$	-	Unspecified	-	Hyperglycemia, 7	-

F, female; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; M, male; MDMP, mega dose methylprednisolone; RP, randomized prospective; RO, retrospective observational; PC, Prospective cohort.

None of the studies considered therapy and treatment choice based on bleeding severity.

Response to MDMP

The overall response to MDMP was evaluated in 11 studies and 362 patients. The response was observed in 348 patients (96.1%) without distinction between PR and CR. In 10 of the 11 studies^{12-19,21,22}, CR rates could be extracted and totaled 81.9% (272/332). In studies limiting MDMP to 1 g^{12,17,19,21}, the overall response rate was 96% (72/75). In the other studies without a maximum MDMP dose^{13-16,18,20,22}, the response rate was 96.2% (276/287).

Side effects of MDMP

Side effects of MDMP were reported in seven studies, five of which compared MDMP to IVIG (Table I). Thus, 135 side effects were observed in 225 patients, for a rate of 0.6 per patient. The side effects were weight gain in 102 patients (45.3%), hyperglycemia in 12 (5.3%), gastric discomfort in 11 (4.9%), hypertension in 5 (2.2%), and behavioral changes in 5 (2.2%). All of the side effects were reported as transient.

Chronicity after MDMP

Defining chronicity as a duration exceeding 12 months, three studies^{12,18,19} reported chronicity rates, yielding a pooled incidence of 30.9% (17 patients out of 55). The highest rate (45%) was observed in the study by Akin et al.¹⁹, which restricted the daily MDMP dose to 1 g.

Comparison of MDMP with IVIG

In the seven studies¹²⁻¹⁸ comparing MDMP with IVIG, the overall response rates were 93.6% (205/219) for MDMP and 93.2% (204/219) for IVIG. The complete response rates were 73.1% (160/219) for MDMP and 67.1% (147/219) for IVIG. The side effects were reported in five studies^{12,13,15,16,18}, 118 side effects in 143 patients with MDMP, 0.83 per patient. Thirty-eight side effects in 92 patients with IVIG, for a rate of 0.41 per patient. MDMP side effects were weight gain in 94 patients (65.7%), gastric discomfort in 11 (7.7%), hyperglycemia in 5 (3.5%), hypertension in 5 (3.5%), and behavioral changes in 3 (2.1%). The side effects related to IVIG were headaches in 11 patients (12%), fever in 9 (9.8%), vomiting in 9 (9.8%), chills in 5 (5.4%), aseptic meningitis in 2 (2.2%) requiring hospitalization, and allergic reactions in 2 (2.2%).

Meta-analysis of platelet increment with MDMP and IVIG

A meta-analysis of platelet increment rates in six randomized studies¹²⁻¹⁷ comparing MDMP to IVIG was performed, and the RR was calculated from the platelet count increment rates (Fig. 2). In one of the six studies, MDMP treatment was more successful than IVIG; in two studies, the success rate was the same (RR = 1); and in three studies, IVIG was more successful than MDMP. Given the observed homogeneity across studies ($I^2=0.0\%$; $p=0.475$), a fixed-effects model was employed to combine the study results

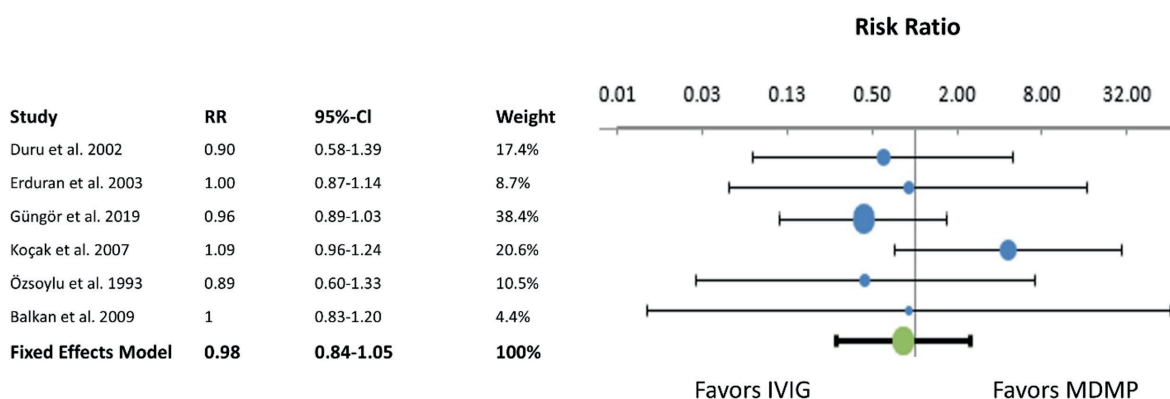


Fig. 2. Forest plot of treatment response, mega dose methylprednisolone versus intravenous immunoglobulin.

statistically. As a result, the pooled RR was 0.98 (95% CI: 0.84–1.05). Therefore, based on the rates of increase in platelet count, there was no statistically significant difference between MDMP and IVIG (RR = 0.98; $Z = -0.45$; $p = 0.65$). Furthermore, visual inspection of the funnel plot demonstrated a symmetrical distribution of effect sizes, suggesting no significant publication bias (Fig. 3). This was statistically confirmed using Kendall's rank correlation test, which yielded a Kendall's τ of 0.20 ($p = 0.573$).

Discussion

Our systematic review and meta-analysis demonstrate that MDMP, when used as a monotherapy, is as effective as IVIG in achieving rapid platelet count increment in pediatric ITP. This finding is important given the current emphasis by hematology societies on restricting and optimizing IVIG use for ITP

due to supply and cost concerns.²³ The MDMP therapy evaluated in this study differed from IV MP suggested in the current guidelines for severe hemorrhage in that the former was not a part of combination therapy, and the treatment lasted for seven instead of three days.^{1,3,5}

The overall reported side-effect rates were acceptable in both the MDMP and IVIG groups in our study (0.83 vs 0.41 per patient); however, the profiles were different. MDMP therapy may lead to endocrinologic, metabolic, and ophthalmologic complications, especially with long-term use. Steroids administered early in the morning for less than two weeks did not suppress the adrenal hypothalamic- pituitary axis.²⁴ Therefore, MDMP should be given at 6:00 a.m. to minimize side effects. However, a significant complication is that MDMP can cause osteonecrosis in acute ITP, particularly at high cumulative doses.²⁵ Children with chronic ITP have been shown to have higher

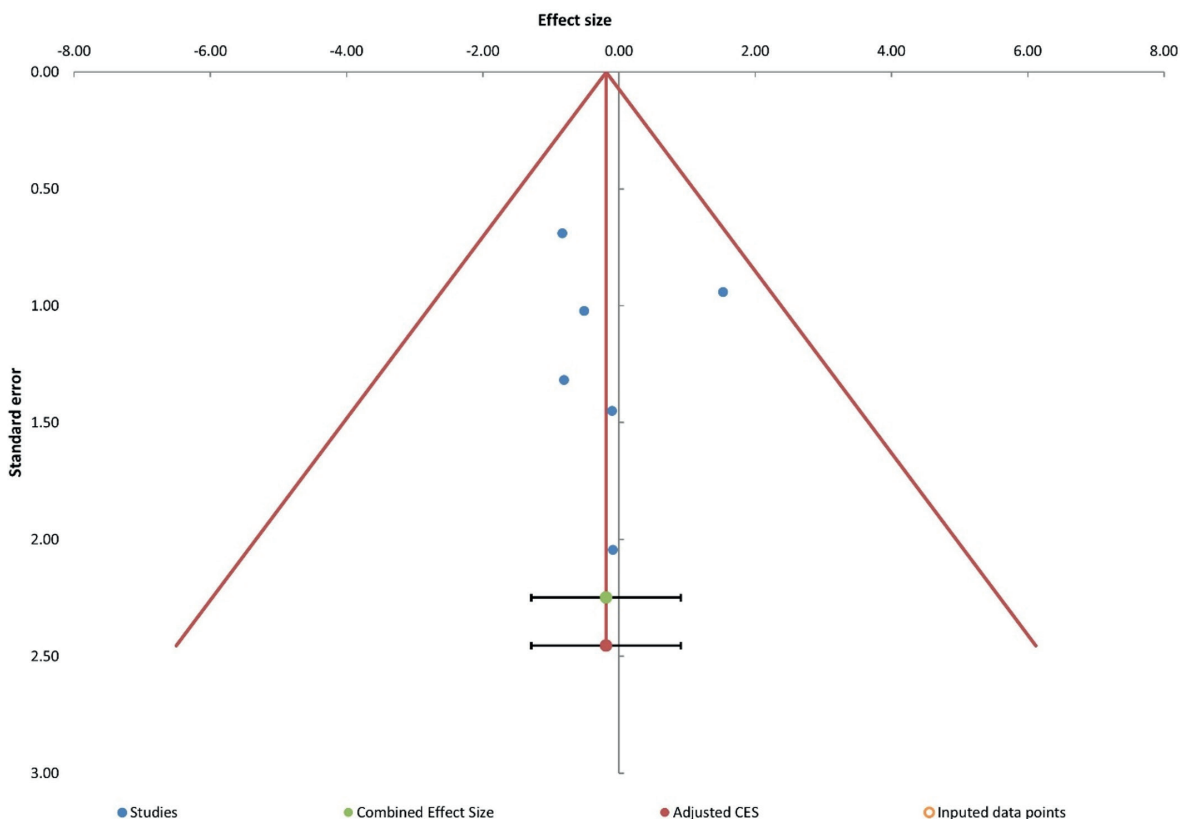


Fig. 3. Funnel plot for assessing publication bias. The symmetry of the distribution suggests no significant publication bias.

rates of osteoporosis, especially those who received more than 10 cycles of MDMP.²⁶ No osteoporosis was observed in our cohort, possibly because long-term outcomes were not tracked. Although there is no systematic review on thrombosis in childhood ITP, adult ITP patients are prone to a prothrombotic state, regardless of treatment type and presence of antiphospholipid antibodies, especially in chronic ITP.²⁷⁻²⁹ Moreover, in childhood ITP, pre-treatment protein C and protein S levels were significantly lower than in controls and improved considerably after MDMP treatment.³⁰ This suggests a preexisting hypercoagulable condition in ITP, which was resolved by MDMP, though larger studies are needed. In our systematic review, no cases of thrombosis were reported. On the other hand, IVIG side effects occur in 5-15% of infusions.³¹ In our review, headache was the most common adverse effect, consistent with the literature. Severe reactions included only aseptic meningitis, which required hospitalization. Other common reactions, like fatigue, abdominal pain, myalgia, and severe issues such as anaphylaxis in some IgA-deficient patients, thrombosis, kidney impairment, severe hemolysis, and neutropenia, were not reported in our cohort.^{3,31}

Steroids are more cost-effective than IVIG.³² Furthermore, suggestions to restrict IVIG use and to favor corticosteroids as the first-line therapy have been made in various treatment guidelines worldwide. Recently, the American and Canadian Hematology Societies have recommended corticosteroids for children newly diagnosed with ITP first, and reserve IVIG for severe bleeding.²³ ITP accounts for 4.6-17% of all diseases treated with IVIG.^{33,34} The supply of IVIG may be insufficient to meet demand, as both the number of IVIG units used across all indications and costs have reportedly increased by nearly 5% recently.³⁴ Although there are no statistics on the frequency and cost of IVIG use in our country, it is observed that IVIG, which is administered in just one day, is often the first treatment choice, regardless of bleeding severity. Although the duration

of therapy with MDMP is longer compared to IVIG, it can be given orally, even at home.¹⁶ It is important to remember that MDMP offers advantages such as oral administration, low cost, easy availability, rapid action as a non-biological agent, and as a reliable alternative to IVIG. Since MDMP was as effective as IVIG in rapidly increasing platelet counts, it can be used in ITP cases requiring a quick platelet increase.^{3,5,35}

In our review, two patients developed ICH during follow-up. Currently, patients with ICH or those at risk of developing ICH, or who have major bleeding according to bleeding scores, are recommended to receive combination therapies. In our review, MDMP was used as monotherapy, but the role of MDMP as part of combination therapy and whether seven days of MDMP is more effective for patients with autoimmune or rheumatologic disorders, which were initially masked as ITP, should be investigated in future studies. Additionally, in our cohort, treatment decisions did not depend on the severity of bleeding; therefore, monotherapy with MDMP may be necessary for moderate to severe bleeding (grades 3a-5).

Limitations

Despite following the PRISMA guidelines and conducting a rigorous meta-analysis, our study has several limitations. First, while the meta-analysis demonstrated a high level of statistical homogeneity, the included studies exhibit methodological diversity in patient populations, study designs, and thresholds for assessing platelet count increments. Although we addressed this by using the lowest threshold reported in each study, this variability should be considered when interpreting our findings. Furthermore, all included studies were conducted in Türkiye, which may limit the generalizability of our results to other populations. Second, many studies lacked data on baseline bleeding severity or standardized assessment scores, restricting a comprehensive evaluation of safety and efficacy in high-risk patients. Third, long-term outcomes, such as

osteoporosis rates, were based on a limited number of studies with short follow-up periods, preventing firm conclusions on long-term safety. Finally, while our assessment of publication bias did not indicate significant bias, the small number of included studies remains a constraint.

Conclusions

Our study concludes that MDMP treatment is a reliable, cost-effective, and practical choice for pediatric ITP, demonstrating efficacy equivalent to IVIG in achieving rapid platelet count increment. MDMP provides a strong, non-biological first-line alternative, especially advantageous in situations that demand high cost-efficiency and ease of administration. Further high-quality studies are essential to fully clarify MDMP's role, particularly in patients stratified according to high-grade bleeding scores, and to confirm its long-term safety profile.

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We dedicate this work to the memory of the late Prof. Dr. Şinasi Özsoylu, the pioneer in megadose methylprednisolone therapy whose legacy inspired this study. We also extend our thanks to Prof. Dr. Namık Yaşar Özbek for his valuable guidance.

Ethical approval

Ethics committee approval was not required.

Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: DK, LO, MAO; literature review: DK, LO; draft manuscript preparation: DK, LO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Investigating the clinical significance and predictive value of miR-146a rs2910164 polymorphism in retinopathy of prematurity: a case-control study

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ABSTRACT

Background. Retinopathy of prematurity (ROP) remains a leading cause of childhood blindness. The microRNA-146a (miR-146a) rs2910164 polymorphism, implicated in angiogenesis and inflammation, may influence ROP pathogenesis, but its role is undefined. This study aimed to investigate the association of the miR-146a rs2910164 polymorphism with ROP susceptibility, disease severity, and complications.

Methods. This retrospective case-control study included 196 preterm infants with ROP and 185 healthy preterm (HC) infants who were treated from January 2020 to December 2021 at our hospital. rs2910164 genotyping and miR-146a expression analysis using quantitative reverse transcriptase polymerase chain reaction were performed. Diagnostic potential was evaluated by receiver operating characteristic analysis. Associations with clinical features, disease severity (need for treatment for ROP), and complications were assessed.

Results. Infants with ROP demonstrated significantly lower gestational age/birth weight and higher rates of intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis than the HC infants (all $P < 0.001$). miR-146a expression was an excellent diagnostic biomarker for ROP (AUC :0.918, 95% CI: 0.87-0.96). The CC genotype and C allele conferred a reduced risk of ROP. Among patients with ROP, CC/GC carriers had a lower likelihood of developing severe ROP that required treatment versus GG homozygotes. GG carriers also showed more severe manifestations and complications.

Conclusion. The rs2910164 C allele is associated with protection from ROP susceptibility, correlates with upregulated miR-146a expression, and is further associated with milder disease manifestations, fewer complications, and a reduced need for clinical intervention. This polymorphism is a valuable predictive biomarker for ROP risk, severity, and prognosis, potentially mediated via miR-146a regulation.

Key words: retinopathy of prematurity, miR-146a, rs2910164, genetic polymorphism, biomarker.

Retinopathy of prematurity (ROP) is a sight-threatening condition marked by abnormal proliferation of retinal blood vessels and associated inflammation, constituting a major contributor to visual impairment in children.¹⁻³ While advancements in neonatal intensive care have markedly increased survival among extremely preterm and extremely low birth weight infants, this success has paradoxically elevated the incidence of ROP, imposing a

substantial public health challenge.^{4,5} The central pathophysiological mechanism of ROP involves an initial arrest of retinal vascular development, followed by pathological neovascularization.^{6,7} Crucially, inflammatory processes are recognized as fundamental drivers in both retinal vascular injury and defective repair mechanisms, playing a pivotal role across all stages of ROP development.⁸

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Research indicates that the microRNA-146a (miR-146a) rs2910164 G→C polymorphism is strongly linked to an elevated risk of various inflammatory and vascular conditions, including inflammatory bowel disease (IBD)⁹ and acute coronary syndrome / coronary heart disease (ACS/CHD).¹⁰⁻¹² This genetic variant is also associated with heightened inflammatory activity and poorer clinical outcomes.^{13,14} Located within the stem-loop region of the miR-146a precursor¹⁵, this polymorphism disrupts mature miR-146a expression and function. Consequently, its ability to regulate inflammation is diminished, leading to varying inflammatory responses among individuals exposed to the same environmental factors.¹⁶ However, the specific contribution, clinical significance, and potential biomarker value of this polymorphism in ROP remain undefined. Considering the critical involvement of inflammatory pathways in ROP pathogenesis and the key regulatory role of miR-146a in inflammation^{1,2,9,10}, dedicated investigation into its impact within the context of ROP is warranted.

Given that the functional genetic variant rs2910164 in the miR-146a gene may influence inflammatory and angiogenic pathways by modulating rs2910164 expression, thereby contributing to the pathogenesis of ROP, this study hypothesizes that the rs2910164 polymorphism is associated with ROP susceptibility, severity, related complications, and the necessity of therapeutic intervention, which serves as a proxy for severe disease. To systematically test this hypothesis, we will utilize a well-characterized cohort of preterm infants to comprehensively analyze the impact of this polymorphism on ROP risk, miR-146a expression levels, key clinical phenotypes, major prematurity-associated complications, and the requirement for treatment, reflecting disease severity.

Materials and Methods

Research design and sample data

This study employed a single-center, retrospective design. All serum samples were residual aliquots obtained from routine clinical biochemistry tests performed on hospitalized patients with ROP between January 2020 and December 2021. Following the completion of clinical testing, the samples were anonymized using a coding system and temporarily stored in accordance with our hospital's Standard Operating Procedures for Clinical Specimen Management. They were subsequently transferred to the institutional biobank for long-term preservation at -80 °C. The storage and subsequent research use of these samples strictly complied with the Interim Regulations for the Use of Clinical Residual Samples in Scientific Research, established jointly by the Research Administration Department and the Institutional Review Board (IRB). Sample collection from January 2020 to December 2021 preceded the IRB application. Notably, these samples were not originally collected for the purposes of this study. The study protocol was submitted in March 2022, and ethical approval was granted on April 14, 2022 (Approval No. 2022030).

Participants and data collection

The study was approved by the Ethics Committee of Jiujiang Maternal and Child Health Care Hospital in Jiangxi Province. Written informed consent was obtained from the guardians of all participants. A total of 196 premature infants with ROP were enrolled in this retrospective study. The condition resolved spontaneously in 98 infants, while the other 98 required treatment. All cases were compared with 185 preterm controls without ROP. These control subjects were matched to the case group by mode of delivery and had no retinal

pathology. Based on the prespecified clinically significant effect size (Cohen's $d = 0.5$), the actual sample sizes (196 vs. 185) and $\alpha = 0.05$, we assessed the statistical power of the study, which was 0.998. This indicates that the sample size in this study was sufficient to detect an effect of this magnitude.

Experienced pediatric ophthalmologists diagnosed and classified all ROP cases according to the International Classification of ROP (ICROP) guidelines. Inclusion in the study required the following: (1) gestational age below 37 weeks at delivery; (2) birth weight under 2,500 g; and (3) hospital admission within 24 hours of birth. Exclusion criteria encompassed neonates who: (1) died within the first 24 hours after admission; (2) had severe congenital malformations; and (3) were diagnosed with inherited metabolic diseases. Retrospective data collection included detailed demographic and clinical parameters: gestational age (weeks), birth weight (grams), mode of delivery (vaginal/cesarean section), sex, Apgar scores (at 1 and 5 minutes), duration of mechanical ventilation (days), and the occurrence of major complications such as intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC).

Ethical statement

The research protocol was submitted in March 2022. Ethical approval was granted on April 14 of the same year (Approval No. 2022030). Due to the retrospective nature of the study, the anonymization of all data, and the use of residual samples that posed only minimal risk, the Ethics Committee granted an exemption from the requirement to obtain renewed informed consent. This decision was made in accordance with the national "Measures for the Ethical Review of Biomedical Research Involving Human Subjects."

Furthermore, during the initial sample collection phase (2020-2021), all patients had previously provided written informed consent using a standard clinical form. This form included a clause permitting the use of anonymized samples for medical research purposes. Patients retained the right to refuse such use at that time. This study involved no interventions beyond standard clinical practice and was conducted in strict adherence to the ethical principles of the Declaration of Helsinki.

Genotyping

Genomic DNA was isolated from peripheral blood samples using a standard salting-out method. The rs2910164 (G>C) polymorphism within miR-146a was genotyped using a TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) on a real-time quantitative PCR system.

Analysis of miR-146a expression

The study quantified the relative expression levels of mature miR-146a in representative serum samples from HC and ROP participants using quantitative reverse transcription PCR (qRT-PCR). TRIzol reagent was employed for total RNA isolation. Complementary DNA (cDNA) synthesis was performed using miRNA-specific stem-loop reverse transcription (RT) primers. Using the $2^{-\Delta\Delta Ct}$ method, we normalized expression levels to U6 small nuclear RNA (snRNA). Results are presented as relative expression levels normalized to a calibrator sample.

Statistics

Statistical analyses were performed using SPSS (version 26.0) and GraphPad Prism (version 9.0). Continuous variables were first examined for normality using the Shapiro-Wilk test and for homogeneity of variance using Levene's test. For variables that were normally distributed with homogeneous variance, comparisons

between the two groups were performed using the independent samples t-test, and the results were presented as the mean $\pm$ standard deviation. For variables that did not meet the assumptions of normality or homogeneity of variance, the Mann-Whitney U test was applied, and the results were reported as the median (interquartile range). Categorical variables were expressed as frequencies (%) and compared using the chi-square (χ^2) test. Hardy-Weinberg equilibrium (HWE) was evaluated within the HC cohort. To assess associations between genotypes and ROP risk, odds ratios (OR) with 95% confidence intervals (CI) were calculated under codominant, dominant (GC+CC vs GG), recessive (CC vs. GG+GC), and allelic genetic models. The diagnostic potential of miR-146a expression for ROP was determined using receiver operating characteristic (ROC) curve analysis, yielding the area under the curve (AUC), sensitivity, and specificity. Multifactorial logistic regression was employed to determine the independent factors associated with the development of ROP. The goodness of fit of the model was evaluated using the Hosmer-Lemeshow test. A *P* value greater than 0.05 indicated that the model had a good fit.

Statistical significance was defined as a two-tailed *P* < 0.05.

Results

Clinical characteristics of retinopathy of prematurity cases versus matched controls

Compared with the HC group, infants with ROP exhibited significantly lower gestational ages, lower birth weights, and reduced Apgar scores at both 1 and 5 minutes. Infants with ROP also required mechanical ventilation for a significantly longer duration. Furthermore, they developed IVH, BPD, and NEC more frequently (Table I).

Diagnostic significance of miR-146a expression

miR-146a expression was significantly lower in the ROP group than in the HC group (Fig. 1A). ROC analysis indicated that miR-146a levels effectively distinguished infants with ROP from healthy preterm controls, with an AUC of 0.918 (95% CI: 0.87-0.96, *P* < 0.001), a sensitivity of 88.3% and a specificity of 84.3% (Fig. 1B). Notably, miR-146a levels did not significantly

Table I. Comparative analysis of clinical characteristics between HC and infants with ROP.

Items	HC, n=185	ROP, n=196	<i>P</i> value
Mode of delivery, n (%)			0.721
Vaginal	94 (50.8)	96 (49.0)	
Caesarean section	91 (49.2)	100 (51.0)	
Gestational age at birth (weeks), mean $\pm$ SD	27.80 $\pm$ 4.16	25.03 $\pm$ 4.37	<0.001
Birth weight (g), mean $\pm$ SD	1320.80 $\pm$ 317.16	971.41 $\pm$ 211.75	<0.001
Male sex, n (%)	94 (50.8)	91 (46.4)	0.450
Apgar score, median (Q1-Q3)			
1st minute	6.0 (4.0-8.0)	3.0 (2.0-4.0)	<0.001
5th minute	7.0 (6.0-8.0)	6.0 (4.0-7.0)	<0.001
Duration of mechanical ventilation (days), mean $\pm$ SD	11.01 $\pm$ 5.49	29.00 $\pm$ 15.67	<0.001
IVH, n (%)	41 (22.2)	115 (58.7)	<0.001
BPD, n (%)	24 (13.0)	99 (50.5)	<0.001
NEC, n (%)	31 (16.8)	115 (58.7)	<0.001

BPD, bronchopulmonary dysplasia; HC, healthy controls; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SD, standard deviation.

differ between GG genotype carriers and GC/CC genotype carriers within the HC group (Fig. 1C). However, within the ROP group, infants carrying the GG genotype exhibited significantly lower miR-146a expression than those with GC or CC genotypes (Fig. 1D).

Link between the rs2910164 polymorphism and susceptibility to retinopathy of ROP

The distribution of rs2910164 genotypes and alleles in the HC group and ROP groups is presented in Table II. In the HC group, the

observed genotype frequencies were consistent with (HWE; $P = 0.817$). Significant differences in genotype frequencies were observed between the two groups. Under the allelic model, the minor C allele was significantly associated with a reduced ROP risk (OR = 0.745, 95% CI: 0.558–0.996, $P = 0.047$). Similarly, in the codominant model, the CC genotype conferred significant protection compared with the GG genotype (OR = 0.529, 95% CI: 0.291–0.963, $P = 0.036$). Moreover, under the dominant model (GC+CC vs. GG), individuals carrying the C allele (GC or CC genotype) exhibited a significantly lower

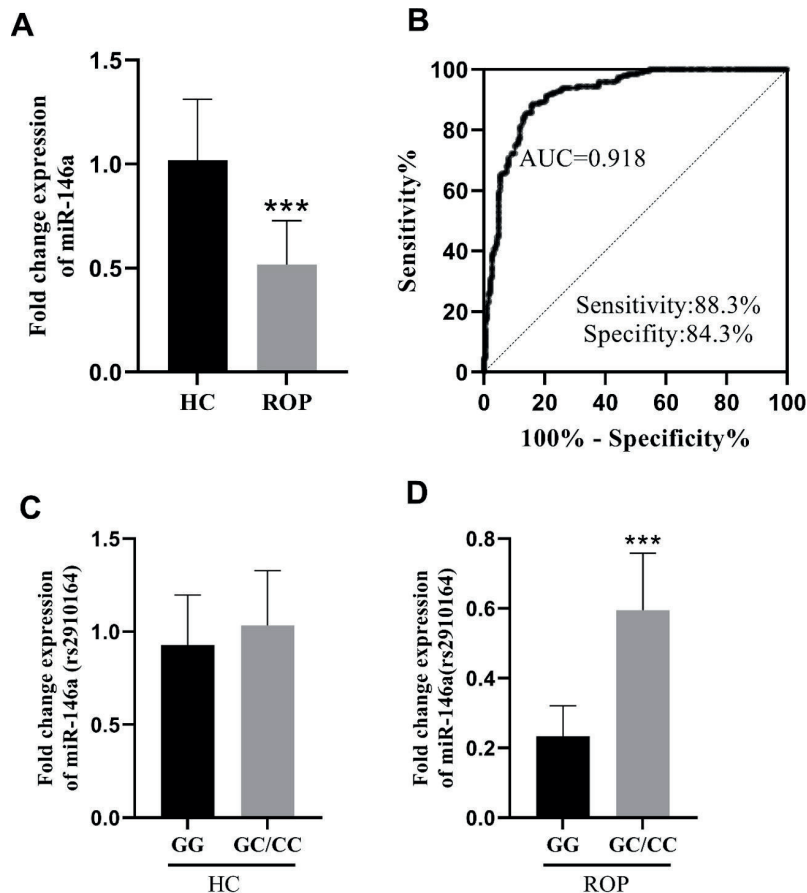


Fig. 1. The expression of miR-146a and its diagnostic value. (A) Relative expression level of miR-146a in healthy controls and the ROP group. (B) ROC curve analysis evaluating the diagnostic potential of miR-146a for ROP group. AUC = 0.918, Sensitivity = 88.3%, Specificity = 84.3%. (C) Distribution of miR-146a expression levels (GG vs. GC/CC) in healthy controls. (D) Distribution of miR-146a expression levels (GG vs. GC/CC) in the ROP group.

*** $P < 0.001$.

AUC, area under the curve; HC, healthy controls; ROP, retinopathy of prematurity.

Table II. Genotype distribution and association analysis of the rs2910164 genetic polymorphism with ROP.

rs2910164	HC (n=185), n (%)	ROP patients (n=196), n (%)	χ^2	OR (95% CI)	P value
Codominant model					
GG	25 (13.5)	42 (21.4)	-	1	-
GC	88 (47.6)	90 (45.9)	2.880	0.609 (0.342-1.083)	0.090
CC	72 (38.9)	64 (32.7)	4.394	0.529 (0.291-0.963)	0.036
Alleles					
G	138 (37.3)	174 (44.4)	-	1	-
C	232 (62.7)	218 (55.6)	3.958	0.745 (0.558-0.996)	0.047
Dominant model					
GG	25 (13.5)	42 (21.4)	-	1	-
GC+CC	160 (86.5)	154 (78.6)	4.114	0.573 (0.333-0.985)	0.043
Recessive model					
GG+GC	113 (61.1)	132 (67.3)	-	1	-
CC	72 (38.9)	64 (32.7)	1.628	0.761 (0.500-1.158)	0.202
p_{HWE}	0.817				

CI, confidence interval; HC, healthy controls; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; ROP, retinopathy of prematurity.

risk of developing ROP than GG homozygotes (OR = 0.573, 95% CI: 0.333–0.985, $P = 0.043$). No significant association was detected in the recessive model.

Multifactorial analysis of the incidence of ROP

To control for confounding effects, all clinical variables listed in Table I were incorporated into a multivariate logistic regression model after confirming the absence of problematic multicollinearity (Supplementary Table S1). The Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 5.481$, $df = 8$, $P = 0.705$) indicated a satisfactory model fit. The adjusted results (Table III) demonstrated that certain clinical parameters and genetic polymorphisms were significantly associated with the development of ROP. Specifically, gestational age, birth weight, and Apgar scores at 1 and 5 minutes were protective factors against ROP, with higher values associated with lower risk. Conversely, prolonged mechanical ventilation and complications including IVH, BPD, and NEC significantly increased the risk of ROP. Notably, the miR-146a gene polymorphism

at rs2910164 was significantly associated with ROP (OR = 3.295, 95% CI: 1.994–5.447, $P < 0.001$), suggesting that this genetic variant could be a strong hereditary risk factor. However, mode of delivery and the gender of the premature infants showed no statistically significant association with ROP. In summary, the occurrence of ROP was closely related to various perinatal clinical factors and the genetic background, with the rs2910164 polymorphism potentially playing an important role.

The association between rs2910164 and clinical characteristics as well as complications of ROP

Stratifying infants with ROP by genotype (GG vs. GC+CC) demonstrated significant differences in disease severity and complication markers (Table IV). Compared with infants carrying the C allele (GC/CC), those homozygous for the G allele (GG) were born at a significantly lower gestational age and had lower birth weights. Their Apgar scores at 1 and 5 minutes were also significantly lower. Additionally, GG homozygotes required mechanical ventilation for longer durations and

Table III. Multivariate logistic regression analysis of risk factors related to ROP.

Items	OR	95% CI	P value
Mode of delivery (Caesarean section vs vaginal)	1.163	0.577-2.344	0.672
Gestational age (weeks)	0.457	0.278-0.749	0.002
Birth weight (g)	0.483	0.257-0.907	0.024
Sex (male vs female)	1.162	0.711-1.897	0.549
Apgar score (1st minute)	0.260	0.155-0.436	<0.001
Apgar score (5th minute)	0.458	0.280-0.748	0.002
Duration of mechanical ventilation (days)	2.102	1.275-3.465	0.004
IVH (yes vs no)	1.953	1.018-3.744	0.044
BPD (yes vs no)	1.791	1.081-2.968	0.024
NEC (yes vs no)	2.089	1.033-4.225	0.040
rs2910164 (GC+CC vs GG)	3.295	1.994-5.447	<0.001

BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; ROP, retinopathy of prematurity.

Table IV. Association of miR-146a rs2910164 polymorphism with clinical characteristics and complications in ROP.

Items	MiR-146a rs2910164		P value
	GG, n=42	GC+CC, n=154	
Mode of delivery, n (%)			0.111
Vaginal	16 (38.1)	80 (51.9)	
Caesarean section	26 (61.9)	74 (48.1)	
Gestational age at birth (weeks), mean±SD	23.54±2.99	25.44±4.60	0.002
Birth weight (g), mean±SD	839.07±151.74	1007.50±211.79	<0.001
Male sex, n (%)	23 (54.8)	68 (44.2)	0.222
Apgar score, median (Q1-Q3)			
1st minute	2.0 (1.0-4.0)	3.0 (2.0-5.0)	0.004
5th minute	5.00 (4.0-6.0)	6.0 (5.0-8.0)	0.001
Duration of mechanical ventilation (days), mean±SD	35.52±11.90	27.17±16.20	0.002
IVH, n (%)	31 (73.8)	84 (54.5)	0.025
BPD, n (%)	32 (76.2)	67 (43.5)	<0.001
NEC, n (%)	34 (81.0)	81 (52.6)	0.001

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SD, standard deviation.

experienced significantly higher rates of IVH, BPD, and NEC.

Association between rs2910164 polymorphism and therapeutic response in ROP

We further analyzed the association between the rs2910164 polymorphism and the risk of progressing to severe ROP requiring treatment.

As shown in Table V, patients possessing at least one C allele (GC or CC genotypes) exhibited a significantly reduced likelihood of needing treatment relative to GG homozygous patients. Under the codominant model, both the GC genotype (OR = 0.350, 95% CI: 0.159-0.769, $P = 0.008$) and the CC genotype (OR = 0.274, 95% CI: 0.119-0.631, $P = 0.002$) were associated with decreased treatment requirements compared

Table V. Association analysis of rs2910164 polymorphism with the severity of ROP.

rs2910164	Treatment requirement, n (%)		χ^2	OR (95% CI)	P value
	Yes (n=98)	No (n=98)			
Codominant model					
GG	12 (12.2)	30 (30.6)	-	1	-
GC	48 (49.0)	42 (42.9)	7.082	0.350 (0.159-0.769)	0.008
CC	38 (38.8)	26 (26.5)	9.656	0.274 (0.119-0.631)	0.002
Alleles					
G	72 (36.7)	102 (52.0)	-	1	-
C	124 (63.3)	94 (48.0)	12.595	0.483 (0.322-0.724)	<0.001
Dominant model					
GG	12 (12.2)	30 (30.6)	-	1	-
GC+CC	86 (87.8)	68 (69.4)	9.818	0.316 (0.151-0.664)	0.002
Recessive model					
GG+GC	60 (61.2)	72 (73.5)	-	1	-
CC	38 (38.8)	26 (26.5)	3.341	0.570 (0.311-1.044)	0.068

CI, confidence interval; OR, odds ratio; ROP, retinopathy of prematurity.

with the GG genotype. The dominant model (GC/CC combined vs. GG) showed that the combined genotype was associated with lower odds of requiring treatment (OR = 0.316, 95% CI: 0.151-0.664, $P = 0.002$). Under the allelic model, the C allele was also associated with lower odds of requiring treatment (OR = 0.483, 95% CI: 0.322-0.724, $P < 0.001$). The recessive model showed no significant association.

Discussion

ROP is a sight-threatening disorder driven by pathological retinal neovascularization and concurrent inflammation, representing a leading cause of childhood visual impairment.^{1,2} Its pathogenesis encompasses hypoxia-induced angiogenic dysregulation, inflammatory pathway activation, and aberrant vascular remodeling. MiRNAs, as critical regulators of gene expression, contribute to ROP pathology by targeting key pathways including vascular endothelial growth factor (VEGF) signaling and inflammatory mediators.^{1,2,17} This study aimed to examine the potential association between the miR-146a rs2910164 polymorphism and susceptibility to ROP, as well as its clinical manifestations. Analysis of baseline

characteristics revealed significant differences between patients with ROP and healthy preterm controls, providing crucial insights into the pathophysiological basis and risk factors for ROP. These differences underscore the complexity of ROP as a systemic disorder of prematurity, closely linked to perinatal stress, immature organ development, and secondary injury.

The study data suggest that infants developing ROP exhibit systemic vulnerability in critical growth parameters: reduced gestational age, lower birth weight, and diminished Apgar scores. This pattern aligns with global ROP epidemiology.¹⁸⁻²² As established markers of fetal maturity, diminished gestational age and birth weight directly correlate with impaired retinal vascularization. Premature birth can disrupt normal intrauterine retinal vascular development, particularly in the temporal peripheral region, leaving vascular endothelial cells exposed to various iatrogenic stressors and risk factors, which may trigger vascular occlusion.^{22,23} Low Apgar scores, indicative of perinatal asphyxia or stress, may potentiate hypoxia-reoxygenation injury and pathological angiogenic signaling. Collectively, these

parameters define a “developmental threshold” for ROP onset, suggesting that retinal screening should be mandatory for infants with extremely low gestational ages and birth weights. The extended duration of mechanical ventilation observed in infants with ROP signals underlying severe pulmonary conditions, such as respiratory distress syndrome, and the need for prolonged oxygen supplementation.²⁴ The repetitive hypoxia-hyperoxia exposure associated with ventilation chronically activates the retina, inducing oxidative stress. This inhibits normal vascular development while promoting the abnormal expression of pro-angiogenic factors such as VEGF. Additionally, research demonstrates a positive correlation between ventilation duration and circulating levels of pro-inflammatory cytokines, notably interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).¹ Such systemic inflammation can compromise the blood-retinal barrier, facilitate inflammatory cell infiltration into retinal tissue, and drive pathological neovascularization. Thus, mechanical ventilation represents a composite measure reflecting both oxygen toxicity and inflammatory load. The markedly higher prevalence of IVH, BPD, and NEC in infants with ROP underscores that ROP is not merely an isolated eye disease but rather a key component of multi-organ dysfunction in preterm infants. These complications interact with ROP in a detrimental cycle: primary conditions (e.g., BPD-related hypoxia) contribute to ROP pathogenesis, and concurrently, while the systemic inflammatory state linked to ROP can aggravate injury to the lungs, intestines, brain, and other organs. Consequently, effective ROP prevention and management demand a comprehensive approach to preterm infant care, extending well beyond isolated ophthalmological treatment.

A marked association was observed between the miR-146a gene polymorphism and ROP risk. The key results revealed that the C allele and GC/CC genotypes function as genetic protective factors against ROP, whereas the GG genotype significantly elevates ROP

susceptibility. This genetic risk profile strongly correlates with the target gene’s expression level, which demonstrates outstanding predictive value for ROP. Collectively, these findings indicate a critical regulatory role for miR-146a in ROP pathogenesis. The heightened risk associated with the GG genotype may stem from insufficient miR-146a expression, thereby attenuating the suppression of inflammatory pathways and increasing vulnerability to aberrant retinal vascular proliferation under stressors such as oxygen therapy. Conversely, carriers of the C allele (GC/CC genotypes) likely sustain more stable miR-146a levels, bolstering retinal anti-inflammatory defenses. Notably, while the GG genotype was overrepresented in the ROP cohort, its distribution in healthy controls strictly adhered to Hardy-Weinberg equilibrium. This makes population stratification or genotyping artifacts less likely to be primary explanations for the observed association, thereby lending support to the potential validity of the genetic effect. These results, showing high predictive capability, offer additional validation of the promise of miR-146a as an ROP biomarker. Consistent with the known downregulation of miR-146a in this disease²⁵, the findings lend support to the concept that microRNA activity modulates inflammatory processes in ROP.^{26,27}

Furthermore, this investigation established a correlation between genotype and treatment requirement, offering deeper insight into the synergistic interplay between genetic susceptibility and environmental factors on ROP progression. Under a dominant genetic model, patients carrying the C allele (GC/CC genotypes) exhibited a substantially reduced risk of needing therapeutic intervention. This suggests that infants with the CC genotype may qualify for low-risk management protocols, potentially reducing the frequency of invasive screening. Compared with C allele carriers, the GG homozygote group was observed to have a lower gestational age and birth weight, which may suggest a tendency toward developmental immaturity. This group also required longer

periods of mechanical ventilation, potentially indicating greater respiratory vulnerability. Additionally, they experienced higher rates of systemic complications, a pattern consistent with observations of reduced compensatory capacity in organ development. Importantly, these clinical phenotypes align closely with the “genetic susceptibility-environmental stress” synergy reported previously.^{21,28} Building upon this concept, this study pioneers risk quantification via genotyping. This advancement transforms prior hypotheses into practical predictive tools: infants with the GG genotype infants, particularly those with low birth weight or extended oxygen therapy, warrant more intensive monitoring.

Limitations

This study has several limitations. Most importantly, given the strong association between ROP and preterm birth, there are inherent and significant differences in key baseline characteristics such as gestational age and birth weight between the ROP case group and the control group. Although case-control methodologies are widely employed in exploratory research, they inherently carry a risk of confounding bias, with observed genetic associations potentially reflecting, in part, the impact of these robust clinical parameters. Adjustment for major clinical covariates via multivariate logistic regression maintained a significant and independent association between the miR-146a variant (rs2910164) and ROP, supporting an independent genetic contribution. Nonetheless, statistical correction cannot wholly substitute for a prospectively matched design based on clinical features, and residual or unmeasured confounding may persist. Thus, our results should be viewed as preliminary and hypothesis-generating, rather than as definitive proof of causation. Subsequent research is needed to verify these findings in prospectively matched cohorts (e.g., by gestational age and birth weight) or through larger, population-based studies, in

order to better ascertain the predictive value of this genetic marker independent of clinical risk factors.

Conclusion

The findings suggest that the miR-146a rs2910164 G>C polymorphism may play a significant role in ROP. The G allele significantly heightens susceptibility compared with the protective C allele which is associated with a better prognosis and reduced treatment requirements. This heightened risk is linked to decreased miR-146a expression, increased disease severity, and higher frequencies of systemic complications such as IVH, BPD, and NEC. Genotyping of rs2910164 can thus be applied to ROP risk stratification in preterm infants. Additionally, miR-146a possesses potential as both a diagnostic biomarker and therapeutic target, especially for high-risk GG genotype infants. This supports early prediction, a better understanding of individual variation, and the development of precision strategies targeting miR-146a.

Supplementary materials

Supplementary materials for this article are available online at <https://doi.org/10.24953/turkijpediatr.2026.7219>

Ethical approval

The study was approved by Ethics Committee of Jiujiang Maternal and Child Health Care Hospital (date: April 14, 2022, number: 2022030).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: WC, CZ, TW, QG, WT; data collection: WC, CZ, TW, QG, WT; analysis and interpretation of results: WC, CZ, TW, QG, WT; draft manuscript preparation: WC. All authors reviewed the

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Conflict of interest

The authors declare that there is no conflict of interest.

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Structural vulnerabilities and adolescent pregnancy outcomes: a cross-sectional study from a tribal community in Jharkhand, India

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ABSTRACT

Background. Adolescent pregnancy remains a major public health challenge among tribal populations, where social, educational, and healthcare-related disadvantages frequently coexist and contribute to adverse maternal and neonatal outcomes. This study examined the sociodemographic profile, vulnerability factors, maternal and fetal outcomes, and the impact of cumulative vulnerability among pregnant tribal adolescents in Jharkhand.

Methods. A cross-sectional, hospital-based descriptive study was conducted among 197 pregnant adolescents aged 13–19 years belonging to Scheduled Tribes in Jharkhand, recruited through purposive sampling at the point of hospital admission for delivery between December 2023 and November 2025. Data were collected through structured interviews during hospital admission for delivery, supplemented by available hospital records. Sociodemographic characteristics, established risk factors including family dysfunction and educational barriers, maternal complications, and neonatal outcomes were assessed. An exploratory study-specific composite vulnerability score was developed using seven predefined vulnerability indicators and categorized as <4 or ≥4. Associations between vulnerability score and maternal-fetal outcomes were evaluated using unadjusted bivariate analysis.

Results. Most participants were aged 13–15 years (83.8%), illiterate (79.7%), primigravida (87.8%), and had received no antenatal care (73.6%). Poor socioeconomic conditions and lack of sexual and reproductive health information were reported by all participants, while school dropout (81.7%), sexual pressure from peers (71.6%), and family addiction history (38.6%) were also common. Maternal complications included anaemia (65.5%) and pregnancy-induced hypertension (32.5%). Low birth weight (63.5%) was the most frequent neonatal complication, followed by feeding difficulty (20.3%), prematurity (13.2%), and intrauterine fetal demise (4.1%). More than two-thirds of participants (71.1%) had a composite vulnerability score ≥4. Higher vulnerability scores were significantly associated with anaemia ($p<0.001$), pregnancy-induced hypertension ($p=0.004$), low birth weight ($p<0.001$), and prematurity ($p=0.016$).

Conclusion. This study reveals a marked clustering of poverty, illiteracy, family disruption, and healthcare exclusion among pregnant tribal adolescents accessing institutional delivery in this region of Jharkhand, and an association between the cumulative burden of these vulnerabilities and adverse maternal and neonatal outcomes.

Key words: syndemic framework, institutional delivery, maternal outcomes, low birth weight, fetal outcome.

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Adolescent pregnancy remains a pressing global concern, particularly in low- and middle-income countries, where it significantly contributes to maternal and perinatal morbidity and mortality, with an estimated 21 million pregnancies occurring annually among adolescents aged 15–19 years in these regions as of 2019; approximately 50% of which were unintended and resulted in an estimated 12 million births.¹ In India, national estimates from the sixth round of the National Family Health Survey (NFHS-6, 2023–24) place the prevalence of teenage childbearing among women aged 15–19 years at 6.7%, essentially unchanged from the 6.8% recorded in NFHS-5 (2019–21),^{2,3} despite national programs such as Rashtriya Kishor Swasthya Karyakram (RKSK) and the Reproductive, Maternal, Neonatal, Child and Adolescent Health (RMNCH+A) strategy.^{4,5} Encouragingly, NFHS-6 shows a decline in child marriage before age 18 among women aged 20–24 years, from 23.3% (NFHS-5) to 20.1% (NFHS-6); however, disaggregated tribal and Jharkhand-specific estimates from this round were not yet available at the time of writing.^{2,3} Adolescent girls, especially those from tribal communities, remain on the fringes of the healthcare system.

India's legal framework nominally protects adolescents from early marriage and sexual exploitation through the Prohibition of Child Marriage Act, 2006, which sets the minimum legal age of marriage at 18 years for women, and the Protection of Children from Sexual Offences (POCSO) Act, 2012, which criminalizes sexual activity with any person under 18 years irrespective of consent. Enforcement of both statutes remains inconsistent in tribal and rural areas, where early marriage continues to be normalized by community practice.⁶ Recent Indian reviews and multilevel analyses confirm that Scheduled Tribe status is independently associated with higher odds of adolescent pregnancy nationally and that illiteracy, domestic violence, and limited media exposure remain key determinants.⁷ Comparative work from tribal and non-tribal communities

elsewhere in eastern India has similarly documented markedly lower antenatal care utilization among tribal teenage mothers than their non-tribal counterparts.⁸

Jharkhand, with one of the highest tribal populations in India, exhibits a disproportionate burden of early marriage, school dropout, and adolescent childbirth.⁹ Tribal adolescents face entrenched structural vulnerabilities including poverty, illiteracy, substance abuse in the family, and disrupted family systems. These intersecting disadvantages not only increase their susceptibility to early pregnancy but also predispose them to poor maternal and neonatal outcomes.

The phenomenon of adolescent pregnancy in tribal regions must be seen through a syndemic lens, where multiple social and biological adversities cluster and interact synergistically to amplify risk.¹⁰ Traditional biomedical models fail to capture the deeper socioeconomic and cultural mechanisms driving early reproduction. This study investigates adolescent pregnancy in a tribal community of Jharkhand, focusing on the clustering of family-level and structural vulnerability factors, missed preventive health opportunities, and resultant maternal-foetal outcomes among adolescents who accessed institutional delivery services.

Methods

Study design and population

This cross-sectional, hospital-based descriptive study was conducted among adolescent pregnant girls belonging to tribal communities in Jharkhand over a period of 24 months, from December 2023 to November 2025. Participants were recruited at the point of hospital admission for delivery at government or affiliated tribal health centers in collaboration with peripheral health centers and outreach clinics serving tribal populations in rural Jharkhand. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of Tata Main Hospital, Jamshedpur.

Study participants

The study included pregnant adolescents aged 13–19 years who identified as members of Scheduled Tribes and were admitted for delivery at government or affiliated tribal health centers. A total of 197 adolescent girls were enrolled through purposive sampling. This non-probability sampling approach enabled focused recruitment of pregnant tribal adolescents accessing institutional delivery services, a vulnerable and hard-to-reach population with low healthcare utilization rates. However, this sampling strategy and facility-based recruitment introduce important limitations to representativeness: participants were limited to those who accessed institutional care at the time of delivery, and the sample therefore excludes adolescents who delivered at home, who were unable to access institutional care at all, and whose pregnancies ended before delivery (through miscarriage, induced abortion, or undetected loss).

Participants were excluded if they (i) refused informed consent / assent, (ii) had serious medical comorbidities such as diabetes, epilepsy, or congenital heart disease, or (iii) were unable to participate due to cognitive or communication impairments. Adolescents with these comorbidities were excluded because each is independently and strongly associated with adverse pregnancy outcomes; their inclusion would have confounded the interpretation of associations between social vulnerability and the maternal / fetal outcomes that were the primary focus of this study.

Participants received no monetary compensation for their participation. However, as part of routine hospital care, all participants received standard postpartum supplies and newborn care kits provided by the government health program.

Study procedure

Eligible participants were approached during hospital admission for delivery. After obtaining informed written consent from participants

and/or guardians (for minors), a structured interview was conducted using a predesigned and pretested proforma. The proforma was developed based on variables reported in the existing literature on tribal adolescent pregnancy risk factors, reviewed internally by departmental faculty, and pretested on a small pilot sample of tribal adolescents (not included in the final analysis) to check comprehensibility; it was administered orally in the local tribal language by trained field investigators. No formally validated psychometric instrument was used to assess sensitive constructs such as dating violence or peer sexual pressure, which we note as a limitation. The questionnaire captured sociodemographic data (age, education, gravida, antenatal care received), maternal complications (e.g., anaemia, pregnancy-induced hypertension, puerperal infection), and neonatal outcomes (e.g., low birth weight, intrauterine fetal death, feeding difficulty, prematurity).

In addition, a set of predefined risk factors was assessed based on existing literature, including:

- Family factors: single mother, single-parent family, suicide or criminal record in family, history of addiction
- Social and psychological factors: sexual pressure from peers, dating violence, lack of spiritual life
- Educational and informational barriers: school dropout, lack of sexual/reproductive health information

Operational definitions

Illiteracy was defined as inability to read and write a simple sentence in any language, based on self-report and, where available, cross-checked against school records. School dropout was defined as discontinuation of formal schooling before completion of the terminal grade appropriate to the participant's age, for any reason. Socioeconomic status (SES) was assessed using the Modified Kuppuswamy scale and poor SES was defined as belonging to

the lower or upper-lower socioeconomic strata. Lack of prior sexual and reproductive health information was assessed via a single question asking whether the participant had ever received information on reproductive health, contraception, or pregnancy from any source (school, health worker, family, or media) before the index pregnancy; a negative response was scored as present. Sexual pressure from peers and dating violence were assessed through direct interview questions without a validated instrument, as noted above. Specifically, sexual pressure from peers was defined as a participant reporting, in response to a direct interview question, that she had ever felt urged, coerced, or pressured by a peer (a friend or acquaintance close in age) to enter into a romantic or sexual relationship or to engage in sexual activity; any positive response, regardless of the specific circumstances described, was scored as present. Dating violence was defined as a participant reporting, in response to a direct interview question, that she had ever experienced physical, sexual, or emotional violence (including hitting, threats, forced sexual activity, or intimidation) from a romantic partner; any such reported experience was scored as present. As these were single, non-validated items rather than standardized scales, they capture the presence or absence of a self-reported experience rather than its severity, frequency, or context, which we note as an additional limitation. Family-level variables (addiction, suicide, criminal record) referred to first-degree relatives residing in the same household (parents and siblings) unless otherwise specified by the participant, and the recall period for these variables was lifetime/ever. Anaemia, pregnancy-induced hypertension, puerperal infection, prematurity (birth before 37 completed weeks of gestation), and low birth weight (birth weight <2.5 kg) were defined using standard WHO/national clinical criteria and were confirmed from hospital records rather than relying solely on self-report.

All data were collected by trained field investigators fluent in local tribal languages to ensure comfort and comprehension for

participants. To minimize interviewer bias, all field investigators underwent standardized training on neutral questioning techniques and avoiding leading questions. A structured interview protocol was used consistently across all participants. To reduce recall bias, data on pregnancy complications and risk factors were collected during hospital admission (within 24-48 hours of delivery) when events were recent, and were corroborated with available medical records where possible. Data were anonymized and double-entered for quality assurance.

Data analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Descriptive statistics were calculated for all variables. Categorical variables were expressed as frequencies and percentages.

To quantify the cumulative burden of structural and psychosocial vulnerabilities, a composite vulnerability score was developed for each participant; this score has not been externally validated. Based on factors identified from existing literature and observed to be highly prevalent in the study population, one point was assigned for the presence of each of the following characteristics: illiteracy, school dropout, absence of antenatal care, history of addiction in the family, single-parent family, sexual pressure from peers, and history of dating violence. Equal weighting of these seven items was adopted as a simple, transparent approach in the absence of prior data that would permit empirical or theoretically derived weighting. We also note that illiteracy and school dropout, while conceptually distinct in our population may partially overlap and could result in some double-counting of a single underlying disadvantage.

The resulting score ranged from 0 to 7, with higher scores indicating greater cumulative vulnerability. This composite vulnerability score was calculated for each participant by summing the presence of seven predefined vulnerability factors, yielding a score ranging from 0 to 7.

The frequency distribution of vulnerability scores was described, and participants were subsequently categorized into low-vulnerability (<4) and high-vulnerability (≥ 4) groups using a cut-off selected a priori to approximate the median of the observed distribution and to yield a clinically interpretable “high-vulnerability” group; this cut-off has not been externally validated and should be interpreted as exploratory.

Associations between vulnerability score category and maternal outcomes (anaemia, pregnancy-induced hypertension, and puerperal infection) as well as fetal outcomes (low birth weight, feeding difficulty, premature birth, and intrauterine fetal demise) were assessed using the Chi-square test. Fisher’s exact test was applied when the expected cell count in any contingency table was less than five. A two-tailed p-value <0.05 was considered statistically significant. These analyses are unadjusted bivariate comparisons; multivariable analysis to adjust for potential confounders (e.g., maternal age, parity, gestational age, antenatal care utilization, and nutritional status) was not performed in the present study, and reported associations should therefore not be interpreted as independent or causal effects (see Limitations). Recruitment occurred across a network of peripheral health

centers and outreach clinics rather than a single site; clustering by recruitment centre was not formally accounted for in the analysis.

Results

Out of the 197 adolescent pregnancies studied from tribal populations in Jharkhand, the majority of participants were aged 13–15 years (83.8%), and illiterate (79.7%). Most were primigravida (87.8%) and had no antenatal care (73.6%). 21.3% of the deliveries were conducted through caesarean section (Table I).

Among risk factors, 100% reported a lack of sexual and reproductive health information and poor socio-economic conditions. A significant proportion had a history of school dropout (81.7%), experienced sexual pressure from peers (71.6%), and had a history of addiction in the family (38.6%) (Table II).

Regarding maternal complications, anaemia was the most common (n=129, 65.5%), followed by pregnancy-induced hypertension (n=64, 32.5%). Puerperal infection was recorded in four cases (2%). In terms of fetal outcomes, low birth weight (LBW) was observed in 125 cases (63.5%), followed by feeding difficulty (n=40, 20.3%), premature birth (n=26, 13.2%), and intrauterine fetal demise (n=8, 4.1%).

Table I. Sociodemographic and obstetric profile of the study participants (N = 197).

Variable	Category	Frequency	Percentage
Age	13–15 years	165	83.8
	16–19 years	32	16.2
Education	Illiterate	157	79.7
	Literate	40	20.3
Gravida	Primigravida	173	87.8
	Multigravida	24	12.2
Antenatal care (ANC) visits	None	145	73.6
	<2 visits	40	20.3
	>2 visits	12	6.1
Mode of delivery	Normal vaginal delivery	155	78.7
	Caesarean delivery	42	21.3

Table II. Distribution of established risk factors for adolescent pregnancy among the study participants (N=197).

Risk factor	Frequency	Percentage
Single mothers	32	16.2
Mother as single parent	52	26.4
Sexual pressure from peers	141	71.6
Lack of sexual and reproductive info	197	100.0
Criminal record in family	32	16.2
Suicide in family	28	14.2
School dropout	161	81.7
Poor socio-economic conditions	197	100.0
Addiction history in family	76	38.6
Siblings sexually active	24	12.2
Lack of spiritual life	20	10.2
History of dating violence	36	18.3

The distribution of the composite vulnerability score demonstrated a substantial clustering of risk factors among study participants. More than two-thirds of the adolescents (71.1%) had a vulnerability score of ≥ 4 , indicating the co-occurrence of multiple social, educational, and familial risk factors. The most common scores were 4 (31.0%) and 5 (23.4%), while only 9.6% of participants had scores below 3. No participant had a vulnerability score of zero (Table III).

Adolescents with a vulnerability score ≥ 4 experienced significantly higher rates of adverse maternal and fetal outcomes compared with those scoring <4 . Anaemia was significantly more prevalent among participants with higher vulnerability scores (77.1% vs. 36.8%, $p<0.001$),

Table III. Composite vulnerability score of the study participants (N=197).

Vulnerability score	Frequency	Percentage
0	0	0.0
1	4	2.0
2	15	7.6
3	38	19.3
4	61	31.0
5	46	23.4
6	24	12.2
7	9	4.6

as was pregnancy-induced hypertension (38.6% vs. 17.5%, $p=0.004$). Similarly, low birth weight was observed in three-fourths of adolescents with vulnerability scores ≥ 4 compared with one-third of those with lower scores (75.7% vs. 33.3%,

Table IV. Association of composite vulnerability score with maternal and fetal outcomes.

Characteristics	Vulnerability score ≥ 4 (N=140)	Vulnerability score <4 (N=57)	p-value#
Maternal complications			
Anemia	108 (77.1)	21 (36.8)	$<0.001^*$
Pregnancy-induced hypertension	54 (38.6)	10 (17.5)	0.004*
Puerperal infection	4 (2.9)	0 (0.0)	0.326
Fetal complications			
Low birth weight (LBW)	106 (75.7)	19 (33.3)	$<0.001^*$
Feeding difficulty	29 (20.7)	11 (19.3)	0.823
Premature birth	22 (15.7)	4 (7.0)	0.016*
Intrauterine death (IUD)	6 (4.3)	2 (3.5)	1.000

Values are presented as n (%); # p value was calculated using chi-square test or Fisher Exact test; * $p<0.05$ was considered to be statistically significant.

$p < 0.001$). Premature birth was also significantly more common in the high-vulnerability group (15.7% vs. 7.0%, $p = 0.016$) (Table IV).

Discussion

This study highlights the substantial structural vulnerabilities faced by pregnant adolescents in tribal Jharkhand. Most participants were aged 13–15 years (83.8%), indicating pregnancies occurring during early adolescence, a period of ongoing physical, cognitive, and emotional development.^{11,12} Illiteracy was highly prevalent (79.7%), reflecting persistent educational disadvantages in tribal communities. Educational deprivation is particularly important because literacy has been consistently associated with delayed childbearing, improved reproductive health knowledge, and better maternal outcomes.^{13,14} Similar patterns have been reported among tribal populations in Rajasthan and other regions of India, although the predominance of very early adolescent pregnancies observed in our study appears particularly pronounced.¹⁵⁻¹⁷ A recent narrative review of teenage pregnancy among tribal populations in India similarly identifies limited awareness, early/child marriage, and lack of parental or spousal support as recurring themes across settings.⁶

The majority of participants were primigravida (87.8%) and had received no antenatal care (73.6%), indicating major gaps in preventive healthcare access. Despite the availability of national maternal health programmes, antenatal care utilization in this cohort was considerably lower than national estimates among tribal populations.² According to the National Family Health Survey-5, even among tribal populations nationally, antenatal care coverage is typically above 60%.² This disparity suggests that the specific geographic and cultural contexts of Jharkhand's tribal communities create additional barriers to healthcare access beyond those experienced by tribal populations elsewhere in India. Although

most deliveries occurred vaginally, over one-fifth were conducted by caesarean section, suggesting that access to institutional obstetric care was available for at least a proportion of participants.

The universal presence of poor socioeconomic conditions and lack of sexual and reproductive health information underscores the deeply entrenched nature of disadvantage in this population. School dropout (81.7%), sexual pressure from peers (71.6%), family addiction (38.6%), single-parent households (26.4%), and dating violence (18.3%) were also common. These findings are consistent with ecological models of adolescent pregnancy that emphasize the interaction of family, social, and community-level determinants in shaping reproductive outcomes.^{10,18-24} Together, these factors reflect a broader context of social vulnerability that extends beyond individual reproductive behaviour, although we did not formally test for interaction between these factors and cannot determine whether they act synergistically or merely co-occur.

The burden of maternal and neonatal morbidity observed in this study was considerable. Anaemia was the most common maternal complication, affecting 65.5% of participants, substantially exceeding estimates reported among Indian adolescent girls and reflecting the combined effects of nutritional deprivation, early pregnancy, and limited antenatal care.²⁵⁻²⁷ Pregnancy-induced hypertension was observed in nearly one-third of participants (32.5%), a prevalence considerably higher than that reported in most adolescent pregnancy cohorts.²⁸ Among neonatal outcomes, low birth weight was recorded in 63.5% of newborns, far exceeding national averages and highlighting the adverse intrauterine environment associated with maternal undernutrition and poor healthcare access.²⁹ Feeding difficulties, prematurity, and intrauterine fetal demise further underscored the high-risk nature of pregnancies in this population. We emphasize that, because outcome ascertainment in this study was largely

restricted to the 24–48-hour period around delivery, with no structured follow-up after discharge, these figures likely underestimate the true burden of puerperal infection, feeding difficulties, and neonatal complications that manifest later in the postpartum or neonatal period. Collectively, these findings indicate that adolescent pregnancy in tribal communities is associated with significant social vulnerability and a substantial burden of adverse maternal and neonatal outcomes.

A contribution of this study was the development of an exploratory, study-specific composite vulnerability score to quantify the cumulative burden of educational, familial, healthcare-related, and psychosocial disadvantages. More than 70% of participants had a vulnerability score of ≥ 4 , indicating that multiple vulnerabilities frequently coexisted within the same individual. This finding demonstrates a clustering of social vulnerabilities in this population: our analysis summed binary indicators and examined their combined association with outcomes but did not formally test for statistical interaction or synergy between individual vulnerabilities, nor between the co-occurring health conditions themselves. Rigorous testing of the syndemic hypothesis in this population would require dedicated interaction analyses which we recommend for future research.

The co-occurrence of family disruption, single-parent households, and addiction within families in this cohort suggests that adolescent pregnancies often occur within broader contexts of persistent social disadvantage within the family unit. This pattern helps explain why interventions that focus narrowly on individual behaviour change, without addressing family- and community-level determinants, may have limited effectiveness in populations facing such concentrated disadvantage. Breaking cycles of disadvantage is likely to require interventions that extend beyond reproductive health services to include educational support, social protection, nutrition, and community-based empowerment

initiatives, alongside stronger enforcement of the Prohibition of Child Marriage Act, 2006, and child-protection provisions under the POCSO Act, 2012, given that a substantial proportion of participants in this cohort became pregnant below the legal age of marriage and consent. The findings also highlight the limitations of health programmes that focus primarily on service delivery without addressing underlying social determinants. Effective strategies should combine school-retention initiatives, adolescent-friendly reproductive health services, nutrition support, community-based reproductive health education, and social protection measures.

This study has several limitations. First, the cross-sectional design precludes establishing temporal or causal relationships between vulnerability factors and adverse pregnancy outcomes. Second, purposive sampling and hospital-based recruitment may have introduced selection bias, and findings may not be generalizable to all tribal communities in India. Third, some psychosocial variables were assessed using non-validated, study-specific questions and were self-reported, and may be subject to recall or social desirability bias; family-level variables used a lifetime recall period, which may introduce further reporting variability. Fourth, the composite vulnerability score was developed specifically for this study using equally weighted, dichotomized indicators and has not been externally validated; some component variables (illiteracy and school dropout) may conceptually overlap. Fifth, outcome ascertainment was largely restricted to the 24–48-hour period around delivery with no structured post-discharge follow-up, likely underestimating outcomes such as puerperal infection and later-presenting neonatal complications. Sixth, the reported associations between vulnerability score and outcomes are unadjusted; we could not account for potential confounders such as maternal age, parity, gestational age, antenatal care, and nutritional status, nor for clustering by recruitment centre, and these associations

should not be interpreted as independent or causal effects. Moreover, this study did not include a comparison group of non-adolescent (adult) pregnant women from the same tribal population; consequently, we cannot determine whether the sociodemographic and obstetric profile, or the observed maternal complications, are specific to adolescent pregnancy or instead reflect broader characteristics shared by pregnant women in this population regardless of age. Future studies incorporating an adult pregnant comparison group are needed to disentangle age-specific risk from population-level disadvantage. Nevertheless, the study provides valuable descriptive insights into the co-occurrence of structural disadvantage and adverse maternal and neonatal outcomes among a highly marginalized and underrepresented population, and identifies clear directions for future research.

Conclusion

The present study reveals that adolescent pregnancy in tribal communities accessing institutional delivery in Jharkhand occurs within a complex network of educational, familial, socioeconomic, and healthcare-related vulnerabilities. The high prevalence of cumulative vulnerability and its unadjusted association with anaemia, pregnancy-induced hypertension, low birth weight, and prematurity are consistent with a clustering of social disadvantages linked to adverse maternal and neonatal outcomes in this population. These findings underscore the need for comprehensive, culturally appropriate interventions that simultaneously address education, healthcare access, nutrition, social protection, and family-level determinants, alongside adequately powered, adjusted, and longitudinal studies to confirm and extend these findings.

Ethical approval

This study was approved by the Institutional Ethics Committee of Tata Main Hospital, Jamshedpur under reference no. TMH/IEC/NOV/10/2023 dated 29.11.2023.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ID, AK, TP; data collection: ID; analysis and interpretation of results: AK, TP; draft manuscript preparation: ID, AK, TP. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescents: a cross-sectional study

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ABSTRACT

Background. This study aimed to examine the relationships between menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescents, and to evaluate the influence of socio-demographic factors.

Methods. A cross-sectional study was conducted with 215 adolescent girls aged 15–19 years in Türkiye. Data were collected online using a questionnaire including socio-demographic information and three validated scales: Menstrual Poverty Scale (MPS), Menstrual Attitude Questionnaire (MAQ), and Genital Hygiene Behavior Scale (GHBS). Descriptive statistics, t-tests, ANOVA, Pearson correlations, and multiple linear regression analyses were performed.

Results. The mean age at menarche was 12.55 ± 1.16 years. MPS scores indicated moderate menstrual poverty, with the poorest scores for product access. MAQ scores were highest for Anticipation and Prediction and lowest for Denial of Any Effect, while GHBS averaged 87.11 ± 10.15 . Associations between menstrual attitudes and hygiene behaviors were weak. Reporting stigma or shame, rather than economic reasons, as the main barrier to accessing menstrual products predicted lower menstrual poverty scores (adjusted $R^2 = 6.9\%$). Menstrual irregularity was the only independent predictor of genital hygiene behaviors (adjusted $R^2 = 12.9\%$).

Conclusions. Menstrual poverty and genital hygiene behaviors were only partly explained by the variables examined. Economic barriers remained relevant to menstrual poverty, whereas menstrual irregularity was independently associated with higher genital hygiene behavior scores. Menstrual attitudes showed limited independent associations with the outcomes. The modest explanatory power of both regression models suggests that broader structural, familial, educational, and environmental factors should be considered. Interventions should combine affordable access to menstrual products with comprehensive menstrual education and supportive family, school, and community environments.

Key words: adolescent health, genital hygiene, menstrual attitude, menstrual poverty.

Adolescence is a critical developmental stage marked by physical, emotional, and social changes.¹ The onset of menstruation is a key milestone in reproductive maturation², yet for many adolescents it also reflects inequities in access to health and hygiene products.² Menstrual health is essential for global health,^{2,3} the Sustainable Development Goals, and

advancing gender equality.^{3,4} Menstrual poverty that is defined as limited access to products, inadequate sanitation, and insufficient education⁵⁻⁷ is a major global health and human rights concern.^{4,8}

Data from the World Health Organization strikingly reveal the magnitude of global

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deficiencies in menstrual health. Worldwide, only approximately 39% of schools provide menstrual health education, and only 31% have waste bins for menstrual waste in toilets. When regional differences are considered, the situation becomes even more evident. In Central and Southern Asia, 39% of schools provide menstrual education, while this rate declines to 30% in Sub-Saharan Africa. In Least Developed Countries, only 17% of schools have waste disposal facilities. At the local level, data show that the situation is much more critical in some regions: for example, waste bins were observed in only 1% of schools in Tajikistan, and only 3% of students in Ethiopia reported having access to dedicated waste bins. In India, when menstrual waste management facilities such as covered bins or incinerators are included in the criteria, the proportion of schools with basic sanitation service levels decreases to as low as 18%.⁹ In the U.S., nearly half of high school girls had been unable to purchase products and 17% missed school as a result;⁵ among university students, 17.1% reported financial difficulties, 55.8% experienced disrupted coursework, and 47.5% avoided changing products on campus.⁶ In South Africa, poor access to products and sanitation infrastructure has negatively affected attendance and Quality of Life,¹⁰ while in Türkiye, financial difficulties in accessing products were linked to lower genital hygiene behavior scores.¹¹ A nationally representative study from Türkiye conducted among adolescents reported that 15% of participants experienced difficulties in accessing Menstrual Hygiene products due to financial constraints, with a higher prevalence (25%) observed in socioeconomically disadvantaged regions. The study also documented the use of improvised menstrual products (17.4%), menstrual poverty-related school absenteeism (8.9%), prolonged use of menstrual materials due to unsuitable school environments (52%), and feelings of shame when purchasing menstrual products (10.7%), all of which were significantly more prevalent in lower socioeconomic tiers. Furthermore, adolescents experiencing menstrual poverty were three times more likely to report moderate-

to-severe depressive symptoms.¹² Menstrual poverty therefore impacts not only material access but also daily life, school participation, and hygiene behaviors,^{13,14} and affects women even in high-income countries.¹⁵

Although menstruation is natural, cultural stigmatization and taboos persist,^{2,10,11} contributing to perceptions of shame. Menstrual attitudes are critical, as positive attitudes and self-efficacy support safe hygiene, whereas negative attitudes are associated with shame and unsafe practices,¹⁶ with implications for mental health and school attendance.⁹

Menstrual attitudes are critical determinants of health-related behaviors. According to the Health Belief Model (HBM), individuals' perceptions of susceptibility, severity, and self-efficacy shape their engagement in preventive health behaviors, including hygiene practices.¹⁷ Applied to menstrual health, adolescents who perceive menstruation negatively (as debilitating or shameful) may exhibit lower self-efficacy and reduced motivation to maintain hygiene, whereas positive attitudes and stronger self-efficacy are associated with safer practices.¹⁸ The Theory of Planned Behavior (TPB) further suggests that attitudes, subjective norms, and perceived behavioral control jointly predict health-related intentions and actions.¹⁹ In the context of Menstrual Hygiene, cultural stigmatization and taboos may undermine subjective norms and behavioral control, thereby translating negative attitudes into unsafe practices with implications for mental health and school attendance. Despite growing attention to menstrual equity, the interplay of menstrual poverty, attitudes, and genital hygiene behaviors in adolescents remains insufficiently understood. Such insights are needed to improve product access, foster positive attitudes, and promote safe hygiene practices. This study aimed to examine the relationships between menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescent girls aged 15–19 years in Türkiye, and to evaluate the influence of socio-demographic factors on these outcomes.

The following research questions guided the study: (1) What is the level of menstrual poverty, menstrual attitudes, and genital hygiene behaviors among adolescent girls? (2) Are menstrual poverty and menstrual attitudes associated with genital hygiene behaviors? (3) Which socio-demographic factors predict menstrual poverty and genital hygiene behaviors?"

Materials and Methods

Study design and participants

This descriptive, cross-sectional study was conducted among adolescent girls aged between 15–19 years in Türkiye. Eligible participants were those who had experienced menarche, were currently menstruating, and consented to participate. Exclusion criteria included the presence of a chronic illness or cognitive impairment that could interfere with completing the questionnaire. The sample size was calculated using GPower (v3.1.7) software based on Pearson correlation analysis, assuming a medium effect size ($r = 0.20$), a significance level of 0.05 (two-tailed), and a statistical power of 80%. The minimum required sample size was determined to be 273. After exclusion of incomplete questionnaires, the final analytical sample comprised 215 participants. A post hoc power analysis using the final sample size ($n = 215$) yielded an achieved power of 76%. Although this value was lower than the originally targeted 80%, it remained within an acceptable range for detecting small-to-moderate associations. Setting and recruitment

The study was conducted using an online data collection process. Research data were collected between March and June 2025 using an online questionnaire created on Google Forms. Participants were recruited from high school students in İstanbul, Türkiye. The survey link was distributed via WhatsApp to high school students through the researchers' personal and

professional networks. Eligible participants were informed about the study's aims, eligibility criteria, and the voluntary nature of participation in the recruitment message. Before starting the survey, participants accessed an information sheet describing the study procedures. Electronic informed consent was obtained prior to completing the questionnaire.

Data collection tools

Data were collected using a structured online questionnaire consisting of two parts. The first part included 17 items on sociodemographic and menstruation-related characteristics (e.g., age, school grade, age at menarche, menstrual cycle regularity, menstrual pain, and hygiene practices). The second part comprised three scales: Menstrual Poverty Scale (MPS), Menstrual Attitude Questionnaire (MAQ), Genital Hygiene Behavior Scale (GHBS).

Menstrual Poverty Scale (MPS): The MPS was developed by Öz Yıldırım et al. in 2024.²⁰ The scale consists of 13 items and four subscales: Access to Hygiene Products, Quality of Life, Embarrassment, and Receiving Information and Education. It is a 5-point Likert-type scale (ranging from 1 = Strongly Disagree to 5 = Strongly Agree). Higher scores indicate greater menstrual poverty. Items 2, 12, and 13 are reverse-scored. The scale consists of 13 items and four subscales: Access to Hygiene Products (3 items), Quality of Life (4 items), Embarrassment (4 items), and Receiving Information and Education (2 items). In this study, the Cronbach's alpha coefficient of the scale was found to be 0.75.

Menstrual Attitude Questionnaire (MAQ): The MAQ was developed by Brooks-Gunn and Ruble in 1980,²¹ and its Turkish validity and reliability study was conducted by Kulakaç et al. in 2008.²² In its original form, the scale is a 7-point Likert-type instrument; however, the adapted Turkish version uses a 5-point Likert-type format, with scores ranging from 1

(Strongly Disagree) to 5 (Strongly Agree). The scale consists of 31 items and five subscales: Menstruation as a Debilitating Event (7 items), Menstruation as a Bothersome Event (5 items), Menstruation as a Natural Event (5 items), Anticipation and Prediction of the Onset of Menstruation (8 items), and Denial of Any Effect of Menstruation (6 items). Higher mean scores in any subscale or in the overall scale indicate a more “positive” attitude toward menstruation. The Cronbach’s alpha reliability coefficient of the scale is 0.79. In this study, the Cronbach’s alpha coefficient of the scale was found to be 0.77.

Genital Hygiene Behavior Scale (GHBS): The GHBS was developed by Karahan in 2017.²³ The scale consists of three subscales: General Hygiene Behaviors (12 items), Menstrual Hygiene (8 items), and Abnormal Finding Awareness (3 items). It contains a total of 23 items, scored on a 5-point Likert scale, with possible total scores ranging from 23 to 115. The scale measures women’s genital hygiene behaviors, with higher scores indicating a higher frequency of correct genital hygiene practices. In the original form of the scale, Cronbach’s alpha coefficients were 0.80 for the GHBS total, 0.70 for General Hygiene Behaviors, 0.74 for Menstrual Hygiene, and 0.81 for Abnormal Finding Awareness. In this study, the Cronbach’s alpha coefficient of the scale was found to be 0.78.

Data analysis

The data obtained from the research were evaluated using the SPSS for Windows (Statistical Package for Social Science for Windows, Version 28.0) package program. Categorical variables were presented as frequency (n) and percentage (%), while quantitative data were summarized using mean $\pm$ standard deviation (SD), and minimum-maximum values. The normality of data distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests,

along with skewness and kurtosis values. For between-group comparisons, the Independent sample t test and one-way ANOVA test were used for continuous variables. Pearson correlation analysis was used to examine relationships between normally distributed continuous variables. Multiple linear regression analyses were conducted separately for the MPS and GHBS total scores. Candidate predictors were selected using a purposeful model-building strategy. Sociodemographic and menstruation-related variables associated with the relevant dependent variable at $p < 0.20$ in preliminary univariable analyses were considered for inclusion. In addition, the total scores of the other menstrual health scales were included because of their theoretical relevance to the study objectives, regardless of their statistical significance in the preliminary analyses. Categorical variables with more than two categories were dummy coded. All selected variables were entered simultaneously using the enter method. Multicollinearity was assessed using tolerance and variance inflation factor values. The assumptions of linearity, normality, homoscedasticity, and independence of residuals were also evaluated. A p -value < 0.05 was considered statistically significant. The MPS total score was treated as a continuous variable in all analyses, consistent with the original scale development study and with prior research employing this instrument.

Ethics approval

This study was approved by the Istanbul University Social and Human Sciences Research Ethics Committee (Date: 26.02.2025; No: 2025/46). As all participants were aged 15 years or older, individual informed consent was obtained directly from the adolescents themselves, in accordance with the ethics committee’s requirements, which stipulated parental consent only for participants under

the age of 15. Electronic informed consent was obtained from all participants prior to completing the questionnaire. All participants were fully informed about the aim and procedures of the study, and their voluntary participation was ensured. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Results

The socio-demographic and menstrual characteristics of adolescents are shown in Table I. The mean age was 16.22 ± 1.08 years, with a mean menarche age of 12.55 ± 1.16 years. Most of the participants lived with family (94.9%), had regular menstruation ($n=157$, 73.0%), and

Table I. Socio-demographic and menstrual characteristics of the participants ($n=215$).

Variables	Mean $\pm$ SD	Min-Max
Age (years)	16.22 ± 1.08	15-19
Age at menarche (years)	12.55 ± 1.16	9-16
Menstrual cycle length (days)	30.66 ± 8.92	20-90
Menstrual duration (days)	5.85 ± 1.22	3-10
	Categories	n (%)
Living arrangement	Dormitory	11 (5.1)
	With family	204 (94.9)
Family monthly income	Income < expenses	10 (4.7)
	Income = expenses	105 (48.8)
	Income > expenses	100 (46.5)
Mother's education	Primary school	41 (19.0)
	Secondary school	27 (12.6)
	High school	74 (34.4)
	University or above	73 (34.0)
Father's education	Primary school	30 (14.0)
	Secondary school	29 (13.5)
	High school	68 (31.6)
	University	88 (40.9)
Menstrual regularity	Yes	157 (73.0)
	No	58 (27.0)
Received menstrual education	Yes	176 (81.9)
	No	39 (18.1)
Source of menstrual information (multiple responses possible)	Mother	163 (75.8)
	Sister	7 (3.3)
	TV/Internet	5 (2.3)
	Social media	8 (3.7)
	Teacher	6 (2.8)
	Healthcare professional	12 (5.6)
	No information	14 (6.5)
Primary menstrual product used	Sanitary pad	215 (100.0)
Difficulty accessing menstrual products	Yes	7 (3.3)
	No	208 (96.7)
Main barrier to obtaining products	Economic reasons	69 (32.1)
	Product unavailability	41 (19.1)
	Social stigma/shame	46 (21.4)

The item "Difficulty accessing menstrual products" assessed whether participants had personally experienced difficulty obtaining menstrual products (Yes/No). In contrast, the item "Main barrier to obtaining products" was administered to all participants and evaluated the perceived primary barrier to menstrual product access (e.g., economic reasons, product unavailability, or social stigma/shame), irrespective of whether participants had personally experienced access difficulties. SD: standard deviation.

reported receiving menstrual education (n=176, 81.9%). When asked about the perceived primary barrier to menstrual product access, economic reasons were the most frequently reported response (n=69, 32.1%). The mean scores of the Menstrual Poverty, Menstrual Attitude, and Genital Hygiene Behavior Scales are presented in Table II. The mean MPS score was 34.19 ± 7.09 , with subscale means ranging from 6.72 ± 2.34 (Receiving Information and Education about Menstruation) to 14.21 ± 4.77 (Quality of Life). The MAQ total score was 95.13 ± 11.62 , with subscale means ranging from 11.59 ± 4.64 (Denial of Any Effect of Menstruation) to 27.61 ± 4.29 (Anticipation and Prediction of the Onset of Menstruation). The mean GHBS total score was 87.11 ± 10.15 , with subscale means of 44.78 ± 5.72 for General hygiene, 31.90 ± 4.32 for Menstrual Hygiene, and 10.42 ± 2.52 for Abnormal Finding Awareness.

The correlations between the MPS, MAQ, and GHBS are illustrated in the heatmap (Fig. 1). Menstrual poverty showed a weak but significant positive correlation with the

Menstruation as a Debilitating Event subscale ($r = 0.187, p < 0.05$) and no significant association with the total scores of the other scales. Access to Hygiene Products subscale was negatively associated with General hygiene ($r = -0.144, p < 0.05$) and Menstrual Hygiene ($r = -0.231, p < 0.05$). At the subscale level, Menstruation as a Debilitating Event was negatively correlated with Abnormal Finding Awareness ($r = -0.140, p < 0.05$), while Menstruation as a Natural Event was positively correlated with Menstrual Hygiene ($r = 0.140, p < 0.05$). The Denial of Any Effect of Menstruation subscale showed a weak negative correlation with both the GHBS total score ($r = -0.111, p < 0.05$) and the Menstrual Hygiene subscale ($r = -0.221, p < 0.05$).

As shown in Table III, the GHBS scores differed significantly by family monthly income ($F = 3.037, p = 0.048$), with higher scores among participants whose income was lower than expenses compared to those whose income exceeded expenses. Menstrual regularity was also significantly associated with GHBS scores ($t = -3.219, p < 0.001$), with higher scores in

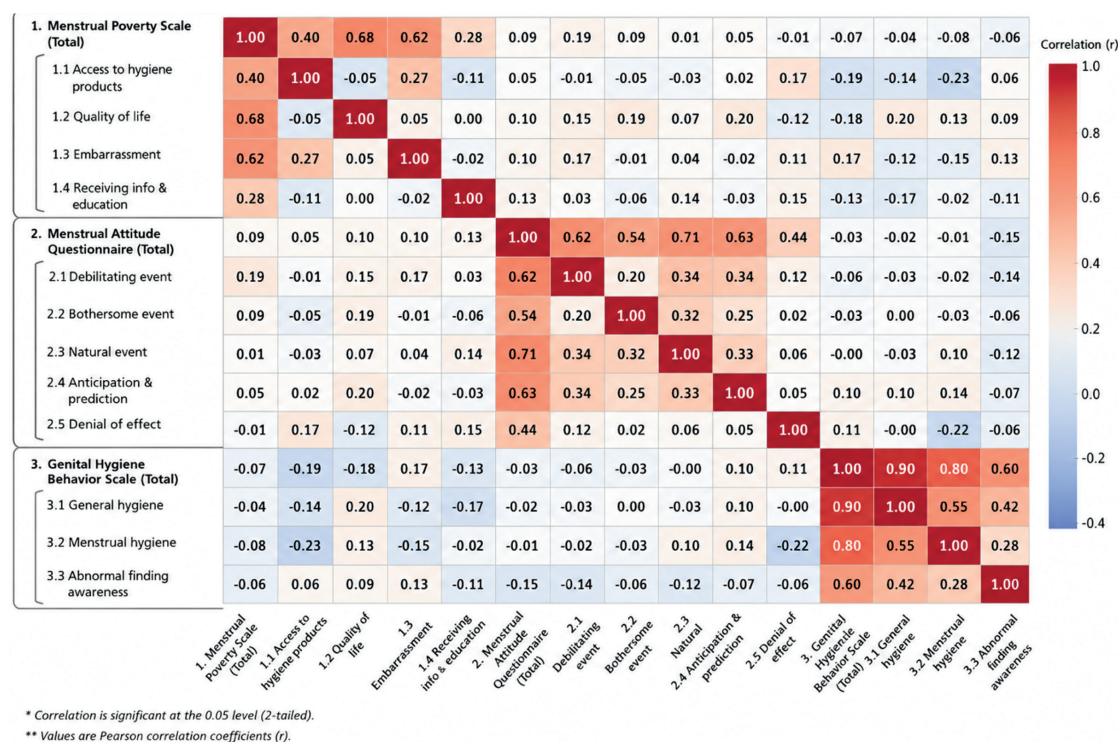


Fig. 1. Correlation heatmap: menstrual poverty, menstrual attitudes, and genital hygiene behaviors scales.

Table II. Mean scores of menstrual poverty, menstrual attitudes, and genital hygiene behaviors scales (total and subscales).

Scale	Subscales	Mean $\pm$ SD	Min–Max
Menstrual Poverty Scale	Access to Hygiene Products	4.95 $\pm$ 2.39	3.0-15.0
	Quality of Life	14.21 $\pm$ 4.77	4.0-20.0
	Embarrassment	8.28 $\pm$ 3.56	4.0-19.0
	Receiving Information and Education about Menstruation	6.72 $\pm$ 2.34	2.0-10.0
	Total	34.19 $\pm$ 7.09	17.0-53.0
Menstrual Attitude Questionnaire	Menstruation as a Debilitating Event	21.91 $\pm$ 3.06	13.0-35.0
	Menstruation as a Bothersome Event	16.59 $\pm$ 3.10	5.0-25.0
	Menstruation as a Natural Event	17.41 $\pm$ 4.53	5.0-25.0
	Anticipation and Prediction of the Onset of Menstruation	27.61 $\pm$ 4.29	12.0-40.0
	Denial of Any Effect of Menstruation	11.59 $\pm$ 4.64	6.0-30.0
	Total	95.13 $\pm$ 11.62	63.0-155.0
Genital Hygiene Behavior Scale	General hygiene	44.78 $\pm$ 5.72	20.0-60.0
	Menstrual Hygiene	31.90 $\pm$ 4.32	17.0-40.0
	Abnormal Finding Awareness	10.42 $\pm$ 2.52	3.0-15.0
	Total	87.11 $\pm$ 10.15	47.0-112.0

SD: standard deviation.

participants reporting irregular menstruation. Additionally, the MPS scores varied significantly according to the main barrier to obtaining menstrual products ($F = 3.523$, $p = 0.016$), with the highest scores observed among those citing economic reasons as the main barrier. No other socio-demographic or menstrual characteristics were significantly related to the scale scores.

The multiple linear regression analyses are presented in Table IV. In the model examining menstrual poverty, paternal education, the perceived main barrier to obtaining menstrual products, MAQ total score, and GHBS total score were included as independent variables. The model was statistically significant and explained 6.9% of the variance in menstrual poverty scores ($R^2 = 0.069$, adjusted $R^2 = 0.037$, $F(7, 207) = 2.183$, $p = 0.037$). Compared with participants who identified economic reasons as the main barrier, those who identified social stigma or shame had significantly lower menstrual poverty scores ($B = -3.195$, 95% confidence interval $-5.331, -1.060$, $\beta = -0.226$,

$p=0.004$). No other variable was a statistically significant independent predictor of menstrual poverty.

In the model examining genital hygiene behaviors, age, living arrangement, family monthly income, maternal education, menstrual regularity, receipt of menstrual education, MPS total score, and MAQ total score were included. The model was statistically significant and explained 12.9% of the variance in genital hygiene behavior scores ($R^2 = 0.129$, adjusted $R^2 = 0.081$, $F(11, 203) = 2.722$, $p = 0.003$). Menstrual irregularity was the only statistically significant independent predictor. Participants reporting irregular menstruation had genital hygiene behavior scores approximately 5.26 points higher than those reporting regular menstruation ($B = 5.258$, 95% confidence interval $[2.232-8.284]$, $\beta = 0.230$, $p=0.001$). Family monthly income, menstrual poverty, and menstrual attitudes were not independently associated with genital hygiene behavior scores in the adjusted model.

Table III. Comparison of scale scores according to socio-demographic and menstrual characteristics.

Variable	Categories	Menstrual Poverty Scale Mean ± SD	Menstrual Attitude Questionnaire Mean ± SD	Genital Hygiene Behavior Scale Mean ± SD	Menstrual Poverty Scale		Menstrual Attitude Questionnaire		Genital Hygiene Behavior Scale	
					Test value	p-value	Test value	p-value	Test value	p-value
Family monthly income	Income < expenses	32.70 ±7.45	99.70 ±8.34	92.80 ±9.17	0.284*	0.753*	0.817*	0.443*	3.037*	0.048*
	Income = expenses	34.10 ±7.21	95.00 ±10.55	87.97 ±10.08						
	Income > expenses	34.43 ±6.97	94.80 ±12.89	85.65 ±10.11						
Menstrual regularity	Yes	33.97 ±6.88	95.52 ±12.24	85.78 ±10.48	-0.734**	0.463**	0.826**	0.410**	-3.219**	<0.001**
	No	34.77 ±7.66	94.05 ±9.76	90.70 ±8.27						
Main barrier to obtaining products	Economic reasons	36.05 ±6.74	94.85 ±11.04	86.73 ±11.59	3.523*	0.016*	0.127*	0.944*	0.201*	0.946*
	Product unavailability	34.85 ±6.42	95.78 ±9.34	87.39 ±9.33						
Social stigma/shame		32.17 ±7.52	95.65 ±14.30	88.02 ±8.96						

p<0.05 indicates statistical significance.
* One-way ANOVA. **Independent Samples t-test
SD: standard deviation.

Table IV. Multiple linear regression analyses of factors associated with menstrual poverty and genital hygiene behaviors among adolescents (n = 215).

Independent variables	B (95% CI)	SE	β	t	p
Model 1. Dependent variable: menstrual poverty scale total score					
Father’s education ^a					
Primary school	−0.131 (−3.045 to 2.783)	1.478	−0.006	−0.089	0.930
Secondary school	−2.300 (−5.282 to 0.682)	1.513	−0.111	−1.520	0.130
High school	−0.613 (−2.830 to 1.604)	1.124	−0.040	−0.545	0.586
Main barrier to obtaining menstrual products ^b					
Product unavailability	−1.234 (−3.942 to 1.474)	1.373	−0.069	−0.899	0.370
Social stigma/shame	−3.195 (−5.331 to −1.060)	1.083	−0.226	−2.950	0.004
Menstrual Attitude Questionnaire total score	0.065 (−0.017 to 0.147)	0.042	0.106	1.548	0.120
Genital Hygiene Behavior Scale total score	−0.039 (−0.131 to 0.054)	0.047	−0.055	−0.830	0.412
Model statistics	R ² = 0.069; adjusted R ² = 0.037; F (7, 207) = 2.183; p = 0.037				
Model 2. Dependent variable: Genital Hygiene Behavior Scale total score					
Age, years	0.629 (−0.603 to 1.861)	0.625	0.067	1.006	0.315
Dormitory residence ^c	5.210 (−1.072 to 11.493)	3.186	0.113	1.635	0.104
Family monthly income ^d					
Income lower than expenses	4.040 (−2.535 to 10.615)	3.335	0.084	1.211	0.227
Income higher than expenses	−1.903 (−4.747 to 0.940)	1.442	−0.094	−1.320	0.188
Mother’s education ^e					
Primary school	1.899 (−2.207 to 6.005)	2.083	0.074	0.912	0.363
Secondary school	−3.606 (−8.094 to 0.882)	2.276	−0.118	−1.584	0.115
High school	0.657 (−2.546 to 3.860)	1.625	0.031	0.404	0.686
Irregular menstruation ^f	5.258 (2.232 to 8.284)	1.535	0.230	3.425	0.001
No menstrual education ^g	2.483 (−0.987 to 5.954)	1.760	0.094	1.411	0.160
Menstrual Poverty Scale total score	−0.082 (−0.269 to 0.105)	0.095	−0.057	−0.863	0.389
Menstrual Attitude Questionnaire total score	−0.044 (−0.160 to 0.072)	0.059	−0.050	−0.746	0.454
Model statistics	R ² = 0.129; adjusted R ² = 0.081; F (11, 203) = 2.722; p = 0.003				

All variables were entered simultaneously using the enter method. Bold p values indicate statistical significance at $p < .05$. Reference categories: ^auniversity or above, ^beconomic reasons, ^cliving with family, ^dincome equal to expenses, ^euniversity or above, ^fregular menstruation, ^greceived menstrual education, B = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; SE = standard error.

Discussion

This study investigated the interrelations among menstrual poverty, menstrual attitudes, and genital hygiene behaviors in adolescents, alongside the influence of socio-demographic factors. The majority of participants resided with their families and identified their

mothers as the primary source of menstrual information, highlighting the family's pivotal role in menstrual health education. The low percentage of participants citing teachers or health professionals as information sources underscores deficiencies in formal education. Although nearly half of the participants reported household income matching expenses,

economic constraints were the predominant barrier to accessing menstrual products. In the present study, households where income equaled expenses were considered to reflect moderate financial status, as this categorization was based on participants' own perceptions of their financial situation rather than an objective income measure. These findings suggest that menstrual poverty may also impact adolescents from households with limited but balanced financial resources, consistent with previous literature.^{7,14,15,24,25} All participants reported using pads, while the lack of alternative products (e.g., tampons, menstrual cups) may be attributed to cultural or accessibility barriers.²⁶

The MPS score was moderate, with the lowest scores in product access, consistent with previous studies.^{13,14} In the MAQ, the highest mean score was observed in the Anticipation and Prediction subscale, and the lowest in the denial of any effect, corroborating Fışkın Siyahtaş et al.²⁶ Elevated scores in the debilitating and bothersome subscales indicated predominantly negative perceptions, in agreement with Borges et al.¹⁶ The GHBS mean score was comparable to earlier research.²⁷⁻³² While general and menstrual hygiene practices were deemed adequate, low scores in awareness of abnormal findings highlighted a limited recognition of unusual symptoms, supporting the findings of Tshivule et al.¹⁰

Correlation analyses revealed weak associations between menstrual attitudes and hygiene behaviors. The denial of any effect subscale showed weak but statistically significant negative correlations with both the GHBS total score and the Menstrual Hygiene subscale, suggesting that adolescents who tend to deny any effect of menstruation may engage in slightly less attentive menstrual hygiene practices. However, given the weakness of these correlations, these findings should be interpreted with caution. A modest positive correlation was identified between anticipation and prediction and general hygiene, suggesting that awareness of menstrual signs may enhance hygiene practices, aligning with previous

research conducted in India.³² Conversely, perceiving menstruation as a debilitating event was negatively associated with awareness of abnormal findings, though the weak correlation coefficient suggests that this association should be interpreted with caution and does not allow for strong conclusions regarding attentiveness to health warning signs. Ghiasi et al.³³ similarly reported that viewing menstruation as "debilitating" was linked to lower symptom awareness and poorer self-care. Overall, menstrual attitudes appear to exert a limited influence on hygiene behaviors, which are more strongly shaped by structural and contextual determinants. This pattern is consistent with a social-ecological perspective, which posits that individual behaviors are embedded within broader environmental, institutional, and socioeconomic systems.² From this standpoint, even adolescents with positive menstrual attitudes may be unable to maintain adequate hygiene practices in the absence of affordable products, functional sanitation infrastructure, or supportive school and family environments. Conversely, structural barriers such as economic hardship and limited access to products may override the potential positive influence of attitudes on behavior. These findings suggest that attitude-focused interventions alone are unlikely to be sufficient, and that structural level changes (including ensuring affordable product access, improving school sanitation facilities, and strengthening family and community support systems) are essential prerequisites for meaningful improvements in adolescent menstrual hygiene behaviors.

Research has documented a correlation between women's monthly income and their genital hygiene behaviors.²⁶ Higher scores in genital hygiene behaviors among women with elevated income levels have been linked to improved living conditions, enhanced access to health services, and increased hygienic practices facilitated by greater economic resources.³⁴ In the present study, an unexpected relationship was identified between family income and genital hygiene behaviors. Adolescents from

households where expenses surpassed income reported higher hygiene scores compared to those from households with greater financial resources. This unexpected finding is difficult to interpret with certainty given the cross-sectional design of the study and the absence of qualitative data on participants' hygiene motivations. One possible explanation is that adolescents from financially constrained households may develop greater awareness of hygiene as a low-cost protective behavior; however, this interpretation remains speculative and should be tested in future research. It is also plausible that unmeasured variables, such as household crowding, access to water and sanitation facilities, or maternal health literacy, may confound this relationship. Similar paradoxical results have been observed in previous studies, suggesting a possible, though modest, association between awareness of menstrual signs and hygiene practices; however, the weak correlation coefficient warrants caution in inferring a directional or causal relationship. Conversely, other studies have reported no significant correlation between monthly income and the mean scores of women's genital hygiene behaviors.²⁵ Although family income was associated with genital hygiene behavior scores in the unadjusted comparison, this association was no longer statistically significant after age, living arrangement, maternal education, menstrual regularity, menstrual education, menstrual poverty, and menstrual attitudes were considered simultaneously. This suggests that the observed income-based differences may partly reflect the influence of other individual or contextual characteristics. Therefore, family income should not be interpreted as an independent determinant of genital hygiene behaviors in the present sample.

Menstrual regularity remained the only statistically significant independent predictor of genital hygiene behaviors in the adjusted model. Adolescents with irregular menstrual cycles had higher genital hygiene behavior scores than those with regular cycles. One possible explanation is that irregular menstruation

may increase attention to bodily changes and encourage more deliberate hygiene practices. However, because of the cross-sectional design, the direction of this relationship cannot be established. Furthermore, the modest explanatory power of the model indicates that menstrual regularity accounts for only a limited proportion of variation in hygiene behaviors. Similarly, previous studies have indicated that menstrual irregularities can heighten adolescents' awareness and attentiveness regarding menstrual management.³⁵⁻³⁷ Regression analysis similarly identified menstrual regularity as a statistically significant predictor of genital hygiene behaviors, though the modest explained variance suggests that this relationship should be interpreted with caution.

Adolescents who identified economic reasons as barriers to accessing menstrual products exhibited significantly higher menstrual poverty scores compared to those who attributed their challenges to product unavailability or social stigma. Economic barriers remained relevant to menstrual poverty; however, the adjusted analysis showed that adolescents identifying economic reasons as the primary barrier had higher menstrual poverty scores than those identifying social stigma or shame. Similar patterns have been observed in low- and middle-income countries, where financial limitations are closely linked to restricted access to menstrual products and adverse menstrual health outcomes.^{38,39} Regression analysis supported this finding; however, the low explained variance indicates that economic barriers, while statistically significant, account for only a small proportion of the variability in menstrual poverty scores, suggesting that additional unmeasured factors may also play an important role. Nevertheless, the relatively low explained variance in both models indicates that menstrual poverty and hygiene behaviors cannot be fully explained by individual or socio-demographic characteristics alone. These findings highlight the importance of considering environmental and contextual

factors-such as school settings, family support, and broader social norms-in shaping adolescent menstrual health outcomes.

This study highlights the multidimensional nature of adolescent menstrual health. The regression analyses showed that identifying social stigma or shame rather than economic reasons as the primary barrier was associated with lower menstrual poverty scores, while menstrual irregularity was the only independent predictor of genital hygiene behaviors. Menstrual attitudes and the other scale scores did not independently predict the outcomes after relevant sociodemographic and menstruation-related characteristics were considered. The modest explanatory power of both models indicates that menstrual poverty and genital hygiene behaviors are likely shaped by broader structural, familial, educational, and environmental factors that were not fully captured in the present study. Interventions should therefore combine affordable product access with comprehensive menstrual education and supportive school and family environments.

Limitations

Several limitations of this study should be acknowledged. Participants were recruited through online convenience sampling via WhatsApp, targeting high school students in Istanbul, Türkiye. This approach may have introduced selection bias, as students without internet access or smartphone use were systematically excluded. Furthermore, the voluntary nature of participation may have resulted in volunteer bias, whereby adolescents with greater awareness of or interest in menstrual health were more likely to participate, potentially overestimating positive attitudes and hygiene behaviors in the sample. Additionally, as the sample was drawn exclusively from high school students in Istanbul, the findings may not be generalizable to adolescents in other regions of Türkiye or to those not enrolled in formal education. These factors limit the representativeness of

the findings, and caution should be exercised when generalizing the results to the broader Turkish adolescent population. Additionally, the socioeconomic distribution of the sample was uneven, with only 4.7% of participants reporting household income below expenses. This underrepresentation of lower-income adolescents may have limited the ability to adequately evaluate the relationship between socioeconomic disadvantage and menstrual poverty, and caution should be exercised when interpreting findings related to income-based comparisons.

Ethical approval

This study was approved by the Istanbul University Social and Human Sciences Research Ethics Committee (Date: 26.02.2025; No: 2025/46). Informed consent form was added to the beginning of the online questionnaire. All participants were fully informed about the aim and procedures of the study, and their voluntary participation was ensured through the collection of written informed consent. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MT, EG, ÖŞ; data collection: EG,ÖŞ; analysis and interpretation of results: MT; draft manuscript preparation: MT, EG, ÖŞ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Trends in adolescent suicide attempts requiring pediatric intensive care across pre-COVID, COVID, and post-COVID periods

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ABSTRACT

Background. The COVID-19 pandemic adversely affected adolescent mental health. This study compares pediatric intensive care unit admissions (PICU) due to adolescent suicide attempts across pre-pandemic, pandemic, and post-COVID periods.

Methods. This retrospective study included adolescents aged 9–18 years admitted to the pediatric intensive care unit of Mersin City Training and Research Hospital for suicide attempts. Data were classified into pre-COVID (January 2019–March 2020), COVID (April 2020–March 2022), and post-COVID (April 2022–August 2024) periods. Variables included demographics, suicide method, psychiatric history, previous attempts, organ support, and outcomes.

Results. Of the 7,074 PICU admissions, 452 (6.4%) were for suicide attempts. Drug ingestion was predominant (95.8%). In the post-COVID period, the proportion of male cases, multiple-drug ingestions, and use of high-lethality methods increased, along with a greater need for intensive organ support. Mortality was observed only in the post-COVID period, with a rate of 1.8%. Logistic regression identified high-lethality methods, psychiatric follow-up, and previous attempts as predictors of severe outcomes in the post-COVID period.

Conclusions. Adolescent suicide attempts requiring PICU admission became more severe after COVID-19. Early risk detection and targeted interventions are essential.

Key words: adolescent, COVID-19, pandemic, pediatric intensive care, suicide attempt.

Suicide is one of the most preventable causes of death in adolescents. It ranks as the second leading cause of death among individuals aged 10–24 in the United States.¹ Periods of social and economic crisis are associated with heightened vulnerability to self-harm and suicidal behavior in this age group, a pattern that became more pronounced during and after the COVID-19 pandemic. This heightened vulnerability

may be driven by prolonged social isolation and educational disruption, compounded by increased family and financial stressors and reduced access to mental health services, collectively creating a fragile psychosocial environment for adolescents.^{2–6} In a meta-analysis including over 100 studies from 31 countries conducted during the COVID-19 pandemic, the prevalence of suicidal ideation

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among adolescents was 22.4%, underscoring the substantial burden of suicide-related risk during this period.⁷ In this context, early identification and effective prevention strategies are critically important.⁸⁻¹⁰ While many studies have investigated psychiatric presentations in emergency departments (ED)^{6,11-17} data on adolescents with suicide attempts (SA) requiring pediatric intensive care unit (PICU) admission remain limited.¹⁸⁻²¹ These cases represent the most severe end of the clinical spectrum and provide a unique opportunity to better understand adolescent suicidal behavior. The current study evaluates adolescents admitted to the PICU for SA across pre-, during-, and post-COVID periods. It aims to characterize changes in case profile and clinical severity, and to inform targeted prevention strategies. To the best of our knowledge, this study is among the few that provide a longitudinal evaluation of pre-pandemic, pandemic, and post-COVID periods in adolescents admitted to the PICU for SA.

Methods

The study was conducted in the PICU of Mersin City Training and Research Hospital. This tertiary-level unit has 30 beds and functions as a regional referral center for critically ill children. Annually, 1,500–2,000 patients are admitted, reflecting a broad referral region encompassing both urban and rural areas. The unit's case mix is heterogeneous, with a wide spectrum of medical and surgical critical illnesses. The study included adolescent patients admitted due to SA during the pre-COVID, COVID, and post-COVID periods. We included patients aged 9–18 years with confirmed SA. A confirmed SA was defined as a self-inflicted, harmful act performed with intent to die, with suicidal intent verified by psychiatric assessment and documented in the medical record. High-lethality was defined as suicide methods with a high probability of death even with timely medical intervention. This category included hanging, firearms, and jumping from heights. Cardiotoxic drug ingestions, as well as massive

or multiple-high-dose drug overdoses, were also classified as high-lethality. All other drug ingestions were considered low lethality. Cases without documented suicidal intent, including non-suicidal self-injury, accidental ingestions, or incomplete medical records, were excluded. Data were collected from electronic medical records and categorized based on the timeline of the pre-COVID (January 2019 – March 2020), during COVID (April 2020 – March 2022), and post-COVID (April 2022 – August 2024) periods. Collected data included demographic characteristics and clinical details such as SA method, Glasgow Coma Scale (GCS) score on admission, comorbidities, psychiatric history, history of previous SA, presence of organ failure, and trauma. In addition, information on treatments and interventions (mechanical ventilation (MV), hemodynamic support, renal replacement therapy (RRT), surgery) and outcomes (length of stay, complications, mortality) was recorded. The severity of illness at admission was assessed using the Pediatric Risk of Mortality III (PRISM III) score, which evaluates physiologic variables within the first 12 hours of PICU admission to estimate the risk of mortality. Higher scores indicate greater clinical severity. Ethical approval for the study was obtained from the Toros University Ethics Committee (Approval Number: 123).

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean $\pm$ standard deviation (minimum–maximum). Categorical variables were expressed as counts and percentages. For comparisons between two groups, the Student's t-test was used for normally distributed variables. For comparisons across the three study periods, the one-way ANOVA or Kruskal–Wallis test was applied depending on distributional assumptions, followed by Bonferroni-adjusted post-hoc tests where appropriate. Categorical

variables were compared using the Chi-square test or Fisher's exact test when expected cell counts were <5 . To identify independent risk factors associated with severe clinical outcomes, a multivariate logistic regression analysis was conducted. For multivariable analysis, logistic regression was used to identify independent predictors of severe clinical outcomes. Severe clinical outcome was defined as the presence of at least one of the following: need for invasive mechanical ventilation, hemodynamic support, renal replacement therapy, surgical intervention, prolonged PICU stay, or mortality. Candidate variables were selected based on clinical relevance and significant or near-significant associations in univariate comparisons. The variables entered into the model were study period, sex, high-lethality method, psychiatric follow-up history, and previous suicide attempt. These variables were chosen because they are established or biologically plausible predictors of clinical severity in adolescent suicide attempts and showed meaningful differences across study periods in the present cohort. Because mortality events were rare, multivariable modeling for mortality was not performed. Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and p-values. Statistical significance was set at a two-tailed p-value <0.05 .

Results

A total of 7,074 pediatric patients were admitted to our PICU during the approximately 6-year study period. Of these, 452 patients (6.4%) were hospitalized due to SA. The patient screening and inclusion process is summarized in Fig. 1. To account for differences in overall PICU activity across the study periods, the incidence of SA per 1,000 PICU admissions was calculated: 83/1000 in the pre-COVID period, 42/1000 during COVID, and 58/1000 in the post-COVID period. Among them, 362 (80.0%) were girls and 90 (20.0%) were boys. The overall mean age of the patients was 15.5 ± 1.5 years (range: 9–18 years). The most common method of SA was drug ingestion, observed in 433 patients (95.8%). This was followed by jumping from a height in 13 patients (2.9%), self-inflicted injuries with sharp objects in 3 patients (0.7%), and hanging in 2 patients (0.4%). A history of psychiatric follow-up was present in 118 patients (26.1%), while 24 patients (5.3%) had a previous history of SA.

In the pre-COVID period, a total of 219 patients (48.4%) were admitted. Of these, 187 (85.4%) were female and 32 (14.6%) male, with a mean age of 15.5 ± 1.4 years. Regarding the method of attempt, drug ingestion was observed in 216 patients (98.6%), while jumping from a height

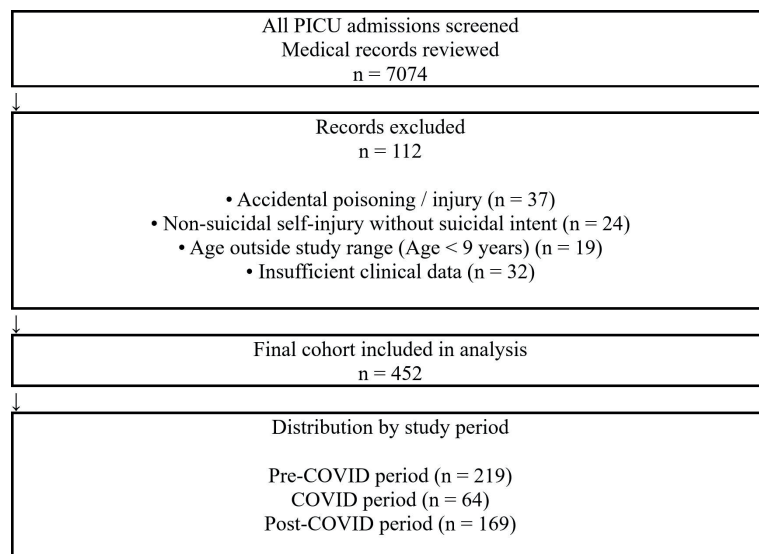


Fig. 1. Flow diagram of patient selection.

was reported in 3 patients (1.4%). Psychiatric follow-up was present in 33 patients (15.1%), and a history of prior attempts was recorded in 5 patients (2.3%). No deaths were reported during this period. The mean PICU length of stay was 1.65 ± 0.8 days (range: 1–6 days). Detailed data are presented in Table I.

During the COVID period, a total of 64 patients (14.1%) were admitted. Of these, 54 (84.4%) were female and 10 (15.6%) male, with a mean age of 15.5 ± 1.6 years. In all cases, the method of attempt was drug ingestion (100%). Psychiatric follow-up was reported in 21 patients (32.8%), and a history of prior attempts was documented

Table I. Patients' characteristics of suicide attempts across study groups.

	Pre-COVID	COVID	Post-COVID	p value
Number of patients	219	64	169	
Age (years), mean $\pm$ SD	15.5 ± 1.4	15.5 ± 1.6	15.6 ± 1.6	>0.05
Sex: F/M, n (%)	187/32 ^a (85/15)	54/10 ^{ab} (84/16)	121/48 ^b (72/28)	<0.05
Suicide method, n (%)				
Drug intoxication				
Female	185 (86)	54 (84)	111 (66)	>0.05
Male	31 ^a (14)	10 ^{ab} (16)	42 ^b (25)	<0.05
Multi-drug ingestion	72 ^a (33)	39 ^b (61)	73 ^a (43)	<0.05
Delayed presentation	13 (6)	4 (6)	14 (8)	>0.05
Jumping from a height	3 ^a (1)	11 ^{ab} (17)	11 ^b (6)	<0.05
Female	2 (0.9)	1 (2)	9 (5)	
Male	1 (0.4)	0 (0)	2 (1)	
Hanging				-
Female	0 (0)	0 (0)	1 (0.6)	
Male	0 (0)	0 (0)	1 (0.6)	
Firearm-related methods				-
Female	0 (0)	0 (0)	0 (0)	
Male	0 (0)	0 (0)	3 (2)	
Psychiatric history				
Psychiatric follow-up	33 ^a (15)	21 ^b (33)	64 ^b (38)	<0.05
Previous suicide attempt	5 ^a (2)	5 ^{ab} (8)	14 ^b (8)	<0.05
Organ support requirements				
Mechanical ventilation	2 ^a (0.9)	1 ^{ab} (2)	11 ^b (7)	<0.05
Renal replacement therapy	1 ^a (0.4)	1 ^{ab} (2)	8 ^b (5)	<0.05
Hemodynamic support	2 ^a (0.9)	1 ^{ab} (2)	11 ^b (7)	<0.05
PRISM III score, mean $\pm$ SD (range)	5.0 ± 1.8 (3–8) ^a	8.5 ± 3.5 (5–18) ^b	13.5 ± 6.0 (7–30) ^c	<0.05
Length of PICU stay, days (mean $\pm$ SD)	1.65 ± 0.8^a	1.93 ± 0.93^{ab}	2.57 ± 3.08^b	<0.05
Mortality, n (%)	0 (0)	0 (0)	3 (2)	>0.05

PICU: Pediatric intensive care unit; PRISM score: Pediatric Risk of Mortality score.

Continuous variables were compared using one-way ANOVA. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. When the overall p-value was significant, pairwise post-hoc comparisons were performed with Bonferroni correction. Different superscript letters within the same row indicate statistically significant differences between groups. Groups sharing at least one common superscript letter are not significantly different from each other.

in 5 patients (7.8%). No deaths occurred in this period. The mean PICU length of stay was 1.93 ± 0.93 days (range: 1–5 days) (Table I).

In the post-COVID period, a total of 169 patients (37.4%) were admitted. Of these, 121 (71.6%) were female and 48 (28.4%) male, with a mean age of 15.6 ± 1.6 years. The methods of attempt included drug ingestion in 153 patients (90.5%), jumping from a height in 11 (6.5%), sharp object injuries in 3 (1.8%), and hanging in 2 (1.2%). Psychiatric follow-up was reported in 64 patients (37.9%), while 14 patients (8.3%) had a history of prior attempts. There were 3 deaths (1.8%) during this period. The mean PICU length of stay was 2.57 ± 3.08 days (range: 1–34 days) (Table I).

Statistically significant differences were observed between periods in terms of sex distribution ($p=0.01$), suicide methods (jumping from a height, $p=0.03$), multiple drug ingestion ($p=0.0002$), psychiatric follow-up ($p<0.0001$), and previous SA ($p=0.0208$), with these findings being more prominent in the post-COVID period. Significant variations were also found in the need for MV ($p=0.005$), RRT ($p=0.016$), hemodynamic support ($p=0.005$) and PICU length of stay ($p<0.001$), all of which were higher in the post-COVID period. Mortality rates did not differ significantly ($p=0.080$). A detailed analysis of these differences is provided in Table I.

Across study periods, the proportion of patients under psychiatric follow-up before SA was 33/219 (15.1%) in the pre-COVID period, 21/64 (32.8%) during COVID, and 65/169 (38.5%) in the post-COVID period ($p<0.05$). Among these patients, depressive disorders, and anxiety disorders differed significantly across periods ($p<0.05$), whereas substance use disorders and attention-deficit/hyperactivity disorder (ADHD) did not ($p>0.05$). Recurrent SA were observed in 5/219 patients (2.3%) in the pre-COVID period, 5/64 patients (7.8%) during the COVID period, and 14/169 patients (8.3%) in the post-COVID period ($p<0.05$). In recurrent cases, depressive disorders differed significantly

across periods ($p<0.05$), while anxiety disorders and ADHD did not ($p>0.05$). The number of patients receiving a new psychiatric diagnosis after SA was 23/219 (10.5%) in the pre-COVID period, 24/64 (37.5%) during COVID, and 50/169 (29.6%) in the post-COVID period ($p<0.05$). New diagnoses of depressive disorders, anxiety disorders differed significantly across periods ($p<0.05$), whereas substance use disorders and ADHD did not ($p>0.05$). Psychiatric status across study periods is presented in Table II.

In the multivariate logistic regression analysis, the post-COVID period was identified as an independent risk factor for severe clinical outcomes (OR = 3.2; 95% CI: 1.9–5.4; $p=0.004$). Because mortality events were extremely rare ($n=3$), multivariate modeling for mortality was not performed. The use of high-lethality methods (hanging, firearms, jumping from a height) was strongly associated with a 5.1-fold increase in severe clinical outcomes (OR = 5.1; 95% CI: 2.8–9.4; $p<0.001$) and an 8.7-fold increase in mortality risk (OR = 8.7; 95% CI: 3.5–16.2; $p<0.001$). A history of psychiatric follow-up was associated with a 1.9-fold increased risk of severe clinical outcomes (OR = 1.9; 95% CI: 1.1–3.3; $p=0.02$). Similarly, a history of previous SA was linked to a 2.3-fold increase in the likelihood of severe clinical outcomes (OR=2.3; 95% CI: 1.2–4.2; $p=0.01$). Male sex was associated with a 1.5-fold increase in severe clinical outcomes (OR=1.5; 95% CI: 0.9–2.4), although this was not statistically significant for mortality ($p=0.08$). The results of the multivariate analysis are illustrated in Fig. 2.

Discussion

In the present single-center PICU cohort spanning three distinct periods (pre-COVID, COVID, and post-COVID), a marked shift in the clinical profile of adolescent SA was observed. We identified (i) a reduction in SA-related admissions during the acute pandemic phase followed by a relative increase in the post-COVID period, (ii) a progressive shift toward higher-lethality methods, including

Table II. Psychiatric status across study periods: follow-up, recurrence, and new diagnoses.

	Pre-COVID	COVID	Post-COVID	p value
Patients under psychiatric follow-up before SA n/n(%)	33/219 ^a (15)	21/64 ^b (33)	65/169 ^b (38)	<0.05
Diagnosis				
Depressive disorders n (%)	15 ^a (7)	13 ^b (20)	35 ^b (21)	<0.05
Anxiety disorders n (%)	5 ^a (2)	5 ^{ab} (8)	21 ^b (12)	<0.05
ADHD n (%)	10 (5)	-	6 (4)	>0.05
Bipolar disorder n (%)	1 (0.5)	-	-	-
Substance use disorders n (%)	2 (0.9)	3 (5)	3 (2)	>0.05
Recurrent SA	5 ^a (2)	5 ^{ab} (8)	14 ^b (8)	<0.05
Diagnosis				
Depressive disorders n (%)	3 ^a (1)	4 ^{ab} (6)	8 ^b (5)	<0.05
Anxiety disorders n (%)	1 (0.5)	1 (2)	4 (2)	>0.05
ADHD n (%)	-	-	2 (1)	>0.05
Bipolar disorder n (%)	1 (0.5)	-	-	-
Substance use disorders n (%)	-	-	-	-
New psychiatric diagnoses after SA	23/219 ^a (10)	24/64 ^b (38)	50/169 ^b (30)	<0.05
Diagnosis				
Depressive disorders n (%)	10 ^a (5)	15 ^b (23)	28 ^b (17)	<0.05
Anxiety disorders n (%)	3 ^a (1)	5 ^b (8)	14 ^b (8)	<0.05
ADHD n (%)	8 (4)	2 (3)	5 (3)	>0.05
Bipolar disorder n (%)	-	-	-	-
Substance use disorders n (%)	2 (0.9)	2 (3)	3 (2)	>0.05

SA: suicide attempts; ADHD: Attention-Deficit/Hyperactivity Disorder.

Continuous variables were compared using one-way ANOVA. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. When the overall p-value was significant, pairwise post-hoc comparisons were performed with Bonferroni correction. Different superscript letters within the same row indicate statistically significant differences between groups. Groups sharing at least one common superscript letter are not significantly different from each other.

among female adolescents, (iii) a marked increase in clinical severity during and after the COVID-19 period, and (iv) a growing burden of psychiatric comorbidity and recurrent SA. Together, these findings suggest that the impact of the COVID-19 pandemic on adolescent suicidal behavior extends beyond the acute phase and may manifest as a delayed and cumulative psychosocial burden. Given that the study periods differ primarily in their temporal relationship to the pandemic, our findings may be more consistent with pandemic-specific stressors than with underlying secular trends. Existing multicenter PICU studies from Germany, the US, and Europe have provided

important insights into the acute pandemic phase but have not examined post-COVID trajectories.¹⁸⁻²¹ In contrast, the longitudinal design of the present study captures changes across the full pandemic timeline, revealing sustained and progressively worsening clinical consequences following the initial COVID-19 period.

The impact of the COVID-19 pandemic on adolescent mental health has been examined primarily through child and adolescent psychiatry-based studies^{5,7,21-35} and ED data.^{2,6,12,15,16,36-46} Child and adolescent psychiatry-based studies have focused on both the mental health impact of the pandemic

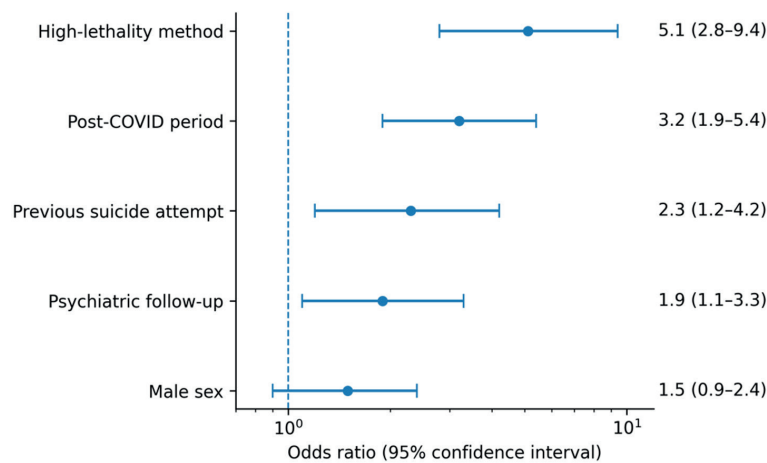


Fig. 2. Risk factors for severe clinical outcomes (multivariate logistic regression results).

This forest plot presents the results of the multivariable logistic regression analysis. For each predictor, the odds ratio (OR) and 95% confidence interval (CI) are shown. An OR greater than 1 indicates increased odds of severe clinical outcomes, whereas an OR less than 1 indicates decreased odds. Horizontal lines represent 95% CIs, and markers indicate point estimates.

and the underlying mechanisms driving these changes in adolescents. Existing evidence, including multi-country reviews and meta-analyses, has consistently demonstrated a marked deterioration in mental health during and after the COVID-19 pandemic, characterized by increased depressive and anxiety symptoms, suicidal ideation, self-harm behaviors, and heightened psychosocial vulnerability.^{5,7,21-35} A summary of child and adolescent psychiatry-based studies is provided in Supplementary Table S1. In parallel, ED-based studies have reported substantial changes in the frequency and temporal distribution of suicide-related presentations among adolescents during the pandemic.^{2,6,12,15,16,36-46} In this context, Madigan et al., in a multicountry meta-analysis including 42 studies from 18 countries, reported increased ED presentations for suicidal ideation and SA among children and adolescents, despite marked regional heterogeneity.⁶ A summary of ED-based studies is provided in Supplementary Table S2. However, ED-based data generally include limited objective indicators of clinical severity and may not adequately capture the most medically severe presentations. In this context, PICU-based studies provide a

complementary perspective by capturing the most medically severe manifestations of suicidal behavior. Multicenter PICU reports have demonstrated heterogeneous patterns during the pandemic. For example Bruns et al. from Germany reported a decline in SA-related PICU admissions during the acute pandemic phase, followed by a substantial increase in subsequent periods.¹⁸ Moral-Larraz et al. examined the 2017–2021 period in a single tertiary-level PICU and reported a significant increase in PICU admissions for SA in 2021 compared with previous years, corresponding to a 230% increase in the median number of admissions.¹⁹ In the United States, Mc Cluskey et al. observed that although the absolute number of PICU admissions for self-harm or SA remained relatively stable, their proportion increased due to a concurrent reduction in overall PICU admissions.²⁰ Conversely, Corrigan and colleagues from Australia identified an early rise in PICU admissions for self-harm during the initial phase of the pandemic.²¹ Taken together, these findings suggest that the impact of the COVID-19 pandemic on severe adolescent suicidal behavior is influenced by country-specific factors, healthcare system

characteristics, and patterns of healthcare utilization.

Pre-pandemic literature consistently demonstrates marked sex-based differences in suicide method lethality, with female adolescents more often using lower-lethality methods and male adolescents more frequently employing highly lethal methods.⁴⁷⁻⁵⁰ Interestingly, over the period from 1999 to 2020, Ormiston and colleagues reported a progressive shift toward higher-lethality suicide methods, most notably among female adolescents, which continued into the first year of the COVID-19 pandemic.⁵¹ Our pre-pandemic findings are consistent with the established literature on sex-based differences in suicide methods. In contrast, in our cohort, the pandemic period—most prominently the post-COVID phase—was associated with a clear shift toward higher-lethality methods in both sexes. This pattern was reflected by a greater use of high-risk methods among girls, such as jumping from a height, and by the emergence of distinctly high-lethality methods among boys, including hanging and firearm-related attempts. In parallel, the pre-pandemic sex gap in method lethality appeared to narrow. This convergence may be driven by two co-occurring patterns: an increase in high-risk, potentially lethal attempts among female adolescents and a relative rise in the proportion of male patients requiring PICU admission. This attenuation of sex differences during and after the COVID-19 pandemic may reflect context-specific psychosocial pressures rather than a simple continuation of long-term secular trends. Although the literature evaluating changes in SA methods during the COVID-19 pandemic remains limited, emerging data support a similar pattern. Consistent with our findings, Auger et al. reported that SA-related hospitalizations increased markedly among girls aged 10–14 years in Quebec during the pandemic; notably, at the beginning of the pandemic, youths aged 10–14 years were more likely to use violent methods, particularly hanging and cutting.⁵² These findings may be related to sex-specific psychosocial

responses to the pandemic. Adolescent girls may have been disproportionately affected by internalizing symptoms (e.g., anxiety and depression) and heightened sensitivity to social disconnection, whereas adolescent boys may have expressed distress through delayed help-seeking and more externalizing trajectories (e.g., impulsivity, anger, and risk-taking). Despite these potentially distinct pathways, shared exposure to prolonged social isolation, educational disruption, bereavement, and reduced access to mental health services may have contributed over time to more planned, high-risk, and clinically more severe SA.⁵³⁻⁵⁷

Independent of the pandemic, it is well established that the increasing lethality of SA methods is accompanied by a stepwise escalation in clinical severity. For example, a large-scale analysis based on the U.S. Virtual Pediatric Systems (VPS) database (2009–2017) demonstrated that mortality among patients admitted to the PICU for SA or deliberate self-harm was predominantly associated with high-lethality methods, such as hanging/asphyxia and firearms.⁵⁸ In parallel with these findings, our study shows that during and after the COVID-19 period, increasing method lethality was accompanied by a marked rise in clinical severity, as evidenced by higher PRISM III scores, greater need for invasive organ support, longer PICU length of stay, and the occurrence of mortality exclusively in the post-COVID period. Although between-period differences in mortality did not reach statistical significance, the exclusive occurrence of fatal outcomes in the post-COVID period is clinically noteworthy. This pattern may indicate an emerging shift toward more severe presentations. These findings are broadly consistent with ED-based reports describing increased clinical severity during the COVID-19 period, including longer ED length of stay, higher hospitalization rates, and a disproportionate rise in severe presentations, particularly among adolescent girls. In contrast, COVID-19 PICU-based evidence specifically addressing a potential increase in the clinical severity of SA remains limited.¹⁸⁻²¹ Much of

the existing PICU literature has focused on changes in admission volumes or proportions, while failing to consistently integrate severity indicators that directly quantify clinical burden, such as validated illness severity scores, invasive organ support requirements, or longitudinal outcomes. Nevertheless, several studies suggest that the pandemic may have influenced not only admission volume but also clinical severity. Bruns et al. reported more severe clinical presentations among adolescents admitted to the PICU for SA during the pandemic, with an approximately threefold increase in the standardized mortality ratio.¹⁸ Similarly, in a national multicenter PICU cohort from Australia, Corrigan et al. observed that although overall PICU admissions declined during the early pandemic period, adolescents admitted for deliberate self-harm experienced clinically significant organ support requirements and mortality.²¹ Against this background, our study contributes to the literature by demonstrating a marked increase in clinical severity during and after the COVID-19 period, supported by objective severity indicators. Overall, the impact of the COVID-19 pandemic on adolescent suicidal behavior does not appear to be limited to a transient acute-phase fluctuation; rather, it may evolve into a delayed, cumulative, and clinically more severe burden.

In our cohort, both the proportion of adolescents with a prior psychiatric history and the rate of recurrent SA increased over time, with this increase becoming most pronounced in the post-COVID period (Table II). Notably, the more frequent use of high-lethality methods among adolescents under psychiatric follow-up points to an escalation of clinical vulnerability associated with the pandemic period. This finding is consistent with the child and adolescent psychiatry literature indicating that the psychological sequelae of the COVID-19 pandemic were more intense and clinically severe among high-risk adolescents. Indeed, in a recent systematic review and meta-analysis by Vardi et al. including 36 studies and data from a total of 1,754,106 adolescents, suicide-

related behaviors followed a heterogeneous trajectory in the general population; in contrast, a marked increase in self-harm and SA was observed among adolescents with a psychiatric history who were followed in clinical settings.⁵⁹ Concordantly, the multicenter PREP-kids study by Ougrin et al. demonstrated that during the COVID-19 period, the proportion of children and adolescents presenting with self-harm who had a pre-existing psychiatric history increased.¹⁵ Carballo et al. (STOP Consortium) emphasized that suicidality in children and adolescents reflects a cumulative risk process arising from the convergence of psychiatric vulnerabilities—particularly depression and anxiety, prior self-harm or SA, impulsivity, and hopelessness—with familial and social stressors, rather than a single triggering event.⁶⁰ This framework provides a compelling explanation for why, under the prolonged and layered stress burden of the pandemic, more severe and recurrent SA became increasingly apparent, especially among high-risk adolescents.

Another notable finding was an increased proportion of adolescents who initiated psychiatric treatment and entered regular follow-up after the index attempt. In the pre-COVID period, SA were predominantly impulsive, typically emerging in the context of an acute crisis and often followed by regret. In contrast, during the pandemic, a marked increase was observed in the proportion of adolescents newly diagnosed with depression and anxiety in the aftermath of a SA. This observation aligns with large-scale child and adolescent psychiatry studies reporting a significant rise in the incidence of depressive and anxiety disorders among adolescents during the COVID-19 pandemic. For example, the European Society for Child and Adolescent Psychiatry led COVID-19 Child and Adolescent Psychiatry Consortium longitudinal survey showed that the mental health burden in children and adolescents increased substantially as the pandemic progressed. Despite a partial normalization of service delivery over time, suicidal crises, depressive

disorders, anxiety disorders, and other severe psychiatric presentations accounted for a growing proportion of referrals and assessment requests.⁶¹ Overall, during the COVID-19 era, we observed increases both in SA among adolescents with pre-existing psychiatric diagnoses and in new-onset cases receiving a first psychiatric diagnosis and entering regular follow-up. Collectively, these findings suggest that the pandemic not only exacerbated existing psychiatric vulnerabilities but may also have precipitated a new, potentially persistent psychopathological process in adolescents who had not previously manifested clinically overt mental health problems.

In multivariate analysis, the post-COVID period was associated with an increased likelihood of severe non-fatal clinical outcomes. High-lethality methods were associated with greater clinical severity and were more frequently observed among fatal cases, while prior psychiatric follow-up and a history of previous SA were linked to increased severity. Male sex was associated with severity but not mortality; however, this finding should be interpreted cautiously given the limited number of deaths and potential shifts in method lethality patterns (Fig. 2).

Our findings suggest increased psychological vulnerability among adolescents in the post-COVID period, highlighting the importance of early risk identification. Targeted mental health screening in high-burden settings, particularly the ED and PICU, may support timely referral and multidisciplinary care. Furthermore, preventive strategies must be adapted to the specific needs of each period. During the pandemic, the expansion of telepsychiatry and digital mental health platforms helped bridge critical gaps in care. In the post-COVID phase, however, school-based mental health programs, stress resilience training, and accessible psychosocial support services should take precedence. Across all periods, a common necessity is equipping parents, educators,

and healthcare professionals with the skills to recognize early warning signs, respond promptly, and guide adolescents toward appropriate care.

This study has several limitations. This single-center, retrospective design may limit generalizability. Reliance on medical records restricted access to psychosocial data. The three periods differed in duration, which may influence comparisons across time. Mortality findings are limited by the very small number of deaths ($n=3$), and multivariate analysis for mortality was not feasible. Logistic regression is also restricted by the low number of events relative to covariates and findings should therefore be interpreted as exploratory. The absence of long-term follow-up data also restricts the ability to assess subsequent psychiatric trajectories. Therefore, future multicenter prospective studies incorporating psychosocial variables and long-term outcomes are needed.

Conclusion

Suicide attempts requiring PICU admission became progressively more severe during and after the COVID-19 pandemic, pointing to a cumulative psychological burden. This underscores the need for early risk identification and sustained post-COVID mental health surveillance among high-risk adolescents.

Supplementary materials

Supplementary materials for this article are available online at <https://doi.org/10.24953/turkjpediatr.2026.7055>

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Ethical approval

The study was approved by Toros University Ethics Committee (date: June 25, 2024, number: 123).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BK, İK, MK; data collection: ÖKC, MT; analysis and interpretation of results: BK, MK, SE; draft manuscript preparation: BK, SE, FHE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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A comparative analysis of Phoenix, PELOD-2, and pSOFA scores to predict mortality in children with clinical sepsis

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ABSTRACT

Background. Sepsis causes significant morbidity and mortality in children worldwide, despite the development of standardized treatment guidelines, vaccination programs, and advanced techniques for organ support in intensive care. Early mortality prediction is crucial for optimizing care, targeting interventions according to risk, and ultimately reducing mortality. Several scoring systems are used to predict outcomes and mortality for pediatric patients with sepsis, but how they compare in terms of sensitivity and specificity is unclear. This study compares the Phoenix, Pediatric Sequential Organ Failure Assessment (pSOFA), and Pediatric Logistic Organ Dysfunction (PELOD)-2 scores in predicting mortality in children with clinical sepsis.

Method. This retrospective cohort study was conducted at Dr. Cipto Mangunkusumo General Hospital, Jakarta, from January to April 2018. The primary outcome was early pediatric intensive care unit mortality (within 7 days). All data were analyzed using STATA 17 and MedCal12. The area under the receiver operating characteristics (AUROC) curves of the Phoenix, pSOFA, and PELOD-2 scores were compared using DeLong's test.

Results. A total of 69 patients were clinically diagnosed with sepsis and 26.1% died. ROC curve analysis showed that the AUROCs of pSOFA, Phoenix, and PELOD-2 for predicting mortality were 0.745, 0.741, and 0.682, respectively. At their respective cutoffs, the pSOFA, Phoenix, and PELOD-2 scores had sensitivities for mortality prediction of 72.2%, 83.3%, and 72.2%, respectively, and specificities of 64.7%, 62.75%, and 54.90%.

Conclusions. The pSOFA and Phoenix scores demonstrated better performance in predicting mortality in children with clinical sepsis than the PELOD-2 score. When selecting an appropriate scoring system, factors such as simplicity and local conditions must be considered to ensure optimal performance.

Key words: Phoenix, Pediatric Logistic Organ Dysfunction-2, Pediatric Sequential Organ Failure Assessment, sepsis.

Sepsis is a major contributor to morbidity and mortality in children.^{1,2} Despite advances in pathophysiological understanding, hemodynamic monitoring, and resuscitation strategies, the incidence and mortality of pediatric sepsis remains high, and may even

have increased in recent years.^{2,3} Based on the 2017 Global Burden of Disease Group data, sepsis incidence shows a biphasic pattern with peak incidences in children and the elderly.⁴ Approximately 25.2 million cases of sepsis occur in children each year, with 84.5%

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occurring in children younger than 5 years and approximately 3 million deaths.^{4,5} A global case fatality rate (CFR) of sepsis and septic shock in children was estimated in a 2019 systematic review and meta-analysis to be 24.7%, with CFR rates in developing countries higher than in developed countries (31.7% vs. 19.3%).⁶

The current definition of sepsis still refers to the sepsis-3 definition of life-threatening organ dysfunction caused by a dysregulated host immune response to infection. These criteria were developed from adult population data, and life-threatening organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score.^{7,8} However, direct application to children is considered inappropriate due to differences in vital sign variability, immune function development and comorbid disease profiles, epidemiology and outcomes. Therefore, the Sepsis-3 definition cannot be adopted directly in children. Nevertheless, the Sepsis-3 definition formed the basis for the development of revised criteria for pediatric sepsis.⁸

Early and accurate recognition of pediatric sepsis is crucial for reducing mortality. Effective identification of sepsis in the pediatric population requires accurate criteria for the assessment of disease progression. Therefore, many scoring systems have been developed over time.² Various scoring systems have been proposed to diagnose and stage pediatric sepsis after the release of the sepsis-3 definition such as the pediatric Sequential Organ Failure Assessment (pSOFA) score, the Pediatric Logistic Organ Dysfunction (PELOD / PELOD-2) score and the pediatric multiple organ dysfunction (pMODS) score.^{9,10} In Indonesia, the diagnosis of pediatric sepsis uses the PELOD-2 score to assess life-threatening organ dysfunction. This is outlined in the National Guidelines for Medical Services for the management of sepsis in children, which was published in 2021.¹¹ In 2024, a decade after the release of the sepsis-3 definition, international criteria for pediatric sepsis were released based on international surveys, systematic reviews, analysis of 3

million children, and a modified Delphi consensus process, with organ dysfunction assessed using the Phoenix score. These sepsis criteria were developed from data on children in high- and middle-income countries.⁸

Scoring systems standardize the assessment of disease severity, risk of morbidity and mortality, and patients' clinical status.¹² Scoring systems are generally categorized into two groups: prognostic scores estimate the risk of death, and descriptive or outcome scores provide information on disease progression.^{2,12} In the context of prognostic scores, the following have been included: the prognostic stability index (PSI), the pediatric risk of mortality (PRISM), and the pediatric index of mortality (PIM). Meanwhile, the following descriptive scores have been included: the PELOD, the pMODS, and the pSOFA scores.² Since the Phoenix score was introduced in 2024, it has been studied only to a limited extent, and challenges remain in its application and effectiveness.¹³ This study aims to compare the performance of PELOD-2, pSOFA, and Phoenix scores in predicting mortality in children with clinical sepsis.

Methods

We conducted a secondary analysis of data from children with clinical sepsis admitted to Dr. Cipto Mangunkusumo Hospital, Jakarta, from January to April 2018. The subjects were patients aged 1 month to 18 years with a diagnosis of clinical sepsis. Clinical sepsis was established based on suspected infection and clinical evidence of organ dysfunction. Suspicion of infection was established based on evidence of infection (signs, symptoms, and physical examination findings consistent with a focus of infection) and signs of an inflammatory response, according to the criteria of the 2005 International Pediatric Sepsis Consensus Conference. Organ dysfunction was suspected when at least one of the following was present: decreased consciousness (Glasgow Coma Scale (GCS) <11), cardiovascular dysfunction, or respiratory dysfunction. Patients with

autoimmune disease, malignancy, trauma or postoperative conditions were excluded. Secondary data from the subjects were used to calculate the PELOD-2, pSOFA and Phoenix scores. All subjects were then followed during management while monitoring the primary outcome of early death within 7 days of treatment. The management of sepsis during the study followed the Surviving Sepsis Campaign 2012 guidelines. Ethical approval was obtained from Faculty of Medicine Universitas Indonesia Institutional Review Board (approval number 0046/UN.F1/ETIK/2018). No additional ethical approval was required for this secondary analysis, and all procedures were performed in accordance with institutional and federal ethical standards for human experimentation and the 1975 Declaration of Helsinki.

Statistical analysis was performed using STATA version 17. The Kolmogorov-Smirnov test was used to assess the normality of the data. Normally distributed continuous variables were presented as means $\pm$ standard deviations and compared using the independent samples t-test, while non-normally distributed variables were presented as medians (ranges) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive performance of each score. The area under the receiver operating characteristics (AUROC) curves, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to assess diagnostic performance. Comparisons between AUROCs were performed using the DeLong test. The optimal cutoff value for each score was determined using the Youden index.

Post-hoc power analyses were performed to assess the statistical power for the observed differences in AUROCs and correlations. A p-value < 0.05 was considered statistically significant.

Results

A total of 69 pediatric patients with clinical sepsis were included in this study, with a mortality rate of 26.1%. The majority of the subjects were male (60.9%) and 68.1% of the patients received mechanical ventilation. The complete characteristics of the study subjects are presented in Table I.

Fig. 1 shows the ROC curves of the three scoring systems used (pSOFA, Phoenix, and PELOD-2) to predict mortality in children with clinical sepsis. The analysis revealed that the pSOFA score had the highest AUROC value of 0.745, followed by Phoenix (0.741) and PELOD-2 (0.682). This indicates that all three scores showed moderate to good predictive performance. The Phoenix and pSOFA scores demonstrated comparable predictive performance in assessing mortality among children with clinical sepsis ($p=0.732$). Both scores significantly outperformed the PELOD-2 score in predicting patient mortality ($p<0.05$).

Table II shows the predictive performance of each score. The Phoenix score, with an optimal cut-off value of 3.5 determined using Youden's index, demonstrated the highest specificity (70.59%) and the highest PPV (44.44%) among the three scores. In contrast, while the pSOFA and PELOD-2 scores demonstrated the same highest sensitivity of 72.2%, the pSOFA score alone achieved the highest overall accuracy of 66.67%. These findings indicate that the cut-offs selected using Youden's index provide a balance between sensitivity for predicting mortality in children with clinical sepsis.

The comparative predictive performance of the scores for pediatric clinical sepsis mortality was evaluated using the AUC and compared using the DeLong test. The results are presented in Table III.

The distribution of mortality among children with clinical sepsis according to pSOFA, Phoenix and PELOD-2 scores can be seen in Fig. 2.

Table I. Characteristics of the study population.

Parameters	Total (n=69)	Survived (n=51)	Died (n=18)	P
Age; median (range), month	14 (1-212)	12 (1-211)	37.5 (3-212)	0.226
Male sex; n (%)	42 (60.9)	32 (62.7)	10 (55.6)	0.395
Focus of infection				0.083
Respiratory, n (%)	56 (81.1)	42 (82.4)	14 (77.8)	
Gastrointestinal, n (%)	7 (10.1)	4 (7.8)	3 (16.7)	
Central nervous system, n (%)	5 (7.2)	5 (9.8)	0 (0)	
Others, n (%)	1 (1.5)	0 (0)	1 (5.6)	
Leukocytes; median (range), /mm ³	15,000 (1,120-72,490)	14,800 (1,120 – 432,000)	15,015 (8,420 – 72,490)	0.512
Platelets; median (range), /mm ³	228,000 (4,380-431,000)	242,000 (4,380-674,000)	164,500 (22,500-432,000)	0.237
Creatinine; median (range), mg/dL	0.57 (0.12-18.64)	0.50 (0.12 – 18.64)	0.80 (0.20 – 3.07)	0.107
Lactate; median (range), mmol/L	2.0 (0.3-9.3)	1.70 (0.30 – 9.30)	2.75 (1.00 – 9.30)	0.027
Procalcitonin (n=46); median (range), ng/mL	5.77 (0.02-368)	4.70 (0.02 – 316.80)	9.68 (0.21 – 368)	0.486
Total bilirubin; median (range), mg/dL	0.7(0.07-42.05)	0.65 (0.07 – 35.96)	1.62 (0.35 – 42.04)	0.016
Mechanical ventilation, n (%)	47 (68.1)	32 (62.7)	15 (83.3)	0.145
Mortality, n (%)	18 (26.1)			
Phoenix score; median (range)	2.0 (0-8)	2.0 (0-8)	4.0 (1.0-7.0)	0.001
PELOD-2 score; median (range) or mean $\pm$ SD	5.76 (0-14)	5.18 $\pm$ 3.22	7.44 $\pm$ 3.70	0.016
p-SOFA score; median (range) or mean $\pm$ SD	9 (3-17)	8.37 $\pm$ 2.87	11.39 $\pm$ 3.40	0.001

Non-normally distributed data are presented as a median with a range, normally distributed data as mean $\pm$ SD, and categorical data as n (%).

PELOD-2, Pediatric Logistic Organ Dysfunction-2; pSOFA, pediatric Sequential Organ failure Assessment; SD, standard deviation.

Table II. Predictive performance of the pSOFA, Phoenix, and PELOD-2 scores for mortality in children with clinical sepsis.

	pSOFA score	Phoenix score	PELOD-2 score
AUROC	0.745	0.741	0.682
Cut-off	9.5	3.5	6
Sensitivity	72.2%	66.67%	72.2%
Specificity	64.7%	70.59%	54.90%
PPV	41.94%	44.44%	36.11%
NPV	86.84%	85.71%	84.85%
PLR	2.05	2.27	1.60
NLR	0.43	0.47	0.51
Accuracy	66.67%	65.57%	59.42%
95% CI	0.614 to 0.875	0.608 to 0.863	0.539 to 0.826

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; NLR, negative likelihood ratio; PELOD-2, Pediatric Logistic Organ Dysfunction-2; PLR, positive likelihood ratio; PPV, positive predictive value; pSOFA, pediatric Sequential Organ Failure Assessment.

Table III. Comparative predictive performance scores for pediatric clinical sepsis mortality.

Comparison	AUROC1	AUROC2	Δ AUROC	n	Data	P-value
Phoenix vs pSOFA	0.741	0.745	0.004	69	same	0.732
Phoenix vs PELOD-2	0.741	0.682	0.059	69	same	0.021
pSOFA vs PELOD-2	0.745	0.682	0.063	69	same	0.018

AUROC, area under the receiver operating characteristic curve; PELOD-2, Pediatric Logistic Organ Dysfunction-2; pSOFA, pediatric Sequential Organ failure Assessment

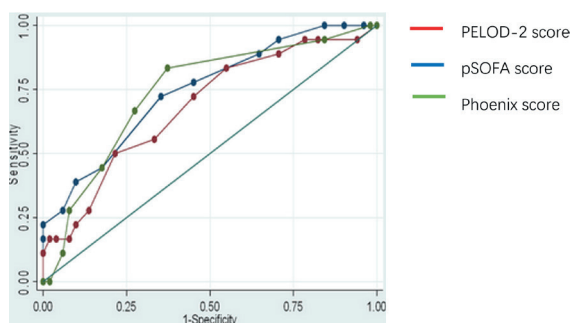


Fig. 1. ROC Curve, cutoff, sensitivity, and specificity of pSOFA, Phoenix, and PELOD-2 scores in predicting mortality in children with clinical sepsis. PELOD-2, Pediatric Logistic Organ Dysfunction-2; pSOFA, pediatric Sequential Organ failure Assessment; ROC, receiver operating characteristics.

Discussion

Sepsis is the most common presentation in the pediatric intensive care unit (PICU) and the leading cause of morbidity and mortality.¹⁴ Consequently, it is important for clinicians to accurately predict patient risk within a few days of treatment. The use of a scoring system in the PICU can facilitate decision-making and appropriate management.^{14,15} Scoring systems are also useful in predicting outcomes and aiding immediate intervention.¹⁴ The ideal prognostic scoring system should be accurate, simple, easy to use, minimally invasive and inexpensive.¹⁶ Various organ dysfunction scores have been developed and validated such as the PELOD-2 score, pSOFA score and more recently, the Phoenix score. This study compared the performance of these three scoring systems in predicting mortality in children with clinical sepsis.

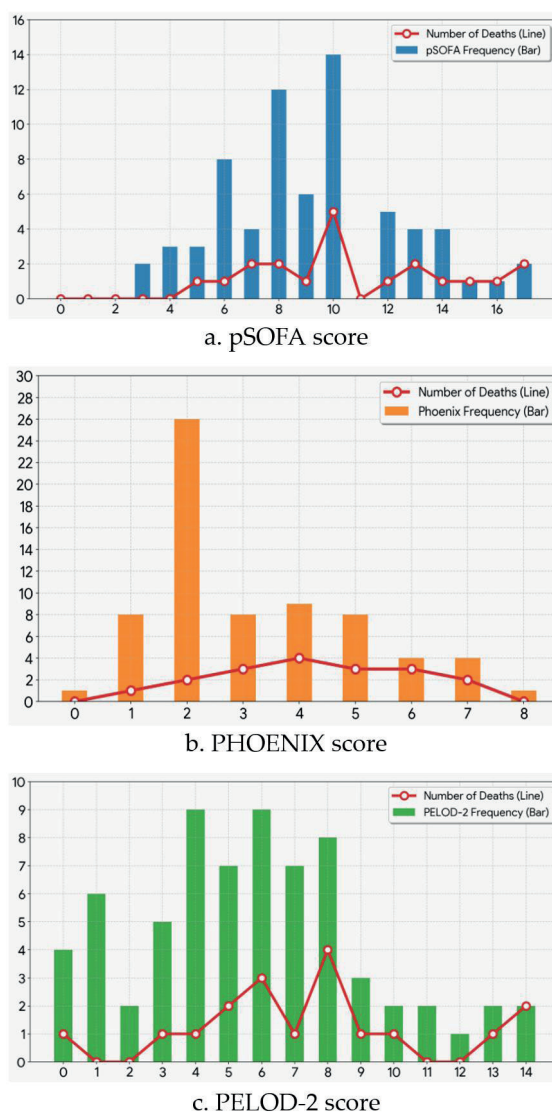


Fig. 2. Distribution of mortality in clinical sepsis children based on: a. pSOFA score; b. Phoenix score, and c. PELOD-2 score.

PELOD-2, Pediatric Logistic Organ Dysfunction-2; pSOFA, pediatric Sequential Organ failure Assessment.

The PELOD-2 score, an update of the original PELOD score, was developed in 2013. This score evaluates 10 variables across 5 organ systems (neurological, cardiovascular, renal, respiratory, and hematologic systems).¹⁷ The PELOD-2 score on the first day was reported as a predictor of mortality in pediatric sepsis patients admitted to PICUs in developing countries¹⁸ and tertiary hospitals in rural areas.¹⁹ A descriptive analytical study conducted from January 2018 to December 2019 in the PICU of Cipto-Mangunkusumo Hospital Jakarta showed that the PELOD-2 score had an AUROC value of 0.842 (95% confidence interval [CI]: 0.843-0.845) in predicting mortality in children with sepsis. This study found an optimal cut-off value of 6.5, with a sensitivity of 77.1% and a specificity of 75%.²⁰ The cut-off value in that study was close to that found in the present study, namely 6.

The pSOFA score was developed in 2017 from the adult SOFA score. Two approaches were used to make modifications. First, age-adjusted renal and cardiovascular variables were validated using the cut-off values of the PELOD-2 score. Second, the respiratory variable score was expanded by measuring the ratio of SpO₂ to FiO₂ as an alternative marker of lung injury.^{21,22} The pSOFA score was reported to have excellent performance in predicting mortality in pediatric patients with suspected or confirmed infection with an AUROC of 0.94 (95% CI: 0.92-0.95),²² assessing the prognosis of pediatric patients with sepsis in PICUs of developing countries (AUROC 0.937; 95% CI: 0.913-0.957),¹⁸ and in predicting mortality among critically ill pediatric patients admitted to the PICU (AUROC 0.86; 95% CI: 0.79-0.93),²³ although the optimal cut-off values differed across studies. Another study reported that the pSOFA score can predict 28-day mortality in pediatric sepsis patients with an AUC of 0.88, but was less effective in predicting length of stay in the PICU.¹⁶ The optimal cut-off point value of the pSOFA score in this study was quite high, at 9.5, which differed from those reported in previous studies.

The Phoenix score was developed in 2024 from an analysis of 218,839 suspected episodes of infection and has been validated internationally.¹² This score assesses only four organ systems: the respiratory, cardiovascular, neurological, and coagulation systems.^{8,24} A large-scale study of 10 hospitals from 5 countries (USA, Bangladesh, Colombia, China, and Kenya) definitively reported that the Phoenix score had area under the precision-recall curve (AUPRC) values of 0.23–0.38 (95% CI: 0.20–0.39) and AUROC values of 0.71–0.92 (95% CI: 0.70–0.92) in predicting mortality in both internal and external validation settings. The Phoenix score was also directly linked to the number of deaths.²⁴ Another study in a tertiary hospital in Vietnam reported that the Phoenix score had good prognostic performance in predicting mortality (AUROC 0.885). The optimal cut-off value in that study was 5.5 with 60% sensitivity, 100% specificity and 100% PPV. The Phoenix score was reported to identify high-risk patients early, thereby facilitating timely intervention and improving outcomes.¹³ The optimal cut-off value differed from that found in the present study which was 3.5.

The implementation of a scoring system in Indonesia must consider the availability of laboratory parameters, the training of medical staff, and the ability to integrate the scores into daily clinical workflows. Of the three scoring systems compared, the Phoenix score is the simplest. The pSOFA score evaluates six organ systems, and the PELOD-2 score evaluates five. Although the pSOFA score was superior to the other two scores, the Phoenix score requires fewer laboratory tests than the other two scoring systems. This makes it more practical to implement in healthcare facilities with limited resources.

This study found that the pSOFA and Phoenix scores were superior predictors of mortality in children with clinical sepsis than the PELOD-2 score. Based on a large-scale database, the AUPRC value of the Phoenix score was reported to be higher than that of PELOD2 score 0.11-0.35 (95% CI: 0.10-0.35) and pSOFA 0.14-0.33

(95% CI: 0.13-0.34). The AUROCs of pSOFA, Phoenix, and PELOD-2 scores ranged from 0.70-0.93, indicating that all three scores can predict mortality in pediatric patients with suspected or confirmed infection.²⁴ Another study in Korea reported that the Phoenix, Phoenix-8, and pSOFA scores had similar performance in predicting mortality among patients with sepsis and septic shock admitted to the PICU, with an AUC range of 0.85 to 0.88.²⁵ The superiority of the pSOFA score over the PELOD-2 score has been widely reported. Retrospective observational cohort studies conducted at Dr. Sutomo Hospital from January to December 2018²⁶ and at RSUD Dr. Moewarli Surakarta from September to March 2019²⁷ demonstrated that the pSOFA score performed better than the PELOD-2 score in predicting mortality in pediatric sepsis patients.

A prospective observational study in India conducted from November 2020 to November 2022 definitively reported that PRISM 4, PIM 3, PELOD-2, and pSOFA scores on the first day of care were positively correlated with mortality among critically ill pediatric patients in the PICU. This indicates that the ability of these scoring systems to differentiate between survivors and non-survivors. The pSOFA score was reported to be better at predicting mortality than the PELOD-2 score.¹⁵ Another retrospective observational study in China from December 2014 to December 2019 demonstrated the superiority of pSOFA in predicting mortality in pediatric sepsis patients over PRISM III, PELOD-2, and pMODS scores (AUROC 0.847 vs. 0.799 vs. 0.780 vs. 0.715). The optimal cut-off point value of pSOFA for predicting mortality was 7, with a sensitivity of 88.07% and a specificity of 64.71%.²⁸

Sandiniurwan et al. reported in 2025 that the PELOD-2 score outperformed the Phoenix score in predicting mortality among pediatric patients with septic shock (AUROC 0.73 vs. 0.59). The optimal cut-off value was 4, which is close to the cut-off value in our study, with a

sensitivity of 62% and a specificity of 62%. The study had a very small sample size of only 16 patients with severe disease, and the mortality rate was 50%.²⁹

The differences in the optimal cut-off values of each scoring system across studies may be due to differences in sample heterogeneity, disease severity at time of assessment, the number of samples, and the underlying conditions of the included patients. The limitations of this study are that (1) it was a retrospective observational study, therefore the available data were insufficient to fully evaluate the coagulation system in the Phoenix score; and (2) the study relied on secondary data and had a relatively small sample size for comparing the scores. A post-hoc power analysis of the AUC differences yielded an estimated power of approximately 5% for the Phoenix vs. pSOFA comparison (Δ AUROC = 0.004), and 70–80% for both the Phoenix vs. PELOD-2 (Δ AUROC = 0.059) and pSOFA vs. PELOD-2 (Δ AUROC = 0.063) comparisons. These results indicate that, although the study was underpowered to detect very small differences, the sample size was sufficient to detect moderate differences in the predictive performance of the scores. Therefore, prospective studies with larger sample sizes are warranted to further compare predictive performance and provide more detailed insights. In conclusion, the pSOFA and Phoenix scores showed better performance in predicting mortality in children with clinical sepsis than the PELOD-2 score. Both scores are suitable for use in clinical practice, taking into account factors such as simplicity, effectiveness, and alignment with local resources. Specifically, the Phoenix and pSOFA scores may be implemented in clinical settings in Indonesia.

Ethical approval

The study was approved by Faculty of Medicine Universitas Indonesia Institutional Review Board [Approval number 0046/UN.F1/ETIK/2018].

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: RC; Data collection: RC; analysis and interpretation of results: RC, IY, RFM; draft manuscript preparation: RC, IY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Quality of life of children with cerebral palsy: an analytical cross-sectional study

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ABSTRACT

Background. Pediatric quality of life (QoL) reflects a child's physical, emotional, social, and cognitive well-being within the cultural and family context. Cerebral palsy (CP), the most common childhood motor disability, significantly reduces QoL. This study aims to describe the QoL of children with CP and healthy children, and to examine whether QoL varies according to the functional abilities of children with CP.

Methods. This analytical cross-sectional study was conducted at the Teaching Hospital, Jaffna, Sri Lanka using an investigator-administered questionnaire. Children with CP comprised the case group, and controls were matched in a 1:1 ratio based on age, sex, socioeconomic status, and geographical area. The Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Communication Function Classification System (CFCs), and Eating and Drinking Ability Classification System (EDACS) were used to assess functional ability. Quality of life was assessed using the PedsQL™ 3.0 CP Module.

Results. A total of 66 children with CP and 66 age-matched controls were recruited. Both groups had a median age of 7 years (interquartile range [IQR]: 6-10 years), with the majority (53%) aged 5-7 years. Quadriplegia was the most common type (34.8%) of cerebral palsy. The median total quality of life score was significantly lower among cases than among controls (59.27 [IQR: 33.80-77.41] vs 100 [IQR: 100- 100]; $p < 0.0001$). Significant differences were observed across all domains between the two groups ($p < 0.0001$). According to the functional classification systems (GMFCS, MACS, CFCs, and EDACS), children with greater dependence in mobility, more limited manual abilities, greater communication restrictions, and greater feeding assistance needs had significantly lower overall QoL scores compared with their more independent counterparts ($p < 0.0001$).

Conclusion. The quality of life of children with CP was significantly lower than that of healthy children. Quality of life scores significantly differed across levels of functional ability, with children with greater functional limitations showing poorer outcome.

Key words: children, cerebral palsy, quality of life.

Pediatric quality of life (PedsQL) is a multidimensional concept encompassing a child's physical, emotional, social, and cognitive well-being, as well as the influence of cultural and familial factors.¹ According to the World Health Organization (WHO), it reflects a child's perception of their position in life in the context of their goals, hopes, and concerns.

Cerebral palsy (CP) is widely acknowledged as the leading motor disability in children, affecting approximately 1.2% of children under 5 years of age globally, with over 98% residing in low-and middle- income countries.² It results from non-progressive brain damage sustained during the prenatal, perinatal, or early postnatal period. According to a population – based study carried

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out in a rural community in Sri Lanka reported a CP prevalence of 3.7% per, 1000 children aged 2 to 5 years, with 75% having severe impairment.³ To address the lack of comprehensive national data, the Sri Lankan CP registry pilot study was launched to improve documentation.⁴

CP significantly impacts the quality of life (QoL) by limiting participation in daily activities for both children and their families. Motor functional status and executive functioning are key determinants of QoL, while visual perception, cognition, communication challenges, and parental stress also play key roles.^{5,6} Children with CP may also face various social and emotional challenges, including social rejection, depression, frustration, anxiety, and anger.⁷ Compared with typically developing peers, affected children often show scores across domains such as social participation, physical functioning, and general health, alongside difficulties with personal care and reduced activity involvement.^{8,9} However, self-reported measures may underestimate these challenges due to differing perceptions.⁹

Caregiver burden significantly impacts parents' physical and social well-being, autonomy, and financial stability.¹⁰ The QoL of parents of children with CP is lower than that of parents of healthy children, with daily activities and physical functioning being particularly affected.¹¹

Assessing QoL in this population is essential for informing clinical care, rehabilitation, and policy planning.¹² Condition-specific tools like the CP QoL-Child questionnaire improve assessment accuracy by targeting areas most affected by the disorder.¹³ Evidence also highlights the benefits of integrating QoL evaluation into routine care to support a holistic, person-centered approach. Notably, active participation in daily routines enhances psychosocial outcomes, especially among ambulatory children, underscoring the importance of promoting engagement through rehabilitation.¹³

Previous studies assessing QoL in children with CP have predominantly relied on parent-proxy reports, have not included healthy control groups, and often lacked comprehensive functional classification; some included only partial Gross Motor Function Classification System (GMFCS) assessment^{14,15} while others did not apply any functional classification at all.^{16,17}

Our study aims to incorporate both child self-reports and parent-proxy assessments, compare QoL with that of age-matched healthy controls, and analyze whether functional abilities such as mobility, manual dexterity, communication, and eating and drinking skills are associated with QoL in children with CP.

Materials and methods

Study design and setting

An analytical cross-sectional study was conducted at the Teaching Hospital, Jaffna, Sri Lanka, a tertiary care center serving approximately 232,000 people in Jaffna District, one of the five districts of the Northern Province. The study was carried out over 13 months, from September 2023 to October 2024.

Participants

The study population comprised children diagnosed with CP (cases) and healthy controls who were individually matched for age (± 6 months), sex, geographical location (within a 1 km radius of the index case), and socioeconomic status. Children aged 2 to 16 years with a confirmed diagnosis of CP, characterized by a non-progressive motor disorder affecting movement, balance, and posture were included. The diagnosis was verified by the principal investigator through a review of medical records. Control participants who visited the outpatient department for minor acute self-limiting clinical conditions were recruited from the outpatient department of the same hospital and had no history or clinical evidence

of neurological or motor impairment. Children with motor dysfunction due to peripheral causes and without evidence of an insult to the developing brain were excluded from this study.

Variables and measurements

The outcome variable in this study was health-related quality of life (HRQOL), which was assessed using the Pediatric Quality of Life Inventory (PedsQL™) 3.0 CP Module, a validated tool specially designed to evaluate the multidimensional aspects of QoL in children with CP. This instrument includes both child self-report and parent proxy-report versions. The parent-proxy report was used in cases where the child was unable to provide reliable responses due to cognitive or communication limitations.

It contains seven subscales with 35 items: nine on daily activities (self-care tasks such as dressing and toileting), four on school activities (use of school tools such as writing instruments and computers), five on movement and balance (physical mobility and postural control), four on pain and hurt (musculoskeletal pain and sleep interference), four on fatigue (tiredness and low energy), five on eating activities (ability to eat independently), and four on speech and communication (clarity and effectiveness of verbal expression).¹⁸

A 5-point Likert scale was employed, with 0 denoting that there was never a problem, 1 denoting that there was seldom a problem, 2 denoting that there was occasionally a problem, 3 denoting that there was frequently a problem, and 4 denoting that there was almost always a problem. Responses were scored in reverse and linearly transformed into a 0 – 100 scale (0=100, 1=75, 2=50, 3=25, 4=0) during data processing. To ensure that higher scores indicated better functioning and less impairment, the total score was calculated as the mean of item responses. The PedsQL™ 3.0 CP Module has demonstrated internal consistency reliabilities that generally

exceed the minimum acceptable Cronbach's alpha coefficient of 0.70.

The primary exposure variable for the case-control comparison was group status (CP vs. healthy children) while for the within-group analysis among children with CP, the exposure variables were the WHO-endorsed functional classification systems: Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Communication Function Classification System (CFCs), and Eating and Drinking Ability Classification System (EDACS).¹⁹ Each functional classification system categorizes children into five levels (I – V), with Level I representing the highest functional ability and Level V indicating the most severe limitations. For analysis, levels were grouped into two categories based on established definitions.

GMFCS classification

The GMFCS categorizes children based on self-initiated movements, such as sitting, standing, and walking. For analysis, children were grouped into two categories. Those in Levels I – II were classified as having independent mobility, meaning they could walk without limitations or with only minor difficulties. Children in Levels III – V were categorized as having dependent mobility, which includes walking with a handheld device, relying on a wheelchair, or having severely restricted self-mobility even with assistive technology.¹⁹

MACS classification

The MACS assesses how children use their hands to handle objects in daily life. Children classified at Levels I – II were described as having better manual ability, indicating that they could manage objects independently or with minimal difficulty. In contrast, those in Levels III – V were considered to have limited manual ability, often requiring assistance, the use of adapted tools, or being unable to manipulate objects effectively.¹⁹

CFCS classification

The CFCS evaluates how effectively children communicate with both familiar and unfamiliar individuals. Children in Levels I – II were categorized as having effective communication, meaning they could reliably convey messages across various contexts. Those in Levels III – V were classified as having restricted communication, characterized by inconsistent, unclear, or limited communication that often requires assistance or the use of alternative communication methods.¹⁹

EDACS classification

The EDACS classifies children's safety and efficiency in eating and drinking. Those in Levels I – II were considered to have independent feeding ability, as they were able to eat and drink safely with little or no assistance. Children in Levels III – V were described as having assisted or unsafe feeding, which includes the need for significant help, the use of modified textures, or tube feeding due to safety concerns or inefficiency.¹⁹

Data collection

Data were collected by trained personnel using interviewer-administered questionnaires and validated clinical assessment tools during scheduled clinical visits. Demographic and perinatal information was obtained from caregivers and verified against medical and birth records when available. Eligible participants were identified through clinic records and selected based on predefined matching criteria. Interviews were conducted directly with the children when they were able to provide reliable responses; otherwise, interviews were carried out with their primary caregivers. All assessments were performed using standardized procedures to ensure consistency and data reliability across participants.

Sample size

Sample size was calculated based on a 1:1 matched case-control design. Assuming an

exposure prevalence of 50% in controls, a correlation coefficient of 0.2 for matched pairs to account for within-pair correlation, a true odds ratio of 3, and 80% power with a 5% significance level, the required sample size was estimated to be 66 cases and 66 matched controls (total n=132).

Data analysis

Data analysis was performed using SPSS version 25. Descriptive statistics were used to summarize participants characteristics. Normality of continuous variables was tested using the Shapiro-Wilk test. As PedsQL™ 3.0 CP Module scores were not normally distributed, non-parametric tests were employed. The Mann-Whitney U test was used to compare QoL scores between cases and controls and across functional subgroups (GMFCS, MACS, CFCS, and EDACS). Results were reported as medians with interquartile ranges (25th – 75th percentile). Missing data were minimal and handled through pairwise deletion. No complex sampling strategies or sensitivity analyses were performed.

Ethical approval

This study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Review Committee of the Faculty of Medicine, University of Jaffna (J/ERC/23/148/NDR/0301). Written informed consent was obtained from parents or legal guardians, and assent was obtained from children aged 5–16 years.

Results

The study included 132 children, comprising 66 with CP and 66 age- and sex-matched healthy controls. The mean age was 8.14 ± 2.80 years for the cases and 8.14 ± 2.72 years for the controls.

The median age was 7 years (interquartile range [IQR]: 6-10 years) in both groups. In each group, 34 (51.5%) were males, and 32 (48.5%)

Table I. Clinical characteristics of children with CP (N=66).

	n (%)
Type of CP	
Quadriplegic	23 (34.8)
Diplegic	21 (31.8)
Hemiplegic	7 (10.6)
Athetoid	1 (1.5)
Other*	14 (21.2)
Use of assistive device	
Yes	38 (57.6)
No	28 (42.4)
GMFCS score	
Independent movements (I, II)	30 (45.5)
Dependent movements (III, IV, V)	36 (54.5)
MACS score	
Better handling (I, II)	42 (63.6)
More limited handling (III, IV, V)	24 (36.4)
CFCS score	
Effective communication (I, II)	32 (48.5)
Restricted communication (III, IV, V)	34 (51.5)
EDACS score	
Independent feeders (I, II)	49 (74.2)
Assisted feeders (III, IV, V)	17 (25.8)

*Other types include: 1. Mixed types: Quadriplegic + diplegic: 3 (4.5%), diplegic + triplegic: 1 (1.5%), quadriplegic + hemiplegic: 2 (3.0%), quadriplegic + athetoid: 3 (4.5%), diplegic + hemiplegic: 1 (1.5%), hemiplegic + athetoid: 2 (3.0%) 2. Not clearly diagnosed: 2 (3.0%)

CFCS = Communication Function Classification System, CP = cerebral palsy, EDACS = Eating and Drinking Ability Classification System, GMFCS = Gross Motor Function Classification System, MACS = Manual Ability Classification System.

were female. The male-to-female ratio among participants was 1.1:1.

Table I presents the clinical characteristics of children with CP; the most common type was quadriplegic observed in 23 (34.8%) children, followed by diplegic in 21 (31.8%), hemiplegic in 7 (10.6%) children, athetoid CP in 1 (1.5%) child, and other types in 14 (21.2%), comprising mixed-type CP in 12 (18.2%) and cases that were not clearly classified by subtype in 2 (3.0%). Nearly 38 (57.6%) children used assistive

devices. Based on GMFCS levels, 30 (45.5%) had independent mobility, while the remainder required assistance. Regarding manual ability, 42 (63.6%) had better handling skills. Nearly half of the children demonstrated effective communication (n=32, 48.5%), and 49 (74.2%) were independent feeders.

Table II highlights the differences between cases and controls. Preterm birth was significantly more common among children with CP (n=16, 22.9%), than among controls (p=0.006). Abnormal newborn examination findings were also significantly more common in the CP group (n=43, 65.2%), than in the control (p<0.0001). The type of questionnaire respondent also differed significantly between groups, with more parent reports in the CP group and more self-reports in controls (p<0.0001). No significant difference was observed in the mode of delivery (p=0.113).

Table III shows that QoL was significantly lower in children with CP compared with healthy children across all domains assessed by the PedsQL™ 3.0 CP Module. The median total QoL score in cases was 59.27 (33.80-77.41), markedly lower than that of controls, 100 (100-100), with this difference being highly significant (p<0.0001). The domains of daily activities, school functioning, movement and balance, fatigue, eating activities, and speech and communication showed significantly lower scores in cases than in controls (p < 0.0001). Although both groups reported high scores in the pain and hurt domain, the CP group still had a significantly lower scores (median: 100, IQR: 75 – 100) compared with controls (median: 100, IQR: 100 – 100) (p < 0.0001).

Table IV shows that children with lower functional abilities had significantly lower QoL scores across multiple domains. For example, those with dependent mobility had a lower median daily activities score of 0.00 (0.00 – 25.00) compared with 66.66 (46.52-86.81) in those with independent mobility (p < 0.0001). Similarly, school activities were markedly lower in children with limited handling ability (median: 0.00, IQR: 0.00 – 15.63), compared to those with

Table II. Comparison of perinatal background and respondents of questionnaire in study groups.

	Children with CP (N=66), n (%)	Controls (N=66), n (%)	p value
Gestational age at birth			0.006
Preterm	16 (22.9)	4(6.1)	
Term	50 (75.8)	62 (93.9)	
Mode of delivery			0.113
Normal vaginal delivery	39 (59.1)	42 (63.6)	
Instrument / vacuum	3 (4.3)	1 (1.5)	
Elective / emergency LSCS	24 (34.3)	23 (34.9)	
Detail of newborn examination			<0.0001
Normal	23 (34.8)	62 (93.9)	
Abnormal	43 (65.2)	4 (6.1)	
Reporter			<0.0001
Children	14 (21.2)	59 (89.4)	
Parents	52 (78.8)	7 (10.6)	

Chi-square test.

CP = cerebral palsy, LSCS = lower segment Caesarean section.

Table III. Quality of life scores in children with CP vs. controls.

PedsQL 3.0™ CP Module	Number of questions	Children with CP (N=66)	Controls (N=66)	p value
Daily Activities	9	29.17 (0.00-66.67)	100 (100-100)	<0.0001
School Activities	4	46.88 (0.00-75.00)	100 (100-100)	<0.0001
Movements and Balance	5	55.00 (33.765-85.00)	100 (100-100)	<0.0001
Pain and Hurt	4	100 (75.00-100.00)	100 (100-100)	<0.0001
Fatigue	4	75.00 (23.44-87.50)	100 (100-100)	<0.0001
Eating activities	5	55.00 (30.00-96.25)	100 (100-100)	<0.0001
Speech and Communication	4	50.00 (0.00-95.32)	100 (100-100)	<0.0001
Total QoL	35	59.27 (33.80-77.41)	100 (100-100)	<0.0001

Mann-Whitney U test. Data presented as median (interquartile range).

CP: cerebral palsy, QoL: quality of life.

better handling ability (median: 75.00, IQR: 43.75 – 95.31) ($p < 0.0001$). Speech and communication scores were also significantly lower in children with restricted communication, compared to those with effective communication, (median: 9.38, IQR: 0.00 – 31.25 vs. median: 96.88, IQR: 75.00-100.00; $p < 0.0001$). Overall QoL scores were also significantly reduced in all lower-functioning subgroups ($p < 0.0001$). In contrast, the pain and hurt domain did not show statistically significant differences across any functional classification ($p > 0.05$).

Discussion

This study aimed to evaluate the QoL of children with CP compared with that of age-matched typically developing peers. The findings revealed significantly lower QoL scores across all domains for children with CP, underscoring the profound impact of the condition on various aspects of daily functioning. These findings are consistent with previous studies that have consistently shown that children with CP report lower QoL compared to healthy controls.^{18,20,21}

Table IV. Quality of life by functional classification systems in children with CP.

Functional classification	Daily activities	School activities	Movements and balance	Pain and hurt	Fatigue	Eating activities	Speech and communication	Overall qol
Dependent movements	0.00 (0.00-25.00)	12.5 (0.00-75.00)	40.00 (15.00-55.00)	87.5 (71.87-100)	59.37 (0.00-75.00)	40.00 (0.00-78.75)	18.75 (0.00-87.5)	37.50 (9.37-61.07)
Independent movements	66.66 (46.52-86.81)	59.38 (35.94-84.38)	87.5 (73.75-100.00)	100 (75.00-100.00)	84.38 (50.00-100.00)	77.5 (50.0-100.0)	71.88 (31.25-100.00)	71.02 (61.80-86.05)
P	<0.0001	0.001	<0.0001	0.216	0.001	<0.0001	0.015	<0.0001
More limited handling	0.00 (0.00-0.00)	0.00 (0.00-15.63)	22.50 (0.00-48.75)	81.25 (18.75-100)	15.63 (0.00-75.00)	5.00 (0.00-40.00)	0.00 (0.00-28.13)	20.77 (0.63-38.57)
Better handling	63.88 (31.25-76.39)	75.00 (43.75-95.31)	75.00 (53.75-100.00)	100 (75.00-100)	78.13 (54.69-100.00)	87.50 (55.00-100.00)	87.50 (37.50-100.00)	71.35 (61.25-85.26)
P	<0.0001	<0.0001	<0.0001	0.055	<0.0001	<0.0001	<0.0001	<0.0001
Restricted communication	0.00 (0.00-27.78)	3.125 (0.00-45.31)	47.50 (11.25-76.25)	100 (75.00-100)	50.00 (0.00-75.00)	35.00 (0.00-50.00)	9.38 (0.00-31.25)	36.17 (6.30-60.18)
Effective communication	65.28 (34.03-79.17)	75.00 (50.00-100.00)	62.50 (45.00-93.75)	100.00 (75.00-100.00)	81.25 (68.75-100)	90.00 (60.00-100.00)	96.88 (75.00-100.00)	65.28 (34.03-79.17)
P	<0.0001	<0.0001	0.019	0.788	<0.0001	<0.0001	<0.0001	<0.0001
Assisted feeding	0.00 (0.00-0.00)	0.00 (0.00-0.00)	15.00 (0.00-42.50)	71.88 (0.00-96.88)	0.00 (0.00-53.13)	0.00 (0.00-12.50)	0.00 (0.00-15.63)	7.30 (0.00-20.83)
Independent feeding	58.33 (23.61-72.22)	68.75 (31.25-81.25)	70.00 (47.50-95.00)	100.00 (75.00-100.00)	75.00 (53.13-96.88)	75.00 (50.00-100.00)	75.00 (34.38-100.00)	69.40 (54.91-84.07)
P	<0.0001	<0.0001	<0.0001	0.420	<0.0001	<0.0001	<0.0001	<0.0001

Mann-Whitney U test. Data presented as median (interquartile range).
GMFCS I-II = Independent movements; GMFCS III-V = Dependent movements. MACS I-II = Better handling; MACS III-V = More limited handling. CFCS I-II = Effective communication; CFCS III-V = Restricted communication. EDACS I-II = Independent feeding; EDACS III-V = Assisted feeding.
CFCS = Communication Function Classification System, CP = cerebral palsy, EDACS = Eating and Drinking Ability Classification System, GMFCS = Gross Motor Function Classification System, MACS = Manual Ability Classification System, QoL = quality of life.

Similarly, a study from Türkiye found that children with CP have lower participation in out-of-school activities and reduced QoL compared to typically developing peers and that children with limited participation often show a strong preference for such activities, highlighting a gap between desire and opportunity.⁸ The median total QoL score was 59.27 in children with CP, which aligns with previous studies conducted in Pakistan, India, and South Africa.^{14,15,17} In Indonesia, using the same PedsQL™ 3.0 CP Module, 76.9% of participants had impaired or poor QoL.¹⁶ In our study all 6 domains were affected, whereas the pain and hurt domain showed relatively high scores. This finding contrasts with several previous studies that reported consistently lower pain-related QoL scores among children with CP, suggesting that pain is a common and impactful symptom.²¹ A possible explanation for our differing result may be the way parents or caregivers interpreted pain. Recognizing pain in children may have been difficult in some cases.

Children with CP who had dependent mobility demonstrated significantly lower median QoL scores across all domains compared to those with independent mobility, a finding that has also been reported in other studies.^{7,22} As the GMFCS level increases, it not only impacts the child's functional abilities but also significantly contributes to a higher burden on caregivers. Caregivers of children with more severe motor impairments experience moderate to high levels of burden, with both GMFCS level and number of children being significant predictors.^{10,23} Regarding mobility devices our study found that only half of the children with CP had access to mobility devices, while the remainder did not. These play a crucial role in enhancing the QoL and development of children with CP. These devices can improve independence and social participation across various settings.²⁴

As measured by the MACS classification, children with CP who had more limited manual handling abilities reported significantly lower QoL scores across multiple domains, particularly daily activities, school activities,

eating, and speech and communication. A similar finding has been reported, with manual ability showing a strong correlation with HRQOL measures.²⁵ Several factors may contribute to poorer manual ability in children with CP, including the severity of fine motor impairment, the presence of spasticity or contractures, associated conditions such as cognitive disability and access to follow-up rehabilitation.²⁶

According to the CFCS, our study found that the greatest QoL difference was seen in the speech and communication domain, with lower scores among children with restricted communication. This finding is consistent with an Indian study reporting that functional levels, including communication abilities, are significantly associated with QoL in young children with CP.²⁷ Intellectual functioning and manual ability have been shown to significantly influence communication function in children with CP.²⁸

Based on the EDACS classification, children with CP who required assistance with feeding had significantly lower QoL scores compared with independent feeders. Eating activities and speech and communication showed the largest differences between groups. Similarly, an Indian study found that EDACS, along with other classification system, was an independent predictor of QoL impairment in young children with CP.²⁷ EDACS levels are strongly associated with dietary intake, with children at higher GMFCS levels showing lower energy and nutrient intake compared with those with less severe impairments.²⁹

Although no significant difference was found in the pain and hurt domain between cases and controls, this result may not accurately reflect the true experience of pain in children with CP. A large proportion of responses in the CP group were completed by parents through interviews rather than the children themselves, which may have led to underreporting particularly by children with limited communication abilities. This highlights the potential overestimation

of well-being in this domain and underscores the need for future studies to incorporate observational and behavioral pain assessment tools. Such approaches are especially important when evaluating children with communication difficulties to ensure a more accurate understanding of their pain experiences.

The study was conducted with a limited sample size and at a single center. Therefore, the generalizability of the findings may be limited. Quality of life depends on several other factors such as seizures and cognitive impairment, which were not investigated in this study. Preterm birth was significantly more common in children with CP than in controls ($p=0.006$), indicating a potential baseline confounder. Parent-proxy reporting was also more frequent in the CP group ($p<0.0001$), which may have introduced reporting bias.

This study highlights the significant impact of CP on the QoL in affected children, as compared to their typically developing peers. Using the PedsQL™ 3.0 CP Module, children with CP demonstrated markedly lower QoL scores across all domains, with the greatest impairments observed in daily activities, school functioning, speech and communications, and eating and drinking abilities. Overall, the results emphasize the importance of comprehensive, multidimensional assessments when evaluating QoL in children with CP. Tailored interventions that address functional limitation and communication challenges are essential to enhance participation and well-being in this vulnerable population.

Ethical approval

The study was approved by the Ethical Review Committee of the University of Jaffna (date :27.09.2023, number: J/ERC/23/148/NDR/031).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MGS;

data collection: VM, YS, KN; analysis and interpretation of results: MGS, VM, YS, KN; draft manuscript preparation: VM. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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Flexible bronchoscopy in pediatric atelectasis: bronchoscopic findings, management changes, and factors associated with radiographic resolution

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ABSTRACT

Background. Flexible bronchoscopy (FB) is widely used in children with atelectasis; however, the optimal timing of FB and the influence of underlying disease on radiographic resolution remain uncertain. We aimed to describe bronchoscopic and microbiological findings, subsequent management changes, radiographic outcomes, and factors associated with atelectasis resolution in children who underwent FB.

Methods. This retrospective cohort included 108 children (0–18 years) who underwent FB for atelectasis between 2017 and 2022 with chest radiograph-based follow-up. Outcomes were immediate radiographic response and final radiographic status. An exploratory Cox model assessed time to complete resolution and included detection-to-FB interval, macroscopic pathological findings, congenital heart disease, primary ciliary dyskinesia, immunodeficiency, asthma and cystic fibrosis.

Results. Median age at FB was 4.9 years (IQR: 2.5–8.8; range: 14 days to 18 years). 67/108 patients (62.0%) had underlying disorders. Macroscopic pathological findings were observed in 95.4%. Bronchoalveolar lavage cultures were positive in 75/105 patients (71.4%) and additional treatment was administered in 67/108 patients (62.0%). At final radiographic status, complete, partial, and no resolution were observed in 44/108 (40.7%), 30/108 (27.8%), and 34/108 patients (31.5%), respectively. In the exploratory Cox model, each 30-day increase in detection-to-FB interval was associated with a lower hazard of complete resolution (HR: 0.88, 95% CI: 0.80–0.98; $p=0.018$), but this association was attenuated after excluding intervals >365 days ($p=0.169$). Procedure-related complications occurred in 4/108 patients (3.7%).

Conclusions. In selected children undergoing FB for atelectasis, bronchoscopy frequently revealed clinically relevant bronchoscopic and microbiological findings, informed subsequent management, and was followed by partial or complete radiographic resolution in more than two-thirds of patients. Although the timing-related findings should be interpreted cautiously, particularly because the association was attenuated in sensitivity analysis, this study supports the role of FB as a complementary diagnostic and management-guiding tool in pediatric atelectasis.

Key words: atelectasis, bronchoscopy, pediatrics, treatment outcome, time-to-treatment.

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Atelectasis is a common respiratory complication in children, characterized by lung volume loss due to airway obstruction. While the etiology often involves endogenous mucus plugging or exogenous foreign bodies secondary to inflammatory processes¹⁻⁴, the condition is generally reversible with appropriate management.² Flexible bronchoscopy (FB) has become a crucial modality for both investigating the underlying etiology and providing therapeutic interventions.⁵

Despite the widespread use of FB, the optimal timing for the intervention remains controversial. Existing literature and expert opinions frequently suggest considering FB if atelectasis persists for more than two to three weeks despite conservative therapy.⁶ However, this empirical “wait-and-see” approach lacks robust evidence and may not be universally applicable, especially in urgent cases such as suspected foreign body aspiration. Furthermore, pediatric atelectasis encompasses a highly heterogeneous patient population. It remains unclear how distinct underlying pathophysiological mechanisms, such as those seen in cystic fibrosis (CF), primary ciliary dyskinesia (PCD), neuromuscular disorders, or congenital heart disease (CHD), affect the clinical response to FB. To date, most pediatric studies have relied on univariate analyses^{3,7,8}, leaving a critical knowledge gap regarding how the timing of FB and underlying comorbidities are associated with atelectasis resolution.

Therefore, the primary objective of this study was to describe the bronchoscopic and microbiological findings and subsequent management changes in children who underwent FB for atelectasis. The secondary objectives were to evaluate radiographic outcomes after FB and to explore clinical, radiological, and bronchoscopic factors associated with atelectasis resolution during follow-up.

Material and methods

Study design and ethics

This retrospective observational cohort study was conducted at a tertiary pediatric pulmonology department. The study protocol was approved by the institutional non-interventional clinical research ethics committee (Project No: GO 21/1231, Decision No: 2021/19-20). Given the retrospective design of the study and the use of anonymized data extracted from medical records, the requirement for informed consent was waived in accordance with institutional ethical guidelines.

Study population and definitions

The study included pediatric patients (aged 0–18 years) diagnosed with atelectasis who underwent FB for diagnostic and therapeutic purposes between January 1, 2017, and December 31, 2022. Atelectasis was confirmed on posteroanterior and lateral chest radiographs (CXR). To differentiate atelectasis from consolidation, all baseline and follow-up CXRs were re-reviewed by a single investigator (a pediatric pulmonologist), with specific attention to definitive signs of volume loss (e.g., fissure displacement, mediastinal shift, diaphragmatic elevation). Patients were required to have complete follow-up data, including post-bronchoscopy imaging and clinical outcomes.

In pediatric respiratory practice, routine follow-up of atelectasis relies predominantly on CXR to adhere to the ALARA (As Low As Reasonably Achievable) principle for radiation safety. Consequently, to ensure a standardized and comparable evaluation of radiological resolution, patients whose diagnosis and follow-up were based solely on computed tomography (CT) findings without corresponding CXR evidence were excluded from the analysis.

Data collection and bronchoscopy procedures

Patient data were obtained retrospectively from the hospital's electronic database and the national health system. The national health system is a comprehensive, mandated electronic registry that integrates all medical records and DICOM-format radiological images from every healthcare facility nationwide (including rural, private, and state hospitals). This centralized database allowed for the complete chronological tracking and independent re-evaluation of all X-rays, regardless of the patient's location or admitting center.

At our institution, FB is generally indicated for pediatric atelectasis when the condition persists despite appropriate conservative management (e.g., chest physiotherapy, antibiotics) or when an underlying airway anomaly or foreign body aspiration is highly suspected. Conservative management before FB was individualized according to the patient's clinical condition and suspected etiology and generally included chest physiotherapy/airway clearance therapy and antibiotics when bacterial infection was suspected. Because of the retrospective design and heterogeneous clinical background of the cohort, the exact frequency, intensity, and duration of these treatments were not standardized across all patients.

During the procedure, airway inspection and suctioning were performed in all patients, and bronchoalveolar lavage (BAL) was performed when clinically and technically feasible. BAL culture results were available for 105 of 108 patients. In the remaining three patients, BAL culture data were not available in the retrospective records; therefore, these patients were excluded from BAL culture percentage calculations. Data extracted included the timing, location, extent, and suspected cause of atelectasis; underlying comorbidities; and presenting clinical symptoms. Macroscopic findings observed during FB (e.g., purulent secretions, mucous plugs, anatomical

anomalies) and BAL culture results were also recorded. In this study, bronchoscopic evidence suggestive of lower airway infection was defined as the macroscopic presence of purulent secretions during FB. BAL culture results were reported separately as microbiological yield, acknowledging that culture positivity may reflect infection or colonization, particularly in chronic suppurative lung diseases.

Radiological resolution of atelectasis was assessed on CXR using prespecified, objective signs of volume loss (e.g., fissure displacement, mediastinal shift, diaphragmatic elevation) to minimize misclassification with consolidation, consistent with our diagnostic approach.

Given the retrospective design, formal blinding to all clinical data was not feasible; however, the investigator reviewing the imaging was blinded to the precise timing of the FB and the patients' subsequent clinical outcomes during the radiological evaluation. To further minimize observer bias, radiologic categorization was based strictly on the predefined, objective radiographic criteria rather than subjective global assessment.

Radiographic outcomes were evaluated at two predefined time points. The immediate radiographic response was defined as the status on the CXR obtained within 24 hours after FB. The final radiographic status was defined as the status on the last available follow-up CXR within the study period. At both time points, resolution was categorized as complete, partial, or no resolution. Complete resolution was defined as full re-expansion of the affected lobe or segment with disappearance of radiographic signs of volume loss; partial resolution was defined as definite radiographic improvement with residual volume-loss signs; and no resolution was defined as no meaningful radiographic improvement compared with baseline. For descriptive purposes, the time from FB to the first CXR demonstrating complete or partial resolution was also recorded when applicable.

Time to complete resolution was defined as the number of days from FB to the first CXR demonstrating complete radiographic resolution.

Statistical analysis

Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using visual inspection (histograms and Q-Q plots) and the Shapiro-Wilk test. Continuous variables were summarized as mean (SD) when approximately normally distributed and as median (IQR) when skewed; categorical variables were presented as n (%). Between-group comparisons were performed using the independent-samples t-test or Mann-Whitney U test for two groups and one-way ANOVA or Kruskal-Wallis test for ≥ 3 groups, as appropriate. Associations between categorical variables were evaluated using the chi-square test (or Fisher's exact test when needed). For within-subject comparisons of oxygen saturation before and after radiologic resolution, the paired-samples t-test or Wilcoxon signed-rank test was used depending on distribution. A two-sided p value <0.05 was considered statistically significant.

An exploratory Cox proportional hazards regression model was constructed to evaluate factors associated with time to complete radiographic resolution while accounting for variable follow-up durations and potential clinical confounders. The time-to-event variable was defined as the number of days from FB to the first CXR demonstrating complete radiographic resolution. Patients who did not achieve complete resolution were censored at their last available follow-up CXR. The multivariable model included seven prespecified variables: the interval from radiologic detection of atelectasis to FB, the presence of macroscopic pathological findings during FB, CHD primary ciliary dyskinesia, immunodeficiency, asthma, and cystic fibrosis. The interval from radiologic

detection to FB was entered into the model as a continuous variable and rescaled per 30-day increase to improve clinical interpretability. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The model included seven variables and 44 complete-resolution events, corresponding to an events-per-variable ratio of approximately 6.3. Because the interval from radiologic detection to FB included very prolonged values, a sensitivity analysis was performed by excluding patients with an interval longer than 365 days. The same Cox proportional hazards model was then repeated in this restricted cohort. Because of the retrospective design, limited event count, and absence of bootstrapping or penalized regression, the multivariable analysis was interpreted as exploratory.

Results

Study population and baseline characteristics

Between January 1, 2017, and December 31, 2022, a total of 342 FB procedures were performed at our pediatric pulmonology department. Of these, 150 (43.8%) were indicated for the diagnosis and/or management of atelectasis. After excluding 7 repeat procedures and 35 patients diagnosed solely via CT scans (due to the lack of appropriate CXR follow-up), 108 patients were included in the final analysis (Fig. 1).

The median age at the time of FB was 4.9 years (IQR: 2.5–8.8; range: 14 days to 18 years), with a slight female predominance (54.6%). Clinical symptoms were present in 95.4% of patients at admission, with dry cough being the most frequent (42.6%). Atelectasis was most frequently located in the right middle lobe (40.7%) and left lower lobe (40.7%). Radiologically, 51.9% of the cohort had additional findings accompanying atelectasis, most commonly inflammatory changes (consolidation/infiltration/ground-glass opacities) (33.3%). At the time of detection,

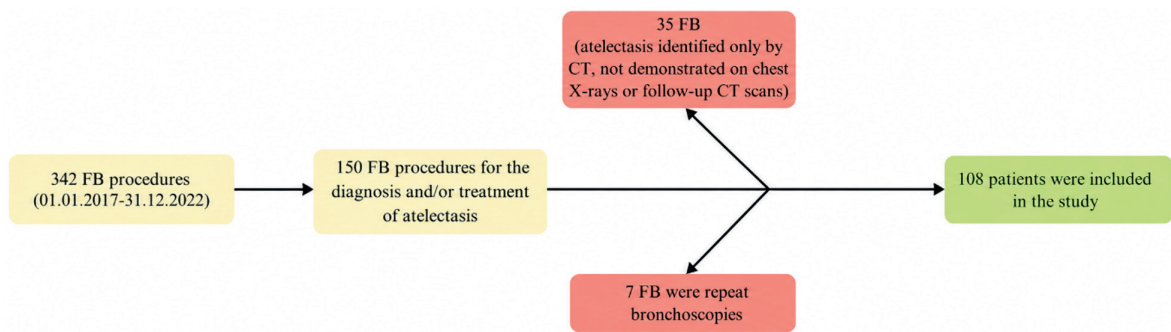


Fig. 1. Flow chart of the study.

FB Flexible bronchoscopy, CT computed tomography.

the study population demonstrated marked clinical heterogeneity; 62% of patients had at least one underlying comorbidity. The most common underlying conditions were asthma (14.8%) and CHD (14.8%), followed by immunodeficiencies (8.3%), neuromuscular diseases (7.4%), and primary ciliary dyskinesia (PCD) (7.4%) (Table I). Based on the medical records at the time of initial presentation, patients with CHD exhibited a significantly higher rate of respiratory failure (62.5%, $p < 0.001$), while those with neuromuscular diseases frequently presented with hypoxia (62.5%, $p = 0.004$). These clinical manifestations were present concurrently with the initial radiological detection of atelectasis upon hospital admission.

Furthermore, the anatomical distribution of atelectasis demonstrated significant disease-specific radiological patterns. In patients diagnosed with asthma, the rate of right middle lobe atelectasis was statistically significantly higher (75.0%, $p = 0.006$). Among patients diagnosed with CHD, the rate of total left lung atelectasis was statistically significantly higher (25.0%, $p = 0.026$).

Bronchoscopic findings and therapeutic interventions

The median interval from radiological detection of atelectasis to FB was 55 days (IQR: 24.3–152.5; range: 1–2000 days). In our practice, FB

is typically performed when atelectasis persists despite conservative management or when airway obstruction is suspected. FB revealed macroscopic pathological findings in 95.4% of patients. Purulent secretions, as a bronchoscopic finding suggestive of lower airway infection, were the most common macroscopic abnormality, observed in 72.2% of the cohort (Table II). Additional structural anomalies, such as bronchomalacia and tracheomalacia, were significantly more prevalent in patients with underlying CHD compared to those without ($p = 0.002$).

BAL culture results were available in 105 patients, of whom 75/105 (71.4%) had positive cultures. *Haemophilus influenzae* was the most frequently isolated pathogen, detected in 23/105 patients (21.9%). Following FB, additional treatment was administered in 67/108 patients (62.0%), including intravenous antibiotics in 35/108 patients (32.4%) and oral antibiotics in 25/108 patients (23.1%) (Table II).

Resolution of atelectasis after flexible bronchoscopy and associated conditions

On the same day as the FB, complete resolution of atelectasis was observed in 12.0% of patients ($n = 13$), partial resolution in 26.9% ($n = 29$), and no resolution in 61.1% ($n = 66$). The underlying diseases and FB findings of patients with partial or complete resolution are detailed in Table III.

Table I. Demographic and clinical characteristics of patients.

Variables		n (%)
Sex	Female	59 (54.6)
	Male	49 (45.4)
Radiological location of atelectasis	Right upper lobe of the lung	20 (18.5)
	Right middle lobe of the lung	44 (40.7)
	Right lower lobe of the lung	26 (24.1)
	Left upper lobe of the lung	21 (19.4)
	Left lower lobe of the lung	44 (40.7)
	Right lung total	2 (1.9)
	Left lung total	9 (8.3)
Pathological findings Accompanying atelectasis Radiologically	Number of patients with pathological findings	56 (51.9)
	Radiographic inflammatory changes (consolidation/infiltration/ground-glass opacities)	36 (33.3)
	Bronchiectasis	25 (23.1)
	Chest deformity	7 (6.5)
	Scoliosis	7 (6.5)
	Dextrocardia	3 (2.8)
Symptoms at presentation with atelectasis	Number of patients with symptoms	103 (95.4)
	Dry cough	46 (42.6)
	High fever	35 (32.4)
	Wet cough	23 (21.3)
	Hypoxia	19 (17.6)
	Respiratory failure	14 (13.0)
	Wheezing	14 (13.0)
	Respiratory distress	8 (7.4)
	Other (fatigue, shortness of breath, runny nose, nasal congestion, difficulty swallowing)	19 (17.6)
Underlying disease at the time of atelectasis detection	Patients with underlying diseases	67 (62.0)
	Asthma	16 (14.8)
	Congenital heart disease	16 (14.8)
	Immunodeficiency	9 (8.3)
	Neuromuscular disease	8 (7.4)
	PCD	8 (7.4)
	CF	6 (5.6)
	BPD	3 (2.8)
	Wheezy infant	3 (2.8)

PCD: Primary ciliary dyskinesia, CF: Cystic fibrosis, BPD: Bronchopulmonary dysplasia

Some patients had more than one underlying disorder; therefore, subgroup counts are not mutually exclusive and may exceed the total number of patients with underlying disease.

Table II. Bronchoscopic findings and post-bronchoscopy treatments in children undergoing flexible bronchoscopy for atelectasis.

Variables		n (%)
Macroscopic findings during FB	Purulent secretions (bronchoscopic)	78 (72.2)
	Bronchomalacia	25 (23.1)
	Airway anomaly	25 (23.1)
	Tracheomalacia	18 (16.7)
	Mucus plug	17 (15.7)
	Normal macroscopy	5 (4.6)
	Foreign body	4 (3.7)
BAL culture	Growth in BAL culture	75 (71.4)
	Haemophilus influenzae	23 (21.9)
	Moraxella catarrhalis	11 (10.5)
	Streptococcus pneumoniae	10 (9.5)
	Pseudomonas aeruginosa	9 (8.6)
	MSSA	5 (4.8)
	Aspergillus	4 (3.8)
	Candida	4 (3.8)
	Klebsiella pneumoniae	3 (2.9)
	Stenotrophomonas maltophilia	3 (2.9)
	MRSA	2 (1.9)
Additional treatments administered after FB	Serratia marcescens	1 (1.0)
	Number of patients receiving additional treatment	67 (62.0)
	IV antibiotics	35 (32.4)
	Oral antibiotics	25 (23.1)
	Antireflux therapy	14 (13.0)
	Inhaled ipratropium bromide	3 (2.8)

FB: Flexible Bronchoscopy, BAL: Bronchoalveolar Lavage, MRSA: methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-Sensitive *Staphylococcus aureus*, IV: Intravenous.

Percentages for BAL culture results were calculated among patients with available BAL culture data (n=105). Percentages for bronchoscopic findings and post-bronchoscopy treatments were calculated using the total cohort as the denominator (n=108).

Out of the 95 patients who did not achieve complete resolution on the same day as FB, 10 did not attend their initial outpatient follow-up appointments. Among the 85 patients who did not achieve complete resolution on the immediate post-FB CXR and had subsequent follow-up imaging, complete resolution was documented in 31/85 patients (36.5%), partial resolution in 21/85 patients (24.7%), and no resolution in 33/85 patients (38.8%).

The median time from FB to complete resolution was 90 days (IQR: 29–450; range: 2–2430 days),

while the median time from FB to partial resolution was 165 days (IQR: 68.3–675; range: 10–1440 days). At final radiographic status, complete resolution was observed in 44/108 patients (40.7%), partial resolution in 30/108 patients (27.8%), and no resolution in 34/108 patients (31.5%). (Table III and Fig. 2). The final status of atelectasis in patients who missed their initial follow-up appointments was successfully determined based on other available medical records in the national database.

Table III. Immediate radiographic response of atelectasis after flexible bronchoscopy according to underlying disorders and bronchoscopic findings.

Variables	Complete resolution (n=13)	Partial resolution (n=29)	No resolution (n=66)	P value
Underlying disorders				
Asthma (n=16)	3 (23.1)	6 (20.7)	7 (10.6)	0.298
Congenital heart disease (n=16)	3 (23.1)	2 (6.9)	11 (16.7)	0.313
Immunodeficiency (n=9)	1 (7.7)	0 (0.0)	8 (12.1)	0.143
Neuromuscular disease (n=8)	0 (0.0)	1 (3.4)	7 (10.6)	0.261
Primary ciliary dyskinesia (n=8)	0 (0.0)	1 (3.4)	7 (10.6)	0.261
Cystic fibrosis (n=6)	0 (0.0)	2 (6.9)	4 (6.1)	0.639
Bronchopulmonary dysplasia (n=3)	0 (0.0)	1 (3.4)	2 (3.0)	0.804
Wheezy infant (n=3)	0 (0.0)	0 (0.0)	3 (4.5)	0.375
Bronchoscopic findings				
Purulent secretions (bronchoscopic) (n=78)	5 (38.5)	23 (79.3)	50 (75.8)	0.014
Bronchomalacia (n=25)	6 (46.2)	4 (13.8)	15 (22.7)	0.071
Airway anomaly (n=25)	2 (15.4)	7 (24.1)	16 (24.2)	0.778
Tracheomalacia (n=18)	2 (15.4)	5 (17.2)	11 (16.7)	0.989
Mucus plug (n=17)	2 (15.4)	3 (10.3)	12 (18.2)	0.627
Foreign body (n=4)	1 (7.7)	2 (6.9)	1 (1.5)	0.317
Normal macroscopy (n=5)	1 (7.7)	1 (3.4)	3 (4.5)	0.832

Values are presented as n (%). Percentages are calculated within each immediate radiographic response group. P values were calculated using the Pearson chi-square test. Some patients had more than one underlying disorder and/or more than one bronchoscopic finding; therefore, row totals may exceed the number of patients in a given subgroup.

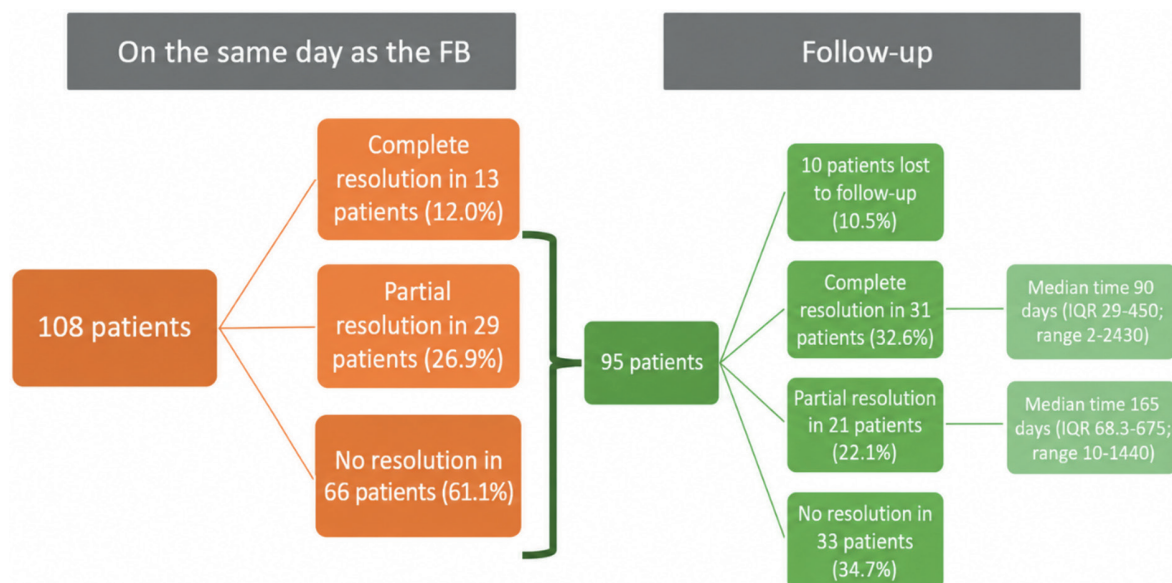
**Fig. 2.** Radiographic outcomes of atelectasis after flexible bronchoscopy.

Table IV. Interval from radiologic detection of atelectasis to flexible bronchoscopy according to radiographic outcome.

Outcome time point	No resolution, n	No resolution, median (IQR), days	Partial or complete resolution, n	Partial or complete resolution, median (IQR), days	P value
Immediate radiographic response	66	59.5 (27.2–232.5)	42	48.0 (20.0–123.0)	0.266
Final radiographic status	34	124.0 (49.0–330.0)	74	34.0 (17.0–121.0)	0.001

Values are presented as median (IQR). Immediate radiographic response was defined as the status on the chest radiograph obtained within 24 hours after FB. Final radiographic status was defined as the status on the last available follow-up chest radiograph within the study period. P values were calculated using the Mann–Whitney U test. FB, flexible bronchoscopy; IQR, interquartile range.

Twelve patients had an interval from radiologic detection to FB longer than 365 days. All had at least one underlying disorder, most commonly PCD (5/12). Macroscopic bronchoscopic abnormalities were present in 11/12 patients, most frequently purulent secretions (10/12). Regarding final radiographic outcomes, partial resolution was observed in 4/12 patients, whereas no radiographic resolution was observed in 8/12 patients. No patient in this subgroup achieved complete radiographic resolution. Initial univariate analyses revealed statistically significant differences in the time interval between the detection of atelectasis and the performance of FB. The interval from radiologic detection of atelectasis to FB was significantly shorter among patients who achieved partial or complete resolution at final radiographic status than among those with no resolution [median (IQR): 34 (17–121) vs 124 (49–330) days; $p=0.001$] (Table IV). Regarding other clinical factors, patients without additional pathological findings on CXR or CT had a significantly higher rate of complete resolution than those with additional pathological findings [28/51 (54.9%) vs 16/54 (29.6%); $p=0.006$]. Similarly, the complete resolution rate was higher among patients without scoliosis than among those with scoliosis [43/98 (43.9%) vs 1/7 (14.3%); $p=0.034$].

An exploratory Cox proportional hazards regression model was used to evaluate factors associated with time to complete radiographic resolution. The model included seven prespecified variables: the interval from radiologic detection of atelectasis to FB, the presence of macroscopic pathological findings during FB, CHD, PCD, immunodeficiency, asthma, and CF. The interval from radiologic detection to FB was entered into the model as a continuous variable and rescaled per 30-day increase to improve clinical interpretability. In the primary model, each 30-day increase in the interval from radiologic detection to FB was associated with a lower hazard of complete radiographic resolution (HR: 0.88, 95% CI: 0.80–0.98; $p=0.018$). CHD was also associated with a higher hazard of complete radiographic resolution (HR: 2.10, 95% CI: 1.05–4.20; $p=0.036$). Other variables in the model did not reach statistical significance.

In the sensitivity analysis excluding patients with an interval from radiologic detection to FB longer than 365 days, the association between the detection-to-FB interval and complete radiographic resolution was attenuated and was no longer statistically significant (HR per 30-day increase: 0.92, 95% CI: 0.81–1.04; $p=0.169$). In this restricted model, CHD remained associated with complete radiographic resolution (HR: 2.11, 95% CI: 1.05–4.23; $p=0.035$).

Finally, among patients who achieved partial or complete radiological resolution at their final follow-up, a statistically significant clinical improvement in oxygen saturation was observed. The mean oxygen saturation increased from 93.1% at the time of initial detection to 96.9% following resolution ($p < 0.001$).

Recurrence and procedure safety

Atelectasis recurrence during the follow-up period was observed in 10 patients (9.3%), with a median time to recurrence of 49 days. The FB procedure demonstrated a favorable safety profile, with complications occurring in only 4 patients (3.7%). These included transient severe hypoxia in three patients with underlying CHD and mild bleeding in one patient, which necessitated the early termination of the procedure.

Discussion

This study describes the bronchoscopic findings, microbiological results, management changes, and radiographic outcomes of children who underwent FB for atelectasis in a tertiary pediatric pulmonology setting. The main finding was that FB provided clinically relevant information in most patients and was followed by management changes in a substantial proportion of the cohort. Partial or complete radiographic resolution was observed in more than two-thirds of patients at final radiographic status, although same-day resolution was less frequent. These findings suggest that, in selected children with persistent or clinically concerning atelectasis, FB may contribute to care not only through direct airway inspection and suctioning, but also by clarifying the underlying mechanism and guiding subsequent individualized treatment.

The timing-related findings should be interpreted cautiously. In the univariate analysis and in the primary exploratory Cox model, a longer interval from radiologic detection of atelectasis to FB was associated with a lower

likelihood of complete radiographic resolution. However, this association was attenuated and was no longer statistically significant after excluding patients with intervals longer than 365 days. This suggests that the timing variable may partly reflect differences between acute atelectasis and chronic or recurrent atelectasis in medically complex patients rather than a direct causal effect of earlier FB alone. The subgroup with intervals longer than 365 days supports this interpretation: all had underlying disorders, most commonly primary ciliary dyskinesia, and none achieved complete radiographic resolution. Therefore, the Cox model findings should be considered exploratory and hypothesis-generating rather than definitive evidence that earlier FB independently determines resolution.

Our cohort's clinical heterogeneity further underscores the necessity of understanding disease-specific mechanisms. We observed distinct anatomical patterns of atelectasis that were consistent with underlying morbidities. For instance, the higher frequency of total left lung atelectasis in patients with CHD may reflect mechanical compression. The close anatomical proximity of an enlarged left atrium or pulmonary artery in various CHD anomalies can externally compress the soft, cartilaginous left main bronchus of infants, leading to collapse and subsequent atelectasis.⁹⁻¹² Correspondingly, we found significantly higher rates of structural airway anomalies (bronchomalacia, tracheomalacia) in this group. Furthermore, the predominant involvement of the right middle lobe in patients with asthma reflects the unique anatomical vulnerability of this lobe; its relatively narrow and long bronchus, combined with a sharp branching angle, makes it particularly susceptible to obstruction by the thick mucus plugs characteristic of asthmatic airway inflammation.¹³ Recognizing these distinct pathophysiological mechanisms emphasizes that pediatric atelectasis is not a single clinical entity; therefore, diverse etiologies should not be managed under a uniform therapeutic approach.

The bronchoscopic, microbiological, and radiographic findings also emphasize the practical value of FB in this population. Macroscopic pathological findings were present in most patients, and purulent secretions were the most frequent abnormality. BAL cultures were positive in a high proportion of patients with available culture data, with *Haemophilus influenzae* being the most commonly isolated pathogen. These findings are consistent with previous pediatric bronchoscopy series showing that FB can reveal infectious, obstructive, and structural contributors to persistent atelectasis.¹⁴⁻¹⁷ Same-day partial or complete radiographic resolution was observed in 42/108 patients (38.9%), which is lower than some previous reports describing immediate response rates as high as 87%.^{16,18} This difference may reflect the high clinical complexity and chronicity of our cohort. Nevertheless, partial or complete resolution increased to 74/108 patients (68.5%) at final radiographic status, and radiographic improvement was accompanied by a significant increase in oxygen saturation. Because conservative and post-procedural treatments were individualized, these improvements should not be attributed solely to the mechanical effect of FB. Rather, FB may be best viewed as a diagnostic and management-guiding procedure that can contribute to resolution through both direct airway clearance and subsequent targeted therapy. The overall complication rate was low; however, all episodes of transient severe hypoxia occurred in patients with CHD. Thus, children with CHD and other medically complex conditions warrant careful pre-procedural assessment, close monitoring, and subgroup-specific vigilance.¹⁹⁻²¹

This study has several limitations. Its retrospective, single-center design may introduce referral bias, and the cohort included only children who underwent FB; therefore, the findings cannot be generalized to all children with atelectasis or used to determine when FB should be performed compared with conservative management alone. Follow-up CXR were obtained at variable time points

according to clinical judgment rather than a standardized imaging protocol, which may have introduced systematic bias into the time-to-resolution analysis. Radiographic assessment relied primarily on CXR and was performed by a single reviewer, although predefined objective criteria were used and the reviewer was blinded to procedural timing and subsequent outcomes. Conservative and post-procedural treatments were individualized, making it difficult to separate the direct mechanical effect of FB from the effect of bronchoscopy-guided medical therapy. Finally, the Cox model included a limited number of complete-resolution events, with an events-per-variable ratio of approximately 6.3; therefore, the multivariable findings should be interpreted as exploratory.

In conclusion, FB in selected children with atelectasis provides high bronchoscopic and microbiological yield, may guide clinically relevant management changes, and should be considered as a complementary diagnostic and management-guiding tool. Decisions regarding timing and expected benefit should remain individualized according to the patient's underlying disease, clinical severity, and suspected mechanism of atelectasis.

Ethical approval

The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (Decision No: 2021/19-20, Project No: GO 21/1231). The requirement for informed consent was waived due to the retrospective design.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ÖFİ, EY; data collection: ÖFİ; analysis and interpretation of results: ÖFİ, EY, DD, UÖ, NK, ÖÖ, BS, NEO; draft manuscript preparation: ÖFİ, EY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Primary hypoparathyroidism in childhood: clinical and etiological spectrum in a tertiary referral center from southeastern Türkiye

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ABSTRACT

Background. Primary hypoparathyroidism is a rare endocrine disorder in childhood; data on its clinical and etiological spectrum in pediatric populations remain limited. We aimed to characterize the clinical, biochemical, etiological, and therapeutic spectrum of pediatric primary hypoparathyroidism at a tertiary center in Southeastern Türkiye.

Methods. A retrospective, single-center observational cohort study was conducted between January 2016 and January 2026. Medical records of 27 children (0–18 years) with nonsurgical primary hypoparathyroidism were reviewed. The diagnosis required persistent hypocalcemia with hyperphosphatemia and inappropriately low or normal intact parathyroid hormone on at least two measurements, in the absence of secondary causes. Demographic, clinical, biochemical, imaging, genetic testing (fluorescence in situ hybridization/multiplex ligation-dependent probe amplification for 22q11.2; targeted sequencing for candidate genes), and treatment data were collected.

Results. Median age at diagnosis was 3 months (interquartile range: 1.6–111 months; range: 3 days–17 years); 9 patients (33.3%) were diagnosed in the neonatal period. Seizures were the most frequent presenting feature in 12 patients (44.4%). A specific etiological diagnosis was established in 11 patients (40.7%): DiGeorge syndrome in 5 (18.5%), Kenny–Caffey syndrome type 1 in 3 (11.1%), Sanjad–Sakati syndrome in 1 (3.7%), autoimmune polyglandular syndrome type 1 in 1 (3.7%), and autosomal dominant hypocalcemia type 1 due to an activating calcium-sensing receptor (CASR) mutation in 1 (3.7%). Twenty-four patients (88.9%) received combined oral calcium and calcitriol therapy. Two patients (7.4%) died from sepsis.

Conclusions. In this Southeastern Turkish pediatric cohort, DiGeorge syndrome and tubulin-specific chaperone E gene (TBCE)-related disorders were the most prominent identified etiologies; the enrichment of TBCE-related disorders likely reflects regional consanguinity and Arab-origin demographics. An integrated diagnostic approach combining clinical, biochemical, and genetic evaluation is essential in similar populations. Prospective multicenter studies with systematic genetic testing are warranted.

Key words: primary hypoparathyroidism, hypocalcemia, childhood, genetic etiology, DiGeorge syndrome, tubulin-specific chaperone E gene.

Primary hypoparathyroidism in childhood is an uncommon endocrine disorder characterized by deficient production or secretion of parathyroid hormone (PTH) leading to

persistent hypocalcemia accompanied by hyperphosphatemia. Hypoparathyroidism may result from intrinsic abnormalities of the parathyroid glands, including developmental

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defects, genetic disorders, and autoimmune destruction, or from acquired causes such as surgical removal or damage to the parathyroid glands. While postsurgical hypoparathyroidism represents the most common form overall, the present study focuses on nonsurgical primary hypoparathyroidism and its underlying intrinsic etiologies.¹ Only a few population-based studies have evaluated the epidemiology of nonsurgical primary hypoparathyroidism. Reported prevalence estimates range from 0.7 per 100,000 in Japan to 5 per 100,000 in Rochester, USA, while a nationwide Danish study reported a prevalence of 2.3 per 100,000 inhabitants.²⁻⁴ Although rare, pediatric hypoparathyroidism carries significant clinical consequences, ranging from subtle biochemical abnormalities to life-threatening neuromuscular and neurodevelopmental complications such as seizures and tetany; early recognition is therefore essential to prevent acute morbidity and long-term sequelae.⁵ The variable clinical spectrum and potential for atypical presentations complicate timely diagnosis and management in children.

The etiologic landscape of pediatric nonsurgical primary hypoparathyroidism is heterogeneous, encompassing isolated genetic defects, syndromic conditions, and developmental anomalies of the parathyroid glands.⁶ Among syndromic causes, 22q11.2 deletion syndrome (DiGeorge syndrome) represents one of the most frequently identified etiologies in pediatric cohorts.⁷ In regions with high rates of consanguineous marriage, autosomal recessive conditions such as Kenny–Caffey syndrome type 1 (KCS1) and Sanjad–Sakati syndrome (SSS), both caused by pathogenic variants in the tubulin-specific chaperone E (*TBCE*) gene, are disproportionately represented.^{8,9} Genetic mechanisms implicated include defects in calcium-sensing receptor (CaSR) signaling, abnormalities of parathyroid development, and perturbations in transcriptional regulators of parathyroid function (e.g., *GCM2*, *GATA3*, and *PTH*), as well as autoimmune polyendocrine syndrome type 1 (APS-1) caused by pathogenic

variants in the autoimmune regulator (*AIRE*) gene.^{7,10,11}

Despite the clinical importance of pediatric hypoparathyroidism, published data from the Eastern Mediterranean and Middle Eastern regions remain sparse. Southeastern Türkiye is characterized by elevated rates of consanguineous marriage and a noteworthy Arab-origin population, demographic factors that may substantially influence the etiological spectrum of rare recessive disorders.^{12,13} The aim of this study was to characterize the clinical, biochemical, etiological, and therapeutic profile of children with nonsurgical primary hypoparathyroidism, with particular emphasis on intrinsic genetic and syndromic etiologies who were followed at a tertiary pediatric endocrinology center in this region.

Materials and Methods

This retrospective, single-center observational cohort study was conducted in the pediatric endocrinology department of a tertiary care center in Southeastern Türkiye. Medical records of children diagnosed with nonsurgical primary hypoparathyroidism and followed between January 2016 and January 2026 were reviewed. Patients aged 0–18 years with a diagnosis of primary hypoparathyroidism, defined as persistent hypocalcemia with hyperphosphatemia and inappropriately low or normal PTH levels in the absence of secondary causes, were included. Patients with postsurgical hypoparathyroidism, vitamin D deficiency, renal insufficiency, transient neonatal hypocalcemia, malabsorption disorders, or hypomagnesemia-related syndromes were excluded.

Demographic data collected included age at diagnosis, sex, and parental consanguinity. Clinical data comprised presenting symptoms (e.g., seizures, tetany, lethargy), age at symptom onset, family history of hypoparathyroidism or unexplained infant deaths, comorbid conditions, and dysmorphic features. Laboratory data

obtained from electronic medical records at diagnosis and during follow-up included total serum calcium, ionized calcium, serum phosphate, magnesium, alkaline phosphatase (ALP), intact PTH, 25-hydroxyvitamin D, creatinine, spot urine calcium-to-creatinine ratio, and 24-hour urinary calcium excretion when available. Clinical characteristics and biochemical parameters reported in this study were obtained at the time of diagnosis. All biochemical measurements were performed in the hospital laboratory using standard automated analyzers; assay-specific reference ranges and units recorded at the time of testing were noted in the dataset when available. Serum intact PTH concentrations were measured using an electrochemiluminescence immunoassay (ECLIA) on Cobas e402 and Cobas e801 analyzers (Roche Diagnostics, Mannheim, Germany). The laboratory reference range for intact PTH was 15–65 pg/mL. Age-adjusted phosphate reference ranges and urine Ca/Cr reference values were applied according to local laboratory standards.

Imaging data included renal ultrasonography to assess nephrocalcinosis and cranial computed tomography (CT) or magnetic resonance imaging (MRI) to detect basal ganglia calcifications when clinically indicated. Audiological and transthoracic echocardiographic evaluations were performed in patients with syndromic features or clinical suspicion, and available results were recorded. Treatment modalities, including oral calcium supplementation, active vitamin D analogues (calcitriol), magnesium replacement, and recombinant PTH when applicable, were documented. Treatment-related data, including elemental calcium and calcitriol doses, were recorded from the most recent follow-up visit available in the medical records. Treatment response was evaluated based on biochemical parameters, clinical improvement, and treatment-related complications such as hypercalciuria and nephrocalcinosis.

Genetic analysis

Available genetic test results were retrospectively reviewed. Genetic investigations had been performed during routine clinical care according to clinical suspicion and test availability. Targeted testing for 22q11.2 deletion was performed using fluorescence in situ hybridization (FISH) and/or multiplex ligation-dependent probe amplification (MLPA). In selected patients with characteristic phenotypic findings, candidate genes including *TBCE* and *CASR* were analyzed by targeted Sanger sequencing. Comprehensive next-generation sequencing panels and whole-exome sequencing were not routinely available during the study period. Accordingly, genetic confirmation could not be obtained for all patients with clinically suspected syndromic diagnoses.

Statistical analysis

Descriptive statistics were used for all analyses. Continuous variables were summarized according to their distribution characteristics. Variables with skewed distributions are presented as median (interquartile range, IQR: 25th–75th percentile), whereas normally distributed variables are presented as mean $\pm$ standard deviation (SD). Categorical variables are expressed as frequencies and percentages. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Adnan Menderes University (approval number: 2026/101), and the requirement for informed consent was waived given the retrospective design.

Results

Patient demographics

A total of 27 patients were included in the study, comprising 15 males (55.6%) and 12

females (44.4%). The median age at diagnosis was 3 months (IQR: 1.6–111 months; range: 3 days–17 years), and 9 patients (33.3%) were diagnosed during the neonatal period. Parental consanguinity was present in 23 patients (85.1%). The median duration of follow-up was 3.75 years (IQR: 2.2–6.5 years; range: 3 months–15 years).

Presentation and clinical features

Seizures were the most frequent presenting symptom in 12 patients (44.4%), followed by neonatal detection of hypocalcemia in 9 patients (33.3%) and muscle cramps in 4 patients (14.8%). One patient (3.7%) was diagnosed incidentally during treatment for pneumonia and one (3.7%) during routine follow-up for previously known as APS-1. Dysmorphic features were observed in 10 patients (37.0%). Cardiac anomalies were present in 8 patients (29.6%): ventricular septal defect in 2 patients (7.4%), pulmonary stenosis in one patient (3.7%), atrial septal defect in one patient (3.7%), patent foramen ovale in 3

patients (11.1%), and left ventricular dilatation in one patient (3.7%). Sensorineural hearing loss occurred in 4 patients (14.8%) and renal anomalies in 2 patients (7.4%). Cranial imaging was performed in only 3 patients (11.1%); basal ganglia calcification was detected in 1 of these 3 (33.3%) patients, which likely resulted in an underestimation of its true prevalence.

Biochemical findings at diagnosis

All patients fulfilled the diagnostic criteria for primary hypoparathyroidism and therefore presented with hypocalcemia and hyperphosphatemia at diagnosis. Biochemical findings are summarized in Table I. Two patients (7.4%) had PTH levels within the normal reference range despite documented hypocalcemia, whereas one patient (3.7%) had a slightly elevated PTH level. These patients were subsequently diagnosed with an activating CASR mutation, DiGeorge syndrome, and APS-1, respectively.

Table I. Baseline characteristics of study patients (n = 27).

Characteristic	Value
Number of patients	27
Female/Male	12/15 (44.4%/55.6%)
Median age at diagnosis (months)	3 (1.6–111)
Neonatal presentation	9 (33.3%)
Parental consanguinity	23 (85.1%)
Presenting symptoms	
Seizures	12 (44.4%)
Neonatal hypocalcemia	9 (33.3%)
Muscle cramps	4 (14.8%)
Incidental diagnosis	2 (7.4%)
Biochemical data at diagnosis	
Total serum calcium (mg/dL)	5.54 (5.31–6.19)
Serum phosphate (mg/dL)	9.30 (8.42–10.25)
Intact PTH (pg/mL)	4.14 (1.36–10.29)
25-Hydroxyvitamin D (ng/mL)	20.3 (16–25)
Serum magnesium (mg/dL)	1.68 (1.54–1.78)
Urinary calcium/creatinine (mg/mg creatinine)	0.095 (0.04–0.23)
Median follow-up duration (years)	3.75 (2.2–6.5)

Data are given as median (IQR) or n (%).

IQR: interquartile range, PTH: parathyroid hormone.

Etiology of primary hypoparathyroidism

A specific etiological diagnosis was established in 11 patients (40.7%) based on clinical and/or genetic findings (Table II). Among these, molecular confirmation was available in 8 patients, whereas the remaining diagnoses were established on the basis of characteristic clinical features and associated findings. The identified etiologies included DiGeorge syndrome in 5 patients (18.5%), KCS1 in 3 patients (11.1%), SSS in one patient (3.7%), APS-1 in one patient (3.7%), and autosomal dominant hypocalcemia type 1 (ADH1, CASR mutation) in one patient (3.7%). All genetic variants identified in our cohort had been previously reported in the literature and were consistent with the corresponding clinical phenotypes.^{7,8,14} However, segregation analysis could not be performed because of the retrospective design of the study and the unavailability of parental genetic testing. The remaining 16 patients (59.3%) had no confirmed genetic or clinical diagnosis, commonly due to limited access to genetic testing during the study period. The etiological distribution is illustrated in Fig. 1. Among the patients without genetic testing or a definitive clinical diagnosis, 4 patients (25%) exhibited foramen ovale or mild cardiac abnormalities, and only one patient (6.2%) had sensorineural hearing loss. Most did not display characteristic syndromic features suggestive of a specific genetic syndrome. Nevertheless, because comprehensive molecular testing was not available for all patients, an underlying genetic etiology cannot be excluded. Detailed individual clinical and genetic characteristics of patients with established etiological diagnoses are presented in Table II.

Treatment and outcomes

Three patients (11.1%) received calcitriol monotherapy, and 24 patients (88.9%) received combined oral calcium and calcitriol therapy. At the most recent follow-up visit, the median elemental calcium dose was 28 (IQR: 22–33)

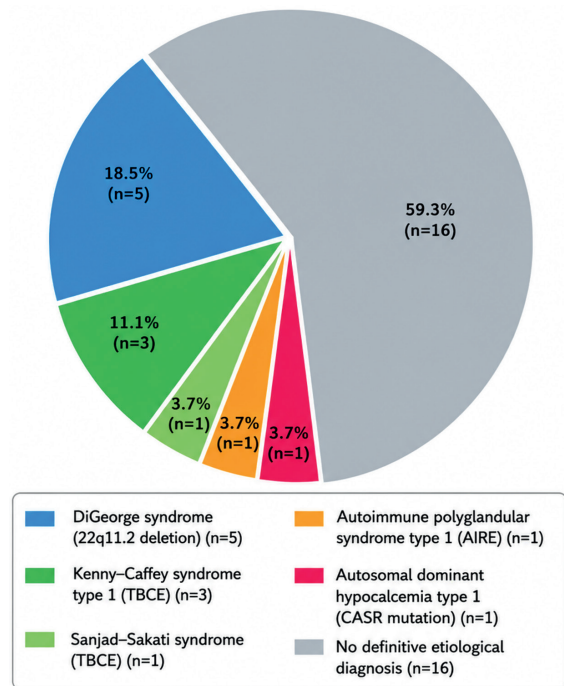


Fig. 1. Etiological distribution of non-surgical primary hypoparathyroidism in 27 pediatric patients followed at a tertiary center in Southeastern Türkiye (2016–2026).

ADH1: autosomal dominant hypocalcemia type 1; APS: autoimmune polyglandular syndrome; CASR: calcium-sensing receptor gene; TBCE: tubulin-specific chaperone E gene.

mg/kg/day and the median calcitriol dose was 18.75 (IQR: 13–25.75) ng/kg/day. The wide range in calcitriol dosing reflects age-related pharmacokinetic differences (neonates and infants typically require higher weight-adjusted doses), as well as dose adjustments made in response to treatment-related complications such as hypercalciuria, particularly in the patient who developed nephrocalcinosis and chronic kidney disease (CKD). Hypercalcemia and nephrocalcinosis occurred only in one patient with KCS1, who subsequently developed CKD; no patient progressed to end-stage renal disease. Overall mortality was 7.4% (2/27). One patient with 22q11.2 deletion syndrome died during the neonatal period due to sepsis. The second patient, who had KCS1, died from sepsis at 3 years of age.

Table II. Clinical, laboratory, and genetic characteristics of patients with genetically or syndromically defined primary hypoparathyroidism.

Pt	Diagnosis	Age at Dx	Sex	Initial presentation	Dysmorphic features	Ca (mg/dL)	P (mg/dL)	PTH (pg/mL)	Echo	Nephrocalcinosis	Genetic finding	BGC
1	DiGeorge syndrome	NB	F	Neonatal hypocalcemia	Yes	5.2	8.4	9.0	Pulmonary stenosis	No	NA	ND
2	DiGeorge syndrome	NB	M	Neonatal hypocalcemia	Yes	4.9	9.3	20.0	Normal	No	22q11.21 microdeletion	ND
3	DiGeorge syndrome	NB	M	Neonatal hypocalcemia	Yes	6.18	9.94	8.8	VSD	No	NA	ND
4	DiGeorge syndrome	NB	M	Neonatal hypocalcemia	Yes	6.5	8.82	10.9	VSD + PFO	No	22q11.21 microdeletion	ND
5	DiGeorge syndrome	NB	M	Neonatal hypocalcemia	Yes	5.05	9.59	1.2	ASD	No	22q11.21 microdeletion	ND
6	KCS1	NB	F	Convulsion	Yes	5.56	8.48	1.2	Normal	No	TBCE: c.155_166del (p.Ser52_Gly55del), homozygous	No
7	KCS1	NB	M	Convulsion	Yes	6.4	8.5	1.2	Normal	No	TBCE: c.155_166del (p.Ser52_Gly55del), homozygous	No
8	KCS1	3 mo	F	Convulsion	Yes	5.4	7.5	4.5	Normal	No	TBCE: c.155_166del (p.Ser52_Gly55del), homozygous	ND
9	Sanjad-Sakati syndrome	NB	M	Convulsion	Yes	5.5	8.8	1.2	Normal	No	TBCE: c.155_166del (p.Ser52_Gly55del), homozygous	ND
10	APS type 1	9 yr	M	Follow-up exam	No	7.83	4.5	84.0	Normal	No	NA	ND
11	ADH1	9 yr	F	Muscle cramps	No	7.43	8.23	24.0	Normal	No	CASR: c.407C>T (p.Pro136Leu), heterozygous	ND

ADH1: autosomal dominant hypocalcemia type 1; APS: autoimmune polyglandular syndrome; ASD: atrial septal defect; BGC: basal ganglia calcification; CASR: calcium-sensing receptor gene; Dx: diagnosis; Echo: echocardiography; KCS: Kenny-Caffey syndrome; mo: months; NA: not available (genetic analysis could not be performed); NB: newborn; ND: not done (imaging not performed); PFO: patent foramen ovale; TBCE: tubulin-specific chaperone E gene; VSD: ventricular septal defect; yr: years.

Discussion

DiGeorge syndrome was the most frequent identifiable cause in our series, affecting 5 patients (18.5%), consistent with prior pediatric reports that show a wide prevalence range (approximately 10–59%) depending on cohort composition and the extent of genetic evaluation.¹⁵ All five affected children in our cohort presented during the neonatal period, consistent with the well-described early manifestation of 22q11.2 deletion-related hypoparathyroidism, although later presentations have been documented in other series. Genetic confirmation was achieved in only 3/5 patients due to technical and access limitations, representing an important constraint on etiological ascertainment. None of the patients with DiGeorge syndrome had a documented family history of 22q11.2 deletion syndrome, consistent with the predominantly de novo occurrence of this condition. We recommend routine consideration of 22q11.2 deletion testing in neonates with unexplained hypocalcemia, even in the absence of overt cardiac or immunological features.

KCS1 (n = 3) and SSS (n = 1) together accounted for 4 patients (14.8%), a proportion higher than typically reported in non-Middle Eastern pediatric series but consistent with reports from Saudi Arabia and Kuwait, where *TBCE*-related disorders are relatively common.^{16–18} Both conditions are autosomal recessive and result from pathogenic variants in the *TBCE* gene; they have been repeatedly associated with Arab ancestry and increased parental consanguinity, factors known to elevate the prevalence of recessive disorders.^{8,12,18} The demographic features of Southeastern Türkiye, including high rates of consanguineous marriage and a substantial Arab-origin population, likely underlie the observed enrichment of *TBCE*-related diagnoses in our cohort.^{12,13,19} Consanguinity is well established as a major driver of autosomal recessive pediatric endocrine disorders across the Eastern Mediterranean region.²⁰ Intrafamilial variability is illustrated by two affected siblings

with KCS1 who had divergent clinical courses, emphasizing variable expressivity even with the same genotype.^{16,18} Although KCS1 and SSS share a genetic basis, they differ phenotypically: SSS typically presents with more severe neurodevelopmental impairment, whereas KCS1 is notable for skeletal features such as cortical thickening and medullary stenosis of long bones.^{17,18} This genotype–phenotype complexity suggests that modifying genetic, epigenetic, or environmental factors should be considered during genetic counseling and prognostic discussions.¹⁷

Among our 27 patients, two had inappropriately normal PTH levels despite documented hypocalcemia and were diagnosed with an activating *CASR* mutation and DiGeorge syndrome, whereas one patient with APS-1 had a slightly elevated PTH level despite hypocalcemia. This finding illustrates that a “normal” PTH in level the setting of low calcium reflects an inadequate parathyroid response rather than true euparathyroidism. This phenomenon may result from partial gland dysfunction, impaired parathyroid reserve, altered CaSR signaling, or early autoimmune destruction.^{21,22} Clinically, PTH must always be interpreted alongside concurrent serum calcium levels to avoid false reassurance.

The patient with an activating *CASR* mutation did not develop nephrocalcinosis or hypercalciuria despite the established renal risk associated with such mutations;^{22,23} early diagnosis and maintenance of conservative serum calcium targets may have mitigated this risk. The APS-1 case demonstrated the classic sequential evolution of disease, consistent with natural history cohorts reporting hypoparathyroidism in approximately 79–84% of patients,^{24,25} underscoring the need for long-term multidisciplinary endocrine surveillance in suspected APS-1. Nephrocalcinosis developed in one patient with KCS1, who subsequently progressed to CKD, underscoring the renal vulnerability described in *TBCE*-related disorders.^{17,18} No patient progressed to end-stage renal disease during follow-up.

Basal ganglia calcification was identified in only one patient; however, cranial imaging had been performed in just 3 patients, a limitation that likely led to substantial underestimation of intracranial calcifications compared with reported prevalences of 40–70% in long-standing hypoparathyroidism.^{22,23} Routine neuroimaging, preferably cranial CT, in patients with chronic disease should be considered to detect subclinical calcifications and guide long-term management.

The majority of patients (24/27, 88.9%) were managed with combined oral calcium and calcitriol, consistent with standard-of-care recommendations.²³ All patients included in the present study had persistent primary hypoparathyroidism by definition; therefore, treatment discontinuation due to transient hypoparathyroidism was not expected.

Two patients (7.4%) died from sepsis during follow-up; both had genetically confirmed syndromic diagnoses (22q11.2 deletion and KCS1), conditions associated with immune dysfunction and infection susceptibility. While mortality data in pediatric hypoparathyroidism series are limited, the available literature suggests that deaths are uncommon in isolated hypoparathyroidism but occur at higher rates in syndromic forms, particularly in DiGeorge syndrome, where T-cell deficiency predisposes to serious infections.^{7,15} Our mortality rate, while seemingly elevated for a pediatric endocrine cohort, must be interpreted in the context of the predominantly syndromic composition of our diagnosed subgroup and the limited access to specialized immunological care in the region during the study period. Despite generally favorable metabolic control, these observations suggest a potential increased susceptibility to infections in these subgroups, emphasizing the need for vigilant multidisciplinary supportive care.

The majority of patients in this cohort (16/27, 59.3%) remained without a confirmed genetic or

clinical diagnosis. This likely reflects the limited availability of comprehensive next-generation sequencing during the study period rather than a true absence of genetic etiology. Candidate genes not fully evaluated in this cohort include *GCM2* (the most common cause of isolated familial hypoparathyroidism), *GATA3* (associated with HDR syndrome: hypoparathyroidism, deafness, and renal anomalies), *SOX3* (X-linked hypoparathyroidism), and *FAM111A* (Kenny–Caffey syndrome type 2). Given the high consanguinity rate (85.1%), novel autosomal recessive variants are plausible in a substantial proportion of the undiagnosed group. Whole-exome or whole-genome sequencing would be the recommended next diagnostic step for these patients.

The present study adds to the limited literature on pediatric nonsurgical primary hypoparathyroidism by providing data from Southeastern Türkiye, a region characterized by high rates of parental consanguinity and a substantial burden of rare autosomal recessive disorders.^{12,13,20} Furthermore, the presence of patients with inappropriately normal PTH concentrations despite hypocalcemia underscores an important diagnostic challenge and emphasizes the need to interpret PTH values in relation to serum calcium concentrations rather than relying solely on laboratory reference intervals.^{1,7,21} However, the retrospective single-center design introduces potential selection bias and incomplete data ascertainment, and the small sample size ($n = 27$), while reflective of disease rarity, limits generalizability. Another major limitation of this study is the relatively low etiological diagnostic yield (40.7%). This likely reflects restricted access to comprehensive molecular testing during much of the study period rather than a true absence of identifiable genetic causes. Therefore, the reported frequencies should be interpreted as the distribution of confirmed etiologies within the cohort and may underestimate the actual prevalence of specific genetic disorders.

Conclusions

In this cohort of 27 children from Southeastern Türkiye, a specific etiological diagnosis was established in 40.7% of patients, with DiGeorge syndrome and *TBCE*-related disorders being the most prominent identified causes; the latter likely reflects the region's high consanguinity rates and substantial Arab-origin population. A normal PTH concentration does not exclude hypoparathyroidism and must always be interpreted alongside simultaneous serum calcium measurements. 22q11.2 deletion testing should be considered in all neonates with unexplained hypocalcemia, and routine neuroimaging merits consideration given the likely underestimation of intracranial calcifications. Children with *TBCE*-related disorders require vigilant infection surveillance. An integrated diagnostic strategy combining clinical assessment, targeted biochemical evaluation, and systematic genetic testing is essential in populations with high consanguinity. Prospective multicenter studies with routine next-generation sequencing (including whole-exome and/or whole-genome sequencing) are needed to improve etiological yield and guide management in pediatric hypoparathyroidism.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Adnan Menderes University (approval date: 13.03.2026 number: 2026/101), and the requirement for informed consent was waived given the retrospective design.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HM, PA, BK; data collection: HM, PA, BK; analysis and interpretation of results: HM, PA, BK; draft manuscript preparation: HM, PA, BK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Exploratory epigenetic analysis of host gene-dependent regulation of miR-197-3p in familial Mediterranean fever

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ABSTRACT

Background. Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease caused by mutations in the *Mediterranean Fever (MEFV)* gene. Despite its monogenic basis, FMF shows marked clinical heterogeneity, suggesting additional regulatory mechanisms. This exploratory study aimed to investigate host gene-dependent mechanisms underlying altered miR-197-3p expression in FMF.

Materials and Methods. Peripheral blood mononuclear cells from homozygous FMF patients (n=6) and matched healthy controls (n=6) were analyzed. miR-197-3p expression was quantified using RT-qPCR. DNA methylation patterns in regulatory regions of the *GNAI3* promoter and the *MIR197* upstream candidate regulatory region were assessed by bisulfite sequencing.

Results. miR-197-3p expression was significantly reduced in FMF patients compared with controls, as expected. No evidence supporting regulation through the *MIR197* upstream candidate regulatory region was observed. Differential methylation within the *GNAI3* promoter was statistically significant (p = 0.0093), supporting biological relevance despite the limited cohort size.

Conclusion. These pilot findings provide preliminary molecular evidence supporting host gene-dependent regulation of miR-197-3p in FMF. Given the small cohort size, these findings should be considered exploratory and require validation in larger, independent cohorts.

Key words: autoinflammation, DNA methylation, *GNAI3*, Familial Mediterranean Fever, microRNA, miR-197-3p.

Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent episodes of fever and serosal inflammation and is caused by mutations in the *Mediterranean Fever (MEFV)* gene encoding the pyrin protein.^{1,2} Although FMF is inherited as an autosomal recessive disorder, patients carrying identical *MEFV* mutations frequently exhibit substantial variability in disease severity, attack frequency, and response to treatment,

indicating that factors beyond genetic variation contribute to disease pathogenesis.³

Epigenetic regulation has emerged as an important modifier of inflammatory and rheumatic diseases, influencing gene expression without altering the underlying DNA sequence.^{4,5} Among epigenetic mechanisms, microRNAs (miRNAs) play a central role in the post-transcriptional regulation of genes involved in innate

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immune signaling, cytokine production, and inflammasome activation.⁴ Altered miRNA expression profiles have been reported in several rheumatic and autoinflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and periodic fever syndromes.^{6,7}

miR-197-3p has been identified as an inflammation-associated miRNA with regulatory effects on cytokine signaling pathways. In our previous work, we demonstrated that miR-197-3p expression is significantly reduced in homozygous FMF patients compared with healthy controls.^{8,9} Functional analyses further showed that miR-197-3p has anti-inflammatory effects by modulating cytokine release, caspase-1 activation, and cell migration.⁸ Despite these findings, the molecular mechanisms responsible for the decreased expression of miR-197-3p in FMF have remained unclear.

miR-197-3p is encoded from the *MIR197* gene within the G Protein Subunit Alpha I3 (*GNAI3*) gene, and to date, no independent promoter has been described for the *MIR197* locus.¹⁰ This genomic organization suggests that miR-197-3p expression is likely regulated in coordination with transcriptional control of its host gene rather than through a separate promoter-driven mechanism. Epigenetic modifications affecting host gene transcription, such as DNA methylation, therefore may contribute to miR-197-3p dysregulation.^{11,12}

In this context, investigating regulatory features of the *GNAI3* locus may provide insight into miR-197-3p expression changes observed in FMF patients. Clarifying whether altered miR-197-3p levels are linked to host gene-dependent regulation is essential for understanding miRNA-mediated control of inflammation and may reveal novel regulatory pathways relevant to autoinflammatory disease pathogenesis.^{12,13}

In the present study, we aimed to investigate the molecular basis of miR-197-3p dysregulation in FMF, focusing on transcriptional and epigenetic mechanisms associated with its host gene, *GNAI3*.

Materials and Methods

Study group

The study group consisted of six patients with FMF homozygous for the M694V variant and six healthy controls without *MEFV* mutations. The FMF and control groups each included three female and three male participants. The mean age was 11.35 ± 3.60 years in the FMF group and 12.25 ± 3.88 years in the healthy control group. Disease duration among FMF patients ranged from 2.9 to 12 years. All patients were receiving colchicine treatment at the time of sampling (1 mg/day, n=5; 2 mg/day, n=1) and had an Autoinflammatory Disease Activity Index (AIDAI) score of 0, indicating clinically inactive disease. No patient had clinical evidence of an acute FMF attack at the time of sampling. *MEFV* mutation analysis was performed using restriction enzyme digestion-based mutation analysis, and homozygosity for the M694V variant was confirmed in all FMF patients. Available hematological parameters and C-reactive protein levels were recorded at the time of sampling. All procedures involving human participants were approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: 20.09.2022, number: 2022/14-35). Written informed consent was obtained from all participants or their legal guardians prior to enrollment, and the study was conducted in accordance with institutional ethical standards.

Peripheral blood mononuclear cell isolation and stimulation

Peripheral blood samples were collected into heparinized tubes. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation using lympholyte-poly solution. Isolated PBMCs were washed and incubated in serum-free Roswell Park Memorial Institute (RPMI) (Gibco) 1640 medium for 30 minutes. Following incubation cells were harvested for RNA and DNA isolation.

DNA isolation and bisulfite treatment

Genomic DNA was isolated from PBMCs using phenol–chloroform–isoamyl alcohol extraction method. DNA concentration and purity were assessed by spectrophotometry. Bisulfite conversion of genomic DNA was performed using the EpiTect Bisulfite Kit (QIAGEN) according to the manufacturer's instructions to assess DNA methylation patterns. Following conversion, bisulfite-treated DNA was purified and stored at -20°C until further analysis in Tris-EDTA (TE) buffer.

DNA methylation analysis

DNA methylation analysis was conducted using the EpiTect Bisulfite Kit (QIAGEN) according to the manufacturer's instructions by bisulfite sequencing. Regions selected for analysis included regulatory sequences associated with the promoter of *GNAI3* and the region upstream of the *MIR197* gene. Bisulfite-specific primers were designed to amplify CpG-rich regions while avoiding CpG sites within primer sequences. PCR amplification of bisulfite-converted DNA was performed using DreamTaq DNA Polymerase (5 U/ μL ; Thermo Scientific) on a SimpliAmp Thermal Cycler (Applied Biosystems). Sanger sequencing was conducted using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems), followed by capillary electrophoresis on an ABI 3130 Genetic Analyzer (Applied Biosystems). Methylation levels at individual CpG sites were determined by direct analysis of sequencing chromatograms.

Because no experimentally validated independent promoter has been established for *MIR197*, the upstream region was investigated as a candidate regulatory region rather than a confirmed promoter. The analyzed regions were selected to evaluate two alternative regulatory models: host gene-dependent regulation associated with the *GNAI3* promoter and possible local regulation associated with the genomic region upstream of *MIR197*. Region selection was guided by genomic position,

CpG density, CpG-associated features, and regulatory annotations within the *GNAI3/MIR197* locus.

Primer sequences used for amplification of bisulfite-treated DNA targeting regulatory regions of the *GNAI3* locus and regions upstream of *MIR197* are listed in Table I. Primer design was based on the length, CpG density, and sequence characteristics of the target regions to ensure efficient amplification of bisulfite-converted DNA and accurate region-specific methylation assessment.

RNA isolation and reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Total RNA was isolated from PBMCs using RNeasy Mini Kit (QIAGEN) according to the manufacturer's instructions. RNA concentration and quality were assessed prior to reverse transcription. For analysis of miR-197-3p expression, complementary DNA (cDNA) synthesis was performed using miRNA-specific reverse transcription protocols with the TaqMan® MicroRNA Reverse Transcription Kit (Applied Biosystems). All reactions were carried out using MicroRNA TaqMan® hsa-miR-197-3p, 000497 and U6 snRNA, 001973 assays (Applied Biosystems) with TaqMan® Universal PCR Master Mix and no AmpErase® UNG (Applied Biosystems) kit. The reactions were conducted on the BioRad IQ5 (Biorad). Small nuclear RNA U6 were used as internal controls, as appropriate. Relative expression levels were calculated using the comparative Ct method ($2^{-\Delta\text{Ct}}$).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 10.4.1 (GraphPad Software). Data distribution was assessed using the Shapiro–Wilk test, and no significant deviation from normality was detected ($p > 0.05$). Differences between patient and control groups were evaluated using an unpaired t-test with Welch's correction, which does not assume

Table I. Primer sequences used in this study. List of primers used for amplification of bisulfite-treated DNA targeting regulatory regions of the *GNAI3* locus and regions upstream of the *MIR197* gene. Primer sequences are provided in the 5'-3' direction.

Gene	Primer	Sequences
MIR197	1	Fw: TTTTGTAGGTGATTTTGATGTAGTTAAT Rv: CCACTATACTCAACCTATATTAATCTTT
	2	Fw: GAGTGTTATGTTGTTATTTAAAAAGTTT Rv: CCACCATACTCAACTAATTTTATATTTT
	3	Fw: GTTAATATGGTGAAATTTTGTTTATT Rv: CCCAACAATTTTCAATAATTTTCTTAAT
	4	Fw: ATTAAGAAAATTATTGAAAATTGTTGGG Rv: ACTAACACTAAACATACAAAACTTTTA
	5	Fw: TATGTAAAAGTTTTGTATGTTTAGTGT Rv: AAAACCTTTATCCTACATAAAACAAAAAT
	6	Fw: TTGTTTTGTTATTTTGTGTTATGTAGG Rv: ACGTTAAATACCTTTATTAATACTACCT
	7	Fw: AGGTAGTATTAATAAAGGTATTTAACGT Rv: TTCTATCTTTTACCATAAAAAAACACT
GNAI3	1	Fw: TTAAATTAGGTAGTCGAAAGGTAAATG Rv: TTAAACCACTCTCCTCAAAAAAAA
	2	Fw: TTGATAGAATTCGAAATTTGTAGATT Rv: AAATAAAAACACCGTCTATTACTAAA
	3	Fw: GAGAGGGTTATCGTTTAGTAATAGA Rv: GAATAACAACAACCTTCACTTCTTT
	4	Fw: GTTAAAGAAGTGAAGTTGTTGTTAT Rv: ATACTCCCAAATCTCTCTACTAAAC

Fw, forward; Rv, reverse.

equal variances between groups. Average CpG methylation values (ranging from 0 to 1) were derived from normalized C/(C+T) ratios and are presented as percentages for clarity. Direct bisulfite sequencing was chosen to assess regional methylation patterns rather than single-allele resolution, as the aim of the study was to compare overall methylation differences between FMF patients and healthy controls. Data are presented as mean $\pm$ standard deviation. A p value of ≤ 0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

Six patients with FMF homozygous for the M694V variant and six healthy controls without *MEFV* mutations were included. The groups were balanced for sex, with three females and three males in each group, and had comparable age distributions. The mean age was 11.35 ± 3.60 years in the FMF group and 12.25 ± 3.88 years in the healthy control group. Disease duration among FMF patients ranged from 2.9 to 12 years.

All FMF patients were receiving colchicine treatment and had an AIDAI score of 0 at the time of sampling, indicating clinically inactive disease. No patient had clinical evidence of an acute FMF attack at the time of sampling. Demographic, clinical, and available laboratory characteristics of the study population are summarized in Table II and Table III.

DNA methylation analysis of the *GNAI3* and *MIR197* locus

Bisulfite sequencing was used to evaluate DNA methylation patterns within regulatory regions including a ~500 bp region within the putative *GNAI3* promoter and a ~2000 bp region upstream of the *MIR197* gene (Fig. 1A). Representative bisulfite sequencing chromatograms of the *selected regions* confirm successful bisulfite conversion and enable discrimination between methylated and unmethylated CpG sites (Fig. 1B), while distinct CpG methylation patterns are observed between FMF patients and healthy controls within the *GNAI3* promoter region (Fig. 1C).

Expression levels of miR-197-3p were evaluated in PBMCs from FMF patients and healthy controls. miR-197-3p expression was significantly reduced in FMF patients compared with healthy controls under basal conditions (0.00500 ± 0.00393 vs. 0.01872 ± 0.00884 , respectively; mean $\pm$ SD; * $p = 0.0106$) (Fig. 2A). In parallel, bisulfite sequencing analysis revealed increased DNA methylation within the *GNAI3* promoter region in FMF patients compared with healthy controls ($58.33 \pm 4.37\%$ vs. $44.00 \pm 8.99\%$, respectively; mean $\pm$ SD; ** $p=0.0093$). In contrast, methylation levels in the regions upstream of the *MIR197* gene did not differ significantly between FMF patients and healthy controls ($51.90 \pm 8.07\%$ vs. $48.55 \pm 8.34\%$, respectively; mean $\pm$ SD; $p=0.4957$) (Fig. 2B). These findings suggest that reduced miR-197-3p expression in FMF may be linked to epigenetic regulation of the host gene *GNAI3*, while no significant methylation difference was detected in the examined upstream candidate regulatory region of *MIR197*.

Table II. Individual and summary of demographic and clinical characteristics of FMF patients and healthy controls.

	Date of Birth	Age (years)	Age (years), mean $\pm$ SD	Sex	Sex, female/male	Date of diagnosis	Disease duration (years)	Disease duration (years), mean $\pm$ SD	Colchicine treatment status	Disease activity measures (AIDAI)
MEFV ^{M694V/M694V} patients	1	15.08.2011	12.3	11.35 $\pm$ 3.60	Male	3/3	01.01.2012	12	8.15 $\pm$ 3.00	1 mg/day 0
	2	28.03.2014	9.7		Female		01.10.2015	8.2	1 mg/day 0	
	3	21.03.2014	9.7		Male		01.06.2016	7.5	1 mg/day 0	
	4	16.09.2017	6.2		Female		01.02.2021	2.9	1 mg/day 0	
	5	24.06.2007	16.5		Female		01.12.2014	9	2 mg/day 0	
	6	07.04.2010	13.7		Male		01.09.2014	9.3	1 mg/day 0	
Healthy controls	1	25.09.2012	11.2	12.25 $\pm$ 3.88	Male	3/3				
No MEFV mutation	2	31.10.2017	6.1		Female					
	3	29.01.2014	9.9		Female					
	4	10.02.2008	15.9		Female					
	5	03.10.2008	15.2		Male					
	6	03.10.2008	15.2		Male					

AIDAI, Autoinflammatory Disease Activity Index; SD, standard deviation. All FMF patients were attack-free at the time of sampling (AIDAI score = 0) and were receiving colchicine treatment. Dates are presented in DD/MM/YYYY format.

Table III. Individual laboratory characteristics of FMF patients and healthy controls at the time of sampling.

		Leukocyte x10 ³ /μL	Lymphocyte %	Monocyte %	Neutrophil %	Eosinophil %	Basophil %	Thrombocyte x10 ³ /μL	C-reactive protein (CRP) mg/dL
Reference Values		4.31 - 11	15.5 – 56.6	4.2 – 12.3	28.6 – 74.5	0 – 4.7	0 – 0.7	206 - 369	0 – 0.8
<i>MEFV</i> ^{M694V/M694V} patients	1	6.5	43.9	8.1	46.3	1.1	0.6	389	0.976
	2	6.3	42.3	6.4	46.1	4.2	1.0	291	0.384
	3	6.8	33.0	7.0	57.5	1.6	0.9	277	0.892
	4	6.8	35.6	6.9	54.8	2.1	0.6	318	5.06
	5	6.4	40.9	8.2	45.9	4.7	0.3	284	0.320
	6	6.5	41.7	8.6	48.6	0.8	0.3	284	0.141
Healthy controls No <i>MEFV</i> mutation	1	8.7	26.7	8.9	61.4	2.4	0.6	246	4.55
	2	5.9	41.1	7.3	49.0	1.9	0.7	233	RV: < 5 mg/L*
	3	6.2	34.4	9.7	50.4	4.7	0.8	289	RV: < 5 mg/L*
	4	5.6	45.1	7.7	44.0	2.7	0.5	261	RV: < 5 mg/L*
	5	4.5	41.3	8.7	47.1	2.5	0.4	221	RV: < 5 mg/L*
	6	5.5	31.6	8.9	56.7	2.4	0.4	219	RV: < 5 mg/L*

RV, Reference Value.

*The analytical instrument was changed; therefore, reference ranges and units were updated accordingly.

Discussion

In this study, we investigated the molecular basis of miR-197-3p dysregulation in FMF, focusing on epigenetic mechanisms associated with its host gene, *GNAI3*. Our results demonstrate a significant reduction in miR-197-3p expression in FMF patients and suggest that this dysregulation is not driven by an

independent *MIR197* upstream candidate regulatory region but may be linked to host gene-dependent regulatory mechanisms.

Previous studies¹⁴⁻¹⁶ have demonstrated that miRNA dysregulation in FMF is heterogeneous and may be influenced by genotype, treatment status, and disease activity. Hortu et al.¹⁴ evaluated 15 inflammation-associated miRNAs

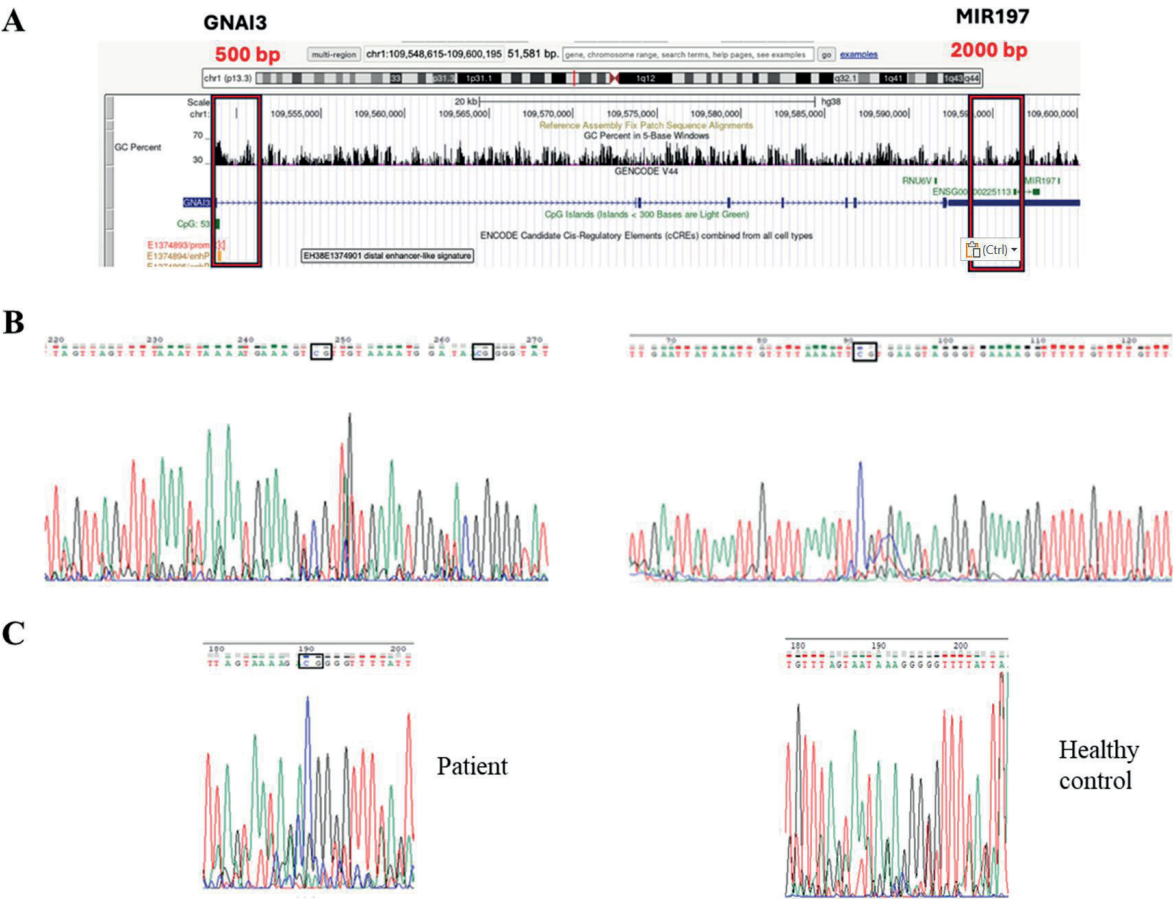


Fig. 1. Epigenetic landscape of the *GNAI3*/*MIR197* locus and bisulfite sequencing analysis. A. Genomic organization of *GNAI3* and intronic *MIR197* with regions analyzed by bisulfite sequencing indicated. CpG density, CpG islands, and ENCODE regulatory features are shown to illustrate the epigenetic landscape of the analyzed regions. B. Representative bisulfite sequencing chromatograms showing methylated (C) and unmethylated (T) CpG sites. C. Representative chromatograms of the *GNAI3* promoter regions from an FMF patient and a healthy control.

and reported reduced expression of multiple miRNAs in FMF, with additional differences related to colchicine treatment and attack status. Kahraman et al.¹⁵ identified a distinct pattern involving both upregulated and downregulated miRNAs and further reported genotype-associated variation, including prominent changes in miR-107 among patients carrying homozygous M694V. In a mechanistically oriented study, Latsoudis et al.¹⁶ linked *MEFV* perturbation to altered miRNA expression and identified an association between miR-4520a, pyrin mutations, and RHEB/mTOR-related signaling. Together, these studies indicate that miRNA dysregulation is a recurring but

molecularly heterogeneous feature of FMF. The present study differs from previous profiling approaches by focusing on a previously identified FMF-associated miRNA, miR-197-3p, and exploring a potential upstream epigenetic basis for its reduced expression. Our findings therefore extend the existing literature from the identification of altered miRNA profiles toward investigation of a possible host gene-associated regulatory mechanism.

Consistent with previous reports implicating miR-197-3p in the regulation of inflammatory pathways, we confirmed that miR-197-3p expression is significantly reduced in FMF patients compared with healthy controls under

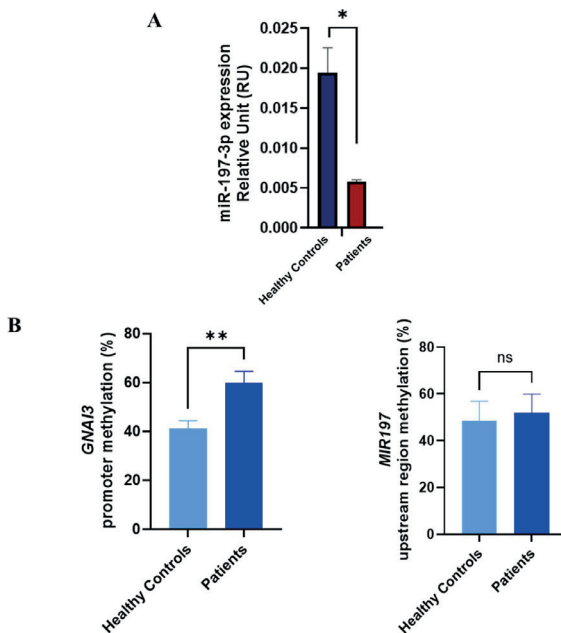


Fig. 2. Reduced miR-197-3p expression and differential promoter methylation of *GNAI3* in FMF patients. A. Relative expression levels of miR-197-3p in healthy controls and FMF patients under basal conditions, measured by RT-qPCR and expressed as relative units (RU). B. DNA methylation analysis of the *GNAI3* promoter region and the *MIR197* upstream region in healthy controls and FMF patients. Bars represent mean $\pm$ SD. Statistical comparisons between FMF patients and healthy controls were performed using unpaired t test with Welch's correction.

* $p < 0.05$ and ** $p < 0.01$ were considered statistically significant. ns, not significant.

basal conditions.⁹ As a possible cause of this reduction, we identified differential DNA methylation within the promoter region of the *GNAI3* gene in FMF patients compared with healthy controls. In contrast, no consistent methylation differences were detected in regions upstream of the *MIR197* gene. Given that no independent *MIR197* upstream candidate regulatory region has been described to date, these results are consistent with a host gene-dependent regulatory model in which epigenetic modifications of *GNAI3* may indirectly influence miR-197-3p expression.

Intronic miRNAs are frequently co-regulated with their host genes, and alterations in host gene transcription can directly affect miRNA

expression levels.¹⁷ Epigenetic mechanisms, particularly DNA methylation, have been shown to regulate both host gene transcription and intronic miRNA expression.¹⁸ miR-197-3p has previously been reported to exert anti-inflammatory effects by modulating inflammatory signaling pathways.⁸ Importantly, the present findings demonstrate an association rather than a causal relationship between increased methylation within the analyzed *GNAI3* promoter region and reduced miR-197-3p expression. The current study did not directly assess *GNAI3* transcription or experimentally manipulate DNA methylation. Therefore, it cannot be concluded from these data alone that altered *GNAI3* promoter methylation causes the reduction in miR-197-3p expression. Functional studies combining *GNAI3* expression analysis with targeted methylation editing, demethylation approaches, or promoter activity assays will be required to establish a direct regulatory relationship.

Dysregulated miRNA expression has been increasingly implicated in autoinflammatory and autoimmune diseases, including FMF.⁵ Reduced miR-197-3p expression may, in turn, impair its anti-inflammatory functions, thereby contributing to enhanced inflammatory responses characteristic of FMF.

This study should be considered a pilot molecular investigation. Although the cohort size is limited, statistically robust methylation differences ($p = 0.0093$) were identified. The analysis was intentionally restricted to M694V homozygous patients to reduce genetic variability. Therefore, the findings should not be generalized to FMF patients with other *MEFV* genotypes without further validation.

The principal limitation of this study is the small sample size. Accordingly, the findings should not be interpreted as establishing the general importance of miR-197-3p across the broader FMF population. Rather, they provide preliminary evidence of a possible association between altered methylation within the *GNAI3* regulatory region and reduced miR-197-3p

expression in a genetically homogeneous group of patients homozygous for the M694V variant. Taken together, our results provide evidence supporting a host gene-dependent regulatory mechanism underlying miR-197-3p dysregulation in FMF. This study adds to the growing body of literature highlighting the role of miRNA regulation in autoinflammatory diseases and underscores the importance of considering host gene-miRNA interactions when investigating epigenetic regulatory networks.

Given the demonstrated anti-inflammatory role of miR-197-3p, its downregulation may contribute to excessive inflammasome activation and cytokine production in FMF. Future studies should explore upstream regulators of *MIR197* transcription and post-transcriptional processing pathways.

Ethical approval

The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: 20.09.2022, number: 2022/14-35). Written informed consent was obtained from all participants or their legal guardians prior to enrollment, and the study was conducted in accordance with institutional ethical standards.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: YZAU; data collection: YZAU, EN, YB, BB, THA, SO; analysis and interpretation of results: YZAU, EN; draft manuscript preparation: YZAU, BBP. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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A rare congenital malformation of the external iliac artery in a term neonate

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ABSTRACT

Background. Congenital malformations of the external iliac arteries (EIAs) are rare and may be associated with other congenital anomalies, such as vertebral, cardiac, or limb anomalies, anal atresia, and tracheoesophageal fistula (VACTERL). These anomalies can be classified into three categories: anomalies of origin or course, hypoplasia or atresia with a persistent sciatic artery, and isolated hypoplasia or atresia. We report a term neonate with left leg cyanosis within the first 48 hours of life due to an isolated congenital EIA malformation.

Case Presentation. A male term neonate was delivered by emergency cesarean section at 40 weeks' gestation for suspected asphyxia (birth weight 4040 g, length 52 cm, Apgar scores 10, 10). The pregnancy was uncomplicated except for gestational diabetes. The neonate showed no signs of distress or cyanosis at birth. Asymptomatic hypoglycemia was corrected with oral glucose. On the second day of life, the neonate developed cyanosis of the left lower limb, accompanied by delayed capillary refill (6 seconds), weak distal pulses, and reduced oxygen saturation (60–70%) as measured by pulse oximetry. Echocardiography excluded cardiac defects. Doppler ultrasound revealed high-grade stenosis of the left EIA, which was confirmed by magnetic resonance angiography, showing collateral circulation and no persistent sciatic artery. Coagulation tests were normal, and the neonate remained asymptomatic. At the 1-year follow-up, he demonstrated normal growth and neurodevelopment, with clinically normal development of the affected lower limb.

Conclusions. Neonatal limb cyanosis should prompt further evaluation after excluding other, more common conditions. Persistent cyanosis, especially when accompanied by weakness, atrophy, or length discrepancy, should raise suspicion for EIA malformations. To the best of our knowledge, this is the third reported case of EIA malformation and the first case of congenital segmental stenosis in a neonate. Despite their rarity, these malformations require consideration and early non-invasive imaging in unilateral limb cyanosis.

Key words: external iliac artery, external iliac artery malformation, limb cyanosis, neonate.

Congenital malformations of the external iliac arteries (EIAs) are rare and have been described only a few times in the literature.¹ The first reported case was published in 1957.² The precise incidence remains undetermined.³ These arterial malformations have been

classified into three categories by Tamisier et al: 1) anomalies in the origin or course of the artery, 2) hypoplasia or atresia compensated by a persistent sciatic artery (PSA), and 3) isolated hypoplasia or atresia.⁴ Unlike the first group, which is usually discovered at autopsy, the

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remaining categories are more likely to cause chronic ischemia of the leg, especially the third group, due to thrombotic tendency or intrinsic arterial wall abnormalities associated with obstructive lesions.^{4,5} Chronic leg ischemia due to hypoplasia or atresia usually occurs in childhood or young adulthood, however two cases of congenital malformation of the EIAs in neonates (aged 1 to 6 days) have been described in the literature.^{6,7} We report a case of a term neonate who developed cyanosis of the left leg within the first 48 hours of life due to an isolated congenital malformation of EIA, documented with corresponding clinical and radiographic images.

Case presentation

A male term neonate was delivered by emergency cesarean section at 40 weeks' gestation due to suspected asphyxia to a 36-year-old mother. Birth weight was 4040 g (83rd centile), length 52 cm (65th centile), with Apgar scores of 10 and 10 at the 1st and 5th minutes, respectively. The neonate was in good clinical condition at birth, displaying no signs of distress or cyanosis, with normal cardiorespiratory function. As part of routine screening for neonates of mothers with gestational diabetes, asymptomatic hypoglycemia was detected, and successfully corrected with oral glucose, with subsequent blood glucose measurements remaining within normal range.

On the second day of life, the neonate developed cyanosis of the left lower limb, accompanied by delayed capillary refill (6 seconds), weak distal pulses, and reduced oxygen saturation (60–70%) as measured by pulse oximetry. The other extremities demonstrated normal saturation levels. Both legs were symmetrical in length and circumference, with normal spontaneous movements and no tenderness. Femoral pulses were palpable on both legs. The neonate was admitted to the neonatal intensive care unit (NICU) for further evaluation (Fig. 1).



Fig. 1. Localized, cyanotic appearance of the left leg in a term neonate on the second day of life.

Due to elevated inflammatory markers (C-reactive protein [CRP] 63.7 mg/L), a seven-day course of antibiotics was administered. Blood cultures remained negative. Acute onset of unilateral limb cyanosis warrants consideration of thromboembolism, catheter-related thrombosis, and traumatic vascular injury in the differential diagnosis. There was no history of umbilical or femoral arterial catheterization or traumatic procedures, and physical examination did not reveal signs of soft tissue injury or hematoma. The coagulation profile was within normal limits. Cranial, renal, and urinary tract ultrasound findings were normal, and echocardiography revealed no structural cardiac defects or intracardiac thrombi. Doppler ultrasound was performed, revealing high-grade stenosis of the left external iliac artery. Peak systolic velocity reached 200 cm/s at the stenotic segment with reduced post-stenotic flow, consistent with hemodynamically significant stenosis. Doppler findings localized to the external iliac artery without evidence

of embolic occlusion in more distal vessels made an acquired thromboembolic event less likely and favored an underlying congenital arterial malformation. Magnetic resonance angiography (MRA) of the abdominal aorta and pelvic arteries on the third day of life showed a segmental absence of signal in the left external iliac artery, while the pelvic arteries on the right side displayed normal continuity. Collateral circulation was observed via circumflex branches of the iliac artery. No evidence of a PSA or other vascular anomalies was seen (Fig. 2). This lesion can be classified as an isolated EIA malformation (group 3) according to Tamisier's classification⁴, representing a congenital segmental stenosis.

The neonate remained stable during hospitalization. No further episodes of cyanosis were observed, and the neonate maintained satisfactory oxygenation levels in the affected limb prior to discharge. Given the absence of acute complications, progressive ischemia or neurologic deficit, presence of collateral circulation, and spontaneous improvement in

limb perfusion, a conservative management approach was chosen in agreement with pediatric surgery and vascular teams. Surgical/endovascular intervention was deferred, because the risk of procedural complications in a clinically stable neonate was considered to outweigh the potential benefit. Close clinical and outpatient follow-up were planned to monitor limb growth, function, and perfusion over time. At subsequent evaluations and pediatric surgical follow-ups, the infant remained symptom-free and demonstrated normal growth and development at 1 year of age. A follow-up MRA is planned at 2 years of age.

Written informed consent was obtained from the patient's legal guardians for publication of this case report.

Discussion

The development of the arterial system of the lower extremities starts in a 6 mm human embryo (approximately 35-37 days of gestation). When the umbilical artery reaches the dorsal aspect of the Wolffian duct, it develops a branch called the axial artery which is the main embryonic lower extremity artery.⁸ Its proximal portion is referred to as the sciatic artery. EIA develops shortly thereafter, proximal to the origin of the axial (sciatic) artery, and then gives rise to the femoral artery, which forms an anastomosis with the sciatic artery by 42 to 49 days of gestation.⁷ As the femoral vessels form, the sciatic artery usually regresses. Therefore, in cases of inadequate development of the femoral or external iliac arteries, the sciatic artery may persist.⁹ The definitive arterial anatomy is usually completed by the third month of gestation. There have been speculations that hyperglycemia and/or hyperinsulinemia may contribute to the development of arterial malformations. However, no studies have confirmed this association to date.⁷

The average age of patients with EIA anomalies at diagnosis is 28 years, but ages range from 1

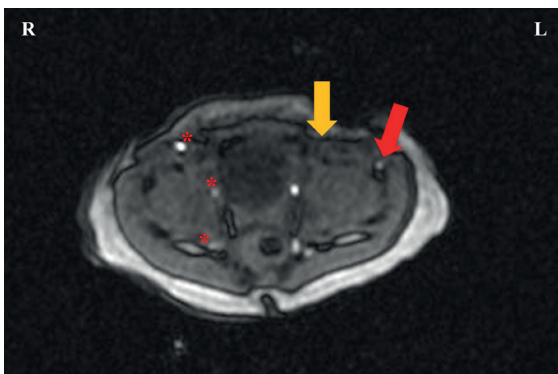


Fig. 2. Magnetic resonance angiography (MRA) of the abdominal aorta and pelvic arteries performed on the third day of life shows absent signal in the left external iliac artery (yellow arrow), consistent with severe stenosis, with collateral circulation via circumflex branches (red arrow) and normal right-sided arteries (red asterisks; in order from anterior to posterior: external iliac artery, internal iliac artery, and gluteal arteries). Image quality is limited due to acquisition on a 2-Tesla MRI scanner, the inability to perform MRA under anesthesia, and motion artefacts related to infant movement.

day to 73 years old with male predominance. Laterality of EIA anomalies have been reported as 42.9% on the right side and 57.1% on the left side.¹ The PSA occurs with an estimated incidence of 0.03-0.06%.^{1,10}

Growth of the lower extremities appears to be unaffected in utero despite arterial malformations, owing to the rich supply from the primary capillary plexus and the development of adequate collateral circulation.¹¹ However, chronic limb ischemia in later life may lead to limb atrophy, leg length discrepancy, general weakness, and consequently motor delay.⁷

The presence of PSA mandates close monitoring, as almost 50% of patients develop an aneurysm of this remnant artery, which often manifests as sciatic neuropathy due to nerve compression. The lack of arterial elastic tissue in the PSA can contribute to aneurysm formation and thrombosis, leading to lower limb ischemia.¹² Therefore, early surgical or endovascular intervention may be required when indicated.⁷

Some of these cases have been associated with other organ anomalies such as vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistulas, renal anomalies and limb abnormalities (VACTERL association).¹ The associated cardiac defects (3.8%) include type B1 distal interruption of the aortic arch, aortopulmonary window, patent ductus arteriosus and persistent foramen ovale.⁶ In our case, echocardiography excluded cardiac defects.

The molecular control of vascular development is not well understood and variations in regulation, genetic predisposition, and environmental factors (hypoxemia) can lead to variations in vessel growth and patterning.¹³

In our case, the diagnosis of external iliac artery malformation was established using duplex doppler ultrasound and MRA. Doppler ultrasound allows non-invasive, real-time assessment of arterial flow and hemodynamic significance of stenoses, while MRA provides detailed visualization of the aorto-iliac and femoropopliteal segments, including collateral

pathways, and avoids ionizing radiation or iodinated contrast in neonates. Although three-dimensional reconstructions are sometimes used, only limited-quality cross-sectional images could be obtained in our case due to the use of a 2-Tesla system, the inability to perform MRA under anesthesia, and motion artefacts. Despite these limitations, the combination of doppler ultrasound and MRA was sufficient to confirm an isolated external iliac artery malformation and to guide conservative management. Consistent with our approach, previous reports have emphasized the role of doppler ultrasound and cross-sectional angiographic techniques (computerized tomography or MRA) in visualizing external iliac or iliac artery malformations in neonates and children.^{14,15}

In conclusion, limb cyanosis in infants should prompt further diagnostic evaluation after exclusion of more common neonatal conditions, such as infection, respiratory distress syndrome, cardiac anomalies, or hypothermia. Persistent cyanosis, particularly when accompanied by leg weakness, atrophy or length discrepancy, should raise suspicion for EIA anomalies. Although rare, these malformations may have significant long-term consequences if not recognized. To the best of our knowledge, this represents only the third reported neonatal case of EIA malformation and the first case of congenital segmental stenosis, emphasizing its exceptional rarity and adding to the limited existing literature.^{6,7}

Ethical approval

Written informed consent was obtained from the patient's legal guardians for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AS, GŽ, EPB, VV, AŠ, KB; data collection: AS, GŽ, EPB, VV, AŠ, KB; analysis and interpretation

of results: AS, GŽ, EPB, VV, AŠ, KB; draft manuscript preparation: AS, GŽ, EPB, VV, AŠ, KB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Megalopapilla in oculodentodigital dysplasia: a novel ocular finding in a rare genetic disorder

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ABSTRACT

Background. Oculodentodigital dysplasia (ODDD) is a rare autosomal dominant disorder caused by pathogenic variants in the *GJA1* gene and characterized by variable craniofacial, dental, digital, and ocular abnormalities. Reported ocular manifestations include microcornea, microphthalmia, glaucoma, cataract, and retinal abnormalities. We report a genetically confirmed case of ODDD with bilateral megalopapilla, a finding that has not previously been described in association with this disorder.

Case Presentation. An 11-year-old boy presented with decreased vision and was found to have characteristic craniofacial, dental, and digital features suggestive of ODDD, including a narrow pinched nose, enamel hypoplasia, dental caries, and fifth-finger clinodactyly. Ophthalmologic examination revealed bilateral microcornea, myopia, persistent pupillary membrane, and markedly enlarged optic discs. Fundus photography demonstrated optic disc areas of 6.95 mm² and 6.07 mm² in the right and left eyes, respectively, consistent with megalopapilla. Optical coherence tomography showed choroidal thinning, while retinal nerve fiber layer thickness and visual field testing were normal. Genetic analysis identified a heterozygous NM_000165.5(*GJA1*): c.119C>T; (p.Ala40Val) variant in the *GJA1* gene, confirming the diagnosis.

Conclusion. This report describes megalopapilla as a previously unrecognized ocular finding in genetically confirmed ODDD, which may expand the phenotypic spectrum of the disease. Comprehensive ophthalmologic evaluation, including optic nerve head assessment, is essential in patients with ODDD to better characterize its full phenotypic spectrum.

Key words: oculodentodigital dysplasia, *GJA1*, connexin 43, megalopapilla, optic disc anomaly, microcornea.

Oculodentodigital dysplasia (ODDD) is a highly penetrant autosomal dominant congenital disorder characterized by developmental anomalies of the craniofacial structures, eyes, limbs, and dentition. The condition exhibits significant phenotypic variability both within and between affected families.¹ Mutations in the *GJA1* gene, which encodes the transmembrane protein connexin 43 (Cx43), are responsible for the disease. Under normal conditions, six Cx43 subunits assemble to form a hemichannel known as a connexon. This connexon aligns with another connexon on a neighboring cell

membrane, creating a gap junction that enables direct communication between adjacent cells.²

Clinically, ODDD presents with a distinct combination of features. Craniofacial abnormalities may include a thin nose with hypoplastic alae nasi, a prominent columella, small nares, and microcephaly. Dental findings typically consist of enamel hypoplasia, microdontia, and premature tooth loss. Digital anomalies frequently involve syndactyly, particularly between the fourth and fifth fingers, as well as clinodactyly of the fifth finger.²

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Ocular abnormalities are also well recognized and may include microphthalmia, microcornea, iris atrophy, glaucoma, and cataracts. Glaucoma, in particular, can have a significant impact on visual prognosis if not identified and managed early.³ Additionally, neurological involvement has been increasingly reported, with manifestations such as spasticity, ataxia, and white matter changes on neuroimaging found in approximately 30% of patients.⁴

Herein, we present a genetically confirmed case of ODDD with megalopapilla, a previously unreported ocular finding, occurring in the absence of neurocognitive impairment. By documenting this case, we aim to contribute to the expanding pleiotropic phenotypic spectrum of ODDD and emphasize the relevance of comprehensive ophthalmologic evaluation in affected individuals.

Case Presentation

An 11-year-old male patient with a known diagnosis of congenital hypothyroidism presented to our clinic with complaints of decreased vision in both eyes. He was born at 41 weeks of gestation via spontaneous vaginal delivery after an uneventful pregnancy. At the time of birth, both the mother and father were 31 years old. He is the third child in the family; his two older siblings are healthy, phenotypically and developmentally normal. Congenital hypothyroidism was identified at 18 days of age during routine newborn screening. The patient was started on thyroid hormone replacement therapy, which was continued until the previous year, when treatment was discontinued due to normalization of thyroid function. He remains under regular follow-up by the endocrinology department.

At three months of age, he was diagnosed with benign extracranial hydrocephalus, based on cranial ultrasonography findings of non-ventricular dilation without compression of the cerebral gyri. The condition was managed conservatively, with serial transcranial

ultrasonography confirming complete resolution by the age of one year, without the need for surgical intervention. Neurological development has since proceeded within normal age-appropriate milestones, and the patient currently demonstrates normal cognitive function and satisfactory academic performance.

The patient exhibited a normocephalic head shape with sparse, wispy scalp hair. At the time of presentation, his anthropometric measurements were as follows: weight 38 kg (50th – 75th percentile), height 152 cm (50th – 75th percentile), and head circumference 55 cm (50th – 75th percentile), based on the reference values reported by Neyzi et al.⁵ for Turkish children.

Craniofacial examination revealed a narrow, pinched nose with hypoplastic alae nasi and a prominent columella. The ears were low-set and anteverted. The patient had no history of hearing loss, and routine otolaryngologic evaluations have been normal. His orthopedic examination was normal except for clinodactyly of the fifth fingers of hands. The patient was noted to be under regular dental follow-up for ongoing management of his dental anomalies. Dental evaluation revealed multiple dental caries, yellow discoloration of the teeth, and enamel hypoplasia (Fig. 1).

The best-corrected visual acuity at presentation was 0.1 logMAR in the right eye (OD) (spherical equivalent: -3.75) and 0.7 logMAR in the left eye (OS) (spherical equivalent: -3.25). The eyes were orthophoric in primary position, with no signs of strabismus.

Anterior segment examination revealed irregular pupil margins, iris strands adherent to the anterior lens capsule compatible with mild persistent pupillary membrane, and posterior embryotoxon in the cornea; the lenses appeared clear. Horizontal corneal diameters of 10.8 mm (OD) and 10.6 mm (OS), met the diagnostic criteria for mild microcornea. Intraocular pressure measurements were within normal limits, recorded as 19 mmHg

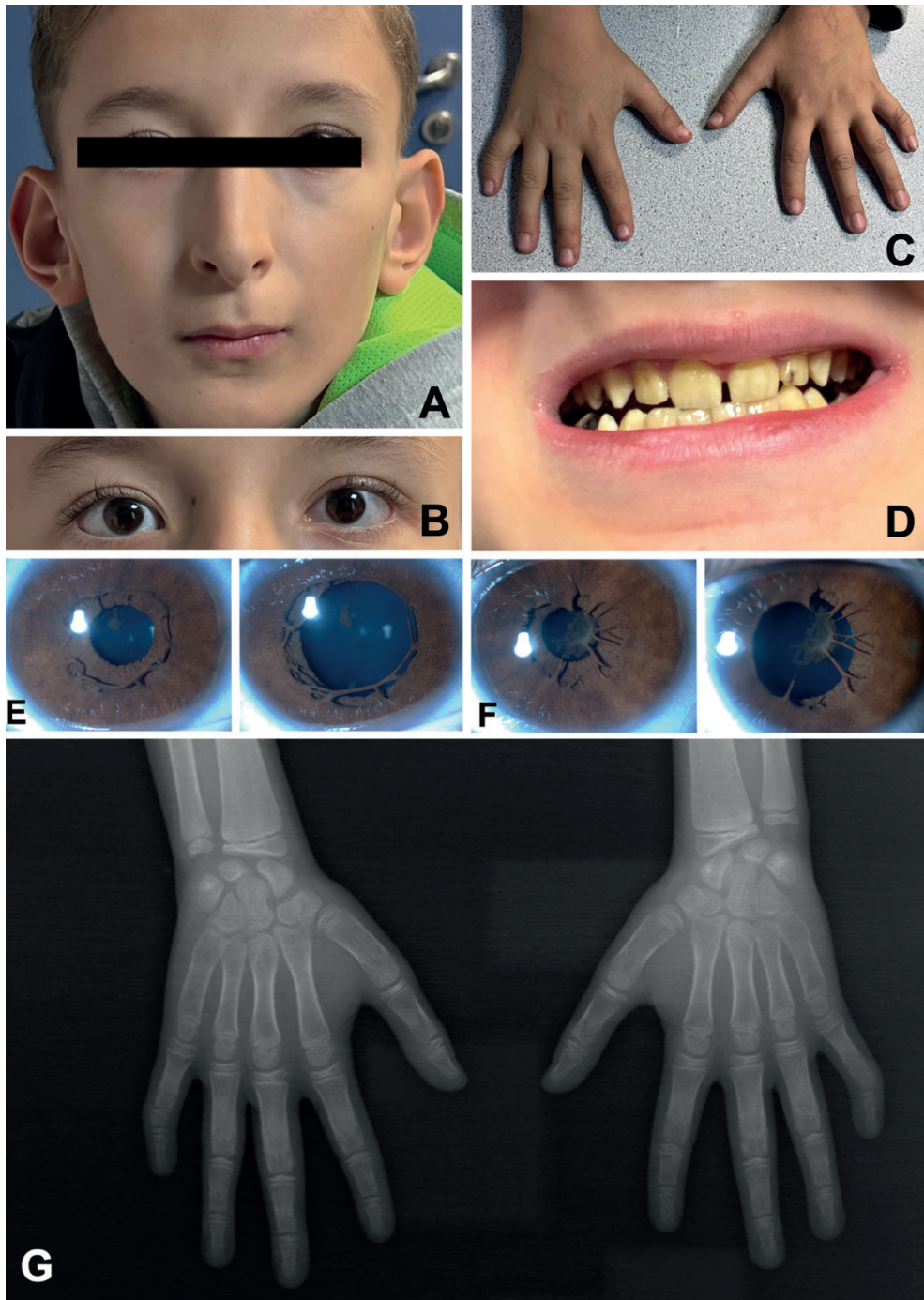


Fig. 1. (A) Craniofacial features including a narrow, pinched nose with hypoplastic alae nasi, prominent columella, and low-set, anteverted ears. (B) The photograph of the eye demonstrates mild microcornea. (C) Bilateral clinodactyly of the fifth fingers. (D) Clinical photograph showing multiple dental caries, yellow discoloration and enamel hypoplasia. (E, F) Slit-lamp photographs revealing iris strands extending toward the anterior lens capsule, consistent with mild persistent pupillary membrane. Iris strands adherent to the pupillary margin in a pharmacologically dilated pupil, along with irregular pupillary contours. (G) Bilateral hand radiographs demonstrate clinodactyly of the fifth digits.

(OD) and 21 mmHg (OS). Pachymetric analysis revealed central corneal thicknesses of 572 μm OD and 590 μm OS, and anterior chamber angles (ACA) measured 34° in both eyes. Additionally, axial lengths were 25.0 mm OD and 25.4 mm OS. Fundus examination revealed bilaterally enlarged optic discs, a tigroid retinal background, and prominent choroidal vessels. Fundus photography confirmed marked optic disc enlargement. Device-integrated software calculated the optic disc areas of 6.95 mm^2 in the right eye and 6.07 mm^2 in the left eye. Optical coherence tomography (OCT) showed choroidal thinning and retinal nerve fiber layer (RNFL) thickness was within normal limits in all four quadrants in both eyes, and standard automated perimetry demonstrated no glaucomatous visual field defects (Fig. 2).

Based on the constellation of craniofacial anomalies (narrow pinched nose with

hypoplastic alae nasi and prominent columella), dental abnormalities (enamel hypoplasia, tooth discoloration, and multiple dental caries), and digital findings (clinodactyly of the fifth fingers), a syndromic condition was suspected. Given the characteristic combination of these findings, ODDD was considered the most likely clinical diagnosis, and the patient was referred to the Division of Pediatric Genetics for further evaluation. Genetic analysis was conducted using Sanger sequencing, covering all coding exons and exon-intron boundaries of the *GJA1* gene. A heterozygous NM_000165.5(*GJA1*): c.119C>T; (p.Ala40Val) variant (rs1554200992) was identified. The Sanger sequencing electropherogram demonstrating the heterozygous variant in the index patient is provided in Fig. 3.

According to the American College of Medical Genetics and Genomics and Association for

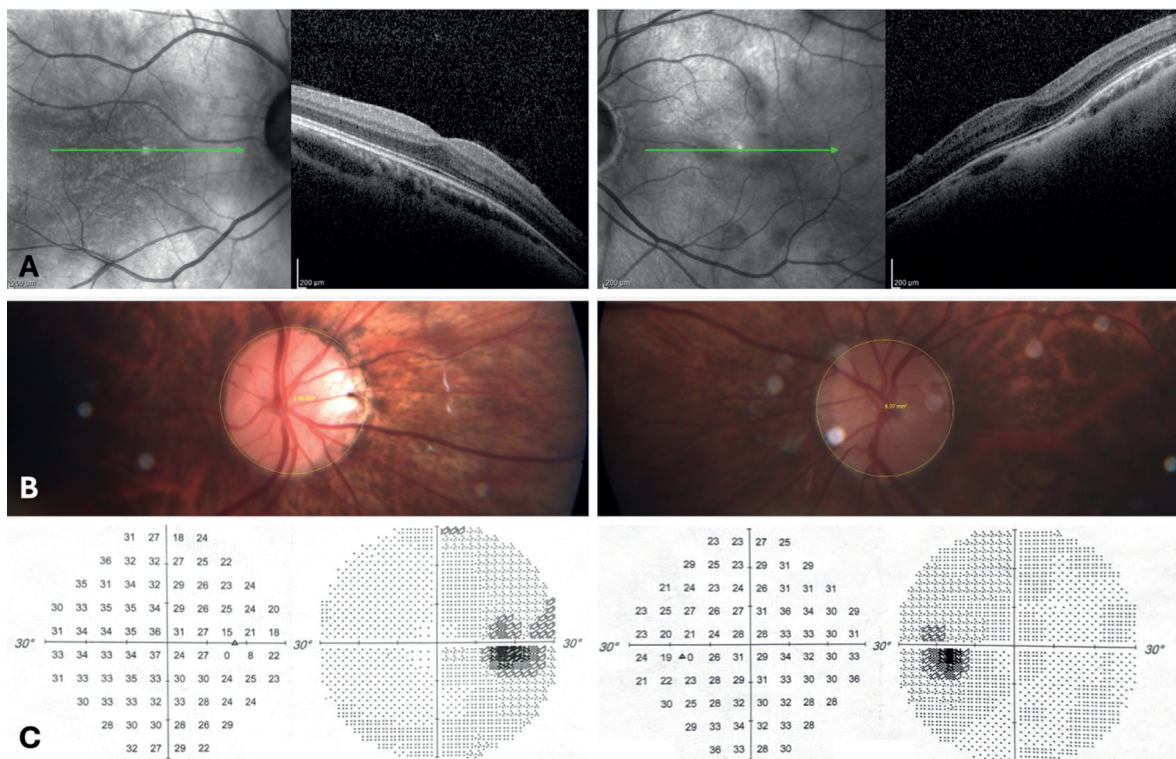


Fig. 2. (A) Macular optical coherence tomography (OCT) of the patient demonstrates thinning of the choroid. (B) Measurements of the optic disc areas in both eyes from fundus photography device software (right: 6.95 mm^2 ; left: 6.07 mm^2) are shown, consistent with megalopapilla. (C) Visual field testing revealed no additional abnormalities other than enlargement of the blind spot, which can be attributed to the increased disc size.

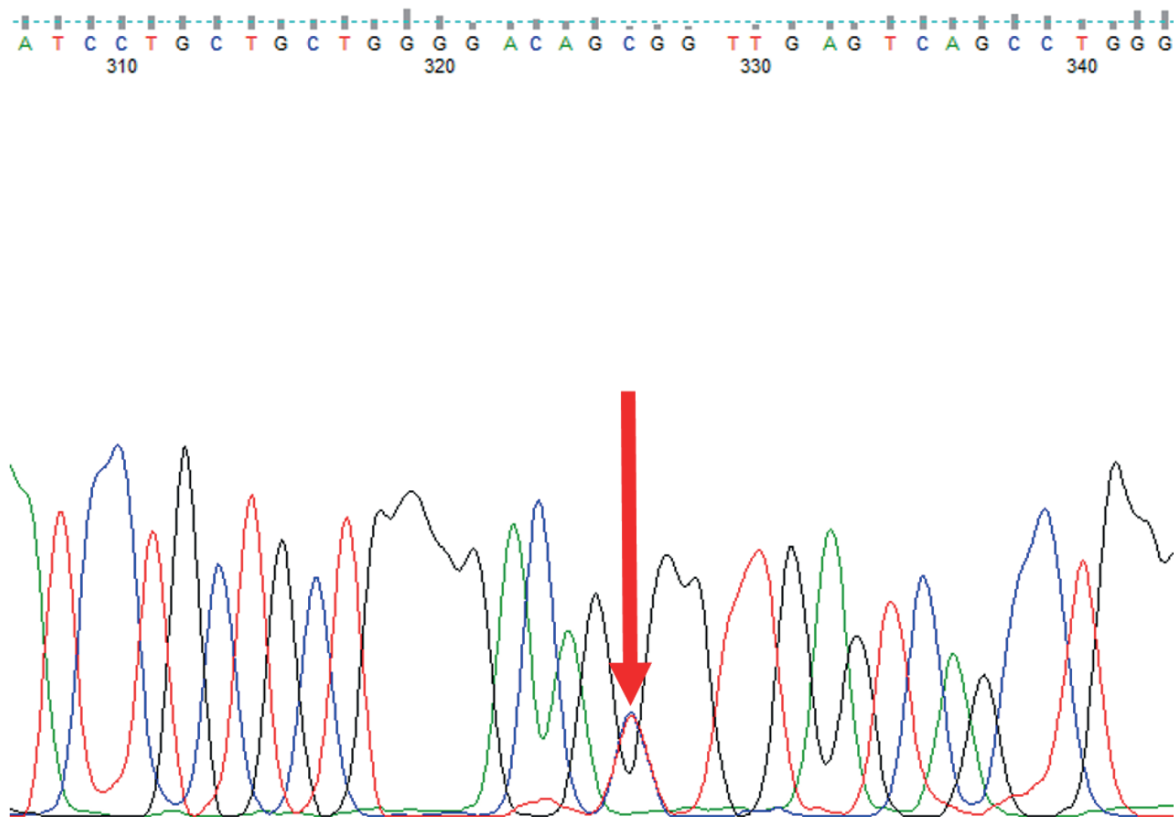


Fig. 3. Sanger sequencing electropherogram of the *GJA1* gene showing the heterozygous NM_000165.5: c.119C>T (p.Ala40Val) variant in the index patient. The arrow indicates the nucleotide substitution.

Molecular Pathology (ACMG/AMP) guidelines⁶, the detected *GJA1* variant was evaluated for pathogenicity. The variant fulfills the criteria PM2 (absence from large population databases), PP3 (multiple in silico prediction tools suggesting a deleterious effect), and PP4 (patient's phenotype highly specific for a disease with a single known genetic etiology) and published functional data (PP5), the variant may be classified as likely pathogenic according to ACMG/AMP 2015 criteria. Parental segregation analysis was recommended; however, genetic testing of the parents could not be performed due to the unavailability of parental DNA samples. Neither parent exhibited craniofacial, dental, digital, or ocular features suggestive of OCDD, and the patient's siblings were phenotypically and developmentally normal. There was no known consanguinity between the parents.

Based on these findings, the variant provides supportive evidence of pathogenicity according to ACMG/AMP 2015 criteria. Written informed consent was obtained from the patient's parents for genetic testing and publication.

Discussion

Oculodentodigital dysplasia is a rare autosomal dominant disorder caused by variants in the *GJA1* gene, which encodes the gap junction protein connexin 43. Mutations in the *GJA1* gene, which encodes connexin 43 and is located on chromosome 6q22–q24, impair Cx43-mediated intercellular communication. This disruption interferes with normal morphogenetic patterning during development and alters cellular function in differentiated tissues.⁷ The syndrome presents with a spectrum of craniofacial, dental, digital, and

ocular anomalies, with considerable phenotypic variability.¹ With an estimated prevalence of 1 in 10 million, ODDD is exceptionally rare, and around 300 cases have been reported worldwide.⁷

In a comprehensive review by Kumar et al.³, 295 ODDD cases were compiled, including 165 genetically confirmed cases encompassing 73 distinct *GJA1* variants. Microcornea and microphthalmia were the most frequently observed ocular findings, present in 111 and 110 patients, respectively, followed by short palpebral fissures and glaucoma.³

Recent analyses have suggested that the location of the *GJA1* variant within the Cx43 protein may influence the pattern of ocular involvement. In particular, variants located within the first intracellular domain of Cx43, as in our case, have been associated with posterior segment abnormalities, including dysplastic optic discs, macular hypoplasia, and dysplastic fundus.³ Gabriel et al.⁸ reported a patient with a variant in this domain who exhibited a dysplastic optic disc, poorly developed retinal pigment epithelium (RPE), and prominent choroidal vessels, further supporting this structure-function relationship.

Our patient harbored the NM_000165.5(*GJA1*): c.119C>T; (p.Ala40Val) variant in *GJA1*, one of the three most frequently reported mutations in the literature, along with c.605G>A (p.Arg202His) and c.389T>C (p.Ile130Thr). While ocular findings such as microcornea (n=9) and myopia (n=4) have been reported in this group, both were also present in our patient, posterior segment anomalies, including optic disc abnormalities, have not been documented in association with this specific variant.³ To date, 19 patients with the c.119C>T variant have been reported, systemic and ocular findings, when available, are summarized in Table I. The pathogenicity of the detected *GJA1* variant was evaluated in accordance with the ACMG guidelines. The c.119C>T; (p.Ala40Val) variant affects a highly conserved amino acid residue located within the N-terminal intracellular domain of connexin 43, a region known to be critical for

gap junction assembly and function. The variant has been reported in multiple individuals with clinically confirmed ODDD and shows strong phenotype-genotype concordance. In addition, the variant is absent or extremely rare in large population databases, and multiple in silico prediction tools support a deleterious effect on protein function. Functional studies further support the biological relevance of this variant. Specifically, mutations affecting the N-terminal and transmembrane domains of connexin 43, including A40V, have been shown to result in preserved gap junction plaque formation but complete loss of intercellular electrical coupling, indicating significant functional impairment.⁹ Based on these findings, the variant fulfills ACMG criteria including PM2, PP3, PP4 and PP5 providing supportive evidence of likely pathogenicity.⁶ Additionally, because parental molecular testing was not available, the variant could not be confirmed as de novo, and parental mosaicism or very mild parental expression cannot be excluded.

Megalopapilla is characterized by an enlarged optic disc with a surface area greater than 2.5–3.0 mm² in the absence of glaucomatous damage^{10,11}, and is often considered a benign anatomical variant. In our case, optic disc areas were measured as 6.95 mm² and 6.07 mm² in the right and left eyes, respectively, significantly larger than the defined threshold. While megalopapilla is a nonspecific finding, its presence in this genetically confirmed ODDD case broadens the posterior segment spectrum associated with the disorder. However, a direct genotype-phenotype association between megalopapilla and the c.119C>T variant cannot be established based on a single observation, and this finding should be interpreted with caution. Although posterior segment abnormalities have been described in ODDD, including optic disc and retinal findings, megalopapilla has not, to our knowledge, been specifically reported in association with ODDD or with the recurrent *GJA1* p.Ala40Val variant. In addition, persistent pupillary membrane, a relatively uncommon anterior segment finding noted in only 13 previously reported cases, was also observed.³

Table I. Previously reported ocular and systemic findings in oculodentodigital dysplasia patients with the *GJA1*: c.119C>T (p.Ala40Val) variant.

First author, year	Country	Age (yr) and sex	Ocular findings	Extraocular findings
Park et al. ¹³ 2019 (3 patients of 1 family)	Korea	32, F	Bilateral microcornea, glaucoma, shallow anterior chamber	Narrow, pinched nose; hypoplastic alae nasi; thin anteverted nares; narrow nasal bridge; prominent epicanthic folds; and hypertelorism
	Korea	37, F	Bilateral microcornea, glaucoma, shallow anterior chamber	Narrow, pinched nose; hypoplastic alae nasi; thin anteverted nares; narrow nasal bridge; prominent epicanthic folds; and hypertelorism together with small and carious teeth and yellow palms
	Korea	10, M	Tigroid fundus, tilted disc, esotropia, shallow anterior chamber	Narrow, pinched nose; hypoplastic alae nasi; thin anteverted nares; narrow nasal bridge; prominent epicanthic folds; hypertelorism; and small and carious teeth
Paznekas et al. ² , 2009 (11 patients of 2 family)	USA	8 patients	Not reported	Not reported
	USA	3 patients	Glaucoma	Not reported
Hayashi et al. ¹⁴ , 2014	Japan	4, M	Strabismus, glaucoma, macular hypoplasia of retina	Sparse scalp hair, low-set ear, narrow nose, brittle nails of fingers and toes, brachydactyly, enamel hypoplasia, hypodontia
Debeer et al. ¹⁵ , 2005 (2 patients of 1 family)	Belgium	Not reported	Not reported	Brachydactyly of the fifth fingers, camptodactyly of fingers 4 and 5
	Belgium	9, M	Hypotelorism	Poor dentition (microdontia, caries, enamel hypoplasia), bilateral 4–5 syndactyly, thin sparse hair, small mandibula, thin nose
Richardson et al. ¹⁶ , 2004	UK	Not reported	Not reported	Not reported
Paznekas et al. ¹⁷ , 2003	USA	Not reported	Not reported	Not reported
Current study, 2025	Türkiye	11, M	Bilateral microcornea, myopia, persistent pupillary membrane, megalopapilla, choroidal thinning	Sparse scalp hair, narrow, pinched nose with hypoplastic alae nasi, prominent columella, low-set, anteverted ears, clinodactyly, dental caries, yellow discoloration and enamel hypoplasia

The differential diagnosis encompassed glaucoma, morning glory disc anomaly, optic nerve hypoplasia, and optic nerve coloboma.¹² In this case, although the optic disc was enlarged, it retained normal color, prominent margins, and typical anatomical vascular configuration.

The patient had a medical history of congenital hypothyroidism and transient benign extracranial hydrocephalus, raising the question of whether these comorbidities might have influenced optic nerve morphology. However, the hypothyroidism was diagnosed through

neonatal screening and treated promptly until age 10, with normal neurodevelopmental milestones and cognitive function throughout childhood. The hydrocephalus, diagnosed at three months of age, was extracranial in nature (non-ventricular and non-compressive) and completely resolved without intervention by age one, as confirmed by serial transcranial ultrasounds. There was no history of increased intracranial pressure or visual developmental delay. Given this clinical context and in the absence of any optic atrophy or other signs of optic nerve compromise, the observed megalopapilla was unlikely to be secondary to these early-life conditions.

Although intraocular pressures were in the upper-normal range (19 mmHg OD, 21 mmHg OS), corrected values based on central corneal thickness (572 μ m OD, 590 μ m OS) remained below the threshold for ocular hypertension. Anterior chamber angles were wide open in both eyes (34°), effectively ruling out angle-closure mechanisms. Axial lengths measured 25.0 mm in the right eye and 25.4 mm in the left eye, which are consistent with moderate myopia. While increased axial length can be associated with certain anatomical variations in the posterior segment, it does not necessarily explain the marked optic disc enlargement observed in this patient. Furthermore, structural evaluation with OCT showed normal RNFL thickness in all quadrants, and standard automated perimetry revealed no glaucomatous visual field defects, supporting the diagnosis of megalopapilla without evidence of glaucoma as a novel optic disc phenotype for the NM_000165.5(GJA1):c.119C>T; (p.Ala40Val) variant.

This case highlights the importance of comprehensive ophthalmologic evaluation, including posterior segment imaging and optic nerve head assessment, in patients with ODDD. Given the emerging evidence linking variant localization within Cx43 to phenotypic expression, further genotype-phenotype studies are warranted to better define the full spectrum of ocular involvement in ODDD.

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Ethical approval

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

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: FBA, GDU; data collection: GDU, İÖ; Supervision: SK; draft manuscript preparation: FBA. All authors reviewed the results and approved the final version of the manuscript.

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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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Beyond the usual: coronary artery abnormalities in Noonan syndrome

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ABSTRACT

Background. Noonan syndrome (NS) is a multisystemic genetic disorder primarily affecting the cardiovascular system. While pulmonary valve stenosis and hypertrophic cardiomyopathy are common cardiac manifestations, coronary artery anomalies (CAAs) are rare but potentially life-threatening complications.

Case Presentation. A 12-year-old boy with genetically confirmed Noonan syndrome due to a *PTPN11* mutation (p.Asn308Asp, c.922A>G) had been followed since infancy. He initially had mild pulmonary valve stenosis that regressed spontaneously. He received intermittent growth hormone therapy, which was discontinued for two years and restarted 1.5 years prior to presentation. Routine echocardiography revealed newly detected coronary artery ectasia involving the left main coronary artery (LMCA) and the left anterior descending (LAD) artery. Coronary computed tomography angiography confirmed ectatic dilation of the LMCA and LAD, with an intramyocardial course of the mid-LAD. Further evaluation with cardiopulmonary exercise testing, myocardial perfusion scintigraphy, and selective coronary angiography demonstrated normal myocardial perfusion, an absence of ischemia, and diffuse coronary ectasia without discrete aneurysm formation. The patient remained asymptomatic, and no flow-limiting lesions were identified.

Conclusion. This case highlights a rare vascular manifestation of NS and underscores the importance of vigilant cardiovascular surveillance. Due to the rarity of such cases and the lack of standardized monitoring or treatment protocols, individualized risk stratification remains essential. Reporting such cases is critical for raising awareness and guiding future management strategies for coronary anomalies in Noonan syndrome.

Key words: Noonan syndrome, coronary ectasia, heart diseases, protein-tyrosine phosphatase non-receptor type 11.

Noonan syndrome is an autosomal dominant genetic disorder that affects multiple organ systems, particularly the cardiovascular system. It is characterized by distinctive facial features, short stature, developmental delay, and multisystem involvement. The syndrome is caused by pathogenic variants in genes involved in the RAS/MAPK signaling pathway, most commonly *PTPN11*.¹⁻³

Cardiovascular abnormalities are among the most important clinical manifestations of Noonan syndrome and occur in approximately 50–80% of affected individuals. Pulmonary valve stenosis and hypertrophic cardiomyopathy are the most frequently observed cardiac findings.¹⁻³ Although advances in genetic testing and cardiac imaging have improved the diagnosis of cardiovascular involvement in

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Noonan syndrome, uncommon cardiovascular manifestations remain insufficiently characterized in the literature. Recognition of these rare findings is important because they may influence clinical surveillance, therapeutic decision-making, and long-term patient outcomes.

Among these uncommon manifestations, coronary artery anomalies (CAAs) have been reported only rarely. Nevertheless, their presence may be associated with serious complications, including thrombotic or ischemic events and even cardiac arrest.¹⁻³ Owing to the limited number of reported cases, the clinical characteristics, management strategies, and prognosis of coronary artery involvement in Noonan syndrome remain incompletely understood. This report discusses a patient with Noonan syndrome and coronary ectasia, highlighting its clinical implications.^{1,2}

Case presentation

A 12-year-old boy with Noonan syndrome, carrying the *PTPN11* mutation p.Asn308Asp (c.922A>G), had been under medical surveillance since infancy. Initially, he presented with mild pulmonary valve stenosis, which regressed spontaneously. He underwent intermittent growth hormone (GH) therapy, which was paused for two years before being resumed 1.5 years before presentation. On examination, he displayed characteristic stigmata of Noonan syndrome. The patient had been followed annually from 6 months of age to 8 years of age with a diagnosis of mild pulmonary stenosis without right or left ventricular hypertrophy. At the time of the diagnosis of coronary ectasia, the patient had not attended follow-up visits for four years. Previous echocardiographic examinations showed no evidence of coronary artery ectasia. Routine echocardiography revealed newly detected coronary ectasia in the left main coronary artery (LMCA; 5.7 mm, z-score +5.4) and the left anterior descending (LAD; 4.1 mm, z-score +4.8) (Fig. 1). Coronary computerized tomography angiography (CTA)

demonstrated ectatic dilation of the LMCA and LAD, with the midportion of the LAD exhibiting an intramyocardial course, narrowing during systole (Fig. 2).

Therefore, a cardiopulmonary exercise stress test, myocardial perfusion scintigraphy and selective coronary angiography were planned for further evaluation. Myocardial perfusion scintigraphy with ^{99m}Tc-MIBI showed no anginal symptoms or ST-T changes on ECG during maximal exertion. Myocardial perfusion was normal in all segments of the left ventricle, with no evidence of ischemia or scarring. Cardiopulmonary exercise stress testing was also normal. Selective coronary angiography revealed moderate dilation of the LMCA, along with ectasia of the LAD and left circumflex (Cx) artery (Fig. 3, and Video 1, which is available online in the Supplementary Materials). No discrete aneurysms were detected. The LMCA diameter measured 5.7 mm (z-score: +6.16), while the LAD diameter was 4.5 mm (z-score: +5.39). Additionally, echocardiography indicated mild dilation of the Cx artery, measuring 3.5 mm (z-score: +2.66). Hemodynamic assessment during catheterization revealed the following findings: Right ventricular systolic pressure: 34 mmHg, Main pulmonary artery pressure: 26/11 mmHg (mean 17 mmHg) indicating mild pulmonary valvar stenosis; and aortic pressure: 112/72 mmHg (mean 93 mmHg). The patient remained asymptomatic, and no flow-limiting lesions were identified. At the one-year follow-up after the diagnosis of coronary ectasia, no evidence of progression was detected. Informed consent was obtained from the patient's parents for the publication of this case report.

Discussion

Coronary artery anomalies in Noonan syndrome are rare but clinically significant.^{1,2} Fewer than 20 cases of coronary aneurysms or ectasia have been reported in the literature, mostly in adults.¹ Most cases were detected incidentally during routine imaging or after patients presented with nonspecific symptoms such as chest pain

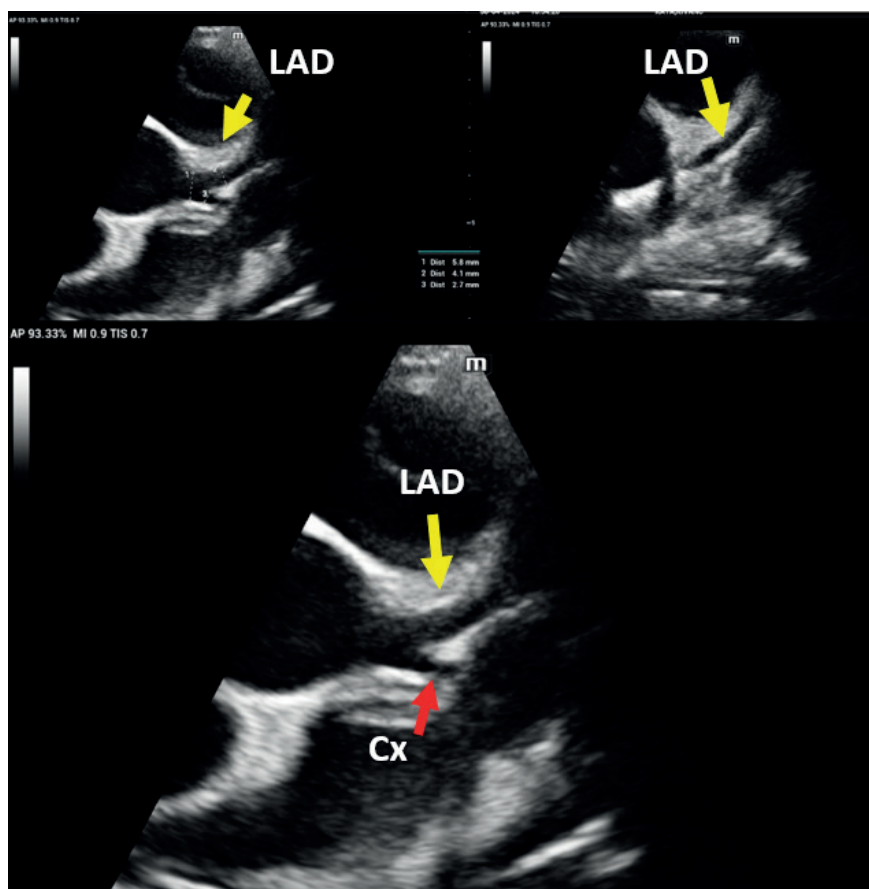


Fig. 1. Transthoracic echocardiography demonstrating ectatic dilatation of the left main coronary artery (LMCA) and the left anterior descending artery (LAD) (yellow arrow). The left circumflex artery (Cx) is also visualized (red arrow).

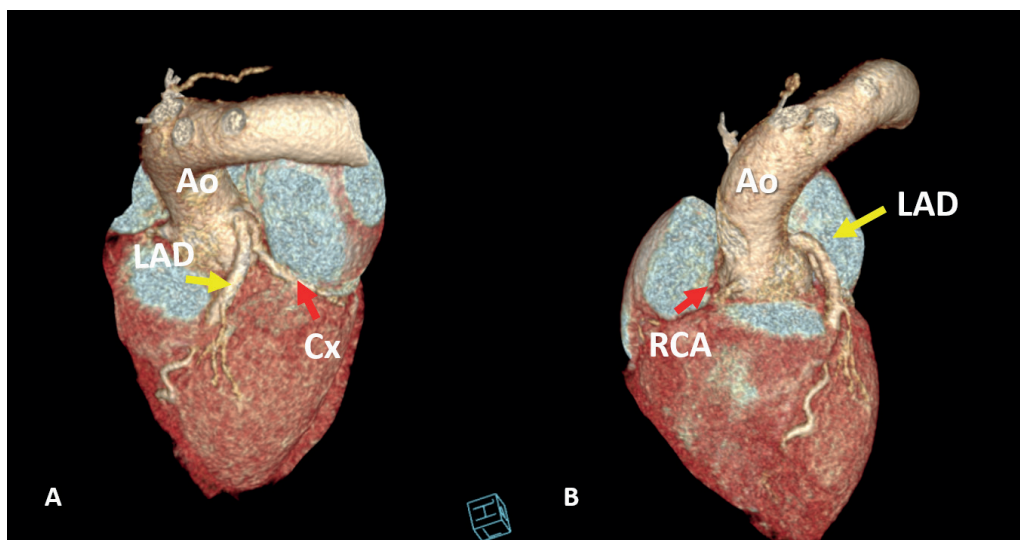


Fig. 2. A) Coronary computed tomography angiography (CTA) demonstrating the left anterior descending artery (LAD) (yellow arrow). The left circumflex artery (Cx) is also visualized (red arrow). **B)** CTA image showing ectatic dilatation of the LAD (yellow arrow). The right coronary artery (RCA) is also visualized (red arrow).

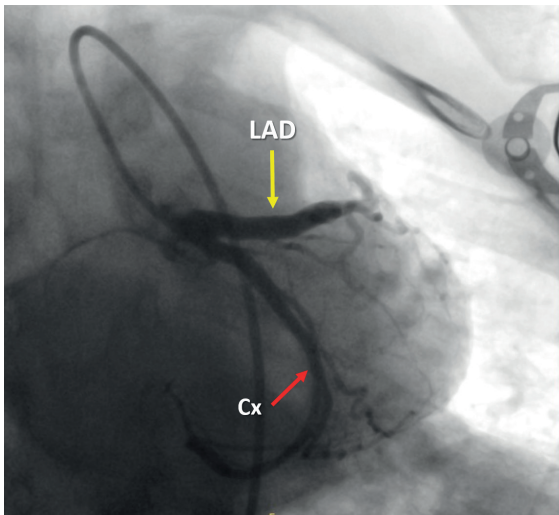


Fig. 3. Selective left coronary angiography clearly demonstrating ectatic dilatation of the left anterior descending artery (LAD) (yellow arrow). The left circumflex artery (Cx) is also visualized (red arrow).

or exertional fatigue. There are no clear reports of myocardial infarction, sudden cardiac death, or thrombotic occlusion directly attributed to coronary artery ectasia in Noonan syndrome, although these remain potential risks especially in adult patients.²⁴

The precise etiology of CAAs in Noonan syndrome remains unclear. Mutations in the *PTPN11* gene, which encodes the SHP2 phosphatase, are thought to increase SHP2 activity, thereby weakening arterial wall structure through dysregulation of the RAS-MAPK signaling pathway.^{2,5,6} Moreover, histopathological studies have identified significant inflammatory changes within the walls of coronary aneurysms, suggesting the involvement of unknown inflammatory triggers in disease progression.^{2,6-9} Cases associated with *SOS1* mutations have also been reported.¹⁰

Detecting CAAs in Noonan syndrome is challenging, as many patients remain asymptomatic. When present, symptoms are typically vague and may include fatigue or mild chest discomfort.² In our case, the patient was asymptomatic, and the coronary ectasia was discovered incidentally during routine echocardiographic screening. This underscores

the importance of regular cardiovascular evaluations in Noonan syndrome. Nevertheless, transthoracic echocardiography (TTE) may not always be adequate for detecting subtle coronary anomalies. Contrast-enhanced CTA is recommended for early detection and longitudinal monitoring. However, there remains uncertainty regarding the optimal timing and frequency of CTA or selective coronary angiography in the diagnostic algorithm. Additionally, the fact that most cases in the literature were incidentally identified further complicates surveillance strategies. Consequently, a consensus on the appropriate monitoring approach is lacking, and further studies are needed to define this clinical spectrum and inform standardized guidelines.

The presence of coronary ectasia or aneurysms raises concerns regarding thrombotic and ischemic risks, especially since these abnormalities can remain subclinical for extended periods.^{2,5} In asymptomatic patients with smooth, non-tortuous ectatic vessels, conservative management with routine follow-up is generally favored.^{2,5} In our patient, antiplatelet or anticoagulant therapy was not indicated due to the absence of irregular or tortuous coronary anatomy, as confirmed by both CTA and coronary angiography. Coronary angiography revealed no stenosis in the myocardial bridge segment. However, cases in the literature have documented the use of antiplatelet therapy in asymptomatic individuals with more complex coronary anatomy.¹ In cases in which thrombotic events occurred, warfarin therapy was instituted.²

The rarity of these cases contributes to uncertainty in diagnosis and management, emphasizing the need for individualized, case-based decisions. Current evidence does not support a clear algorithm regarding the timing of CTA or coronary angiography, or the initiation or antiplatelet/anticoagulant therapy. Thus, reporting such cases is essential for expanding the knowledge base and guiding clinical practice.

Moreover, the incidental nature of most reported cases calls for heightened awareness and comprehensive cardiovascular evaluation in patients with Noonan syndrome. Further research is required to better characterize the clinical course and establish evidence-based monitoring and treatment strategies.

Supplementary materials

Supplementary materials for this article are available online at <https://cdn.turkjpediatr.org/html-files/TJP-6871-Suppl-Video-1.mp4>

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Ethical approval

Ethics committee approval was not required for this case report. Informed consent was obtained from the patient's legal guardian for publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BBB, HHA, and ET; data collection: BBB, HHA, and ET; analysis and interpretation of results: BBB, HHA, and ET; draft manuscript preparation: BBB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Colonic arteriovenous malformations in children: a missed cause of lower gastrointestinal bleeding

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ABSTRACT

Background. Arteriovenous malformations (AVMs) are rare causes of lower gastrointestinal bleeding in the pediatric population.

Case Presentation. We report two female children aged 3 and 7 years old with multiple episodes of hematochezia and severe anemia who underwent computed tomography angiography. The first case demonstrated diffuse concentric wall thickening with small calcifications (phleboliths) involving the sigmoid colon and rectum. The affected segments demonstrated moderate progressive enhancement, along with an arcade of prominent vascular channels in the pericolic fat. The second case demonstrated hyperdense wall thickening involving the descending colon and proximal sigmoid colon with intense homogeneous contrast enhancement and an arcade of prominent vessels along the left colon. In both cases, the feeding arteries arose from the inferior mesenteric artery and the venous drainage was into the inferior mesenteric vein. Our first case was subjected to ligation of inferior mesenteric vascular pedicle feeding and draining the AVM, which succeeded in controlling bleeding episodes, while the second patient, who presented with relatively milder symptoms, underwent embolization therapy.

Conclusion. Vascular malformations of the bowel should be considered in pediatric age group in cases of lower gastrointestinal bleed.

Key words: radiology, pediatric surgery, gastrointestinal bleeding, gastroenterology, gastrointestinal surgery.

Pediatric lower gastrointestinal (GI) bleed is most commonly caused by intussusception, Meckel's diverticulum, infectious enterocolitis, juvenile polyposis and anal fissures.¹

Angiodysplasias are vascular malformations more commonly seen in elderly patients, frequently involving the right colon, and are well recognized causes of lower intestinal bleeding in the elderly.² Their development in the elderly population is attributed most commonly to degenerative changes. Conversely, vascular malformations of the GI tract in the pediatric population are rarely documented, and many

of them may be asymptomatic, or present with non-specific abdominal pain. Rarely, they may clinically present as obstruction or intestinal perforation.³ However, they may present as massive lower gastrointestinal bleed, associated with severe anemia requiring repeated blood transfusions. Such cases may produce catastrophic hemorrhage and prove to be life-threatening. The severity of this clinical scenario warrants a definitive management in the form of embolization of the feeding artery, ligation of the vascular pedicle or surgical resection of the involved bowel segments, as decided by the treating physician. The physician takes into

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consideration the age and clinical condition of the patient, as well as the available facilities and infrastructure.

In this report, we present two pediatric cases of arteriovenous malformation (AVM) of the distal large bowel, predominantly involving the sigmoid colon and rectum, who underwent computed tomography (CT) angiography to localize the cause of recurrent fresh bleeding per rectum.

Case Presentations

Case 1

A 3-year-old girl was admitted to our hospital with recurrent episodes of massive fresh lower GI bleed and intermittent abdominal pain. She was severely anemic and had previously undergone repeated blood transfusions in a local primary care facility. Diagnostic colonoscopy and biopsy had been performed at another health center, which reportedly revealed bluish venous congestion in the walls of the rectosigmoid colon and anal canal. The colonoscopic biopsy showed evidence of colonic wall edema, non-specific lymphoplasmocytic infiltrate and focal crypt formation. A differential diagnosis of hemangioma or venous malformation was considered based on the colonoscopic findings. Radionuclide scan for Meckel's diverticulum was normal. The child was being managed conservatively with iron, calcium and multivitamin supplements, and propranolol. However, she suffered from intermittent rectal bleeding and resultant chronic anemia.

There was no history otherwise suggestive of any bleeding dyscrasias. All the developmental milestones were appropriately attained. The child was born at term, assisted by Cesarean delivery, with good APGAR scores at birth. Past history was also significant for not having received any vaccinations.

At presentation to our center, physical examination was remarkable for evident pallor, a heart rate of 90 per minute and a respiratory rate of 18 per minute. She had a body weight of 13.5 kg (10th to 25th percentiles) and a height of 100 cm (50th percentile for age). Her abdomen was soft, non-tender and non-distended. Rectal examination revealed no growths or polyps, however, blood staining was observed. The child had a hemoglobin level of 3.9 g/dL at the time of presentation, which, after blood transfusions, increased to 6 g/dL and subsequently to 10.6 g/dL. Other blood investigations including liver function, renal function, electrolytes, platelet count and coagulation profile were within normal limits.

Transabdominal sonography revealed mild concentric rectal wall thickening (maximum thickness of 7mm). Other abdominal organs appeared normal on sonographic evaluation. As magnetic resonance imaging (MRI) was not available at the health facility, CT angiography was performed for further and more definitive evaluation. The study was done on a 16-slice helical CT scanner (Philips®). Multiphase scanning was done for proper characterization of the lesion and accurate determination of arterial supply and venous drainage. Arterial, venous and delayed phase images were acquired at 15, 60 and 180 seconds respectively. Subsequently, intravenous non-ionic contrast was administered, at the rate of 3 mL/min, with a pressure pump injector. Non-contrast images revealed diffuse concentric hyperdense thickening of the walls of anal canal, rectum, and sigmoid colon. Few phleboliths, appearing as small nodular calcific foci, were also noted in the walls of these segments of the large bowel (Fig. 1a and Fig. 1b). Following administration of the contrast material, the thickened walls of the affected segments of the large bowel demonstrated moderate enhancement in the arterial phase, which also increased in the venous phase and persisted into the delayed phase. Prominent vascular channels in the pericolic / perirectal fat were also noted (Fig. 1c and Fig. 1d). Early opacification of mesenteric

veins was noted on the arterial phase images (obtained at 15 seconds), which indicated arteriovenous shunting. The lesion received its arterial supply from branches of the inferior mesenteric artery. The venous drainage of the lesion was predominantly into the inferior

mesenteric vein (Fig. 1e and Fig. 1f). The portal vein, superior and inferior mesenteric veins were dilated. The imaging-based diagnosis was a high flow vascular malformation. Adjuncts to the diagnosis of AVM were the moderate mural enhancement of the involved bowel

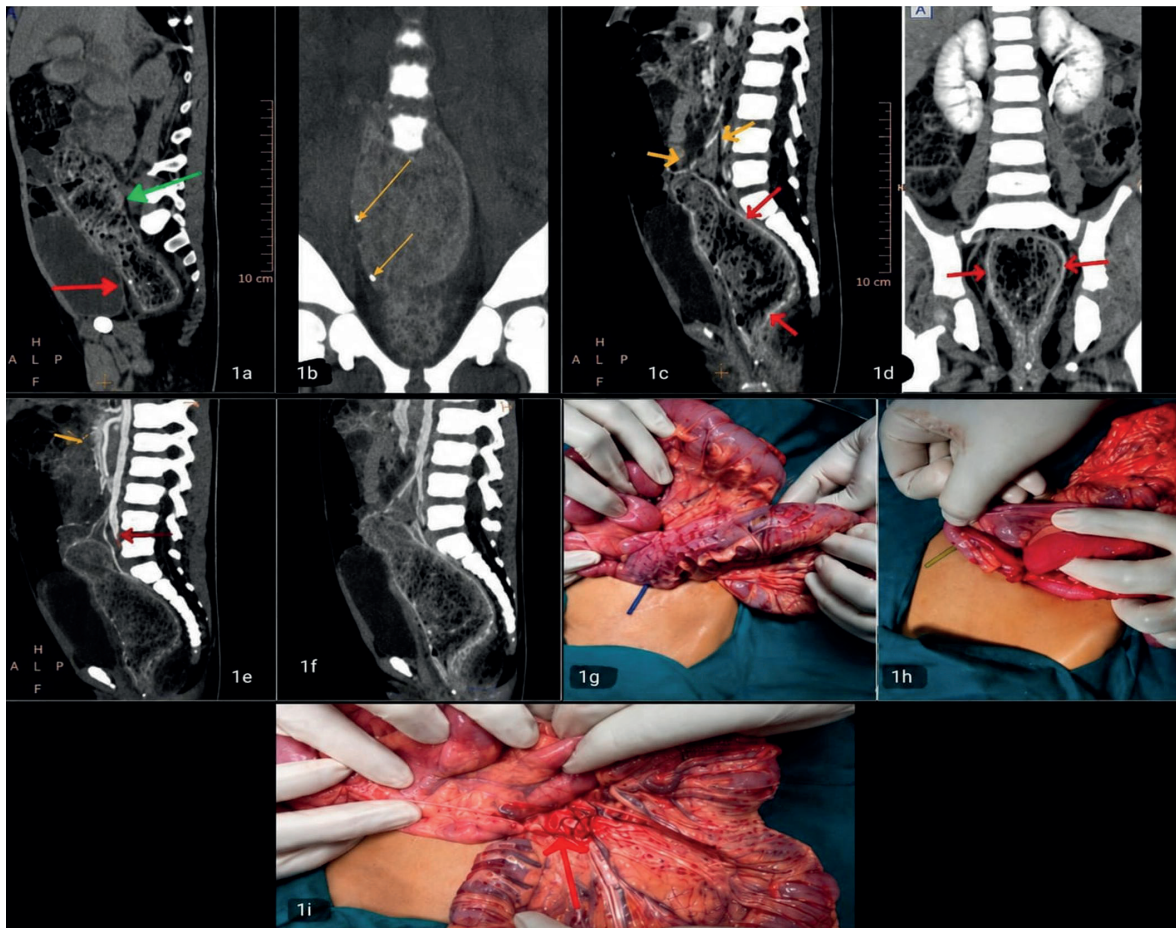


Fig.1. Radiological and intra-operative images of Case 1. **a)** Non-contrast CT image in sagittal plane, demonstrating hyperdense wall thickening involving the sigmoid colon and rectum (green arrow) with phleboliths, seen as calcified nodular foci, in rectal wall (red arrow). **b)** 3D maximum intensity projection (MIP) shows multiple phleboliths in the rectal wall (yellow arrows) **c and d)** Contrast enhanced CT images in sagittal (c) and coronal (d) planes show intense homogenous persistent enhancement of the thickened recto-sigmoid wall (red arrows), with prominent perirectal vessels (yellow arrows). **e)** CT angiography- 3D MIP on arterial phase shows arterial supply from branches of inferior mesenteric artery (red arrow). Early opacification of the draining mesenteric veins is also noted on the arterial phase image (yellow arrows), signifying arteriovenous shunting. **f)** Portal venous phase image shows vascular arcade around the recto-sigmoid and anal canal. The venous drainage at recto-sigmoid junction is into the inferior mesenteric vein. Phlebolith noted in the wall of anal canal (blue arrow) **g-i)** Intra-operative pictures demonstrating the high flow vascular malformation of sigmoid colon and rectum (g), with multiple dilated vascular channels (blue arrows), the congested appendix with vascular malformation (h), which on histopathology was proved to be an arteriovenous malformation (yellow arrow), and the ligated inferior mesenteric vessels as a measure to control bleeding due to the AVM (red arrow).

AVM: arteriovenous malformation, CT: computed tomography.

segments, early opacification of draining veins on the arterial phase, prominent pericolic and perirectal vessels, and dilated mesenteric and portal veins.

Thereafter, an exploratory laparotomy was performed, which revealed a vascular lesion, associated with prominent bright red vessels, involving the anal canal, rectum & sigmoid colon, extending up to the descending-sigmoid colonic junction (Fig. 1g). Increased pulsatility of the feeding arteries to the affected segment was noted. The draining veins were also found to be dilated and surgical diagnosis of AVM of the large bowel was considered. Another similar vascular lesion was noted involving the cecum and appendix (Fig. 1h) so an appendectomy was performed. However, as it was deemed difficult to excise the diseased segment without affecting anal continence in the young child, the inferior mesenteric vascular pedicle (including both the inferior mesenteric artery and vein) was ligated (Fig. 1i). Histopathological evaluation of the appendectomy specimen confirmed the diagnosis of an AVM, with evidence of congestion and hemorrhage on the appendiceal surface, and numerous dilated and congested vessels in the submucosa, serosa and adherent mesentery of the appendix. The child is doing well with an uneventful follow-up period of the last 30 months.

Case 2

A 7-year-old girl presented to the pediatric outpatient clinic with the chief complaint of a few episodes of recurrent rectal bleeding over the past four weeks. The patient had no relevant history suggestive of any infectious cause for the bleeding. At presentation, the child was hemodynamically stable, with no clinically evident pallor, heart rate of 89 beats per minute, and a blood pressure of 106/76 mm Hg. Physical examination was normal, except for mild tenderness in the left flank on deep palpation. Digital rectal examination was within normal limits with no evidence of any polyps, fissures, or hemorrhoids. Blood count revealed hemoglobin of 11.2 g/dL, with normal total

leucocyte and platelet counts. The peripheral smear and prothrombin time were also within normal limits.

Colonoscopic evaluation revealed congested hyperemic mucosa of the descending colon, with a few bleeding spots. The child underwent CT angiography on a 64-slice CT scanner (Siemens®) with contrast enhancement, including arterial and venous phase imaging for definitive characterization and determination of the extent of the lesion. The study demonstrated diffuse concentric wall thickening of the distal descending colon and proximal sigmoid colon, with intense homogeneous mural enhancement of the affected bowel on post contrast scans (Fig. 2a and Fig. 2b). An arcade of vessels surrounding the involved segment, with arterial supply from a hypertrophied inferior mesenteric artery, and early opacifying veins draining into the inferior mesenteric vein was noted. The inferior mesenteric vein was dilated and coursed superiorly, parallel to the inferior mesenteric artery, and drained at the junction of the splenic and superior mesenteric veins (Fig. 2c). The child was initially treated conservatively. Subsequently, she underwent embolization of the AVM at a referral center, after which the symptoms resolved.

Informed consent was obtained from the parents of both patients for this publication and use of intra-operative and radiological images.

Discussion

The ISSVA (International Society for the Study of Vascular Anomalies) classification divides vascular anomalies into 2 broad groups-vascular tumors and vascular malformations.⁴ Hemangiomas (infantile and congenital), tufted angiomas and angiosarcomas are the vaso-proliferative tumors. Vascular malformations include slow flow i.e., venous (previously erroneously called cavernous hemangiomas), lymphatic and veno-lymphatic (or lymphangioma) and high flow (arteriovenous malformations or arteriovenous fistulae).⁵

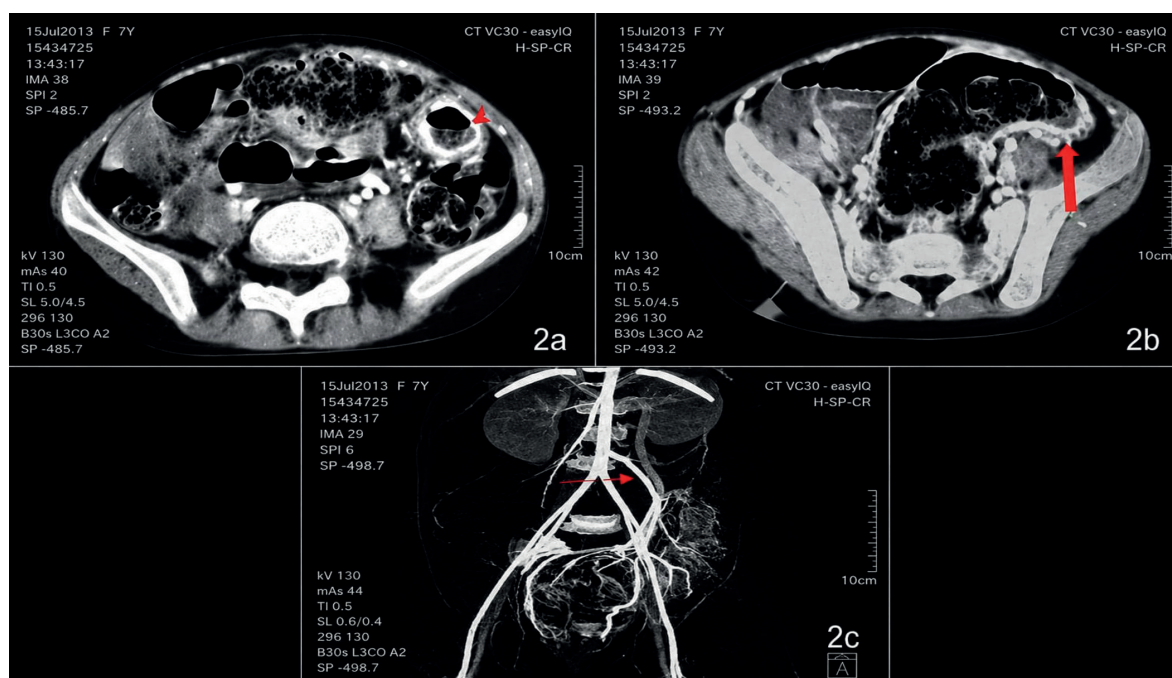


Fig. 2. Radiological images of Case 2. a and b) Contrast enhanced CT – arterial phase images showing intense homogenous mural enhancement in the thickened walls of descending & sigmoid colon (red arrows) with dilated pericolic vessels. c) Coronal MIP reconstruction of CT angiography of abdomen- arterial phase demonstrating arterial supply from hypertrophied inferior mesenteric artery (red arrow). Early draining veins into prominent inferior mesenteric vein (blue arrow) are noted. There is an extensive tuft of vessels surrounding the descending and sigmoid colon.

CT: computed tomography, MIP: maximum intensity projection.

The vascular anomalies may be a rare cause of bleeding per rectum in children and need proper work up and management.

Venous malformations are one of the most common low- flow vascular malformations. They are most often located superficially within the head and neck or limbs and can rarely involve the viscera. The most common venous lesions found on CT evaluation for obscure GI bleed are venous angiomas and small bowel varices. Albeit rare, venous angiomas of the small bowel may be sporadic or associated with Klippel-Trenaunay or blue rubber nevus syndrome.⁶ Calcified phleboliths are characteristic of venous stasis along with typical monophasic flow on Doppler sonography.⁷ In the setting of mesenteric venous hypertension, varices form within the adhesions between adjacent bowel loops or between the bowel and peritoneum.⁸ Such adhesions provide a pathway

for the varices to form. On multiphase CT enterography, venous lesions show progressive enhancement; i.e., they are non-enhancing on the arterial phase and intensely enhancing on enteric and delayed phases.⁹ Treatment of venous malformations is determined by their extent and location. Although many are managed expectantly, involvement of vital organs or extensive symptoms may necessitate treatment in the form of sclerotherapy and surgical excision.^{10,11}

Arterio- venous malformations (AVMs) are the fast-flow vascular malformations. They usually involve the brain and peripheral extremities and comprise a feeding artery, central nidus, and an early draining vein, and exhibit an extensive vascular network.¹² The feeding artery and the vascular lake may vary from being extremely obvious to very subtle. The early draining vein is usually very prominent, and tends to be parallel

to the feeding artery. It is almost invariably visualized in the late arterial phase, when the peripheral branches of the mesenteric arteries and the vasa recta still exhibit the contrast material-induced opacification.¹³ Extensive vascularity with arterial flow waveforms is seen on Doppler sonography and MRI exhibits prominent flow voids.

AVM of the bowel in the pediatric population is considered to be a developmental anomaly - mostly sporadic, or may be associated with syndromes such as hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome. Therapy for high-flow malformations is preceded by angiography for complete mapping of vessels. The first-line therapy for AVMs and arteriovenous fistulas (AVF) is embolization. Surgery, or a combination of therapies, may be needed in some children.¹⁴ Angiodysplasia may be a differential diagnosis, which is characterized by dilation and proliferation of blood vessels in the submucosal and mucosal layers. However, angiodysplasia is a disease of the elderly, that predominates in the right colon. It is postulated to be a degenerative change in the basement membrane of the colon under high tension. Angiographically, it presents as focal nodular areas of enhancement in an intramural location, which appears brightest on venous phase and gradually fades away in delayed phase.⁹ They generally do not show an enlarged feeding artery or prominent draining vein. These lesions are thus different from arterial lesions or AVMs which enhance most in the arterial phase.

CT angiography is a very useful tool in suspected cases and can accurately depict lesions in the bowel wall, along with their vascular communications, with high spatial resolution and fast scanning time. It is thus better than the conventional, more invasive selective mesenteric angiographic studies. The use of 3D maximum intensity projection (MIP) reconstructions can provide better mapping of abnormal mural vessels, and their arterial supply and venous drainage, thus providing helpful guidance for the surgeon.^{15,16} Although low-

dose pediatric CT techniques and protocols are available in all modern CT scanners, magnetic resonance angiography (MRA) should be used where available, in view its non-ionizing nature for pediatric patients. However, the need for prolonged sedation is an important limitation with MRI studies. Intensely enhancing bowel wall thickening, early opacification of draining veins, and dilated arterial and venous channels, are all classical diagnostic features of an AVM of the bowel.

Both our described cases presented with bleeding per rectum (more severe in the first case), displayed early moderate to markedly enhancing large bowel wall thickening, early opacification of draining veins in the arterial phase signifying arteriovenous shunting, as well as significantly dilated draining veins. All these findings were pointers to the radiological diagnosis of an AVM in both cases.

However, a few points in the CT study of the first case including persistent enhancement of the lesion in the delayed phase and presence of phleboliths, may need discussion, but they may be explained by the possibility of more numerous venous channels as part of the AVM, which was ultimately confirmed as the final diagnosis on surgical and histopathological findings. Also, the presence of phleboliths in AVM is a known entity, though less common, and suggests a chronic venous component. The enhancement pattern in venous malformation is more of gradual as compared to AVM, where it persists throughout the phases. The early opacification of mesenteric veins in the arterial phase is the most definitive sign of arteriovenous shunting, which rules in AVM. The presence of phleboliths and prominent venous structures may suggest a mixed lesion or chronic venous changes secondary to AVM, but not a pure venous malformation. Differential diagnosis of an enhancing lesion involving the bowel wall with increased mesenteric vasculature includes congenital / infantile hemangioma, AVM (high flow), venovenous malformation (slow flow), and angiodysplasia (largely a degenerative disease of the elderly).

Conclusion

Vascular malformations of the bowel should be considered in the pediatric age group in cases of lower GI bleed where the usual suspects such as Meckel's diverticulum and enterocolitis have been ruled out. Although most patients present with mild or insignificant symptoms, an accurate diagnosis and definitive management are imperative for symptomatic patients, as it may present as a life-threatening condition with massive lower GI bleed and severe anemia.

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Ethical approval

The parent's consent taken for publication and using radiological and intra-operative pictures.

As per our hospital policy, Ethics approval not applicable as two cases presented with discussion focused on rare anomaly and were retrospective in nature.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: RL, NG, PK; data collection: RL, NG, PK; analysis and interpretation of results: RL, NG, PK; draft manuscript preparation: RL, PK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Perineal dysmorphism and patellar luxation in SLC35A2-CDG: a new piece in the glycosylation puzzle

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ABSTRACT

Background. Congenital disorders of glycosylation (CDG) represent a group of inherited metabolic diseases characterized by multisystem involvement. SLC35A2-CDG (OMIM #300896) is a rare X-linked subtype resulting from pathogenic variants in the *SLC35A2* gene, which encodes the UDP-galactose transporter. Approximately 70 cases have been documented, predominantly presenting with early-onset epilepsy, developmental delay, hypotonia, and dysmorphic features. Phenotypic variability remains incompletely characterized, and novel features continue to expand the clinical spectrum.

Case Presentation. We report a 6-year-old girl with SLC35A2-CDG harboring a novel *de novo* heterozygous frameshift variant (NM_005660.3: c.105_106insCG, p.K36Rfs*6). The patient presented with epileptic spasms, severe global developmental delay, hypotonia, and distinctive dysmorphic features including strabismus and inverted nipples. Notably, she exhibited bilateral patellar luxation and perineal dysmorphism with a shortened anogenital distance, features that have not been previously associated with SLC35A2-CDG. Additional findings included a thin corpus callosum, a pineal cyst, right-sided aortic arch, bilateral vesicoureteral reflux, and central hypothyroidism. Oral D-galactose supplementation was initiated and resulted in subjective improvements in language comprehension, pain responsiveness, and motor function, although no improvement in seizures was observed.

Conclusions. This case may expand the phenotypic spectrum of SLC35A2-CDG by describing bilateral patellar luxation and perineal dysmorphism as potentially novel clinical features, along with a previously unreported pathogenic variant. Recognition of such unique features is crucial for improving our clinical understanding of this rare disorder, guiding differential diagnosis, and contributing to a more refined characterization of genotype-phenotype correlations.

Key words: SLC35A2-CDG, congenital disorders of glycosylation, epileptic spasms, perineal dysmorphism, patellar luxation, CDG-IIm.

Congenital disorders of glycosylation (CDG) are inherited metabolic diseases characterized by defects in glycan attachment or processing of glycoproteins and glycolipids.¹ The

phenotypic spectrum has expanded rapidly since the condition was first described by Jaeken in 1980.² In 2009, Jaeken et al.³ proposed a revised nomenclature using only the official

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gene symbol followed by ‘-CDG.’ By 2024, the number of recognized subtypes had exceeded 200.⁴ CDG can present with symptoms affecting various organs, primarily the nervous system, including hypotonia, developmental delay, and seizures.⁵ More than half of patients exhibit endocrine abnormalities, as glycoproteins regulated many endocrine functions, with abnormalities reported in the thyroid, adrenal, and growth axes, sexual development, and metabolism.⁶

Among more than 200 known subtypes, SLC35A2-CDG (OMIM #300896) is a rare X-linked dominant disorder caused by pathogenic variants in the *SLC35A2* gene on Xp11.23,⁷ with approximately 70 documented cases.⁸ *SLC35A2* encodes the UDP-galactose transporter (UGT), which transports UDP-galactose from the cytoplasm into the Golgi apparatus for incorporation of galactose into the oligosaccharide chains. Mutations can disrupt glycosylation pathways, leading to incomplete oligosaccharides.⁹

SLC35A2-CDG primarily affects females, with most cases occurring in female heterozygotes with *de novo* mutations. In males, a mutation in a single gene copy is typically lethal, though some survive through somatic mosaicism.¹⁰ Clinically, the disorder manifests in early infancy with refractory seizures, infantile spasms and West syndrome, severe hypotonia, and developmental delay. Dysmorphic features include coarse facial features, broad nasal bridge, thick lips, and strabismus. Patients may also show ocular abnormalities, hepatic dysfunction, and brain MRI findings including cerebral atrophy and a thin corpus callosum.^{10,11}

We report the case of a 6-year-old girl with confirmed SLC35A2-CDG presenting with epileptic encephalopathy, developmental delay, hypotonia, dysmorphic features, and systemic involvement. Our patient also exhibited perineal dysmorphism and bilateral patellar luxation, which have not been previously

reported in SLC35A2-CDG and may represent a potential expansion of the phenotypic spectrum, although a causal relationship between these findings and the disorder remains uncertain.

Case presentation

A 6-year-old girl was initially referred to our clinic at 4 months of age because of new-onset seizures. These seizures commenced 2–3 days after routine vaccination and were classified as epileptic spasms. Electroencephalography (EEG) demonstrated a hypsarrhythmic pattern. The patient was admitted with a diagnosis of West syndrome. At 38 weeks and 5 days of gestation, she was delivered via cesarean section due to cephalopelvic disproportion, with a birth weight of 2880 g (−0.93 SDS) and a length of 46 cm (−1.88 SDS). Her head circumference at birth was not documented. Written informed consent was obtained from the patient’s parents for the publication of this case report and any accompanying images and videos.

At the age of 6 years, anthropometric measurements showed a weight of 17.3 kg (−1.2 SDS), height of 106 cm (−1.93 SDS) which was consistent with the target height (158.8 cm, −0.73 SDS), and a head circumference of 49.3 cm (−1.26 SDS). The sitting height/height ratio was 0.57, indicating a proportionally large trunk. Hair was sparse in both anterior and posterior regions, particularly at the vertex. The forehead was wide and prominent. Joint laxity and hypermobility were observed. Bilateral patellar luxation was evident, with notable mobility of the right patella; the patient had undergone surgery for left patellar luxation (Video 1). Inverted nipples were present. The toes were proximally positioned, and the distal phalanx of the right index finger exhibited radial deviation. Organomegaly was not observed. The anogenital distance (AGD), measured from the posterior fourchette to the center of the anus as described by Andreassen et al.¹² was 17 mm. The dysmorphic features of the patient are shown in Fig. 1.



Fig. 1. Selected dysmorphic features in a patient with genetically confirmed SLC35A2-CDG.

(a) Broad and prominent forehead; (b) Inverted nipple; (c) Shortened anogenital distance; (d) Proximally placed hallux.

During the neonatal period, she experienced significant constipation, necessitating the use of enemas until the age of one year. Spontaneous defecation was subsequently possible without an enema. Recurrent urinary tract infections were observed until the age of two. The patient achieved head control at 2 years of age and independent sitting at 3.5 years. She exhibited persistent food-seeking behavior suggestive of hyperorality, along with repetitive biting episodes involving self-injury. Diminished pain perception was evident based on reduced responses to noxious stimuli. No ocular deviation was observed before the onset of seizures; however, the patient subsequently developed strabismus.

Considering the diagnosis of West syndrome and the presence of multiple dysmorphic features,

a thorough evaluation was conducted. Cranial magnetic resonance imaging (MRI) revealed a thin corpus callosum and a 4 mm pineal cyst. Echocardiography revealed a right-sided aortic arch. Imaging of the urinary system confirmed bilateral grade 3 vesicoureteral reflux (VUR). Endocrine examination at 7.5 months revealed labial hypoplasia with anterior displacement of the anus. The external genital score (EGS) was 0, confirming female sex, with marked labial rugae. Follicle stimulating hormone, luteinizing hormone, and estradiol levels were consistent with minipuberty, with normal growth and adrenal axes. Thyroid function tests suggested central hypothyroidism (thyroid stimulating hormone 3.92 mIU/L, free thyroxine 0.61 ng/dL). Mild hypoglycemia (50 mg/dL) occurred during infancy. Abdominal/pelvic MRI confirmed the presence of the uterus and ovaries. During the follow-up period, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels generally remained within the normal range, although occasional mild elevations were observed.

Whole-exome sequencing revealed a heterozygous pathogenic variant of *SLC35A2* (NM_005660.3: c.105_106insCG, p.K36Rfs*6), confirming the diagnosis of SLC35A2-CDG. This variant was absent in both parents, indicating a *de novo* origin, and was not detected in existing databases (ClinVar, gnomAD, dbSNP), confirming its classification as a novel variant. A transferrin isoelectric focusing study performed prior to the initiation of treatment had been reported as normal, although the corresponding numerical values were no longer available for review. Following genetic confirmation, oral D-galactose therapy was initiated. The most recent transferrin isoelectric focusing panel during therapy revealed the following values: disialotransferrin 0.87% (reference range, 2–2.5%), trisialotransferrin 7.51% (reference range, 4.5–9%), tetrasialotransferrin 76.76% (reference range, 64–80%), and pentasialotransferrin 14.86% (reference range, 12–18%).

Discussion

The clinical presentation of our patient closely corresponded with the established spectrum of SLC35A2-CDG.¹¹ She presented with early infantile-onset epilepsy characterized by epileptic spasms. In alignment with most documented cases, she demonstrated significant global developmental delay, marked by the absence of age-appropriate speech and motor milestones, hypotonia, and intellectual disability.¹¹ Her dysmorphic features were consistent with those described in glycosylation disorders, including strabismus and inverted nipples.^{11,13-15} Brain MRI revealed thinning of the corpus callosum, a recurrent observation in SLC35A2-CDG.^{11,13} In addition, a 4 mm pineal cyst was identified, which, although likely incidental, represents a previously unreported neuroimaging feature of this subtype.

Hepatic involvement in CDG can range from mild to severe transaminase elevation and coagulopathy.¹⁶ In our case, ALT and AST levels largely remained within normal ranges, with only occasional mild elevations. These mild fluctuations were attributed to the long-term use of multiple antiepileptic medications rather than primary hepatic dysfunction. In a review, liver involvement, defined as mild transaminase elevation, was observed in 12 of 30 cases (40%).¹¹

Although there was considerable overlap with the established phenotype, our case also presented features atypical of SLC35A2-CDG. The patient had VUR and a right-sided aortic arch, which are not commonly reported in this disorder. In a series of 30 cases, cardiac anomalies were observed in 8 out of 30 cases (27%) and renal anomalies in 1 out of 30 cases (3%).¹¹ While congenital cardiac and renal/urinary tract anomalies are not characteristic hallmarks of CDG, their presence in this patient suggests that SLC35A2-CDG may have broader systemic manifestations than previously appreciated.

It is well established that glycosylation plays a crucial role in the development of the urogenital system.¹⁷ Notably, the patient exhibited a short anogenital distance (17 mm) with a normal external genital score. To the best of our knowledge, reduced AGD has not been previously reported in SLC35A2-CDG. This raises the possibility that glycosylation defects in *SLC35A2* may subtly influence the embryological development of the caudal midline or genital structures, although the precise pathophysiological link remains unclear. Glycosylation is integral to numerous developmental signaling pathways; thus, impairment of glycan assembly may contribute to abnormal morphogenesis of the perineum. Conversely, it is conceivable that this perineal finding represents an unrelated congenital variant unique to our patient. Given the rarity of SLC35A2-CDG, even isolated anomalies may be significant, and documenting them is valuable because it may enable other clinicians to recognize similar features in future cases.

Given the known association between glycosylation defects and endocrine abnormalities, it has been recommended that all endocrine axes be assessed, together with bone mineralization and glucose metabolism from birth through puberty. The patient's history of constipation may be attributable to central hypothyroidism and/or the abnormal AGD, both of which were present.

A 2021 review by Lipiński et al.¹⁸ systematically examined skeletal involvement in patients with CDG and identified a broad spectrum of abnormalities, including joint laxity, brachydactyly, scoliosis, vertebral malformations, and hip dislocation. However, to date, patellar luxation has not been reported as a clinical feature of any CDG subtype including SLC35A2-CDG. Therefore, the presence of bilateral patellar luxation in our patient may represent a novel skeletal manifestation associated with CDG, expanding the known phenotypic spectrum of SLC35A2-related disorders.

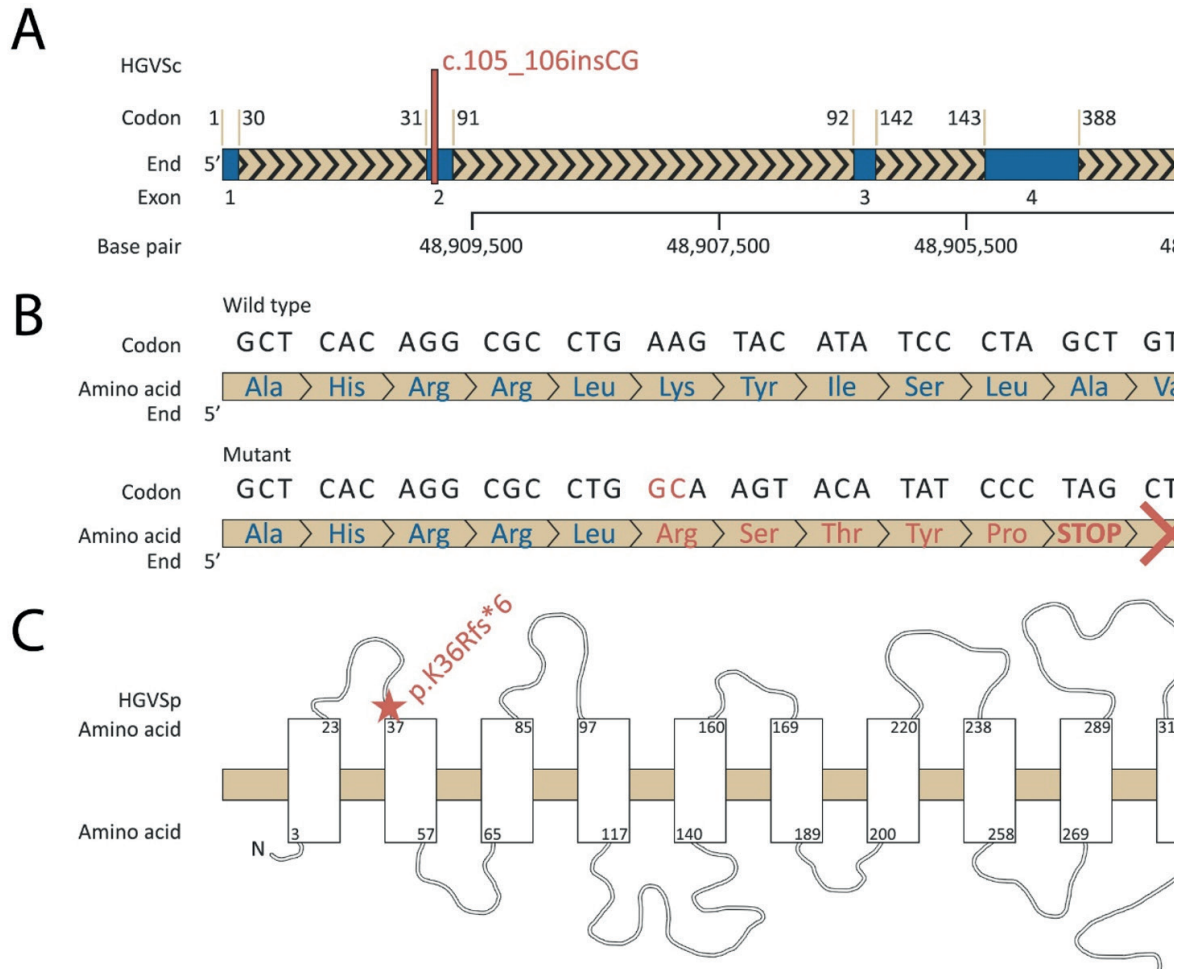


Fig. 2. Schematic representation of the *SLC35A2* variant based on the transcript NM_005660.3. (A) Exon localization, (B) amino acid substitution, (C) protein localization (red mark). The topology of *SLC35A2* was determined using UniProt.

Genetic analysis revealed a heterozygous NM_005660.3: c.105_106insCG (p.K36Rfs*6) variant. At the DNA level, the insertion of CG between nucleotides 105 and 106, located within exon 2 of *SLC35A2*, leads to a frameshift mutation (Fig. 2). The mutant protein is predicted to be severely truncated and likely non-functional or subject to nonsense-mediated mRNA decay. Given its nature as a frameshift variant leading to a premature stop codon in a gene for which loss-of-function is a known disease mechanism, this variant fulfills the PVS1 criterion under the ACMG guidelines.¹⁹ Parental testing confirmed its *de novo* origin (PS2), the variant was absent from population databases (PM2), and the patient's phenotype was highly consistent with

SLC35A2-CDG (PP4). Therefore, the variant was classified as pathogenic. Importantly, this specific variant has not been previously reported in major variant databases and is thus considered a novel mutation.

A broad spectrum of pathogenic *SLC35A2* variants has been reported to underlie this disorder, encompassing missense, nonsense, frameshift, and splice-site variants as well as small in-frame insertions and deletions; the majority arise *de novo* and are predicted to result in loss of function of the UDP-galactose transporter.^{7,9,11} In addition to germline variants responsible for the multisystem congenital phenotype, postzygotic somatic mosaic *SLC35A2*

variants have been increasingly recognized as a recurrent cause of mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE).²⁰ Hemizygous variants in affected males are generally considered lethal, with survival reported mainly in the setting of somatic mosaicism.¹⁰

Oral galactose supplementation has been investigated to enhance UDP-galactose availability for glycoprotein synthesis in patients with SLC35A2-CDG. Witters et al.²¹ administered oral D-galactose to ten patients and demonstrated significant improvement on the Nijmegen Pediatric CDG Rating Scale (NPCRS), with advances in postural control, response to stimuli, and chewing function, as well as improvements in gastrointestinal symptoms. While our patient's quantitative pretreatment biochemical results were unavailable, the family reported enhanced language comprehension, increased pain responsiveness, and the ability to bear weight and stand briefly with support. She was also able to articulate two or three words. However, no beneficial effects on seizures or EEG findings were observed.

In conclusion, we describe a 6-year-old female with SLC35A2-CDG who displays prototypical features of this rare glycosylation disorder along with two previously unreported anomalies: perineal dysmorphism and bilateral patellar luxation. The causative *SLC35A2* variant (NM_005660.3: c.105_106insCG, p.K36Rfs*6) is a novel pathogenic mutation. This case emphasizes that patients with CDG may occasionally manifest unique anatomical variations. Recognition of such atypical features is important, as it can prompt more thorough clinical examinations and help clinicians develop a more complete picture of the manifestations of this disorder. Further reporting of similar cases is essential to determine whether features such as perineal dysmorphism or patellar luxation are recurrent findings associated with *SLC35A2* variants or isolated anomalies. Ultimately, our report contributes a new piece to the puzzle of SLC35A2-CDG.

Supplementary materials

Supplementary materials for this article are available online at <https://cdn.turkjpediatr.org/html-files/TJP-8349-Video-1.mp4>

Ethical approval

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images and videos. The study was conducted in accordance with the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AG, BK, YA; data collection: AG, TÖ, ÖAD, MCB, FCJ; analysis and interpretation of results: AG, TÖ, ÖAD, FCJ, YA; draft manuscript preparation: AG, BK, YA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Precocious puberty as the first clue: mediastinal germ cell tumor revealing previously undiagnosed Klinefelter syndrome

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ABSTRACT

Background. Gonadotropin-releasing hormone-independent precocious puberty (GnRH-independent PP) due to a human chorionic gonadotropin (hCG)-secreting mediastinal germ cell tumor is an exceptionally rare presentation, particularly in the context of Klinefelter syndrome. This case highlights the diagnostic challenges posed by GnRH-independent PP and underscores the importance of considering extragonadal germ cell tumors in the differential diagnosis of virilization with suppressed gonadotropins.

Case Presentation. A 7-year-9-month-old boy presented with rapidly progressive virilization, including pubic hair development, penile enlargement, and voice deepening. Laboratory evaluation revealed markedly elevated testosterone, estradiol, β -hCG, and alpha-fetoprotein (AFP) levels, with suppressed gonadotropins and a prepubertal GnRH stimulation response. Imaging studies demonstrated a large anterior mediastinal mass containing fat and calcifications, while scrotal ultrasonography showed no testicular lesion. The mediastinal mass was completely resected and histopathology confirmed a mixed germ cell tumor composed of seminoma, yolk sac tumor, and Grade II immature teratoma with β -hCG-positive trophoblastic foci. Karyotype analysis revealed 47,XXY, consistent with Klinefelter syndrome. Following surgery and four cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy, tumor markers normalized rapidly, and no recurrence was detected during long-term follow-up.

Conclusions. This case illustrates a rare presentation of GnRH-independent PP due to a β -hCG-secreting mediastinal mixed germ cell tumor in a child with previously undiagnosed Klinefelter syndrome. Routine karyotype analysis should be considered in male patients with mediastinal germ cell tumors. In children presenting with unexplained virilization and suppressed gonadotropins, extragonadal germ cell tumors and their biochemical markers (β -hCG, AFP) must be carefully evaluated. Early recognition, timely surgical intervention, metabolic monitoring, and multidisciplinary care are critical for optimizing outcomes.

Key words: gonadotropin-releasing hormone-independent precocious puberty, germ cell tumor, Klinefelter syndrome, β -hCG, AFP.

Precocious puberty (PP) is defined as the onset of breast development before the age of eight in girls and testicular enlargement before the age of nine in boys, corresponding to pubertal development occurring 2–2.5 standard deviations earlier than population norms.¹ PP

is classified into two major categories based on the underlying mechanism: gonadotropin-dependent central precocious puberty, which results from early activation of the hypothalamic–pituitary–gonadal axis, and gonadotropin-releasing hormone-independent

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precocious puberty (GnRH-independent PP), which arises from mechanisms unrelated to central axis stimulation. GnRH-independent PP is considerably less common than central precocious puberty and is usually caused by exposure to sex steroids, or by excessive production of sex hormones from the adrenal glands or gonads.¹

One of the important etiologic groups of GnRH-independent PP is tumors that secrete human chorionic gonadotropin (hCG). Owing to its structural homology with luteinizing hormone (LH), hCG stimulates LH receptors in the testes, leading to increased testosterone production by Leydig cells. This results in virilization without testicular enlargement. In male children, the coexistence of markedly elevated hCG levels and rapidly progressive virilization should raise strong suspicion for hCG-secreting germ cell tumors (GCTs) in the differential diagnosis. Among the leading causes of elevated hCG in the pediatric population are mediastinal mixed GCTs and choriocarcinomas.²

GCTs are rare malignancies in childhood, accounting for approximately 3–4% of all pediatric cancers. The majority of GCTs arise from gonadal tissue; however, nearly 5% occur at extragonadal sites.³ The mediastinum is the most common location for extragonadal GCTs, followed by the retroperitoneum and the central nervous system. Mediastinal GCTs are more frequently observed in males, are often characterized by elevated hCG or alpha-fetoprotein (AFP) levels, and have been reported to present with precocious puberty at a higher rate compared with other subtypes.⁴

Genetic and chromosomal abnormalities play a notable role in the development of extragonadal GCTs.⁴ Klinefelter syndrome (KS) is the most common sex chromosome abnormality in males, and micropenis, gynecomastia, and delayed puberty constitute the most frequent clinical presentations in childhood. Individuals with KS have an increased risk of malignancy compared with the general population, with

a particularly strong association reported between KS and mediastinal extragonadal GCTs.³ The risk of developing mediastinal GCT is estimated to be 20–30 times higher in males with KS, and approximately 8% of male patients with primary mediastinal GCT have been found to have KS.⁵ Precocious puberty is not a typical feature of KS; however, it may rarely occur in the presence of an hCG-secreting GCT.⁶

In this case report, we present a 7-year-9-month-old boy who was admitted with signs of precocious puberty and was diagnosed with GnRH-independent PP secondary to an hCG-secreting mediastinal GCT. Karyotype analysis revealed KS. This case is presented to highlight this extremely rare clinical association reported in the literature.

Case presentation

A 7-year-9-month-old male patient presented with complaints of genital hair development, rapid penile enlargement, and voice deepening that had been noticed one month earlier. His medical history revealed that he was a Syrian refugee who had previously been evaluated by a pediatric neurologist for delayed language development. As part of that evaluation, cranial magnetic resonance imaging (MRI), electroencephalography, thyroid function tests, liver function tests, renal function tests, and urinary organic acid analyses were all reported as normal. There was no family history of relevant diseases, and the parents were not consanguineous. On physical examination at presentation, the patient's weight was 32 kg (+1.69 standard deviation score [SDS]), height was 135 cm (+1.64 SDS), and body mass index (BMI) was 17.6 kg/m² (+1.12 SDS). Blood pressure was 100/60 mmHg, and cardiac, pulmonary, and abdominal examinations were unremarkable; no hyperpigmentation was noted. Pubertal assessment revealed a testicular volume of 4 mL bilaterally, as measured using a Prader orchidometer, Tanner stage 2 pubic hair, no axillary hair, and a stretched penile length of 9 cm.

Laboratory evaluation at presentation revealed normal thyroid function tests, electrolytes, and liver function tests. Despite suppressed gonadotropin levels (follicle-stimulating hormone [FSH] 0.3 IU/L, LH <0.07 IU/L), the total testosterone concentration was markedly elevated (1442 ng/dL; reference range: 0–25.9). Given the bilateral testicular volume of 4 mL, a GnRH stimulation test was performed to exclude central precocious puberty; the peak levels of FSH and LH were measured at 2.02 IU/L and 0.47 IU/L, respectively. Further investigations for GnRH-independent PP showed cortisol 9.07 µg/dL, adrenocorticotrophic hormone (ACTH) 55.7 pg/mL, 17-hydroxyprogesterone 1.1 ng/mL, dehydroepiandrosterone sulfate (DHEAS) 32.4 mcg/dL, estradiol 102 ng/mL (reference range: <11–39), β-hCG 314 IU/L (reference range: <5 IU/L), and AFP 586 ng/mL (reference range: 0–8.2). Bone age corresponded to a value of 9 years, indicating an advancement of 1 year and 3 months relative to chronological age.

As part of the etiologic evaluation for GnRH-independent PP secondary to hCG secretion, scrotal ultrasonography revealed testicular volumes near the upper limit for age and compatible with early pubertal development; however, no intratesticular mass was detected. Cranial, pituitary, and abdominal MRI findings were normal. Posteroanterior chest radiography demonstrated asymmetric mediastinal widening with tracheal deviation, without evidence of pulmonary infiltration or pleural/pericardial effusion (Fig. 1). Subsequent thoracic computed tomography (CT) showed a 10.5 × 7 × 7 cm anterior mediastinal mass occupying the right hemithorax. The mass exhibited no significant enhancement following contrast administration and showed no signs of invasion into adjacent structures. It extended from the thymic region toward the right hemithorax, compressing the right middle lobe. The lesion contained areas of fat density and coarse calcifications, and thymic tissue could not be clearly distinguished. No pathological lymph nodes or vascular abnormalities were identified in the mediastinum (Fig. 2).

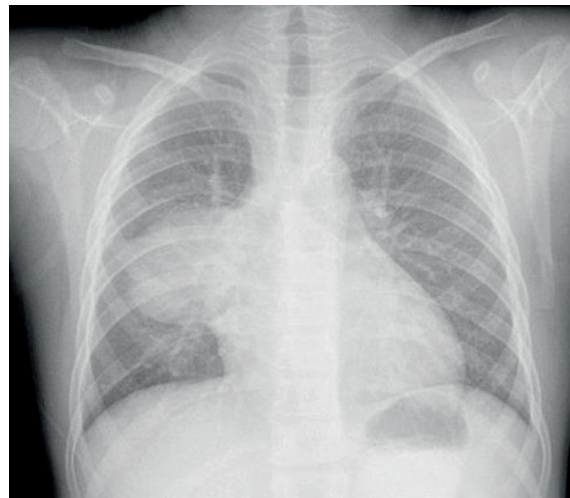


Fig. 1. The posteroanterior chest radiograph demonstrates markedly increased opacity in the right hemithorax with leftward displacement of the mediastinum, consistent with the large mediastinal mass identified on thoracic computed tomography (Fig. 2). Loss of aeration in the right middle lobe due to compressive effect is also evident.

The patient's clinical and laboratory findings were considered consistent with a GCT secreting β-hCG and AFP. The lesion was extragonadal in origin and located in the mediastinum. Given the known association between this tumor group and karyotypic abnormalities, a karyotype analysis was performed, which revealed a 47,XXY pattern consistent with KS.

The mediastinal mass was completely resected via thoracotomy performed by the thoracic surgery team. The patient, who had no preoperative respiratory distress, experienced no intraoperative or postoperative complications. Pathologic evaluation of the mediastinal mass revealed a thymus-derived mixed GCT. Histologically, components representing all three germ layers were identified. Approximately 20% of the tumor consisted of immature neuroepithelial, immature glial, chondroid, and muscular tissues, consistent with a Grade II immature teratoma, accompanied by focal necrotic areas (5%). Surgical margins were reported as tumor-negative. Immunohistochemical analysis confirmed the mixed nature of the tumor, demonstrating D2-

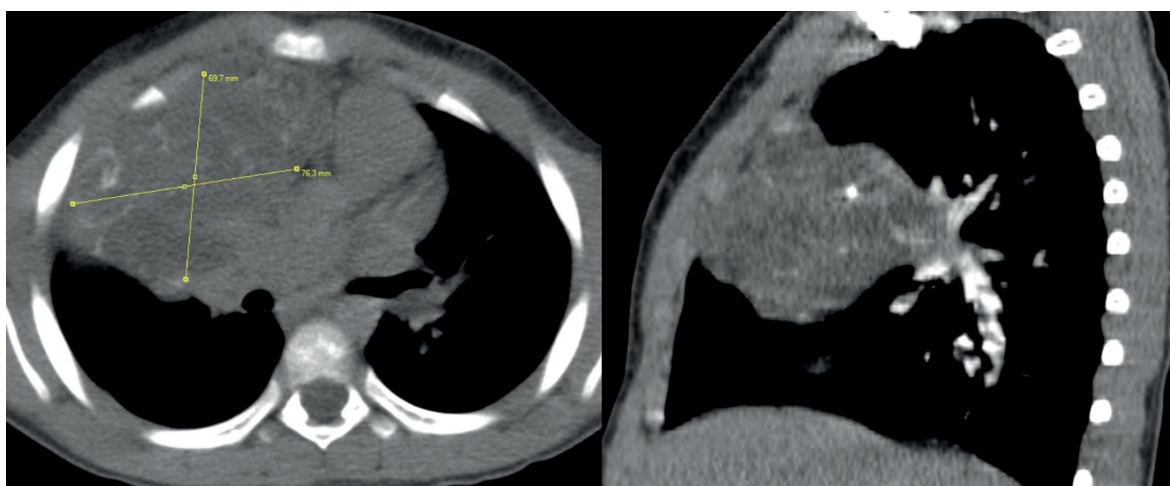


Fig. 2. The contrast-enhanced thoracic computed tomography (axial [left] and sagittal [right] sections) demonstrates a solid mass measuring approximately $10.5 \times 7 \times 7$ cm, originating from the anterior–superior mediastinum and containing areas of fat density and calcification. The mass markedly compresses the right middle lobe and displaces the mediastinum toward the left superior–posterior direction. No contrast enhancement, lymphadenopathy, or vascular invasion was observed.

40, CD117, and placental alkaline phosphatase positivity in the seminomatous component; AFP, low-molecular-weight cytokeratin, and pancytokeratin positivity in the endodermal sinus (yolk sac) component; and strong β -hCG staining in focal trophoblastic areas suggestive of choriocarcinoma. The positivity of synaptophysin within glial regions supported the neuroepithelial component of the immature teratoma. The lesion was classified as a “mixed germ cell tumor composed of seminoma, yolk sac tumor, and Grade II immature teratoma with β -hCG–positive trophoblastic foci” on the basis of the findings of the pathology report.

Postoperative posteroanterior chest radiography demonstrated complete resolution of the mediastinal mass with no complications related to the surgery. Serial tumor marker measurements obtained on postoperative days 3, 7, and 30 showed a rapid and marked decline: β -hCG levels decreased to 82.6 IU/L, 6.4 IU/L, and <2 IU/L; AFP levels to 365 ng/mL, 108.2 ng/mL, and 3 ng/mL; and total testosterone levels to 800 ng/dL, 25.3 ng/dL, and <7 ng/dL, respectively. These findings indicated total resection of the tumor and the elimination of its β -hCG/AFP-producing components.

Post-surgically, the patient was placed under the care of the pediatric oncology unit and classified as having an intermediate-risk mediastinal mixed GCT. Accordingly, the patient received four cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy following the standard treatment protocol. Neutropenia and sepsis that developed during therapy were managed appropriately according to established treatment guidelines.

During follow-up, the patient’s pubertal hormone profile remained appropriate for age, with FSH, LH, and testosterone levels within the expected ranges up to 10 years of age. Clinical examinations, laboratory studies, and imaging assessments revealed no evidence of tumor recurrence. The levels of tumor markers obtained at the initial presentation and throughout the postoperative follow-up period are summarized in Table I. A neuropsychological evaluation performed in the context of KS identified mild perceptual difficulties, while echocardiographic findings were normal.

At the most recent follow-up in April 2025, at 14 years and 1 month of age, no evidence of tumor recurrence was detected based on clinical, laboratory, and imaging findings, and pubertal development was appropriate for

Table I. Tumor markers, total testosterone, and estradiol levels at initial presentation and during postoperative follow-up.

	At admission	Postoperative day 3	Postoperative day 7	Postoperative day 30	Normal value
β -hCG (IU/L)	314	82.6	6.4	<2	<5
AFP (ng/mL)	586	365	108.2	3	0–8.2
Total testosterone (ng/dL)	1442	800	25.3	<7	0–25.9
Estradiol (ng/mL)	102	–	–	19.4	11–39
LDH (U/L)	297	–	–	–	110–295

β -hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase.

age. Laboratory evaluation revealed elevated gonadotropin levels, with FSH at 17.5 U/L (reference range: 1.24–10.37 U/L) and LH at 15 U/L (reference range: 0.2–5 U/L), despite a total testosterone level within the normal male range (449 ng/dL). These findings were considered consistent with hypergonadotropic compensated testicular dysfunction, likely reflecting the combined gonadotoxic effects of KS and BEP chemotherapy. Tumor markers remained within normal limits, with AFP at 1.15 ng/mL (reference range: 0–7 ng/mL) and β -hCG <5 IU/L (reference range: <5 IU/L). Androgen replacement therapy is planned for the later stages of adolescence due to underlying KS.

Informed consent was obtained from the legal guardian for the use of the patient's information in the publication.

Discussion

This case highlights a rare etiology underlying GnRH-independent PP in a 7-year-9-month-old boy: a mediastinal GCT secreting β -hCG and AFP. Despite markedly elevated testosterone and estradiol levels, the suppression of gonadotropins indicated a GnRH-independent mechanism of puberty. The presence of a solid mediastinal lesion containing fat density and calcifications, the absence of testicular masses, and normal abdominal, cranial, and pituitary MRI findings effectively excluded primary testicular or central causes, strongly pointing toward an hCG-secreting mediastinal tumor as the source of the clinical picture. Although

the patient's testicular volume was borderline pubertal (4 mL bilaterally), this finding may be explained by the LH-like activity of β -hCG stimulating Leydig cell testosterone production despite suppressed pituitary gonadotropins. In contrast, the absence of true gonadotropin activation likely limited further testicular enlargement, which remained inconsistent with fully activated central puberty.⁷

Precocious puberty is not a typical feature of KS, although GCTs have been reported in these patients. While most cases of precocious puberty in KS arise from hCG-secreting GCTs, idiopathic central precocious puberty remains extremely rare among these patients.⁶ Although KS had not been previously diagnosed in our patient, the presence of a mediastinal tumor made this association noteworthy. Indeed, KS has been identified in at least 8% of male patients with primary mediastinal tumors, and the syndrome is reported to be nearly 50 times more prevalent among males diagnosed with mediastinal GCTs than in the general population.⁸ These data underscore the importance of routine karyotype analysis in male patients presenting with mediastinal GCTs.

The increased risk of mediastinal GCT development in individuals with KS is supported not only by epidemiological observations but also by several underlying biological mechanisms. The association between KS and mediastinal GCTs may involve genetic factors related to an extra X chromosome.³ Furthermore, the increased incidence of mediastinal GCTs

in KS has been hypothesized to result from the malignant transformation of primordial germ cells misplaced during embryogenesis. This pathogenic association may be further influenced by the susceptibility locus at Xq27, as well as by sustained hypergonadotropism, which may promote germ cell proliferation.³ Additionally, disturbances in steroidogenesis and impaired androgen production may create a permissive environment for the proliferation of extragonadal germ cells. Collectively, these findings support the notion that KS provides a genetic substrate that predisposes individuals to the development of mediastinal GCTs.⁴

In this case, the markedly elevated level of β -hCG (314 IU/L) is consistent with the characteristic biochemical profile described in hCG-secreting mediastinal GCTs.³ As hCG shares an identical α -subunit and a highly similar β -subunit with LH, it stimulates Leydig cells, resulting in increased testosterone secretion. As a natural consequence of this mechanism, gonadotropins are suppressed through negative feedback.⁹ The suppressed gonadotropin levels observed in our patient, together with the blunted FSH/LH response on the GnRH stimulation test, strongly indicate hCG-mediated suppression of the hypothalamic-pituitary-gonadal axis.

The markedly elevated AFP level (586 ng/mL) indicated the presence of a non-seminomatous component within the tumor, a finding commonly associated with yolk sac tumors or embryonal carcinoma, and frequently observed in mixed GCTs.¹⁰ The areas of fat density and calcification detected on thoracic CT were consistent with a teratomatous component. When the biochemical markers and imaging findings were evaluated together, a clinical diagnosis of mixed GCT was strongly favored, and histopathologic examination confirmed this diagnosis. The identification of seminomatous, yolk sac, and trophoblastic components in the pathology samples was fully concordant with the patient's biomarker profile.

In the literature, cases of precocious puberty secondary to hCG-secreting mediastinal

tumors have commonly been associated with elevated testosterone and markedly increased β -hCG levels.³ For instance, in an 8.5-year-old KS case reported by Völkl et al., suppressed gonadotropins, elevated testosterone levels, and markedly elevated β -hCG and AFP levels were documented, and the tumor was histopathologically diagnosed as a mixed GCT.³ Similarly, in our case, the absence of any testicular mass on scrotal ultrasonography definitively supports the mediastinum as the primary site of the tumor.

Primary extragonadal malignant GCTs account for only 5% of all malignant GCTs; however, they may exhibit clinically aggressive behavior. Mediastinal non-seminomatous GCTs, in particular, tend to have a more aggressive course and lower chemotherapy response rates compared with their gonadal counterparts.¹⁰ Therefore, early diagnosis, timely surgical intervention, and a multidisciplinary treatment approach are crucial for improving prognosis. Treatment typically consists of complete surgical resection followed by cisplatin-based chemotherapy regimens.¹⁰ In the pediatric population, coordinated multidisciplinary management involving pediatric oncology, endocrinology, and thoracic surgery teams has been shown to positively influence both survival and long-term recurrence outcomes. In our case, complete tumor resection and the rapid normalization of postoperative tumor markers were considered indicators of favorable prognosis.

Primordial germ cells undergo a well-defined migratory process during embryogenesis, traveling from the yolk sac to the gonadal ridge. Defects in this migration pathway may result in germ cells becoming arrested at ectopic midline locations, including the pineal region, mediastinum, or retroperitoneum. Extragonadal GCTs are thought to arise from these ectopic primordial germ cells.⁴ This theory represents the most widely accepted embryological mechanism explaining the primary mediastinal location of the tumor in our patient. Extragonadal GCTs occur most

commonly in the mediastinum, accounting for approximately 50–70% of all extragonadal GCT cases. Among mediastinal GCTs, the most frequent histologic type is mature teratoma.¹¹

Conclusion

In summary, this case represents an extremely rare and noteworthy clinical presentation of GnRH-independent PP secondary to a β -hCG- and AFP-secreting mediastinal GCT, occurring in association with KS. The literature clearly demonstrates an increased association between KS and mediastinal GCTs, and routine karyotype analysis is of clinical importance in all male children diagnosed with mediastinal GCTs.

This case provides valuable insight into the diagnostic approach to similar clinical presentations and strongly emphasizes that, particularly in cases of unexplained precocious puberty accompanied by suppressed gonadotropins, extragonadal GCTs and their associated biochemical markers (β -hCG, AFP) must be carefully evaluated.

Ethical approval

Informed consent was obtained from the legal guardian for the use of the patient's information in the publication.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AFY, MB; data collection: AFY, HE, BK; analysis and interpretation of results: AFY, HE, BK; draft manuscript preparation: AFY, MB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORTS

- 855 **A rare congenital malformation of the external iliac artery in a term neonate**
Ana Sučić, Gabriela Živković, Edi Paleka Bosak, Vinko Vrdoljak, Alen Švigir, Katarina Bojanić
- 860 **Megalopapilla in oculodentodigital dysplasia: a novel ocular finding in a rare genetic disorder**
Figen Bezci Aygun, Gunes Deniz Ulas, Izlem Ozturan, Sibel Kadayifcilar
- 869 **Beyond the usual: coronary artery abnormalities in Noonan syndrome**
Bilgehan Betül Biçer, Hayrettin Hakan Aykan, Ercan Tutar
- 874 **Colonic arteriovenous malformations in children: a missed cause of lower gastrointestinal bleeding**
Rohan Luthra, Natasha Gupta, Parveen Kumar
- 882 **Perineal dysmorphism and patellar luxation in SLC35A2-CDG: a new piece in the glycosylation puzzle**
Anıl Gök, Tolgahan Özer, Özlem Akgün Doğan, Mehmet Cihan Balci, Filiz Çizmecioğlu Jones, Bülent Kara, Yasemin Alanay
- 889 **Precocious puberty as the first clue: mediastinal germ cell tumor revealing previously undiagnosed Klinefelter syndrome**
Ahmet Fatih Yılmaz, Muammer Büyükinan, Buket Kara, Hıdır Esme