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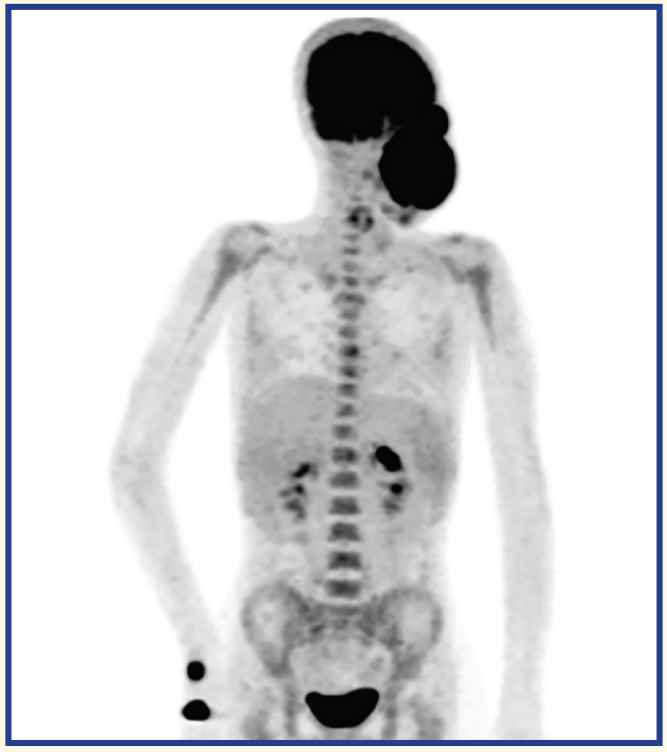

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CONTENTS

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EDITORIAL

New Insights in Pediatric Medicine: A Concise Reflection for the New Year

As we welcome a new year, this issue brings together a diverse collection of studies that advance our understanding of pediatric health and disease. Several contributions highlight the importance of biomarkers and immune-nutritional status in childhood illnesses—such as the meta-analysis linking low serum zinc levels to urinary tract infections and the evaluation of the prognostic nutritional index in pediatric high-grade glioma.

Diagnostic refinement remains a central theme. The review on pediatric penicillin allergy emphasizes the importance of accurate assessment and delabeling strategies to improve antimicrobial stewardship. Complementing this, research into thyroid function and infection severity provides valuable clinical context for interpreting endocrine changes during acute illness.

Innovative methodologies also enrich this issue. A multi-omics Mendelian randomization study explores the causal pathways between neonatal sepsis and later attention-deficit/hyperactivity disorder risk, offering new perspectives on neurodevelopmental outcomes. Procedural and imaging advances are reflected in the report on direct right atrial catheterization in short bowel syndrome and the optical coherence tomography-based iris evaluation in pediatric Behçet's disease.

Digital health and psychosocial domains come forward in the study examining social media and health app use in adolescents with type 1 diabetes, while the validation of a foreign body aspiration scoring system supports improved clinical decision-making in critical care. Rare case reports—including mandibular Ewing sarcoma, Morganella morganii urinary tract infection with hydronephrosis, and Mycobacterium bovis bacillus Calmette–Guérin mastitis—remind us of the diagnostic challenges that require vigilance and multidisciplinary collaboration.

As we step into the new year, these studies collectively reflect our ongoing commitment to evidence-based, innovative, and patient-centered pediatric care. We extend our thanks to the authors and reviewers whose work enriches our scientific community.

Wishing all our readers a healthy, productive, and inspiring new year.

Sanem Yılmaz, MD

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Review

Low Serum Zinc Level is Associated with Urinary Tract Infection in Children: A Systematic Review and Meta-analysis

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ABSTRACT

To review the relationship between serum zinc (Zn) levels and urinary tract infections (UTIs) in children. Databases with published papers from 2015 up to July 2025 from PubMed Central, SpringerLink, EBSCOhost, and ScienceDirect were used in this investigation. The data were processed quantitatively using the Review Manager 5.4 software application. The risk of bias qualitatively was assessed using the New Ottawa Scale and Agency for Health Research and Quality requirements as the threshold. Four out of five studies (80%) reported that lower levels of Zn were found in children with UTIs compared to control subjects. Our analysis results showed that there was an inverse correlation between serum Zn levels and UTIs in children [p<0.0001; mean difference: -10.49, 95% confidence interval (-13.32 to -7.66)]. Low serum Zn levels correlated significantly with UTIs in children.

Keywords: Zinc, urinary tract infection, children

Introduction

Trace elements such as zinc (Zn) are essential for cell proliferation and biochemical reactions in the body. Zn has a significant impact on gene transcription, protein metabolism, lipid metabolism, nucleic acid metabolism, and complement activity (1). Skeletal muscle (approximately 60%), bone (about 30%), skin (about 5%, predominantly in the epidermis), and liver (about 5%) have the greatest tissue Zn concentrations. Additionally, blood serum contains a small quantity of Zn (about 0.1% of total Zn reserves). However, the element is not specifically stored in the human body (2).

Zn homeostasis is regulated by transcriptional pathways and transmembrane transport, which in part, shield the body from the negative consequences of too much or too little Zn in the diet (2). The human body cannot produce Zn, so sufficient levels must be obtained externally. The amount of Zn consumed in food rises with age, from 2 mg/day for children to 9 mg/day for adult females and 11 mg/day for adult men, which makes Zn supplementation now a common practice in primary healthcare services in many developing regions' health policy decisions (3).

Zn deficiency (ZnD) is a health problem with up to 17.3% of the world's population and up to 30% of those

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in South Asia potentially being at risk (4). ZnD usually manifests as growth impairment, sexual dysfunction, inflammation, gastrointestinal urinary symptoms, or cutaneous involvement. ZnD triggers thymic atrophy and lymphopenia, which both suppress innate and adaptive immune responses. It hinders macrophage phagocytosis, intracellular killing activity, and cytokine production; neutrophil and natural killer cell host defence; and T and B cell proliferation, cytokine production, and antibody secretion. These consequences lead to an increased susceptibility to a wide range of infectious agents and a longer duration of infection (5).

Urinary tract infection (UTI) is one of the most common infections in childhood. It can impact either the lower urinary tract (cystitis) or the upper urinary tract (pyelonephritis). Unfortunately, especially in newborns and young children, it may be challenging to differentiate between cystitis and pyelonephritis based solely on clinical symptoms and indicators (6). It is important to diagnose and treat UTIs early in order to avoid more complications.

Around 5% of girls who have not had their periods and 20% of boys get a UTI during the first two months of life in febrile newborns. Uncircumcised males have a ten-fold to twelve-fold higher risk of UTI during their first six months (7). Through to the time they reach seven years old, 1.7% of boys and 7.8% of girls, on average, are predicted to have experienced a UTI. Of the 16-year-old populations, 3.6% of boys and 11.3% of girls will have experienced a UTI at some stage, while the recurrence rates range from 30% to 50% on average (8-10). Inadequate host defences may be the reason for recurrent UTIs (a UTI occurring after the resolution of a previous episode) in certain patients (11). The two major host variables in the pathophysiology of UTIs include a failure in innate immune responses and urothelial barrier function, such as pro-inflammatory cytokine production or protective glycoprotein impairment (12). Thus far, the literature has presented contradictory results from the limited number of studies which have examined children's Zn status during UTIs (13-17). Therefore, evaluating the association between serum Zn levels and pediatric UTIs was the aim of this investigation.

Materials and Methods

The authors independently found articles published from 2015 until July 2025 on PubMed Central, SpringerLink, EBSCOhost, and ScienceDirect, by using titles and abstracts. There was also a manual assessment of the references for every eligible study.

This evidence-based study is structured on the Preferred Reporting Item for Systematic Review and Meta-study 2020 statement. We used a word mesh combining "Zn," "UTI" and "pediatric" to search for the journals used in this study. Overall, the researchers searched for and evaluated the papers included independently. Every issue which arose during the literature search was resolved by consensus. Result journals which mentioned the relationship between serum Zn levels and UTIs were included in this study. We detailed (participants, exposure, comparison and outcome): P: children with UTI, E: low serum Zn levels, C: control subjects, O: incidences of UTI in children. Four conditions had to be met to be included in this systematic review study: (1) observational studies investigating the association between serum Zn levels and UTIs, including case-controls, cross-sectional design, and cohorts; (2) child-related research; (3) non-recurrent UTI; (4) study in human. We did not include conference abstracts, letters, editorial comments, reviewed publications, or items which were published more than 10 years ago in our selection.

Every researcher extracted data individually from the verified articles, compiling it into an Excel spreadsheet. In order to reach a final decision, additional researchers settled any disagreements. The primary author, location, year of publication, number of subjects and population, study design, type of UTIs, diagnostic approach of the studies, and a description of the relationship between serum Zn levels and pediatric UTIs were the data which we gathered from each study.

The Newcastle-Ottawa Scale (NOS) was used to assess the included studies' risk of bias. In order to conduct case-control and cross-sectional research, we examined eight domains: non-response rate, exposure determination, case representativeness, control selection, control definitions, case-control comparability, and adequate case definition (18). Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis controlled for confounders, assessment of outcome, long enough follow-up for outcomes to occur and adequacy of follow-up of cohorts were the eight domains for cohort studies which we evaluated. The Agency for Health Research and Quality criteria were used as a criterion to assess the quality of the studies (19).

Data on serum Zn (µg/dL) were collected both from the children with UTIs and the controls. The findings from individual studies are summarized in the summary tables, and

data for these variables were pooled as relative frequencies and presented as means and standard deviations. Data analysis and graphical plotting was performed using the Review Manager 5.4 software application. Publication bias was assessed using funnel plot visualization and interpreted qualitatively when fewer than 10 studies were included.

Results

The database searches and screening processes are shown in Figure 1. A total of 687 articles (PubMed Central: 72, SpringerLink: 290, EBSCOhost: 86, and ScienceDirect: 239) were identified in accordance with the key terms from the published literature. Of these, 435 articles were excluded before screening, and the remaining 256 articles were further screened by their title and abstract. Four out of five studies (80%) reported that lower levels of Zn were found in children with UTI compared with the control subjects. Only one study stated that the mean difference (MD) between the controls and the cases was not statistically significant (p=0.98). From that one study, the findings may have been related to the weights in the various age groups, gestational age, the severity of leukocytosis and thrombocytosis, the severity of increases in erythrocyte sediment rates or C-reactive protein (CRP), or the durations of hospitalization. The details of the studies included are shown in Table I.

Four studies were further reviewed quantitatively. One research from the prior qualitative evaluation was excluded due to differences in the unit measurements of serum Zn levels. We compared a total of 212 children with UTIs and 212 children as control. This figure shows the pooled analysis of four studies [Mahyar et al. (13), Zabihi et al. (17), Amoori et al. (20), Seifollahi et al. (21)] comparing MDs between those children with UTI and the controls. The pooled MD was -10.49 (95% confidence interval: -13.32, -7.66), indicating that children with UTIs had significantly lower values compared to the controls. The test for overall effect was statistically significant (Z=7.27, p<0.00001), supporting a strong association. However, there was high heterogeneity among the studies (I^2= 93%, p<0.00001), suggesting variability in the study results which may have resulted from differences in the study designs, populations, or their measurement methods. The data analysis and graphical plotting is shown in Figure 2.

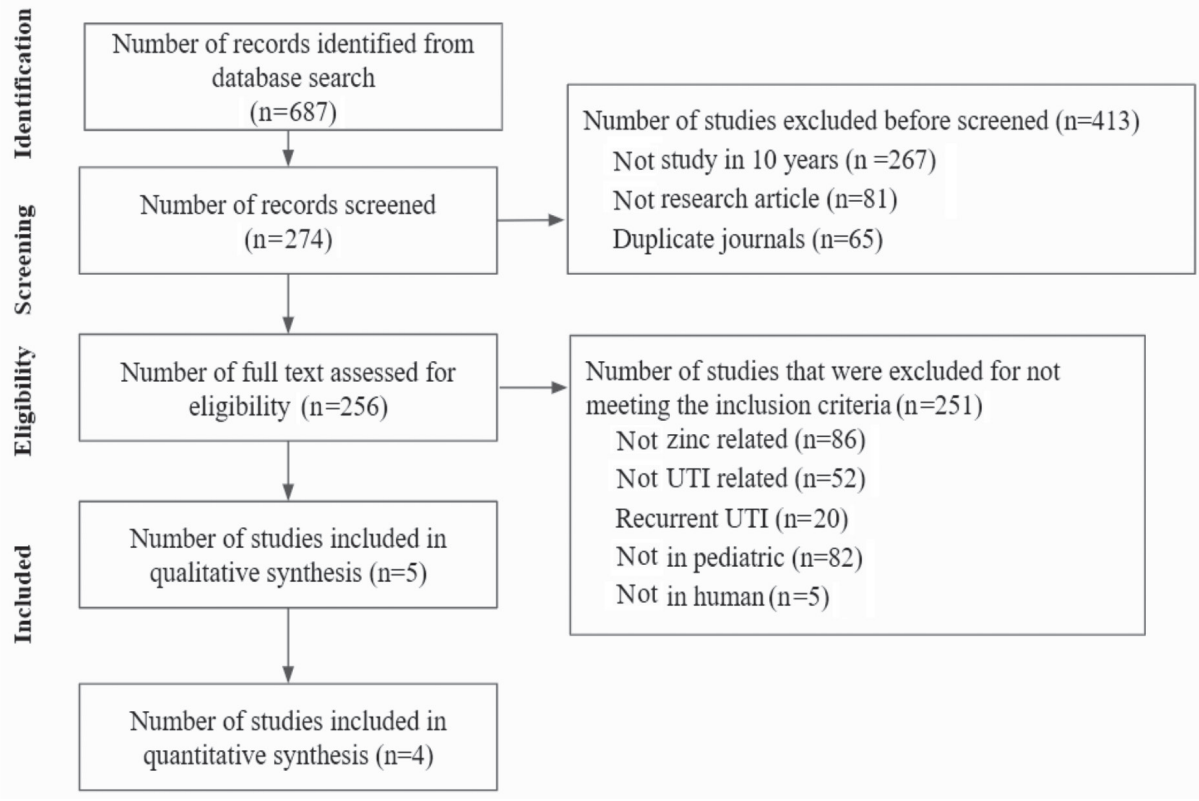

Figure 1. PRISMA study flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses, UTI: Urinary tract infection

Table I. Descriptive information for selected research studies regarding the relationship between the levels of serum zinc and urinary tract infections in children

No	Primary author, Year	Population	Study design	Cut-off serum zinc level	Result zinc & UTI
1	Mahyar et al. (13), 2015	120 children (60 cases and 60 controls) aged 12 months-2 years old	Case control, non-RCT	70-120 µg/dL	Serum zinc levels in the case and control groups were 70.73±14.15 and 87.61±12.68 µg/dL, respectively (p=0.001).
2	Zabihi et al. (17), 2020	104 children (52 cases aged 26.5±20.5 months and 52 controls aged 34.3±16.8 months)	Case control, non-RCT	70-120 µg/dL	Serum zinc level was 60.0±17.1 µg/dL in the case group and 83.0±15.7 µg/dL in the control group (p=0.001). After being adjusted for demographic factors, the zinc deficiency proved to be a significant predictor of UTI (OR=8.633, 95% confidence interval=3.084-24.171, p<0.001).
3	Amoori et al. (20), 2021	120 children (60 children with febrile UTI and 60 healthy children) aged 3 -120 months old	Case control, non-RCT	60-90 g/dL for <1 years old children and 80-110 g/dL for 1 to 10 years old children	Not statistically significant, the mean value was 95.05±11.34 µg/dL in the control group and 94.98±12.24 µg/dL in the case group; (p=0.98).
4	Noorbakhsh et al. (16), 2019	65 children (25 proven UTI cases and 40 controls without infection) aged <5 years old	Cohort study, non-RCT	≥65 µg/dL were considered normal	Lower serum levels for zinc in UTI cases as compared to the normal children (95.43 vs. 106.9 µg/dL; p=0.05).
5	Seifollahi et al. (21), 2024	80 children (40 cases and 40 controls)	Case control, non-RCT	63.8-110 µg/dL	Significant difference between the 2 groups regarding serum zinc levels (p<0.001). Twenty-four children were deficient with (mean ± SD) µg/dL serum level 75.02±56.00 and 7 children were deficient with serum level, 71.40±141.72 for the healthy children.

Diagnostic of UTI in these studies was based on positive urine culture
UTI: Urinary tract infection, RCT: Randomized controlled trial OR: Odds ratio SD: Standard deviation

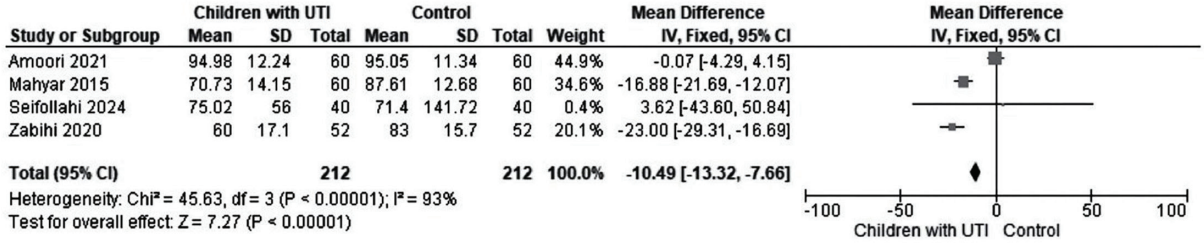

Figure 2. Forest plot of 4 studies assessing the serum zinc levels in children with urinary tract
UTI: Urinary tract infection, SD: Standard deviation, CI: Confidence interval

Finally, five studies were identified for this review. Quality assessment of these studies was performed by NOS. Risk of bias is shown in Table II (case-control study, non-randomized control trial) and in Table III (cohort study, non-randomized control trial). Among the five studies included, two [Mahyar et al. (13), Zabihi et al. (17)] were graded as fair quality due to limitations in selection and comparability. For Mahyar et al. (13) although UTI diagnosis was rigorous, the lack of adjustment for nutritional and socio-economic confounders limited comparability. Similarly, Zabihi et al. (17) reported significant baseline differences between the cases and the controls (age, sex, weight), and despite adjustments, these imbalances introduced residual bias. In contrast, three studies [Amoori et al. (20), Noorbakhsh et al. (16), and Seifollahi et al. (21)] achieved good quality, with more balanced groups and stricter exclusions of confounding factors, thereby fulfilling most NOS criteria and so resulting in a lower risk of bias. Overall, the evidence base appears reasonably strong, with a low-to-moderate risk of bias, although further well-designed studies with broader controls of potential confounding factors would strengthen the conclusions.

Table II. Risk of bias of the case-control studies included. Newcastle-Ottawa Scale and the Agency for Health Research and Quality guidelines were used to evaluate the risk of bias and establish the threshold for defining the research quality

Study	Selection				Comparability	Exposure			Interpretation†
	1	2	3	4	5	6	7	8	
Mahyar et al. (13), 2015	*		*		*	*	*	*	Fair quality
Zabihi et al. (17), 2020	*		*		*	*	*	*	Fair quality
Amoori et al. (20), 2021	*		*	*	*	*	*	*	Good quality
Seifollahi et al. (21), 2024	*		*	*	*	*	*	*	Good quality

1) Is the case definition adequate?
2) Representative of the cases,
3) Selection of controls,
4) Definition of controls,
5) Comparability of cases and controls on the basis of the design or analysis controlled for cofounders,
6) Ascertainment of exposure,
7) Same method of ascertainment for cases and controls,
8) Non-response rate.

†: Thresholds for converting the Newcastle-Ottawa Scales to AHRQ standards (good, fair, and poor):
• Good quality: 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Fair quality: 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Poor quality: 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 star in the outcome/exposure domain.
AHRQ: Agency for Healthcare Research and Quality

Table III. Risk of bias of the cohort study included. Newcastle-Ottawa Scale and the Agency for Health Research and Quality guidelines were used to evaluate the risk of bias and establish the threshold for defining the research quality

Study	Selection				Comparability	Exposure			Interpretation†
	1	2	3	4	5	6	7	8	
Noorbakhsh et al. (16), 2019	*		*	*	*	*	*	*	Good quality

1) Representativeness of the exposed cohort,
2) Selection of the non-exposed cohort,
3) Ascertainment of exposure,
4) Demonstration that outcome of interest was not present at start of study,
5) Comparability of cohorts on the basis of the design or analysis controlled for confounders,
6) Assessment of outcome,
7) Was follow-up long enough for outcomes to occur?
8) Adequacy of follow-up of cohorts.

†: Thresholds for converting the Newcastle-Ottawa Scales to AHRQ standards (good, fair, and poor):
• Good quality: 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Fair quality: 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Poor quality: 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 star in the outcome/exposure domain.
AHRQ: Agency for Healthcare Research and Quality

Discussion

Many children suffer from UTIs, which are linked to serious morbidity. The prevalence rate is up to 30%. UTI is the most dangerous bacterial infection in children under three months old. One in six cases of febrile newborns is caused by a UTI. This condition can cause short-term consequences, such as acute kidney injury, renal abscess and sepsis. Hypertension, end-stage renal disease, preeclampsia, renal scarring, and recurrent infection are the possible long term consequences (22).

An estimated half a million infant and child deaths annually are attributed to ZnD. In five Indian states, a cross-sectional study revealed that 43.8% of infants aged six to sixty months had insufficient Zn. The most frequent causes of ZnD were determined to be insufficient dietary intake, minimal consumption of animal products, restricted Zn bioavailability from cereals, and recurrent diarrheal illnesses which resulted in intestinal Zn loss (23).

To the best of our knowledge, this is the first systematic review and meta-analysis regarding the association between serum Zn levels and non-recurrent UTI in children. In this systematic review and meta-analysis, we aimed to see the relationship between Zn and UTI in children by comparing the serum in those children with UTI and the controls. We

found significantly lower serum Zn levels in those children with UTI than in the controls. This finding is in line with three previous studies (8,17,21). The study by Amoori et al. (20) found contrasting results which showed that there was no relation between low serum Zn levels and UTI in children. Another slightly different study had a similar finding with this meta-analysis which showed that serum Zn levels played a role in recurrent UTI in children (12).

Nonetheless, some studies stated that there was no correlation between Zn deficit and inflammatory cytokines, and the association between ZnD and UTI was independent of inflammation indicators. Through the production of proteins and nucleic acids, Zn contributes significantly to cellular development and differentiation. Some studies have pointed out the role of Zn supplementation in the prevention and treatment of bacterial diseases (13).

The specific mechanism by which ZnD contributes to the pathogenesis of UTIs in humans has not been fully elucidated. Zn itself plays a role in immune system functioning in terms of defending against infections. It helps epithelial cells and leukocyte regulation. Zn homeostasis, intracellularly and extracellularly, is needed for optimal immune response and also to prevent further tissue damage (24). Antioxidant levels are downregulated and oxidative stress is elevated in UTI patients' serum cations. Copper, calcium, and Zn are decreased while indicators of oxidative stress such malondialdehyde are elevated in UTIs (15,25).

In the study by Hancock et al. (26), research was carried out on the antimicrobial and anti-biofilm effects of Zn on *Escherichia coli, Klebsiella*, and urinary tract pathogens. It was found that divalent Zn could apply its antimicrobial mechanism by preventing the above mentioned organisms from forming biofilms. Thus, it is possible to draw the conclusion that stones in the urinary system or the development of biofilm in the urinary tract are the cause of UTIs (26).

A previous systematic and meta-analysis reported that supplemental medicines containing Zn and dietary intake were also shown to have positive effects during infection, specifically in the respiratory and gastrointestinal systems (27). Previous studies have also stated that there was an inverse relation between Zn and inflammatory markers (interleukin-6, tumor necrosis factor-alpha, and CRP). Low levels of Zn were linked to decreased macrophage activation and impaired lymphoid tissue development (28).

Zn is the second most abundant trace element in the body, after iron. One in ten of the proteins found in the human body is a Zn protein. More than 300 enzymes and 1,000 transcription factors depend on Zn activity. Zn is an essential micronutrient involved in many cellular processes such as protein synthesis, nucleic acid metabolism including deoxyribonucleic acid synthesis, gene transcription, cell proliferation and differentiation, and mitosis (5).

The amount of Zn needed rises with age, starting from 2 mg/day for children, which makes Zn intake is an important supplementation (3). Zn can be found in a wide range of dietary and supplementary groups, but its content and bioavailability vary greatly (3). This micronutrient cannot be synthesized in the human body. Therefore, supplementation and foods which contain high Zn are needed in order to maintain adequate serum levels in the body (5,29). Some foods contain high levels of Zn, such as red meat, offal, oysters and shellfish, fortified cereals, and whole-grain products. Of all the foods, oysters provide the highest amount of Zn per serving. However, since beef is so widely consumed in Western nations, it accounts for 20% of total dietary Zn intakes. Zn is also found in eggs and dairy products. Zn is found in beans, nuts, and whole grains, but because plant-based diets are high in phytates, the bioavailability of Zn is reduced (29).

Through this study, the researchers want to enhance the understanding of the role of Zn in maintaining urinary tract health and its implications on more effective prevention strategies for children. Our findings also emphasize the importance of Zn nutrition. This study can be a reference for health guidelines and health promotion in order to raise awareness about the importance of adequate Zn supplementation.

Study Limitations

The limitation of this study was the small number of available studies. This limited evidence base reduces the generalizability of our findings and weakens the strength of our conclusions. Further large-scale, prospective studies are required in order to confirm the associations between serum Zn levels and pediatric UTI. Moreover, while our findings raise the possibility that Zn supplementation may serve as an adjuvant preventive or therapeutic strategy, this implication should be validated through well-designed randomized controlled trials.

Conclusion

This systematic review and meta-analysis demonstrated a significant association between low serum Zn levels and UTI in children. These findings highlight the potential role of Zn status in pediatric urinary health. However, given the

limited number of available studies, the evidence should be interpreted with caution. Further large-scale, prospective studies and randomized controlled trials are warranted in order to confirm this association and to explore whether Zn supplementation could serve as an effective adjuvant strategy in reducing the incidence of pediatric UTI.

Footnotes

Authorship Contributions

Concept: S.Y.U., J.C., M.O., Data Collection or Processing: S.Y.U., J.C., M.O., Analysis or Interpretation: S.Y.U., J.C., M.O., Literature Search: S.Y.U., J.C., M.O., Writing: S.Y.U., J.C., M.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Review

Reevaluating Pediatric Penicillin Allergy: Diagnosis, Clinical Impact, and De-labeling Strategies

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ABSTRACT

Penicillin allergy is the most commonly reported drug allergy in children, yet the vast majority of these labels are incorrect. Approximately 5-10% of pediatric patients are reported to be penicillin-allergic, but over 90% are found to tolerate penicillins after thorough evaluation. Overdiagnosis of penicillin allergy in children leads to significant clinical and public health consequences, including the unnecessary use of broad-spectrum antibiotics, higher rates of antimicrobial resistance (e.g., *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infections), and increased healthcare costs. This narrative review examines the discrepancy between reported and true penicillin allergy prevalence in pediatrics and discusses the immunopathology of hypersensitivity reactions (Types I-IV). We outline current strategies for diagnosing penicillin allergy, from detailed history-taking and risk stratification to skin testing using non-irritating concentrations and drug provocation test, which remains the gold standard. We also review the evidence on β-lactam cross-reactivity, clarifying that cross-allergy with cephalosporins and carbapenems is lower than historically thought and largely related to side-chain structures. The clinical impact of mislabeling children as penicillin-allergic is explored, highlighting the benefits of penicillin "de-labeling" programs and antibiotic stewardship interventions. Ongoing trials aim to demonstrate improved outcomes when incorrect allergy labels are removed. Finally, we address the challenges and practice gaps in low-resource settings, particularly in Asia, where limited access to allergy testing and specialist care complicates penicillin allergy management. By improving the accurate diagnosis of penicillin allergy in children, we can optimize antibiotic use, enhance patient safety, and combat antibiotic resistance.

Keywords: Pediatric allergy, drug hypersensitivity, beta-lactam allergy, allergy de-labeling, drug provocation test

Introduction

Penicillin, first discovered by Alexander Fleming in 1928 and widely used since the 1940s, remains a cornerstone antibiotic for pediatric infections. However, penicillin allergy is commonly reported and often overdiagnosed in children. Approximately 10% of all patients, including 5-10% of children, are labeled "penicillin-allergic," making it the most documented drug allergy in the medical records. In reality, true immunoglobulin E (IgE) mediated penicillin allergy is uncommon: fewer than 1-2% of the population is truly allergic upon formal evaluation (1) (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025). Studies

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have shown that 80-90% of individuals with a reported penicillin allergy can actually tolerate penicillin upon testing or re-exposure [British Society for Antimicrobial Chemotherapy website, "The risk of being risk-averse: penicillin allergy labels (PALs)," accessed June 25th, 2025]. Many pediatric patients lose their penicillin sensitivity over time or were never allergic to begin with. Mislabeling often stems from misinterpreting benign rashes or viral exanthems as allergic reactions (1). For example, common childhood viral infections frequently cause rashes which coincide with antibiotic treatment, leading caregivers and clinicians to mistakenly attribute the rash to a drug allergy.

Overdiagnosis of penicillin allergy in children has important consequences for both individual patients and public health. Once a PAL is attached to a child's medical record, it tends to persist into adulthood. This label can lead to an avoidance of all β-lactam antibiotics, resulting in the use of alternative broad-spectrum agents which may be less effective, more toxic, and more expensive. The downstream effects include longer illness durations, higher rates of treatment failure, antibiotic resistance, and increased healthcare costs (2). Growing awareness of these issues has prompted efforts to "de-label" patients who are not truly allergic and encourage more accurate diagnostic workups for reported penicillin allergies (1). In this review, we examine the epidemiology of reported versus confirmed penicillin allergies in pediatric populations, discuss the immunologic mechanisms and types of hypersensitivity reactions, and describe current best practices for testing and management. We also explore the clinical impact of penicillin mislabeling, including antibiotic stewardship considerations and emerging de-labeling programs, with special attention to challenges in low-resource settings.

Epidemiology of Reported vs True Penicillin Allergies

Penicillin allergy is vastly over-reported relative to its true prevalence. In pediatric populations, an estimated 5-10% of children are believed to have a penicillin allergy based on their history. However, comprehensive allergy evaluations reveal that over 90% of these children are not truly allergic. In other words, only about 1 in 20 children with a PAL have a confirmed immunologic hypersensitivity. This disparity is consistent with findings in adults: around 10% of the general population reports penicillin allergy, but fewer than 1% are truly allergic when formally tested (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

Large cohort studies and meta-analyses have established that the vast majority of PALs are inaccurate. For example, Macy and Contreras (3) examined a large healthcare database and found that 94% of patients with listed penicillin allergy were able to tolerate penicillin upon further evaluation or testing. Similarly, a UK study reported that while 6% of patients in primary care carried PAL, only about 0.6% (1 in 10 of those labeled) had a true allergy on comprehensive testing. Pediatric-specific studies also confirm that over 9 out of 10 children with reported penicillin allergy can be safely de-labeled. Vyles et al. (4), for instance, showed that among children with low-risk histories (e.g., only mild rash without features of anaphylaxis), direct oral amoxicillin challenges were negative in over 95% of cases, indicating no allergy in those children. Moreover, penicillin allergy can be transient; it is well documented that IgE-mediated penicillin sensitivity wanes over time. Approximately 50% of patients lose their penicillin-specific IgE antibodies within 5 years, and about 80% may lose sensitivity after 10 years. Many children "outgrow" their penicillin allergy, especially if their initial reaction was mild (5).

Why is Penicillin Allergy Over Diagnosed?

A major reason is the misattribution of symptoms. Children frequently develop rashes due to viral infections or due to benign drug side effects (e.g., transient gastrointestinal upset or diarrhea), which can be misconstrued as allergic reactions. For example, amoxicillin is often prescribed for viral infections (such as Epstein-Barr virus) which cause rashes. When a rash appears, penicillin is blamed. In one study, viral rashes accounted for a large portion of suspected antibiotic "allergies" in children (1). Another contributor is that detailed allergy evaluations are seldom performed at the time of the reaction. Understandably, if a child has any suggestive reaction during antibiotic therapy, families and physicians may choose to err on the side of caution and avoid penicillins thereafter, without pursuing confirmatory testing (6). Over time, the PAL remains in the chart unchallenged. This highlights a critical epidemiologic point: while PALs are present in up to 10% of pediatric charts, the true prevalence of confirmed penicillin allergy in children is of the order of 1% or less. Most labeled children could safely receive penicillins. Recognizing this gap has led to initiatives to better diagnose and, when appropriate, to remove inaccurate PALs in pediatric practice.

Pathophysiology and Types of Hypersensitivity Reactions

Adverse reactions to penicillins can be broadly categorized as either immune-mediated (allergic) or non-immune in nature. Non-immune reactions (previously

called "Type A" reactions) are predictable from the drug's pharmacology and are not due to the immune system, such as diarrhea from amoxicillin or yeast diaper rash after antibiotics. In contrast, true penicillin allergies are immune-mediated ("Type B" reactions) and involve drug-specific immunologic mechanisms. Penicillin and other β-lactam antibiotics can elicit all four types of hypersensitivity described by the Gell-Coombs classification (Types I-IV), though Type I (immediate IgE-mediated) and Type IV (delayed T-cell-mediated) reactions are the most common in clinical practice.

Type I (Immediate, IgE-mediated) Hypersensitivity

These reactions are classically what physicians think of as "true penicillin allergy." Type I reactions occur when a patient has drug-specific IgE antibodies which trigger an immediate allergic response upon penicillin exposure. Onset is usually within minutes to an hour after administration. Clinical manifestations range from urticaria (hives), flushing, angioedema (swelling of the face/lips), and bronchospasm, to anaphylaxis with hypotension and shock. Anaphylaxis to penicillin, while rare, can be life-threatening. Epidemiological data indicate that the incidence of anaphylactic reactions to penicillin is approximately 0.01% or less (in the order of 1-4 per 10,000 courses). The risk of fatal penicillin anaphylaxis is even rarer, estimated to be around 1 in 50,000 to 100,000 courses. Risk factors for IgE-mediated penicillin allergy include repeated high-dose exposures, parenteral (injectable) administration, and a history of atopy or other drug allergies. Notably, children may be less likely to experience severe IgE-mediated reactions than young adults–for example, epidemiologic studies have noted the highest incidence of serious penicillin anaphylaxis in adults aged 20-49 years, possibly because younger children have fewer cumulative exposures or differences in immune response. Nonetheless, immediate allergic reactions can occur at any age, and penicillin is a leading cause of anaphylaxis in children (7,8).

Type I reactions result from penicillin (a hapten) binding to proteins and forming antigenic complexes which IgE antibodies recognize. The classic allergenic determinant is the penicilloyl moiety (the "major determinant"), but minor determinants and side-chain antigenic determinants also contribute. Upon re-exposure, IgE on mast cells and basophils triggers the release of histamine and other mediators, causing the allergic symptoms. Importantly, IgE-mediated penicillin allergy tends to wane over time. IgE levels decline if the patient avoids penicillin for years, which is why many individuals "lose" their penicillin allergy with time. This transient nature underpins the concept of "impermanent allergy" in children, reinforcing the need to periodically re-evaluate PALs.

Type IV (Delayed, T Cell-mediated) Hypersensitivity

Delayed reactions to penicillins, mediated by T lymphocytes, account for many cutaneous "allergic" reactions which occur more than 1-2 hours after drug administration. These typically manifest as maculopapular rashes, which can arise days into a course of penicillin or even days after completion. The majority of benign amoxicillin or ampicillin rashes in children (often seen in the setting of viral infections) are considered delayed T-cell mediated exanthems. These rashes are generally self-limited and not life-threatening, though they lead to an allergy label if misinterpreted. More severe Type IV syndromes include contact dermatitis, drug fever, and certain severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), although SJS/TEN due to penicillins is exceedingly rare. Delayed hypersensitivity can also manifest as organ-specific reactions (e.g., interstitial nephritis from methicillin) or as part of multiorgan immune reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). These severe T-cell mediated reactions (SJS, TEN, DRESS) are medical emergencies and contraindications to future penicillin use. Fortunately, they are extremely uncommon in pediatrics (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

Other Hypersensitivity Types

Penicillins can, less commonly, cause Type II (cytotoxic antibody-mediated) and Type III (immune complex-mediated) reactions. An example of a Type II reaction is immune-mediated hemolytic anemia: high-dose penicillin can bind to red blood cell membranes and induce IgG antibodies which leads to red blood cell destruction. Type III reactions involve circulating immune complexes; an example is serum sickness-like syndrome, featuring fever, rash, arthralgias, and lymphadenopathy, which can occur days after starting therapy. These are relatively rare and usually associated with high-dose, prolonged penicillin therapy (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

In summary, penicillin hypersensitivity in children can range from acute IgE-mediated anaphylaxis to benign delayed rashes. When evaluating a child with a history of "penicillin allergy," it is critical to characterize the reaction's timing, symptoms, and severity. Many reported

"allergies" in children are actually non-allergic adverse reactions or viral rashes rather than true immune-mediated events. Understanding the type of hypersensitivity not only guides risk assessment (e.g., an isolated delayed rash vs. an immediate anaphylaxis history) but also informs the approach to allergy testing and future antibiotic choices.

Diagnostic Testing Strategies for Penicillin Allergy

Accurately diagnosing penicillin allergy in children is essential in order to distinguish true hypersensitivity from minor reactions or other causes. A comprehensive approach includes a careful clinical history, risk stratification, skin testing (when indicated), and drug provocation (challenge) testing as the gold standard. Recent guidelines also emphasize using validated non-irritating concentrations (NICs) for skin tests to improve specificity.

1. Clinical history and risk assessment: The first step is a detailed history of the reaction. Key details include: the specific drug and dose, timing of symptom onset relative to drug administration, the nature of the symptoms (e.g., hives vs. flat rash vs. respiratory distress), severity, need for hospitalization, and how the reaction was managed. One should also note how long ago the reaction occurred and whether the child has tolerated related antibiotics since then. Historical features help stratify the allergy label as high-risk or low-risk. For example, a child who developed immediate urticaria and wheezing within 30 minutes of a penicillin dose likely had an IgE-mediated reaction and is higher-risk. In contrast, a child who had only a mild rash one day into therapy, or whose reaction was many years ago in infancy, may be low-risk for true allergy. Several risk stratification tools have been developed for penicillin allergies. One example for adults is the Penicillin Allergy Network formula score, which assigns points based on time since reaction, features, and the need for treatment, to predict the likelihood of true allergy. A score <3 suggests low-risk (under 5% chance of true allergy). In pediatrics, simplified approaches often identify children with only benign rashes or remote histories as candidates for direct challenge without extensive skin testing (9). Ultimately, risk assessment guides whether to proceed with immediate challenge or perform skin testing first.

2. Skin prick and intradermal testing: Skin testing for penicillin allergy has been a standard diagnostic tool for decades. Traditional protocols use the major penicillin determinant (penicilloyl-polylysine) and a mixture of minor determinants, as well as the suspect penicillin (e.g., amoxicillin) itself, to increase sensitivity. In skin prick testing, a drop of reagent is placed on the skin, and the skin is superficially pricked; in intradermal testing, a small amount is injected into the dermis. A positive test is a wheal-and-flare reaction at the site, indicating the presence of drug-specific IgE on the patient's mast cells. Modern practice employs NICs of antibiotics for skin testing. NIC refers to the highest concentration of a drug which does not cause non-specific irritation. Using too high a concentration can cause false-positive skin irritation unrelated to IgE; thus, guidelines define appropriate dilutions for skin tests. For penicillins, for example, the recommended NIC for amoxicillin or ampicillin in skin testing is 20 mg/mL, and for benzylpenicillin (penicillin G), it is 10,000 IU/mL. Commercially available penicillin skin test kits (e.g., Pre-Pen, which contains the major determinant) are widely used in North America and Europe, but such reagents may be unavailable in low-resource settings. A positive skin test indicates penicillin-specific IgE and confirms an immediate allergy, and so the patient should avoid penicillin-class drugs. A negative skin test greatly reduces the likelihood of an IgE-mediated allergy, but it does not completely rule it out, especially if only the major determinant was tested and not the full spectrum of metabolites. In practice, when skin tests are negative, an oral challenge is usually performed to conclusively confirm tolerance.

3. Drug provocation test (oral challenge): The drug provocation test, also called an oral challenge, is the gold standard for diagnosing penicillin allergy. In a supervised medical setting, the patient is given a test dose of penicillin (typically an age-appropriate dose of amoxicillin) and observed for any reaction. A stepwise graded challenge may be used–for instance, administering 10% of the dose, then the remaining 90% if no reaction occurs after a set interval. If the patient tolerates the full dose without symptoms, penicillin allergy is effectively ruled out, and the label can be removed. If a reaction does occur, it is managed, and the allergy is confirmed. Drug challenges carry a small risk of inducing an allergic reaction, so they are generally reserved for patients deemed unlikely to react (e.g., those with negative skin tests or very low-risk histories). In children, direct oral challenges without preceding skin tests have been successfully employed for low-risk cases, given the relatively low likelihood of serious reactions (10,11). Several studies have demonstrated the safety of direct amoxicillin challenges in children who have only vague rash histories. For higher-risk histories or where skin testing is available, a negative skin test before challenge adds an extra layer of safety.

4. *In vitro* testing: Blood tests play a more limited role. Serum specific IgE assays for penicillin (radioallergosorbent

tests or newer fluorescence immunoassays) are available, but they have suboptimal sensitivity, often failing to detect many true allergies, and they only address IgE-mediated allergy. A negative IgE test does not rule out penicillin allergy, and a positive test must be interpreted with caution due to false positives. More advanced tests, such as the basophil activation test (BAT), have shown promise in research settings, where a patient's basophils are exposed to the drug *in vitro* and activation markers are measured. BAT can help detect IgE-mediated allergy and may be useful for cases where skin testing is inconclusive or contraindicated. However, BAT and other T-cell assays (for delayed allergy, such as the lymphocyte transformation test or enzyme-linked immunospot for interferon-gamma) are not routinely available in clinical practice and remain research tools.

5. Special considerations: If a patient has a history suggestive of a severe non-IgE reaction (e.g., SJS/TEN or DRESS from penicillin), neither skin testing nor challenge should be carried out due to the risk and the label in these cases should generally be considered permanent, and alternative antibiotics should be used. Desensitization is another procedure used in certain scenarios. If a patient has a confirmed penicillin allergy but absolutely needs a penicillin (for example, a child with neurosyphilis or endocarditis with no good alternatives), an allergist can perform a temporary desensitization. This involves administering gradually increasing doses of the antibiotic under close monitoring, which can induce a temporary state of tolerance. Desensitization carries significant risk and is only performed in hospital settings; once the antibiotic course is finished, the patient will revert to being allergic.

A structured approach to penicillin allergy testing in children involves: (a) identifying those at such low-risk that they can undergo direct oral challenge, (b) performing skin prick/intradermal tests for those with moderate risk or uncertain history (using appropriate NICs to avoid false positives), and (c) confirmatory oral challenge for those with negative or equivocal skin tests (Table I).

When implemented, this approach can safely clarify allergy status in the majority of children and allow those without true allergy to safely receive penicillins again.

Cross-reactivity of Penicillins with Other β-Lactams

A common concern is whether a child with penicillin allergy can safely take other β-lactam antibiotics, such as cephalosporins, carbapenems, or monobactams. Early studies from decades ago suggested up to 8-10% cross-reactivity between penicillins and cephalosporins, leading to a cautious approach where cephalosporins were often avoided in penicillin-allergic patients. However, more recent research has clarified that cross-reactivity risk is generally much lower and is largely related to similarities in chemical structure (specifically, the R1 side chain) rather than the β-lactam ring itself (1).

Penicillins: Within the penicillin class, cross-reactivity is effectively assumed if a patient is truly allergic to one penicillin (e.g., amoxicillin), and so they are usually presumed to be allergic to all penicillin-type antibiotics (ampicillin,

Table I. Risk-stratified diagnostic approach for evaluating pediatric penicillin allergy

Risk category	Typical history features	Recommended evaluation pathway	Outcome
Low-risk	• Benign maculopapular rash only • No mucosal involvement • >12 months since reaction • No features of anaphylaxis	Direct oral amoxicillin challenge (single-or two-step) under supervision	If tolerated → remove allergy label; resume penicillins
Intermediate risk	• Urticaria without respiratory compromise • Reaction within first hour of dose • Unclear medication history	Skin prick±intradermal testing using non-irritating concentrations, followed by oral challenge if negative	Negative tests → safe use; positive → avoid penicillins
High risk	• Anaphylaxis signs: wheeze, angioedema, hypotension • Hospitalization for reaction • Immediate onset of symptoms within minutes	Skin testing plus graded oral challenge in specialist setting; consider avoidance until reviewed by allergist	Confirmed IgE-mediated allergy → avoid penicillins; consider desensitization if no alternative available
Severe cutaneous or organ involvement	• Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • DRESS • Serum sickness-like syndrome	Do not perform skin test or oral challenge; permanent avoidance recommended	Avoid all penicillins; document clearly in the patient's record

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

penicillin G, piperacillin, etc.) due to the shared core penicilloyl determinant. There are exceptions; for instance, some patients have selective allergies to amoxicillin or ampicillin (often manifesting as a delayed maculopapular rash), yet they can tolerate penicillin G. These cases are often due to unique side-chain sensitivities. Overall though, a positive skin test to one penicillin indicates avoidance of all penicillins is prudent. The good news is that 80-90% of those labeled allergic to penicillin are not actually allergic and they can be de-labeled, regaining access to all penicillins.

Cephalosporins: Cephalosporins share the β-lactam ring with penicillins but have a different adjacent ring (dihydrothiazine) and distinct side chains. The historical teaching of a 10% cross-reactivity between penicillins and cephalosporins is an overestimate. The overall risk that a penicillin-allergic patient will have an allergic reaction to a cephalosporin is around 1-3% or even lower. A 2012 literature review by Campagna et al. (12) found the cross-reactivity rate to be approximately 2% between penicillins and first-generation cephalosporins, and negligible for later-generation cephalosporins. Critical to this risk is whether the cephalosporin shares a similar side chain to the culprit penicillin. Immunologic cross-reactivity occurs when the immune system recognizes chemical similarities. For example, amoxicillin and certain early cephalosporins (such as cefadroxil, cefatrizine, and cephalexin) share an identical R1 side chain; hence, an individual allergic to amoxicillin is at higher risk of reacting to those cephalosporins. European studies have documented cross-reactivity rates as high as 30-40% between amino-penicillins (amoxicillin, ampicillin) and amino-cephalosporins (such as cefaclor, cephalexin) which have similar side chains. On the other hand, cephalosporins with dissimilar side chains may be tolerated. For instance, cefazolin (a first-generation cephalosporin often used for surgical prophylaxis) has a unique side chain and exhibits essentially no cross-reactivity with penicillins, and so it can be safely used in most penicillin-allergic patients (13). Clinically, the approach is to avoid cephalosporins which share identical or very similar side chains with the culprit penicillin. Allergy specialists have developed side-chain cross-reactivity charts in order to guide safe antibiotic choices. If a penicillin-allergic child needs a cephalosporin, one strategy is to choose a cephalosporin from a later-generation with a dissimilar structure or perform cephalosporin skin testing if the allergy history was severe. It is worth noting that most data on cross-reactivity pertain to IgE-mediated (immediate) allergies; much less is known about cross-reactivity in delayed T-cell mediated reactions. In severe delayed reactions such as SJS/TEN, some experts recommend avoiding all structurally similar β-lactams entirely due to the life-threatening nature of recurrence.

Carbapenems: Carbapenems (e.g., meropenem, imipenem) also contain a β-lactam ring and initially were thought to pose a high cross-allergy risk in penicillin-allergic patients. Newer studies have dispelled this to a large extent. Reported cross-reactivity between penicillins and carbapenems is under 1% in most recent series. For example, a 2014 multicenter study found that >98% of penicillin skin test-positive patients tolerated meropenem. Therefore, the vast majority of penicillin-allergic individuals can receive carbapenems without incident, especially if their penicillin allergy is not recent or severe. Skin testing protocols for carbapenems have been proposed, and some allergists will perform a test dose or graded challenge to a carbapenem in a penicillin-allergic patient if use is necessary. Overall, current evidence supports that cross-reactivity is low, and carbapenems can be considered with caution or testing, rather than automatically avoided.

Monobactams: Aztreonam is the sole monobactam antibiotic in common use and has a monocyclic β-lactam ring distinct from penicillins. Aztreonam has virtually no cross-reactivity with penicillin allergy at the IgE level. However, an important exception is its side chain, which is identical to that of ceftazidime (a third-generation cephalosporin). Patients allergic to ceftazidime may react to aztreonam due to this shared side chain epitope, but penicillin-allergic patients without ceftazidime allergy are not at an increased risk of reacting to aztreonam. Thus, aztreonam is often a safe alternative in a penicillin-allergic patient if a gram-negative β-lactam is needed (assuming no ceftazidime allergy).

In summary, the fear of cross-reactivity has historically led to overly broad restrictions of β-lactams in penicillin-allergic patients. We now appreciate that, especially for non-critical allergies, many β-lactams can be used safely with appropriate caution. For pediatricians, this means that an allergy to penicillin does not necessarily preclude using all cephalosporins or carbapenems. A careful review of the allergy and possibly consultation with an allergist can identify safe options. For mild penicillin allergies, a cephalosporin with a dissimilar side chain (or even a test dose in a controlled setting) can be reasonable. Avoidance of all β-lactams should be reserved for those with severe, high-risk allergies until they can be formally evaluated. This nuanced understanding helps prevent the unnecessary use

of second-line antibiotics when a safe β-lactam alternative might exist.

Clinical Consequences of Mislabeling Penicillin Allergy

Labeling a child as penicillin-allergic when they are not truly allergic carries significant clinical repercussions. Avoidance of first-line therapy: penicillins (and other β-lactams) are often the preferred treatment for many pediatric infections due to their effectiveness and narrow spectrum. If a child is labeled as allergic, clinicians must resort to second-line or broad-spectrum antibiotics. For example, instead of amoxicillin for an acute otitis media, a "penicillin-allergic" child might receive a macrolide such as azithromycin (which may be less effective against *Streptococcus pneumoniae*). Instead of penicillin for streptococcal pharyngitis, they might receive clindamycin or a cephalosporin. In hospitalized patients, PALs lead to the use of fluoroquinolones, vancomycin, or extended-spectrum agents in place of β-lactams. These substitutes can be suboptimal as they can be broader-spectrum than necessary, potentially more toxic, and sometimes inferior in efficacy. A well-documented example is surgical prophylaxis: patients with a PAL often receive vancomycin or clindamycin instead of a first-generation cephalosporin such as cefazolin, and this has been associated with higher rates of postoperative surgical site infection. In a cohort of over 8,000 surgical patients, those labeled penicillin-allergic had a 50% higher risk of surgical site infection, likely due to less effective prophylactic antibiotics (e.g., vancomycin) being used in place of cefazolin. Mislabeling thus directly impacts patient outcomes.

Higher risk of antibiotic resistance and infections: Perhaps the most concerning consequence is the increased risk of developing infections with resistant organisms. PALs have been linked to greater incidences of *Clostridioides difficile (C. difficile)* infection and methicillin-resistant *Staphylococcus aureus* (MRSA), among others. A landmark population-based study published in 2018 (UK) followed over 300,000 patients and found that those with a documented penicillin allergy had a 69% higher incidence of MRSA and a 26% higher incidence of *C. difficile* infection compared to matched patients without a PAL (14). The primary driver was the use of broader-spectrum, non-penicillin antibiotics in the allergy-labeled group–for instance, an increased use of fluoroquinolones and clindamycin, which are known risk factors for *C. difficile*, and the use of vancomycin or sulfonamides which exert selective pressure for MRSA. The U.S. Centers for Disease Control and Prevention similarly reported significantly higher *C. difficile* rates among hospitalized patients labeled as penicillin-allergic. Thus, carrying a PAL can tangibly harm patients by predisposing them to difficult infections. From a public health perspective, this contributes to the broader problem of antimicrobial resistance. An allergy label leads to more use of broad-spectrum agents, which in turn fosters resistant bacteria– a ripple effect caused by an inaccurate label.

Increased healthcare utilization and cost: Multiple studies have demonstrated that PALs are associated with longer hospital stays and higher healthcare costs. Sousa-Pinto et al. (15) analyzed hospital records and found that patients labeled as penicillin-allergic had significantly longer admissions (on average) and greater hospital expenses than similar patients without such a label, after eliminating confounders. Another study by Mattingly et al. (16) showed that antibiotic costs were higher for penicillin-allergic inpatients, since alternative drugs such as daptomycin or linezolid (for MRSA) and aztreonam (for gram-negatives) are far more expensive than standard β-lactams. In children, if an alternative antibiotic is less effective, it might lead to treatment failures or complications which require additional clinical visits or hospitalizations. All of these add to the healthcare burden (16).

Impact on patient experience and outcomes: Children labeled as penicillin-allergic often face more complex medication regimens. They may receive intravenous antibiotics instead of oral ones (e.g., IV vancomycin for an infection which could have been treated with oral amoxicillin), which can be painful, require hospital stays, and disrupt family life. Broad-spectrum antibiotics such as quinolones can have more side effects (e.g., gastrointestinal upset, musculoskeletal effects) which children must endure unnecessarily. There is also a psychological aspect: families might worry excessively about medication safety due to the label, potentially leading to avoidance of necessary medications or vaccine components (though penicillin allergy does not equate to vaccine allergy, some may misunderstand the risk).

Special cases–rheumatic fever prophylaxis: In some parts of the world, notably low-resource settings with higher rates of rheumatic fever, penicillin (benzathine penicillin G injections) is critical for prophylaxis against recurrent *Streptococcus* infections. If a child is labeled as being allergic, doctors may avoid penicillin prophylaxis, potentially leading to recurrent rheumatic fever and progression of rheumatic heart disease. Unfortunately, false PALs can deprive patients of this life-saving, inexpensive

preventive therapy and necessitate the use of much less established alternatives.

In summary, a PAL is not benign as it can set off a "cascade of consequences." Overdiagnosis negatively impacts individual patient care (through use of suboptimal antibiotics and increased side effects) and contributes to larger issues of antimicrobial resistance and healthcare costs. Recognizing these consequences has been a major driver in improving penicillin allergy evaluation and de-labeling efforts, which we discuss next.

Education of both families and clinicians plays a key role in preventing overdiagnosis. Many reported allergies stem from misinterpretations of benign rashes or viral symptoms, and counseling families about true vs. false allergies reduces avoidance of first-line therapies. Pediatricians who receive focused training in allergy history-taking and direct oral challenge protocols report higher de-labeling success rates.

De-labeling and Antibiotic Stewardship Programs

Given the high frequency of false PALs and their deleterious effects, healthcare systems are increasingly implementing penicillin "de-labeling" programs. De-labeling refers to the process of identifying patients who are not truly allergic and removing the allergy label from their medical record, thereby restoring penicillins as a treatment option. This process aligns closely with antibiotic stewardship goals, as it enables the use of first-line narrow spectrum agents and reduces unnecessary broad-spectrum antibiotic use.

Antibiotic stewardship guidelines: The Infectious Diseases Society of America stewardship guidelines highlight allergy assessment as a key component of optimizing antibiotic use. Hospitals are encouraged to implement protocols whereby patients with reported penicillin allergy, especially those needing antibiotics, are evaluated by allergy or infectious disease specialists. By confirming or refuting the allergy, clinicians can avoid second-line therapies when penicillin (or a cephalosporin) would be more appropriate (17). Many institutions have created penicillin allergy assessment pathways (PAAPs) as part of their routine care, sometimes led by pharmacists, infectious disease physicians, or allergists. For example, some stewardship programs use questionnaires in order to identify low-risk allergy histories and then perform direct oral amoxicillin challenges on the ward or in clinic. Others have developed rapid de-labeling protocols in postoperative patients, intensive care units, or general pediatric wards in order to ensure that patients receive optimal prophylaxis or therapy during their hospital stay (18).

Outcomes of penicillin allergy testing and de-labeling: The benefits of penicillin allergy testing (skin tests and/or challenges) in hospitalized patients are well documented. A 2017 systematic review and meta-analysis by Sacco et al. (19) looked at outcomes following inpatient penicillin allergy. They found that after a negative penicillin allergy evaluation, 80-100% of patients went on to receive penicillin or cephalosporin safely, indicating successful de-labeling. Importantly, such testing was associated with reduced lengths of hospital stay in some studies, fewer readmissions, and no serious adverse reactions from the testing itself in the vast majority of cases (19). Another analysis noted that penicillin allergy evaluation led to changes in antibiotic therapy in over 90% of tested patients, commonly de-escalating to a β-lactam, with resultant cost savings (20). In pediatric patients, a recent systematic review (2021) found that penicillin de-labeling programs in children increased the subsequent use of penicillins for infections and did not lead to increased adverse outcomes (21). Essentially, once cleared, children can reap the benefits of effective β-lactam therapy without harm.

Outpatient de-labeling and special programs: In addition to hospital-based programs, outpatient penicillin allergy clinics have emerged. Blumenthal et al. (22) described a risk-based outpatient pathway in which low-risk patients (e.g., benign rash history) went straight to amoxicillin challenge, while moderate-risk cases underwent skin testing first; this approach was safe and efficient in removing allergy labels. Some centers have even piloted penicillin allergy testing in primary care offices or emergency departments for children, which could provide opportunities when children present for unrelated issues. Education is key, both healthcare providers and families need awareness that penicillin allergies can and should be reevaluated. A notable commentary titled "de-labelling penicillin allergy is not rocket science" Turner (23) underscored that with proper protocols, general pediatricians can identify candidates for de-labeling safely. That said, having allergy specialist support is valuable for higher-risk cases.

The Allergy Antibiotics and Microbial Resistance trial: One of the most significant ongoing efforts to rigorously evaluate penicillin allergy de-labeling is the Allergy Antibiotics and Microbial Resistance (ALABAMA) trial. ALABAMA is a multicenter, parallel-arm randomized controlled trial in the UK designed to measure the impact of a PAAP in primary care. Adults with penicillin allergy records are randomized to either undergo a comprehensive allergy evaluation (including history, skin testing, and/

or direct challenge as appropriate) or to usual care (no testing). The trial's outcomes include the proportion of patients successfully de-labeled, changes in antibiotic prescribing patterns, incidences of infections such as MRSA/*C. difficile*, and cost-effectiveness. While focused on adults, the trial's results (expected in the next couple of years) will provide high-quality evidence on the benefits of penicillin allergy de-labeling on a large scale. The inclusion of "microbial resistance" in its title highlights that a major hypothesis is that removing incorrect allergy labels will lead to more penicillin use and consequently lower rates of resistant infections and overall broad-spectrum antibiotic consumption. Early phases of this work have already shown that integrating allergy assessments into primary care is feasible by using electronic health record prompts and pharmacy support. If ALABAMA demonstrates significant benefits, it could pave the way for broader policy changes encouraging routine penicillin allergy verification as part of standard care in the national health service and beyond (24).

Other Trials and Studies: Another noteworthy initiative is the U.S. based Penicillin Allergy Delabeling Program by the Pediatric Asthma and Allergy community, which tested direct amoxicillin challenges in low-risk children in a community setting with success rates >95% (10). This underscores a growing trend to undo the legacy of penicillin overdiagnosis.

Penicillin allergy de-labeling and stewardship programs have emerged as win-win interventions. They improve patient care by enabling the use of optimal antibiotics and concurrently help combat antimicrobial resistance. The key components for success include education, a standardized pathway (risk assessment, skin testing, challenge), and support from multidisciplinary teams. Even in the absence of an allergist, many centers have shown that trained hospitalists or pharmacists can implement screening and direct challenge protocols safely for low-risk cases. Moving forward, expanding these programs, including to outpatient and resource-limited settings, will be crucial to fully address the penicillin allergy overdiagnosis problem.

Practice Gaps in Low-resource Settings (Indian/Asian Context)

While penicillin allergy de-labeling has gained traction in many high-income countries, significant challenges remain in low-resource settings such as parts of Asia. The epidemiology of PALs differs somewhat in these regions. A recent review on penicillin allergy in India and Sri Lanka noted that the reported prevalence of PALs in those populations (around 1-4% in secondary care) is lower than the 10-20% reported in Western countries. This may be due to under-recognition or under-reporting; however, even a "small" percentage in South Asia translates to millions of individuals because of the large population base. Moreover, once labeled, the impact on care may be even more pronounced given the reliance on penicillin for endemic infections (9).

Limited access to allergy evaluation: Low-resource settings often lack trained allergists and the infrastructure for formal allergy testing. Allergy/immunology as a specialty is still developing in countries such as India. There is a "huge unmet need for allergy specialists" in these regions. For instance, India, with over a billion people, has only a handful of centers which routinely perform drug allergy testing. Consequently, most PALs are assigned (and maintained) based solely on history without verification. The unavailability of standardized skin test reagents is a major barrier. The penicillin skin test kits (major/minor determinants) used in Western countries are often not available or even licensed in South Asian markets. Physicians might attempt ad-hoc testing with the drug itself, but without validated NICs and proper technique, this can yield false positives or even provoke reactions (9).

Non-standard practices: In the absence of guidelines and trained personnel, some practitioners engage in "pre-emptive, non-standardized and unregulated skin testing by untrained operators." For example, a common practice in some Indian hospitals is to administer a small test dose of penicillin (either intradermal or subcutaneous) before giving the full dose, as a crude allergy check. This practice is not standardized, and so concentrations and interpretation vary widely, and it may itself sensitize patients or give misleading results. Without clear protocols, a patient can be mislabeled as allergic due to an irritant reaction from an overly concentrated test dose. The Biswas et al. (25) review highlighted the need for establishing validated NICs and protocols tailored to the local setting in order to avoid false diagnoses. Additionally, in many Asian countries, drug allergy history is not systematically documented; patients may not even be aware of the specifics of a past reaction. This makes subsequent evaluation very difficult (9).

Antimicrobial stewardship challenges: The implications of a PAL in low-resource settings can be especially problematic for diseases such as rheumatic fever, rheumatic heart disease, and syphilis, which are managed with long-acting penicillin injections. As noted, if someone who has been labeled as allergic foregoes penicillin prophylaxis, they risk recurrent disease.

Unfortunately, alternative prophylactic regimens (such as sulfadiazine for rheumatic fever) are less effective. Another example is pediatric sepsis management: in settings where third-generation cephalosporins (e.g., ceftriaxone) are standard for severe infections, a penicillin/cephalosporin allergy label might lead to the use of chloramphenicol or fluoroquinolones (older or more toxic drugs) due to the lack of availability of newer alternatives such as carbapenems. This can adversely affect outcomes.

The weak health system framework in some areas means that there is limited oversight on how drug allergies are recorded or acted upon. Patients might self-report an allergy and have it accepted at face value without further inquiry. Conversely, true allergies may be missed due to a lack of awareness, leading to serious reactions. Global pushes for antibiotic stewardship, such as the World Health Organization's Access, Watch, Reserve (AWaRe) classification to guide antibiotic use, must take these local limitations into account (World Health Organization website, "The WHO AWaRe antibiotic book – Infographics," accessed June 25th, 2025). The 2025 review by Moitra et al. (9) advocates for a "pragmatic, cautious and staged approach" to penicillin allergy mitigation in India and Sri Lanka. This could include measures such as: focusing on identifying low-risk patients who could safely receive penicillin under observation (direct oral challenge), improving physician training in allergy history-taking, lobbying for access to penicillin skin testing reagents, and creating local guidelines for allergy management which align with international best practices but are feasible in resource-limited contexts (9).

Awareness and education: There is also a gap in public and provider awareness. In many Asian countries, the concept of drug allergy is not well understood by patients, some of whom may not differentiate between an adverse effect and an allergy. Educational initiatives are needed to inform healthcare workers about the high false-positive rates of penicillin allergy histories and to encourage referrals or cautious test doses under proper conditions rather than blanket avoidance. Encouragingly, some large tertiary hospitals in India (e.g., in Vellore, Chandigarh) have started antibiotic allergy testing clinics as part of research collaborations. Regional allergy societies (such as the Allergy and Immunology Society of Sri Lanka and the Indian College of Allergy, Asthma and Applied Immunology) are now discussing penicillin allergy in their meetings, indicating a growing recognition (9).

In summary, low-resource settings face unique challenges such as fewer specialists, a lack of testing reagents, and often a greater burden of infections where penicillin is vital. Penicillin allergy overdiagnosis is a global issue but it needs local solutions. Bridging this gap will require international support in order to improve access to diagnostics, local guideline development, and the integration of penicillin allergy assessments into broader antimicrobial resistance strategies. Without addressing penicillin allergy mislabeling, efforts to optimize antibiotic use in these countries will be incomplete.

Conclusion

Penicillin allergy in children is often overdiagnosed, with the vast majority of pediatric patients labeled as "allergic" ultimately found to tolerate penicillins upon proper evaluation. Rethinking our approach to pediatric penicillin allergy is imperative–both to improve individual patient care and to advance public health goals such as antimicrobial stewardship. Clinicians should maintain a healthy skepticism regarding historical penicillin allergy reports and consider formal allergy assessments for children, especially when β-lactam antibiotics are the best therapy. By understanding the immunologic basis of reactions (Types I-IV) and employing available diagnostic tools, such as careful history, skin testing with NICs, and drug challenges, we can accurately identify the rare truly allergic child and, just as importantly, de-label the many who are not allergic. The benefits of penicillin allergy de-labeling are clear: children gain access to optimal antibiotic therapy, experience fewer side effects and complications, and healthcare systems see a reduced emergence of resistant infections and lower costs. Programs around the world are demonstrating that penicillin de-labeling is feasible and safe, and ongoing research, such as the ALABAMA trial, will further quantify its impact.

Penicillin, a drug which has saved countless lives, should not be needlessly avoided due to an unwarranted allergy label. For pediatricians, an important practice point is to revisit allergy histories periodically; a child labeled in infancy may not be allergic a few years later. Incorporating penicillin allergy assessments into routine pediatric care and stewardship protocols will ensure that our young patients receive the most effective treatments. In low-resource settings, tackling penicillin allergy overdiagnosis will require innovative strategies and support in order to overcome resource gaps. Across all contexts, the message is consistent: it is time to replace cautionary avoidance with evidence-based evaluation. By doing so, we can safely "reclaim" penicillin for the majority of children who need it, improving health outcomes and preserving the utility of this invaluable class of antibiotics.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.V., S.M., P.B., V.S.P., S.T.K., Concept: I.V., S.M., P.B., V.S.P., S.T.K., Design: I.V., S.M., P.B., V.S.P., S.T.K., Data Collection or Processing: I.V., S.M., P.B., V.S.P., S.T.K., Analysis or Interpretation: I.V., S.M., P.B., V.S.P., S.T.K., Literature Search: I.V., S.M., P.B., V.S.P., S.T.K., Writing: I.V., S.M., P.B., V.S.P., S.T.K.

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Original Article

Predictive Role of the Prognostic Nutritional Index for the Prognosis of Pediatric High-grade Glioma Patients

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ABSTRACT

Aim: Pediatric high-grade glioma (pHGG) is a highly aggressive malignancy with poor prognosis. The role of nutritional status in pHGG prognosis is understudied. This study examined the prognostic value of the prognostic nutritional index (PNI) in pHGG patients.

Materials and Methods: This retrospective study analyzed data from 67 pediatric pHGG patients admitted to the Department of Neurosurgery at The 904th Hospital of the PLA between October 1st, 2016, and December 1st, 2022. The PNI was calculated at three time points: at admission, post-radiotherapy, and at 12 months. Clinical data including age, gender, Lansky performance status score, World Health Organization glioma grade, treatment, overall survival (OS), and time to progression were collected. Multivariate Cox regression analysis and Kaplan-Meier survival analysis were used to assess the correlation between PNI and the clinical outcomes.

Results: The median survival time was 15.3 months. PNI was highest post-radiotherapy and lowest at 12 months. Higher PNI scores at admission and at 12 months were associated with longer progression-free and OS. Multivariate analysis showed that Grade 3 glioma, isocitrate dehydrogenase mutation, and high PNI at admission were associated with delayed tumor progression and longer OS, while Grade 4 glioma and H3K27M mutation were associated with poorer outcomes.

Conclusion: The PNI is a valuable predictor of prognosis in pHGG patients. Higher PNI scores at admission and at 12 months are associated with better clinical outcomes. Nutritional support during the disease course may improve prognosis in pHGG patients.

Keywords: Prognostic nutritional index, pediatric, high-grade glioma, prognosis, survival

Introduction

Pediatric high-grade glioma (pHGG) is a highly aggressive malignant tumor of the central nervous system, predominantly affecting children and adolescents. While high-grade glioma (HGG) also occur in adults, pediatric cases differ substantially from adult gliomas in their biological characteristics, genetic mutations, and treatment responses, resulting in notably poorer outcomes in children and younger patients (1). The prognosis for pHGG remains grim, with an estimated 3-year event-free survival rate of only 10% and an overall survival rate of 20% in this timeframe's subtypes, with diffuse intrinsic pontine glioma (DIPG) presenting the worst prognosis: the average survival for patients with DIPG is less than a year, typically between 8 and 11 months, with only about 10% of patients surviving beyond two years and less than 2% reaching the five-year mark (2,3).

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The standard approaches for pHGG, namely surgical resection, radiotherapy, and chemotherapy, have limited efficacy in significantly improving long-term survival rates. Children with pHGG often present with early symptoms related to tumor-induced pressure, such as movement difficulties, strabismus, swallowing issues, and loss of appetite, which complicate daily care and the provision of adequate nutritional support. As the disease progresses, these often intensify, leading to a greater risk of malnutrition which can potentially impact patient outcomes (4,5). Despite the critical nature of these issues, the relationship between nutritional status and prognosis in pHGG patients remains understudied.

Thus, this study sought to explore this potential correlation through a detailed retrospective analysis, focusing on how nutritional status at various points during treatment might correlate with clinical outcomes in pediatric patients with HGGs.

Materials and Methods

Patients

This study included a retrospective analysis of pHGG patients admitted to the Department of Neurosurgery at The 904th Hospital of the PLA from October 1st, 2016 to December 1st, 2022. Ethical approval was not needed as it was a retrospective study without additional interventions or new data collection. Informed consent was obtained from the guardians of all participating children. This research was performed in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows: (1) aged between 1 and 18 years; (2) no gender restriction; (3) a diagnosis of pHGG [classified as World Health Organization (WHO) astrocytomas Grades III or IV) based on biopsy results; (4) the availability of relevant clinical data for analysis; and (5) a history of radiotherapy. The exclusion criteria included: (1) a lack of access to the required clinical data for the study; and (2) family refusal for follow-up or the provision of invalid contact information.

Research Content and Methods

The primary objective of this study was to assess the nutritional status of patients using the prognostic nutritional index (PNI) and, in turn, to evaluate any correlation between nutritional status and prognosis in pHGG patients. The peripheral blood albumin level and lymphocyte counts at three stages: at admission (prior to biopsy); within one week after the end of radiotherapy; and at 12 months were used to calculate the PNI in order to assess the patient's nutritional status.

The secondary objective of this study was to analyze the following clinical data with respect to the patients' outcome: age, gender, Lansky performance status (LPS) score, WHO grade, treatment, time to progression [from diagnosis, verified by T2 phase magnetic resonance imaging (MRI) scan and neurological deficiency] and gene mutation.

The formula for calculating PNI was as follows: PNI=10 × serum albumin (g/L) + 0.005 × peripheral blood lymphocyte count (/mm^3).

Statistical Analysis

Statistical analysis was performed using R 4.1.1. Multivariate Cox regression analyses were conducted in order to identify factors influencing treatment outcomes and prognosis in pHGG patients. OS was measured and compared by Kaplan-Meier (KM) survival analysis. The cut-off value for PNI was determined based on previous studies. A cut-off value of 40 was selected to categorize patients into high PNI (PNI≥40) and low PNI (PNI<40) groups which had been used in previous studies for PNI (6-8).

Results

Clinical Characteristics of Patients

A total of 86 patients admitted to The 904th Hospital of the PLA between October 1st, 2016 and December 1st, 2022 were screened (Figure 1). Among them, 14 patients had incomplete records for the primary endpoints, and the families of 5 patients declined to participate in the follow-up. Finally, this study retrospectively analyzed 67 pediatric patients, all of whom were diagnosed with pHGG by MRI scan and their pathological results from biopsies. Table I presents the clinical characteristics of these 67 patients, with a mean age of 10.1±5.2 years, with 47.8% of them being female. Regarding the LPS scores, 3 patients scored 40, 14 patients scored 50, 17 patients scored 60, 25 patients scored 70, and 8 patients scored 80. All patients received radiotherapy; 12 patients underwent chemotherapy, and 5 received conventional treatment. According to the WHO 2021 classification system for brain tumors, 27 patients were classified as Grade 3, and 40 patients were classified as Grade 4. Regarding genetic mutations, 15 patients had an isocitrate dehydrogenase (IDH) mutation, 57 patients had a H3K27M mutation, 4 patients had a BRAF V600E mutation, and all patients had a p53 mutation.

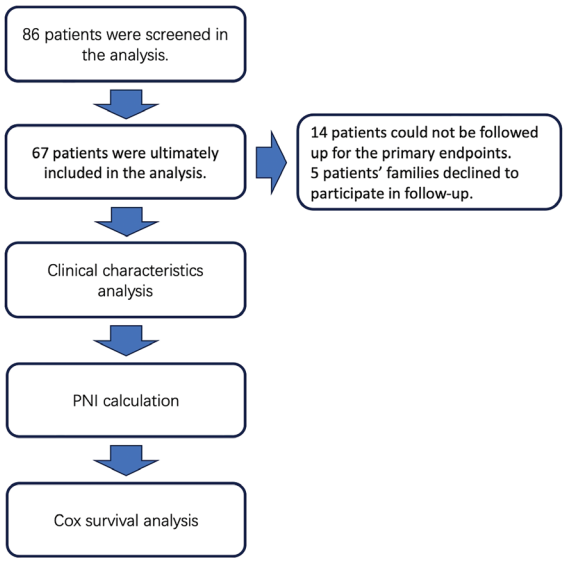

Figure 1. This flowchart illustrates the patient screening and analysis process in this clinical study. A total of 86 patients were initially screened for inclusion in this analysis. Out of these, 67 patients were ultimately included in this analysis. Fourteen patients could not be followed up for the primary endpoints, and 5 patients' families declined to participate in the follow-up. The analysis began with an assessment of the clinical characteristics of the included patients. Next, a prognostic nutritional index calculation was conducted. Finally, Cox survival analysis was performed in order to evaluate survival outcomes

Survival Analysis

According to the KM survival curve, the median survival time was 15.3 months (Figure 2). Median progression time was 14.4 months (Table II). Thirty-eight patients survived over 12 months. We used multivariate Cox survival analysis in order to assess the relationships between the patients' clinical characteristics, tumor progression time and their survival time. The results indicated that age, sex, LPS score, chemotherapy or conventional treatment, BRAF V600E mutation, and the PNI value after radiotherapy had no significant association with tumor progression time after radiotherapy (Figure 3A). However, those patients with Grade 3 glioma, *IDH* mutation, and high PNI at admission experienced delayed tumor progression. In contrast, Grade 4 glioma and H3K27M mutation were associated with faster progression. Regarding OS, there was no significant correlation between age, sex, chemotherapy, conventional treatment, BRAF V600E mutation, and PNI after radiotherapy with OS (Figure 3B). However, higher LPS scores, Grade 3 glioma, IDH mutation, high PNI at admission and at 12 months, and longer progression times were associated with longer OS. Conversely, Grade 4 glioma and H3K27M mutation were associated with shorter survival times.

Table I. Clinical characteristics of patients

N	67
Age (y)	10.1±5.2
Gender (female)	32 (47.8%)
LPS	
40	3 (4.5%)
50	14 (20.9%)
60	17 (25.4%)
70	25 (37.3%)
80	8 (11.9%)
Treatment	
Radiotherapy	67 (100%)
Chemotherapy	12 (17.9%)
Traditional therapy	5 (7.5%)
WHO grade	
Grade 3	27 (40.3%)
Grade 4	40 (59.7%)
Gene mutation	
IDH mut	15 (22.4%)
H3K27M	57 (85.1%)
BRAF V600E	4 (6.0%)
p53	67 (100%)

Numeric variables were expressed in mean ± standard deviation or median (minimum-maximum), and typed variables were expressed in n (n%)
LPS: Lansky performance status, WHO: World Health Organization, IDH: Isocitrate dehydrogenase

PNI Changes for Outcome

We attempted to deepen our understanding of how different levels of the PNI relate to patient prognosis by analyzing OS outcomes. By examining PNI values at three key time points, at admission, at one week post-radiotherapy, and at 12 months, we observed that PNI was highest shortly after radiotherapy but decreased significantly by the 12-month mark, showing marked differences compared to admission and post-radiotherapy levels (Figure 4A).

To further clarify the role of PNI in prognosis, we selected a PNI cut-off of 40, categorizing patients with a PNI ≥40 as having a high PNI and those with a PNI <40 as having a low PNI. We then conducted a KM survival analysis in order to compare OS between these two groups. Our findings revealed that an early high PNI was associated with a significantly better prognosis, suggesting that nutritional

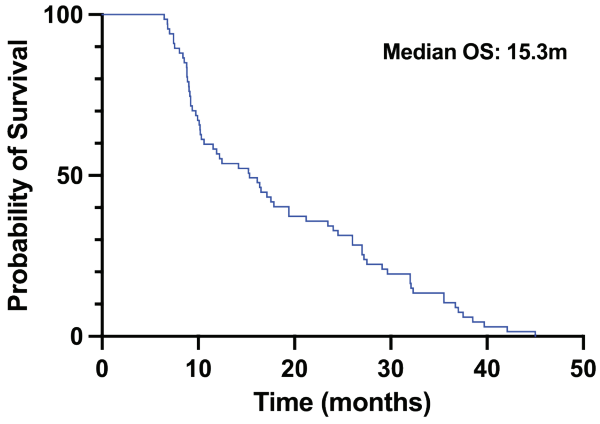

Figure 2. The Kaplan-Meier survival curve for all patients, the median survival was 15.3 months
OS: Overall survival

Table II. Patients outcome	
Progression time (m)	14.4 (2.1-32.3)
Survival at 12 months after onset	38 (56.7%)
Overall survival (m)	15.3 (6.5-45.0)
PNI	
PNI at admission	42.1±5.7
PNI after radiotherapy	45.1±6.1
PNI at 12 months (n=38)	40.1±3.4
Numeric variables were expressed in mean ± standard deviation or median (minimum-maximum), and typed variables were expressed in n (n%) PNI: Prognostic nutritional index	

status at the outset may play a critical role in patient survival (Figure 4B). This positive association, however, was less pronounced immediately following radiotherapy, possibly reflecting transient treatment effects on nutritional status and immune response (Figure 4C).

In those patients who survived beyond 12 months, a high PNI was again linked to longer OS, reinforcing the importance of sustained nutritional and immune health in improving long-term survival (Figure 4D). Collectively, these findings indicate that a high PNI, particularly in the early and later stages (12 months), may serve as a useful predictor of overall survival, highlighting the value of monitoring and supporting nutritional health as part of long-term management in those patients with HGGs.

According to the results of this study, PNI levels at admission and at 12 months have a more significant impact on survival rates. Specifically, those patients with higher PNI at admission tended to have better prognoses. This may be because a good nutritional status provides a

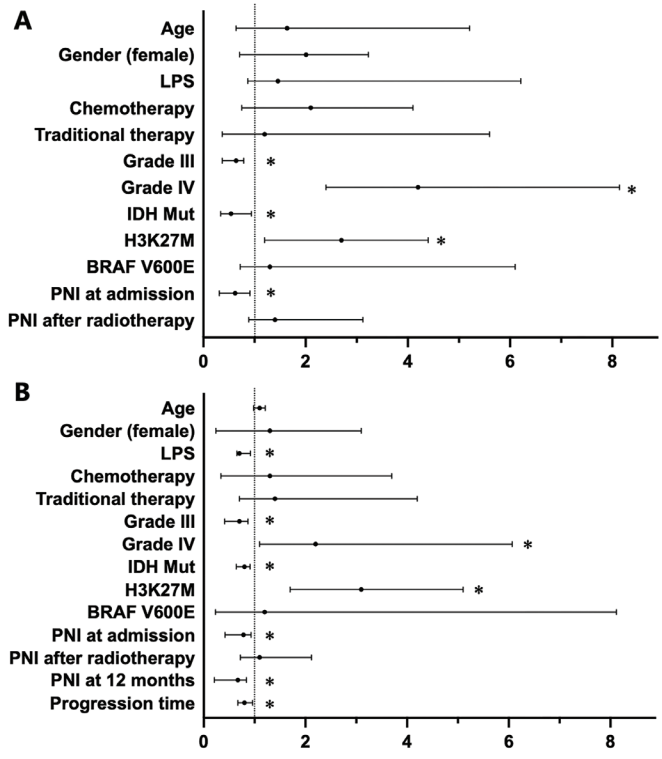

Figure 3. This tree map shows the clinical factors with respect to patient outcomes analyzed by multivariate COX survival analysis (•: Indicates the coef value, the bar represents the 95% confidence interval, and *: Represents p<0.05) (A) This panel primarily illustrates the relationship between clinical characteristics and progression time. The Grade 3 tumor, IDH mutation and high PNI at admission indicated later progression. Grade 4 tumor and H3K27M mutation indicated earlier progression. (B) This panel primarily illustrates the relationship between clinical characteristics and overall survival. High LPS at admission, Grade 3 tumor, IDH mutation, high PNI score at admission and 12 months and later progression were associated with longer survival times. Grade 4 tumor and H3K27M were associated with poorer outcomes
IDH: Isocitrate dehydrogenase, PNI: Prognostic nutritional index, LPS: Lansky performance status

better foundation for subsequent treatments, helping to enhance the body's immune system and tolerance, thereby delaying tumor progression and improving survival rates to some extent. At 12 months, those patients with higher PNI levels also showed longer survival times, indicating that maintaining good nutritional status throughout the disease process is crucial for long-term survival. In contrast, although PNI levels one week after radiotherapy can also reflect the patient's nutritional status to some extent, the correlation with survival rates was relatively weaker. This was likely because radiotherapy itself may have certain effects on the patient's nutritional status and immune function.

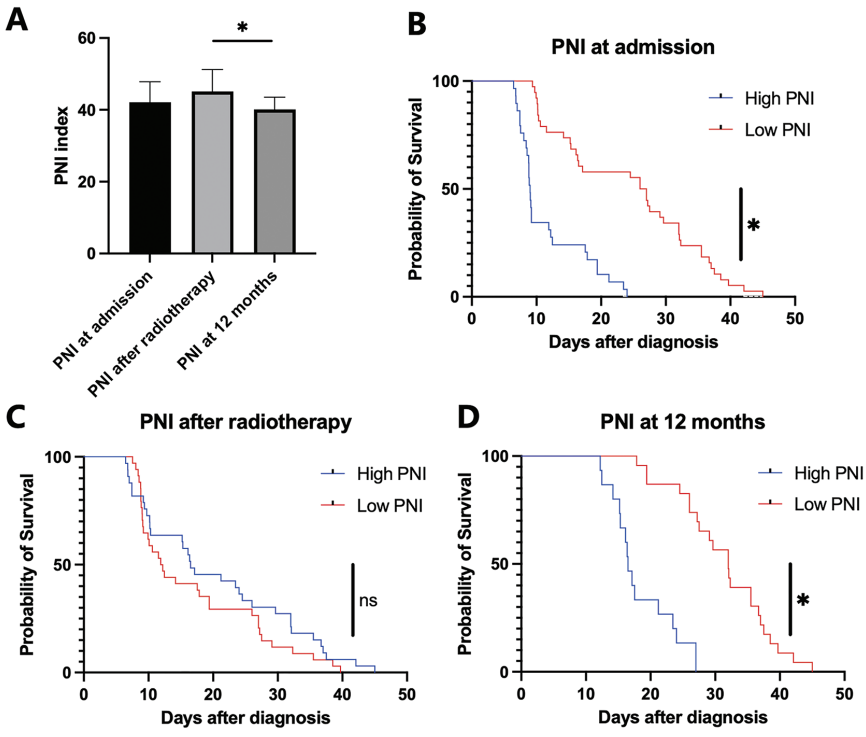

Figure 4. This figure illustrates the relationship between the prognostic nutritional index and survival outcomes across different time points in this clinical study (*: Indicates p<0.05) (A) A bar graph showing changes in PNI at three different time points: at admission, after radiotherapy, and at 12 months. (B) A Kaplan-Meier (KM) survival curve depicting the probability of survival based on PNI at admission. Patients with a high PNI have significantly better survival probabilities compared to those with a low PNI. (C) A KM survival curve showing survival probabilities based on PNI levels after radiotherapy. No significant difference was observed between high and low PNI groups at this time point. (D) A KM survival curve displaying survival probabilities based on PNI at 12 months. High PNI was associated with a significantly better survival rate than low PNI
PNI: Prognostic nutritional index

Discussion

pHGG is the most common malignant brain tumor in children, with a high mortality rate and limited effective treatment options (9). Currently, for pHGG, the concept of multidisciplinary collaboration is indispensable. It is no longer a task which can be accomplished by a single discipline (10). Appropriate and continuous nutritional support is also crucial for a positive patient prognosis (11). pHGG have distinct characteristics compared to adult gliomas. For instance, patients often face inadequate nutritional intake in the early stage. In addition to decreased oral intake, tumor-related cachexia, reduced digestive capacity, gastrointestinal dysfunction, increased catabolism, and the side effects of radiotherapy and chemotherapy all exacerbate the deterioration of the patients' nutritional status (12,13).

In this study, we used PNI to assess patients' nutritional status at onset, after radiotherapy, and at the 12-month mark. Compared to previous single nutritional indicators, PNI incorporates serum protein levels and has greater prognostic value for glioma patients, which has been confirmed by several studies (14). Among the three time points measured, PNI was lowest at 12 months, indicating a decline in nutritional status later in the disease course. This decline is multifactorial, with decreased appetite in the late stage of pHGG, and reluctance among guardians for invasive nutritional support measures (such as gastrointestinal tubes), which further complicates nutritional support. Additionally, most families lack sufficient experience in long-term care and nutritional support, highlighting the importance of continuously providing caregivers with adequate guidance throughout the treatment. Among the three periods, the PNI was highest following radiotherapy,

which may be related to symptomatic relief after radiation therapy, thus improving nutritional intake. We suggest that this period is an opportune time for nutritional intervention.

Given the difficulties in providing nutritional support in the later stages, we recommend implementing personalized interventions in order to support immune functions and overall metabolic health. These interventions may include a high-protein diet to prevent muscle wasting and to maintain lean body mass, which are essential for immune function (15). Additionally, ensuring a sufficient intake of omega-3 fatty acids, vitamins (such as vitamin D and B vitamins), and minerals (such as zinc and selenium) can help modulate inflammation and support tissue repair (16). For patients struggling with oral intake, nutritional supplementation or enteral nutrition may be necessary to meet caloric and protein needs (17,18). Close monitoring of nutritional status throughout the treatment is also critical in order to allow timely adjustments to the intervention plan, although further clinical trials are needed to confirm the effectiveness of these interventions.

The mechanisms by which nutritional status affects the prognosis of children with pHGG are diverse. Improved nutritional status may impact pHGG outcomes through several potential mechanisms. One key area is the role of nutrition in supporting the immune system. A well-nourished state may enhance immune surveillance and response to therapies, including immunotherapy, which is particularly relevant to our research focus (19). Additionally, certain nutrients may influence inflammation, which has been shown to affect tumor progression and treatment response. For instance, omega-3 fatty acids are known to regulate inflammatory pathways which could impact the tumor microenvironment (20). Another potential mechanism involves energy metabolism. Nutritional status can alter metabolic pathways, which could affect cancer cell proliferation, particularly in fast-growing tumors such as DIPG (21). These biological processes and pathways are worth further investigation in the context of DIPG and nutritional interventions.

In order to investigate the relationship with patient prognosis, we conducted a multivariate Cox survival analysis on multiple clinical indicators. Relative to lower-grade gliomas (Grade 3), IDH mutation, and higher PNI (at the early stage of the disease) were associated with a relatively longer progression-free survival and overall survival, consistent with other research findings regarding these clinical features and prognosis. Additionally, the 12-month PNI also indicated a longer survival period for patients. However, both the Cox survival analysis and KM survival curve analysis suggest that the prognostic predictive value of PNI after radiotherapy appears to be smaller than at the other two time points. This may be due to the direct impact of radiotherapy on PNI. Overall, we conclude that maintaining nutritional support throughout the disease course is crucial for patient prognosis.

Currently, studies on the prognostic value of PNI in pediatric tumors are relatively limited. For instance, a study on medulloblastoma patients undergoing surgical resection found that PNI could play a predictive role in overall survival, with an optimal cut-off value of 56.5 (22). Another study on pineal region tumors found that the hemoglobin, albumin, lymphocyte, and platelet score, which includes PNI, was positively associated with survival chances (23). These studies, although not specifically focused on pHGGs, provide a broader context for understanding the potential prognostic value of PNI in pediatric tumors. Our study uniquely contributes to the field by focusing on the temporal dynamics of PNI at admission and at 12 months, demonstrating its significant impact on survival rates in pHGG patients. This detailed temporal analysis is a novel aspect which differentiates our work from previous studies, offering new insights into the importance of sustained nutritional support throughout the disease course (23).

Study Limitations

This study has several limitations. Firstly, we were unable to conduct a prospective cohort study to verify the effectiveness of nutritional interventions, so further validation is needed. Secondly, the low incidence of pHGG makes follow-up challenging. The sample size of this study was small, introducing a degree of sample bias. Additionally, differences in direct therapeutic interventions for each patient may have led to variability in prognosis.

Conclusion

This study conducted a retrospective analysis of the relationship between PNI at different time points and prognosis in pHGG patients. Our results showed that a favorable early PNI level and a high PNI level 12 months post-onset are associated with better prognosis. Therefore, nutritional support during the course of the disease in children with pHGG is essential.

Ethics

Ethics Committee Approval: This study involved a retrospective follow-up analysis of previously collected data and was granted an exemption from the ethic committee of The 904th Hospital of the PLA.

Informed Consent: This study obtained written consent from the guardians of all participants.

Footnotes

Authorship Contributions

Concept: L.S., Y.W., Design: L.S., Y.W., Data Collection or Processing: N.S., Y.S., S.W., L.S., Y.W., Analysis or Interpretation: N.S., Y.S., S.W., L.S., Y.W., Literature Search: N.S., Y.S., S.W., L.S., Y.W., Writing: N.S., Y.S.

Conflict of Interest: All authors declare no conflict of interest.

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Original Article

Direct Right Atrial Catheterization in Pediatric Short Bowel Syndrome: A Durable and Technically Advantageous Solution for End-stage Vascular Access

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ABSTRACT

Aim: Children with short bowel syndrome (SBS) frequently require long-term total parenteral nutrition (TPN), which increases the risk of progressive central vein thrombosis. Once conventional venous access is exhausted, direct right atrial catheterization becomes a necessary salvage technique. In addition to bypassing thrombosed veins, it allows for the placement of larger-caliber catheters than percutaneous approaches.

Materials and Methods: This retrospective study included 17 pediatric SBS patients with end-stage vascular access who underwent direct right atrial catheterization via right anterior thoracotomy. Patient characteristics, vein thrombosis patterns, catheter duration, complications, and reinterventions were analyzed.

Results: All patients (100%) had thrombosed jugular veins. Subclavian, hepatic, and femoral vein thrombosis was observed in 41.1%, 29.4%, and 23.6% of the patients, respectively. The median catheter duration was 14.8 months. Four patients (23.6%) developed catheter-related bloodstream infections, including one Candida parapsilosis infection which required complete catheter and port removal with reinsertion. One mechanical complication (5.9%) occurred due to port chamber torsion. Two patients (11.8%) required surgical reintervention. No cases of catheter-related sepsis, tamponade, or mortality were recorded. Larger-bore catheters were successfully implanted in all patients due to the direct atrial route.

Conclusion: Direct right atrial catheterization is a safe, durable, and technically advantageous vascular access option in children with SBS and depleted venous anatomy. Its capacity to accommodate large-caliber catheters supports high-volume TPN delivery. This technique should be considered early in the multidisciplinary management of complex intestinal failure.

Keywords: Short bowel syndrome, vascular access, total parenteral nutrition

Introduction

Short bowel syndrome (SBS) is a common cause of pediatric intestinal failure, typically resulting from extensive bowel resection in the neonatal period due to conditions such as necrotizing enterocolitis, intestinal atresia, or volvulus (1). Children with SBS often require long-term total parenteral nutrition (TPN), which necessitates durable and reliable central venous access (2). Over time, repeated catheter insertions, catheter-related infections, and thrombotic complications frequently lead to the loss of

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usable central veins, resulting in what is termed end-stage central venous access (3,4).

As central veins become progressively unusable, including the internal jugular, subclavian, femoral, and transhepatic veins, clinicians are forced to consider unconventional access strategies. These include transhepatic lines, intercostal vein approaches, or ultimately, direct right atrial catheterization, a rarely performed but potentially life-saving technique (5,6). This approach, typically executed through a right anterior thoracotomy or sternotomy, enables the direct insertion of a tunneled catheter into the right atrium, bypassing the thrombosed venous system entirely (7).

While direct right atrial access has been described in case reports and small series, especially in children with intestinal failure awaiting intestinal transplantation (5,8), data on its mid- to long-term safety, complication rates, and durability remain limited. Reported concerns include catheter dislodgement, infection, and procedural morbidity, but contemporary experiences suggest that with proper technique and multidisciplinary support, outcomes may be favorable (5,9).

In this study, we present our single-center experience with direct right atrial catheterization in 17 pediatric patients with SBS and end-stage vascular access. Unlike previous reports which described only isolated cases or small cohorts such as Rodrigues et al. (5) (n=6) and Detering et al. (7) (a single case report) our study provides one of the largest pediatric series to date. Furthermore, we offer mid-term follow-up data on catheter durability, infectious outcomes, and surgical reinterventions, thereby expanding the limited literature on this approach in non-transplant SBS populations.

Materials and Methods

Study Design and Patient Population

This retrospective single-center study included pediatric patients with a diagnosis of SBS who underwent direct right atrial catheterization between 2020 and 2025 at our institution. The inclusion criteria were: SBS secondary to extensive bowel resection, long-term TPN dependency, and exhaustion of conventional central venous access routes, including jugular, femoral, subclavian, and hepatic veins. Patients with prior cardiac surgery or structural heart defects were excluded.

Demographic data, prior catheterization history, operative details, duration of catheter use, incidence of catheter-related bloodstream infections (CRBSIs), mechanical complications, and the need for surgical reintervention were collected from the medical records.

Surgical Technique

All procedures were performed under general anesthesia by a pediatric cardiovascular surgeon. A right anterior thoracotomy through the fourth or fifth intercostal space was used to access the pericardial cavity. The right atrium was exposed and a tunneled central venous catheter was inserted via a controlled atriotomy. The catheter tip was secured with a purse-string suture, and the line was tunneled to a subcutaneous chest port on the anterior thoracic wall. Proper positioning was confirmed intraoperatively via direct visualization and intraoperative flushing.

A schematic representation of the anterior thoracotomy and the placement of the tunneled catheter through the right clavicular region into the right atrium is illustrated in Figure 1.

Anticoagulation and Infection Prevention

Postoperative anticoagulation was administered in the form of low molecular weight heparin at a dose of 100 IU/kg subcutaneously twice daily for 3 days. The use of taurolidine lock solutions was recorded when applicable; however, due to challenges in supply and inconsistent documentation

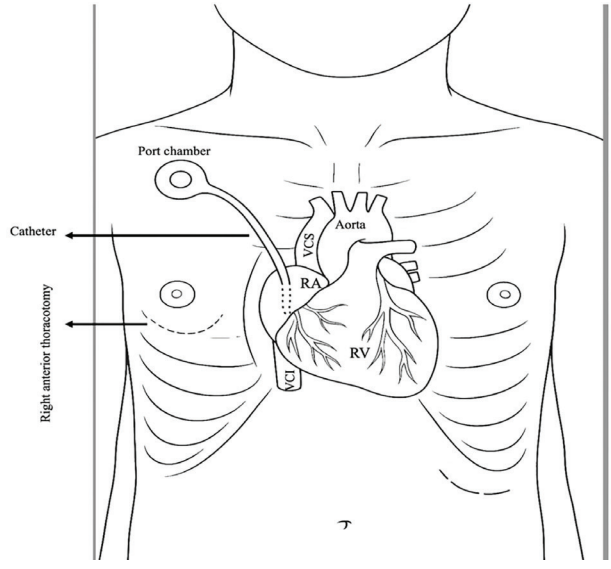

Figure 1. Right anterior thoracotomy and tunneled catheter placement into the right atrium in a pediatric patient. The illustration demonstrates the surgical exposure through the right fourth intercostal space using a retractor. The catheter enters through a subcutaneously placed port under the right clavicle, follows a curved intrathoracic course, and terminates within the right atrium. The cardiac anatomy, rib cage, and port location are anatomically aligned for educational and surgical reference
RA: Right atrium, RV: Right ventricle, VCS: Vena cava superior, VCI: Vena cava inferior

across clinical settings, precise data regarding duration and adherence could not be reliably retrieved for all patients.

Definitions and Outcome Measures

- CRBSI was defined as a positive peripheral blood culture with clinical signs of sepsis and no other identifiable source of infection.
- Mechanical complications included any device-related issues such as port torsion, dislodgement, or subcutaneous migration which interfered with catheter function.
- Reintervention was defined as any surgical procedure required to revise or replace the catheter or port due to infection or mechanical failure.
- End-stage central venous access was defined as thrombosis or anatomic inaccessibility of all major conventional central veins (jugular, subclavian, femoral, and hepatic).

All surgical procedures were performed with written informed consent from the legal guardians. This study was approved by the Non-interventional Clinical Research Ethics Committee of İzmir Bakırçay University (approval no.: 2417, dated: 27.08.2025). The committee confirmed that the study was ethically appropriate and conducted in accordance with the Declaration of Helsinki. Written informed consent for surgical procedures was obtained from the legal guardians of all participants, and the requirement for additional consent for inclusion in this retrospective analysis was waived by the ethics board.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics version 25. Continuous variables, including age, weight, and duration of catheter use, are expressed as medians due to non-normal distribution (assessed using the Shapiro-Wilk test). Categorical variables such as the presence of CRBSI, vein thrombosis status, mechanical complications, and reinterventions are expressed as frequencies and percentages.

Results

Patient Characteristics

A total of 17 pediatric patients with SBS underwent direct right atrial catheterization due to end-stage central venous access. The median age at the time of catheter insertion was 4 years, and the median weight was 10 kg. All patients had previously exhausted conventional central venous access options.

All patients (100%) had documented jugular vein thrombosis. Additionally, thrombosis of the femoral, subclavian, and hepatic veins was observed in 23.6% (n=4), 41.1% (n=7), and 29.4% (n=5) of the patients respectively, highlighting the extent of vascular access compromise in this cohort.

Catheter Duration and Use

The median duration of catheter use following direct right atrial insertion was 14.8 months (7-22 months). All patients were successfully managed with TPN via the intra-atrial catheter during this period, with no early postoperative catheter failures. Taurolidine lock solutions were selectively used in a minority of cases, depending on availability and clinician preference.

Catheter-related Bloodstream Infections

A total of 4 patients (23.5%) developed CRBSIs during the follow-up period. The isolated pathogens included *Staphylococcus aureus*, *Staphylococcus epidermidis*, and Candida parapsilosis. Time to first CRBSI ranged from 1 to 6 months following catheter placement. Three cases were successfully managed with antimicrobial therapy alone. In one case, a Candida parapsilosis bloodstream infection necessitated complete catheter and port system removal. No patients developed sepsis-related complications or endocarditis.

Mechanical Complications

Mechanical complications were rare. Only 1 patient (5.9%) experienced a complication, which was identified as subcutaneous port chamber torsion, resulting in difficult access and requiring repositioning. No cases of catheter migration, pericardial effusion, or tamponade were observed.

Reinterventions

Two patients (11.8%) required surgical reintervention. One underwent catheter revision due to subcutaneous port torsion. The second patient required complete catheter and port removal with subsequent reinsertion due to persistent Candida parapsilosis associated infection. Both patients recovered without further complications and resumed TPN through the new catheter.

A summary of the patient demographics, thrombotic profiles, catheter-related infections, mechanical complications, and reintervention rates is presented in Table I.

Table I. Summary of patient characteristics and outcomes: CRBSI: catheter-related bloodstream infections	
Parameter	Value
Total number of patients	17
Median age at catheter insertion (range)	4 (2-7) years
Median weight (range)	10 (4-15) kg
Median catheter duration (range)	14.8 (7-22) months
Jugular vein thrombosis	17 (100%)
Femoral vein thrombosis	4 (23.6%)
Subclavian vein thrombosis	7 (41.1%)
Hepatic vein thrombosis	5 (29.4%)
Catheter-related bloodstream infections (CRBSI)	4 (23.6%)
Microorganisms identified	*Staphylococcus aureus* 2 (11.8%) *Staphylococcus epidermidis* 1 (5.9%) Candida parapsilosis 1 (5.9%)
CRBSI requiring catheter removal	1 (5.9%) Candida infection
Mechanical complications (e.g., port torsion)	1 (5.9%)
Surgical reintervention required	2 (11.8%)
Mortality	0 (0%)

Discussion

This study presents a single-center experience of direct right atrial catheterization in pediatric patients with SBS and end-stage central venous access. Our findings demonstrate that this technique can be safely performed with relatively low rates of mechanical complications and infectious events, even in a high-risk cohort with extensive venous thrombosis and long-term parenteral nutrition dependence.

Central venous access is critical for maintaining TPN in children with SBS, but it often becomes compromised over time due to catheter-related thrombosis, mechanical failure, and/or infection (4,10). Multiple prior studies have reported progressive loss of venous access in this population, especially among those with prolonged survival and repeated catheter insertions (11,12). In our series, 100% of patients had thrombosed jugular veins, while thrombosis of subclavian, femoral, and hepatic veins was present in 41.1%, 23.6%, and 29.4%, respectively. These data highlight the severity of vascular depletion in this cohort and the necessity of alternative access strategies.

Direct intra-atrial catheterization has historically been reserved for patients in whom all conventional central veins are unavailable. Previous reports, such as those by Rodrigues et al. (5) and Detering et al. (7), described the technique in small series and case reports, typically as a last-resort measure in children awaiting intestinal transplantation. In our series of 17 patients, the median catheter duration was 14.8 months, with no early failures or procedure-related deaths, demonstrating the durability and safety of this approach when performed in experienced hands.

Our findings add to existing evidence by demonstrating the feasibility of this technique outside of transplant-focused cohorts. While Rodrigues et al. (5) reported its use mainly as a bridge to small bowel transplantation, our patient population included those undergoing long-term TPN for intestinal adaptation as well. Compared to the prior literature, our series offers longer follow-ups and a detailed evaluation of complications, and so it supports a broader application of this approach in selected pediatric SBS patients.

Our CRBSI rate of 23.6% is comparable to or lower than reported rates in pediatric patients with long-term central lines (13,14). One case of Candida parapsilosis CRBSI required complete catheter and port removal. Fungal infections involving long-term venous devices often demand more aggressive management, including device explantation, due to the risk of persistent bloodstream infection and biofilm formation (15). While rare, this complication underscores the importance of early diagnosis and organism-specific management strategies in patients with TPN dependence and device-related infections.

The selective use of taurolidine locks may have contributed to this favorable outcome. Although taurolidine locks were selectively used in some patients, limitations in supply and non-standardized clinical documentation precluded accurate quantification of usage patterns. Consequently, a definitive analysis of its effect on CRBSI incidence could not be performed in this study.

Mechanical complications were rare in our cohort. Only one patient (5.9%) experienced a complication, identified as subcutaneous port torsion, resulting in difficult access and requiring repositioning. No cases of catheter migration, pericardial effusion, or tamponade were observed. These findings compare favorably with prior reports, in which mechanical issues such as dislodgement or tamponade have been described as serious complications (7,8). We attribute our low rate to the consistent use of a right anterior thoracotomy approach, secure atrial fixation, and careful subcutaneous tunneling.

While alternative approaches such as transhepatic or intercostal venous access have been described (6), these techniques are often technically demanding, and catheter longevity is typically limited. Direct atrial catheterization, by contrast, offers a central, stable, and durable route for TPN in patients with no other options.

In addition to providing durable access, direct atrial insertion allows for the use of larger-diameter catheters compared to percutaneous techniques. This facilitates improved flow rates, reduced catheter occlusion risk, and more effective long-term parenteral nutrition delivery, which is a critical advantage in children with increasing nutritional demands (16).

Our experience supports the early consideration of direct atrial access in select children with SBS and severely compromised vascular access. In patients awaiting intestinal transplantation or those with the potential for enteral adaptation, this technique may serve as a vital bridge, provided that meticulous surgical technique, anticoagulation, and infection prevention measures are applied.

Study Limitations

This study has several limitations. First, its retrospective design and single-center nature may limit the generalizability of the findings. While the surgical technique and postoperative protocols were consistent, institutional practices (e.g., the use of taurolidine locks or the timing of reintervention) may differ across centers.

Second, the sample size was relatively small (n=17), which limits the statistical power to detect rare complications or perform subgroup analysis (e.g., comparing catheter duration in patients with vs. those without reintervention). Additionally, we did not include a comparison group (e.g., transhepatic access or tunneled central catheters via alternative veins), which would have strengthened the interpretation of catheter longevity and complication rates.

Third, the follow-up period, while sufficient to assess short- to mid-term outcomes, may not fully capture long-term complications such as right atrial thrombus formation, late infections, or impacts on future transplant eligibility. No routine echocardiography or surveillance imaging was performed unless clinically indicated, which may have led to an underestimation of subclinical atrial changes.

Lastly, heterogeneity in infection prevention strategies, particularly the non-uniform use of taurolidine or ethanol locks, limits our ability to draw firm conclusions about CRBSI prevention. Standardized infection control protocols may further improve the understanding of outcomes in future studies.

Despite these limitations, our findings provide meaningful insights into a rarely described yet increasingly important surgical option for children with end-stage venous access.

Conclusion

In pediatric patients with SBS and exhausted central venous access, direct right atrial catheterization via anterior thoracotomy represents a safe and effective salvage strategy for maintaining long-term parenteral nutrition. Our experience demonstrates low rates of mechanical complications and manageable CRBSI incidence, with a median catheter duration of 14.8 months.

This technique, though historically considered a last resort, should be repositioned as a proactive option in selected patients with confirmed multi-site venous thrombosis. With proper surgical execution, perioperative anticoagulation, and infection surveillance, direct atrial access may serve as a bridge to intestinal adaptation or transplantation. The ability to insert larger-caliber catheters through this route further enhances its utility for long-term use.

Future multicenter, prospective studies are needed in order to define the long-term safety, ideal timing for intervention, and standardized postoperative management of this increasingly relevant vascular access approach in complex intestinal failure populations.

Ethics

Ethics Committee Approval: This study was approved by the Non-interventional Clinical Research Ethics Committee of İzmir Bakırçay University (approval no.: 2417, dated 27.08.2025).

Informed Consent: All surgical procedures were performed with written informed consent from the legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.N.T., M.A., Y.A., Concept: O.N.T., E.K.T., Design: O.N.T., E.K.T., Y.A., Data Collection or Processing: O.N.T., M.A., Analysis or Interpretation: O.N.T., Y.A., Literature Search: M.A., E.K.T., Writing: O.N.T., E.K.T., Y.A.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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Original Article

Iris Changes in Patients with Pediatric Behçet's Disease: A Cross-sectional Spectral Domain Optical Coherence Tomography Study

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ABSTRACT

Aim: The study aimed to assess whether pediatric Behçet's disease (PBD) eyes with a history of ocular inflammation in remission exhibit residual iris structural changes compared with BD eyes without ocular involvement and also healthy controls.

Materials and Methods: Twenty PBD patients without ocular involvement (Group 1), 6 PBD patients with inactive ocular involvement (Group 2), and 24 age-sex-matched healthy controls (Group 3) were included in this study. Their demographic characteristics and the patients' anterior and posterior segment examination findings were recorded. Iris thicknesses at 1 mm, 2 mm, and 3 mm from the pupillary margin in the nasal and temporal areas were measured using spectral domain optical coherence tomography (SD-OCT). Iris area measurements in the 3 mm area were evaluated using the ImageJ program.

Results: There was no statistical difference between the three groups in terms of their age or gender (p=0.920, p=0.482, respectively). There was no statistically significant difference between the three groups regarding their iris thicknesses at temporal and nasal 1 mm, 2 mm, and 3 mm (p>0.05). The three groups had no significant difference in their temporal and nasal 3 mm area measurements (p>0.05).

Conclusion: In PBD eyes with a history of uveitis which were in remission at the time of imaging, iris thickness and area did not differ from those of non-ocular BD eyes or healthy controls. These findings suggest that no persistent iris structural damage is detectable by SD-OCT after the resolution of inflammation, although longitudinal follow-up during both active and inactive phases is warranted.

Keywords: Behçet's uveitis, iris area, iris thickness, pediatric Behçet's disease, spectral domain optical coherence tomography

Introduction

Behçet's disease (BD) is a disease first described by a Turkish physician, Hulusi Behçet, in 1937, with a triad of oral ulcers, genital ulcers, and uveitis (1). Its prevalence is higher in the Silk Road Basin (2,3). It is stated that this disease occurs as a result of various unknown infectious or non-infectious agents activating a wide range of inflammatory conditions in genetically susceptible individuals and it can present with multisystem involvement (4,5).

Pediatric BD (PBD) is a sub-classification of BD used to define the age group in which the disease is diagnosed as a result of the clinical picture being established before the age of 16 years (6). Although there is no clear data in the literature regarding the prevalence in this age group, it has

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been stated that the prevalence of this disease is around 15% to 20% of all BD cases (7,8).

The eye is one of the most commonly affected organs in BD, and its presentation is often bilateral non-granulomatous panuveitis, similar in both adult and pediatric groups. However, in children under the age of 10 years, the presentation may differ, often manifesting as anterior uveitis (9,10). Although the ocular progression of BD can vary widely, it can affect all segments of the eye in patients who do not receive proper treatment and it can cause a wide range of complications ranging from decreased vision to blindness (9,11).

Although ocular involvement in BD can affect all uveal tissues, objective and non-invasive quantification of iris structural parameters in pediatric patients remains limited. Spectral domain optical coherence tomography (SD-OCT) enables reproducible and non-invasive assessment of iris morphology, including stromal thickness and area, providing an opportunity to investigate subtle anterior segment changes in this population. Therefore, this study aimed to determine whether the eyes of PBD patients in remission with inactive uveitis exhibit structural alterations in iris thickness and area, compared to the eyes of BD patients without ocular involvement, and with a healthy control group.

The present study, therefore, aimed to evaluate whether PBD eyes with a history of ocular inflammation but currently in remission (inactive uveitis) show residual or permanent structural changes in iris thickness and area compared with BD eyes without ocular involvement and healthy controls.

Materials and Methods

Our study was designed retrospectively between March 2024 and April 2024 and was approved by the Scientific Research Evaluation and Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval no.: AEŞH-BADEK-2024-459, date: 22.05.2024). This study was conducted in accordance with the Declaration of Helsinki. Since this was a retrospective, non-interventional imaging study, written informed consent for the use of clinical and imaging data was obtained from the legal guardians of all participants. This study included 20 patients who were followed up with the diagnosis of PBD and had no ocular involvement, 6 PBD patients with inactive ocular involvement, and 24 age-sex-matched healthy controls. Twenty patients with PBD without ocular involvement were classified as Group 1, 6 pediatric patients with BD who were inactive in terms of ocular involvement were classified as Group 2 and the healthy control patients were classified as Group 3. Only the right eye of each subject was included to avoid inter-eye correlation.

All PBD patients with inactive ocular involvement were patients who had a single uveitis attack (3 eyes with anterior uveitis and 3 eyes with panuveitis) and had no history of uveitis activation within the prior 3 months. In addition, the inactivity of these cases was determined by fundus fluorescein angiography (FA) and flare measurements in the prior 3 months of follow-up; no leakage was detected in angiography and the flare value was measured as being less than 5 in repeated flare measurements. All PBD patients were not receiving any additional medication other than colchicine as systemic treatment.

The demographic characteristics such as age and gender, best-corrected visual acuity (BCVA), intraocular pressure (IOP), spherical equivalents (spherical power + cylindrical power/2), flare values, and detailed anterior and posterior segment examination findings were recorded from the patient files. Flare measurements were evaluated with a Kowa FM 700 laser flare meter (Kowa Company Ltd., Nagoya, Japan), and an average of at least 5 values was recorded. Anterior segment SD-OCT scans were obtained using the Sirius device with the SD-OCT module (CSO, Florence, Italy) in raster mode along the horizontal central pupil line by the same operator. All images were acquired without pharmacologic mydriasis, under standardized room illumination of 300-500 lux measured with a luxmeter, and between 09:00 and 12:00 a.m. in order to minimize diurnal variation. Pupillary diameter at the time of scanning was recorded, and for each eye, three consecutive scans were obtained with the mean value used for analysis. Image quality criteria included adequate signal strength and the absence of motion artefact; scans not meeting these criteria were excluded and reacquired. Iris area was measured via ImageJ (v1.54 g Bethesda, USA) after calibration to the device scale. A 3 mm radial sector from the pupillary margin was marked temporally and nasally, and the enclosed stromal area was recorded (Figure 1). All measurements were performed independently by two masked graders, and the average of their values was used for analysis; discrepancies greater than 10% were resolved by consensus before inclusion.

Patients with a BCVA worse than 0.0 logMAR, a spherical equivalent refractive error beyond ±2.0 D, IOP outside the range of 11-21 mmHg, or anterior chamber flare values ≥6 were excluded, as well as those with a history of intraocular surgery, significant anterior segment pathology (such as

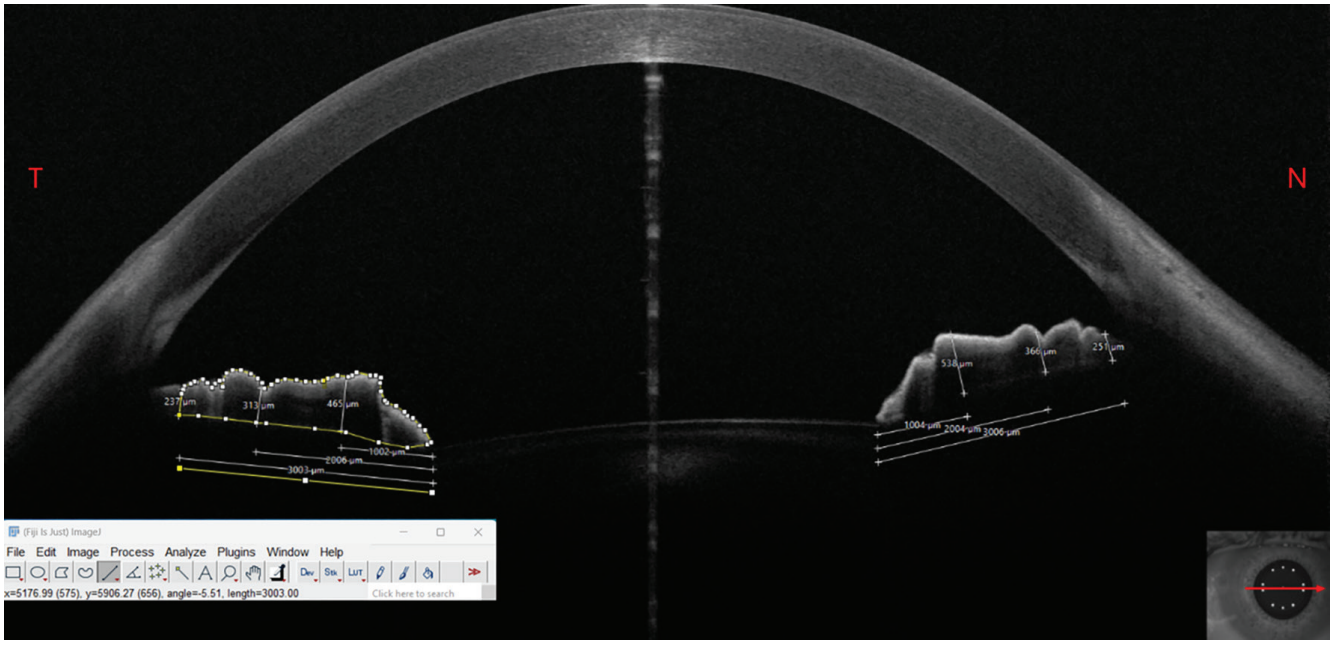

Figure 1. Evaluation of iris thickness using anterior segment optical coherence tomography and marking of the iris area using Image J program

corneal opacity or iris atrophy), active uveitis at the time of imaging, or the use of systemic medications known to affect pupillary function other than colchicine.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). For nominal (categorical) data, frequency and percentage values were calculated. For continuous variables, descriptive statistics including minimum, maximum, median, mean, and standard deviation were reported. The Kruskal-Wallis H test, a non-parametric test, was used to compare continuous variables among the three independent groups. When significant differences were detected, Dunn's post-hoc test with Bonferroni correction was performed for pairwise group comparisons. Effect sizes (η^2) with 95% confidence intervals (CIs) were calculated in order to quantify the magnitude of the observed differences. For comparisons between two independent groups, the Mann-Whitney U test was applied. Fisher's exact test was used for categorical variables. Additionally, post-hoc power analyses were performed based on observed effect sizes in order to evaluate the adequacy of the sample size. In order to check for potential confounding factors, covariate-adjusted analyses including age, spherical equivalent, and sex were conducted as sensitivity tests. A p-value <0.05 was considered statistically significant.

Results

Group 1 patients included 12 (60%) female and 8 (40%) male patients; Group 2 patients included 2 (33.3%) female and 4 (66.7%) male patients; Group 3 patients included 12 (50%) female and 12 (50%) male patients. There was no statistically significant difference between the groups in terms of gender (p=0.482). The mean age of Group 1 patients was 13.4±3.28 years, the mean age of Group 2 patients was 14.67±17.67 years, and the mean age of Group 3 patients was 13.67±3.13 years. No statistically significant difference was found between the mean ages of the patients (p=0.92). There was no statistically significant difference between the disease durations of Group 1 and Group 2 cases (p=0.234) (Table I).

The BCVA of all patients in Group 1, Group 2, and Group 3 was 0.0 logMAR. The biomicroscopic anterior segment and dilated fundus examination were normal in all eyes and Group 2 patients had no posterior synechiae. FA showed no vascular leakage in Group 2. All participants had brown irises.

The median (interquartile range) temporal iris thickness values at 1,000 µm, 2,000 µm, and 3,000 µm from the pupillary border were 446.5 (386-525) µm, 395 (318.75-465.75) µm, and 234.5 (208.5-290.75) µm in Group 1; 495.5 (464.25-518.25) µm, 386 (362.25-405.25) µm, and 269.5 (256-303.75) µm in Group 2; and 455 (412.25-502.5) µm, 365.5 (321.75-412.75) µm, and 269.5 (243-380) µm in Group

3, respectively. The median nasal iris thicknesses at 1,000 µm, 2,000 µm, and 3,000 µm were 483 (420.5-543.25) µm, 417.5 (338.75-471.75) µm, and 286 (255.75-324.5) µm in Group 1; 495 (450.25-550) µm, 375 (347.25-412.25) µm, and 249 (221.75-331.5) µm in Group 2; and 492.5 (448-548.5) µm, 394.5 (367-444) µm, and 289 (237.25-343.25) µm in Group 3, respectively. No statistically significant differences were found among the three groups for any of the temporal or nasal iris thickness parameters (p>0.05, Kruskal-Wallis test; η^2=0.01-0.05, 95% CI (0-0.15). The temporal and nasal iris areas measured up to 3,000 µm from the pupillary border were 1.52 (1.34-1.79) mm² and 1.57 (1.43-1.77) mm² in Group 1; 1.54 (1.48-1.72) mm² and 1.56 (1.09-1.72) mm² in Group 2; and 1.55 (1.47-1.65) mm² and 1.66 (1.52-1.72) mm² in Group 3, respectively. No significant intergroup differences were observed for the iris area measurements (p>0.05, Kruskal-Wallis test; η^2=0.01, 95% CI (0-0.06) (Table II).

Table I. Clinical and demographic characteristics of patients

	Group 1 (n=20)	Group 2 (n=6)	Group 3 (n=24)	p-value
Age (years)	13.4±3.28 Median: 13.5 Min-max: 6-17	14.67±3.20 Median: 16 Min-max: 9-17	13.67±3.13 Median: 14.5 Min-max: 6-17	0.920[K]
Gender				0.482[F]
Female	12 (60%)	2 (33.3%)	12 (50%)	
Male	8 (40%)	4 (66.7%)	12 (50%)	
Duration of pediatric BH (months)	24.75±24.9 Median: 12.5 Min-max: 2-84	14.17±17.7 Median: 6 Min-max: 2-48	-	0.234[M]

[K]: Kruskal-Wallis H-test, [F]: Fisher's exact test, [M]: Mann-Whitney U test, BH: Behçet's disease, Min: Minimum, Max: Maximum

Table II. Comparison of patients' iris thickness and iris areas

Iris thickness (µm)	Group 1 (n=20)	Group 2 (n=6)	Group 3 (n=24)	p-value	Effect size η^2 (95% CI)
Temporal 1000	446.5 (386-525), CI: 396.9-484.5	495.5 (464.25-518.25), CI: 444.6-529.0	455 (412.25-502.5), CI: 430.8-483.8	0.578[K]	0.02 (0-0.12)
Temporal 2000	395 (318.75-465.75), CI: 357.2-431.8	386 (362.25-405.25), CI: 355.7-422.3	365.5 (321.75-412.75), CI: 342.8-394.6	0.649[K]	0.01 (0-0.11)
Temporal 3000	234.5 (208.5-290.75), CI: 222.5-288.1	269.5 (256-303.75), CI: 250.4-303.6	269.5 (243-380), CI: 264.7-330.7	0.110[K]	0.05 (0-0.15)
Nasal 1000	483 (420.5-543.25), CI: 434.7-522.3	495 (450.25-550), CI: 441.1-552.5	492.5 (448-548.5), CI: 470.3-518.1	0.833[K]	0.01 (0-0.09)
Nasal 2000	417.5 (338.75-471.75), CI: 354.9-432.6	375 (347.25-412.25), CI: 333.6-426.4	394.5 (367-444), CI: 383.9-423.7	0.633[K]	0.01 (0-0.10)
Nasal 3000	286 (255.75-324.5), CI: 267.0-310.0	249 (221.75-331.5), CI: 208.8-334.2	289 (237.25-343.25), CI: 259.0-318.0	0.687[K]	0.01 (0-0.10)
Iris area (mm²)					
Temporal	1.52 (1.34-1.79), CI: 1.42-1.66	1.54 (1.48-1.72), CI: 1.45-1.73	1.55 (1.47-1.65), CI: 1.50-1.62	0.758[K]	0.01 (0-0.06)
Nasal	1.57 (1.43-1.77), CI: 1.49-1.68	1.56 (1.09-1.72), CI: 0.89-2.38	1.66 (1.52-1.72), CI: 1.57-1.71	0.711[K]	0.01 (0-0.05)

Data are presented as median (IQR), CI=95% confidence interval
[K]: Kruskal-Wallis H-test, η^2: Eta-squared effect size, IQR: Interquartile range, CI: Confidence interval

Discussion

PBD develops on average between the ages of 4.9 and 12.3 years and affects both sexes approximately equally (8). Ocular involvement can occur at very different frequencies in this group of patients, and it is stated that the frequency of ocular involvement can vary between approximately 9% and 76% of patients (9). These ocular inflammations which may develop can cause a wide variety of ocular complications, making close follow-up of these patients essential (9,11).

There are various data on the prevalence of uveitis in pediatric cases, and it has been stated that it is between 5% and 16%. In these cases, various segments of the eye can be affected depending on the type of uveitis and these cases can present with a wide variety of complications, from band keratopathy to posterior synechiae or optic atrophy to retinal detachment (12). The iris is the only part of the uvea which can be directly observed in biomicroscopic examination. The iris, which has a dynamic structure, consists of irregular superficial cells, sphincter and dilator pupil muscles, stromal cells, and iris pigment epithelium. The iris, which has a spongy structure, can cause changes in its thickness as a result of contractions and relaxations with a structure which allows fluid exchange between the stroma and aqueous. In eyes affected by uveitis, inflammation or iris vasculitis may lead to alterations in the iris tissue which are not easily detectable through biomicroscopic examination. Therefore, we investigated the measurement of iris thickness and area in PBD with and without ocular involvement and compared these results with age-matched healthy controls. In our study, we found no statistically significant differences between temporal and nasal iris thickness changes and iris areas in inactive ocular involvement BD, BD without ocular involvement, and the control group when compared to each other. In this study, we did not find any ocular complications on biomicroscopic examination in eyes with inactive ocular involvement.

In addition to obvious ocular complications, subclinical changes can be observed depending on the pathophysiology of the BD, and these changes may affect all segments of the eye with varying degrees of severity. Furthermore, eyes without ocular involvement have also been reported to be affected by the disease. In one study examining retinal vascular structures in BD without ocular involvement, a significant decrease was found in both superficial vascular density, deep vascular density, and choriocapillaris flow areas in patients when compared to a healthy group, and the results indicated that vascular changes can occur even in eyes without ocular involvement (13). In another study examining retinal vascular structures in PBD without ocular involvement, no difference was found in superficial vascular densities, but decreases in deep capillary plexus vascular densities were found (14). Considering the changes in these vascular structures, the need for close follow-up of these clinically asymptomatic patients emerges and it has been seen that a wide variety of retinal vascular changes occur in patients even in cases which appear to be asymptomatic.

Changes in the vascular system of the iris in patients with BD have been another research subject. In a study conducted by Yoshikawa et al. (15), the iris vascular system of patients with BD was examined in the remission phase and it was emphasized that the damage continued even in the inactive period. Based on these conditions, we wanted to investigate the usability of non-invasively measuring the iris thickness of patients in terms of follow-up, progression, and the detection of developing complications. In addition, retinal vascular involvement can be easily detected by OCT angiography in both eyes either with or without ocular involvement in BD, but iris vascular changes cannot be identified in more detail with the current technology.

In another study, corneal changes in BD which were active with ocular involvement, inactive with ocular involvement, and BD without ocular involvement were examined and the effectiveness of these data in determining the activity of the disease was evaluated. As a result, the researchers stated that endothelial dysfunction developed due to ocular inflammation and corneal thickness increased, but this was not observed in inactive patients and these parameters returned to normal. As a result, the authors stated that they could make an opinion about disease activity based on corneal thickness and that these data could be a guide in determining the best treatment method (16). In a further study examining corneal endothelial changes, the changes in the inactive period of BD patients with ocular involvement were examined. Although the researchers did not detect any difference in corneal thickness between a healthy group and the BD group, they stated that permanent changes in endothelial cell morphology could be observed, but these conditions did not cause decompensation of the cornea (17). Although it has been stated that these inflammation-related effects on corneal parameters do not result in decompensation after the inflammation ends, cellular effects occur and this shows the importance of long-term and close follow-up of the progression in these patients, even if they are asymptomatic. The results of the above studies suggest that inflammation may also have

an effect on iris tissue during acute attacks. In our study, we evaluated eyes with ocular involvement during the inactive phase of uveitis, and our findings suggest that after treatment of active uveitis attacks, inflammatory effects may not lead to measurable changes in the iris tissue of eyes with normal anterior segment findings.

It has also been reported that changes in iris thickness can occur in many ocular diseases. In a study examining the iris thickness in patients with neovascular glaucoma, it was stated that ischemia caused a decrease in iris thickness (18). Another place where iris thickness is examined is in cases with uveitis. Studies investigating changes in iris thickness and area in eyes with Fuchs' uveitis have reported reduced iris thickness and area compared to healthy eyes (19).

We found no statistically significant differences between temporal and nasal iris thicknesses and iris areas among inactive ocular involvement BD, BD without ocular involvement, and the healthy control group. These results should be interpreted with caution due to the limited sample size, right-eye-only analysis, and inclusion of only inactive cases. The small sample, particularly in the inactive ocular-involvement group, also limits the statistical power of this study. The absence of measurable differences may indicate that no permanent iris damage was demonstrated under inactive disease conditions. It is also possible that suppression of inflammation during the inactive phase may have prevented structural iris alterations. From a vascular perspective, ischemia associated with the vasculitis nature of BD might not have occurred because of systemic inactivation of the disease, or the changes may exist below the detection threshold of current imaging methods. Further longitudinal and active-phase studies with larger sample sizes are warranted in order to clarify the pathophysiological changes of the iris in PBD.

Study Limitations

The absence of active PBD with ocular involvement in our study, the fact that our study was a single-centre retrospective study, and the relatively small number of patients can be cited as the limitations of this study.

Conclusion

No permanent changes were demonstrated in iris parameters among PBD cases with inactive disease, and the values were comparable to those of the healthy controls. This study represents, to the best of our knowledge, the first evaluation of iris parameters in PBD using SD-OCT. Larger, longitudinal, and active-phase studies are needed in order to confirm these preliminary findings.

Ethics

Ethics Committee Approval: Approval was granted by the Scientific Research Evaluation and Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval no.: AEŞH-BADEK-2024-459, date: 22.05.2024).

Informed Consent: Informed consent was obtained from all patients and or their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ş., Y.Ö.E., B.K., E.B., N.G.K., S.Ö., Concept: E.Ş., Y.Ö.E., B.K., Design: E.Ş., Data Collection or Processing: E.Ş., Y.Ö.E., B.K., E.B., N.G.K., S.Ö., Analysis or Interpretation: E.Ş., Y.Ö.E., Literature Search: E.Ş., Writing: E.Ş.

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Original Article

Evaluation of the Relationship Between Thyroid Function Tests and Markers of Infection Severity in Children Presenting with Acute Infections

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ABSTRACT

Aim: In cases of mild to moderate infections, a phenomenon known as non-thyroidal illness syndrome may occur, characterized by reduced thyroid hormone levels despite an intact thyroid gland. This study aimed to investigate the relationship between thyroid function tests and inflammatory markers in children with acute infections.

Materials and Methods: Children under the age of 18 years who had previously presented to the Pediatric Outpatient Clinics of University of Health Sciences Türkiye, İzmir City Hospital with acute infections and had blood tests performed were included in this study. Data of thyroid functions and infection markers were collected from the records.

Results: A total of 50 patients and 112 individuals in a control group under the age of 18 years were included in this study. No statistically significant differences were observed between the groups in terms of demographic or baseline clinical characteristics. Serum triiodothyronine (T3) and thyroid-stimulating hormone levels were significantly lower in the patient group, while levels of C-reactive protein (CRP), procalcitonin, and erythrocyte sedimentation rate, as well as the CRP/lymphocyte ratio (CLR), neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) were significantly higher in the patient group. The median T3 level was significantly lower in the patient group. A subgroup analysis was performed in order to assess the relationship between T3 levels and complete blood count/infection markers. A negative correlation was observed between T3 levels and CRP, procalcitonin, neutrophil counts, as well as CLR, NLR, MLR, and disease severity.

Conclusion: Thyroid function tests, in conjunction with infection markers, may serve as potential predictive tools for clinical outcomes. There is a correlation between infection/inflammation markers and thyroid function in pediatric patients with acute infections.

Keywords: Inflammation, disease severity, non-thyroidal illness

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Introduction

Non-thyroidal illness (NTI) is a condition characterized by low thyroid hormone (TH) levels, typically without intrinsic thyroid gland dysfunction (1). As the severity of a critical illness worsens, there is initially a decline in triiodothyronine (T3) levels, followed by significant reductions in thyroxine (T4) and thyroid-stimulating hormone (TSH) over time. The reduction in T4 and TSH levels, particularly when T4 falls below 3 µg/dL, is associated with poor prognosis (2). Studies have shown that in cases of mild illness, serum T3 levels decline, and with an increasing severity and duration of the illness, serum T4 levels also decrease. Unlike primary hypothyroidism, these decreases in serum TH concentrations are not accompanied by an increase in serum TSH levels. This alteration in TH levels has been termed low T3 syndrome, euthyroid sick syndrome, or more recently, NTI syndrome (NTIS). The prevalence of NTIS is particularly high (up to approximately 80%) in critically ill patients with T4 levels below 3 µg/dL (2).

The bidirectional interaction between the hypothalamic-pituitary-thyroid axis and the immune system has been a topic of ongoing discussion for many years (3). Animal models have demonstrated that, in addition to TSH, THs such as T4 and T3 play a crucial role in the homeostatic regulation and functional activity of lymphocyte populations. The essential role of thyroid function in lymphopoiesis has been documented in numerous studies. In critically ill patients, particularly those in intensive care units (ICUs), a marked decline in T3 concentrations is commonly observed, followed by low or normal plasma T4 levels, while TSH concentrations may remain normal or become reduced (3-5).

Patients with severe illnesses have been reported to exhibit reduced TSH levels (6,7). Declines in serum T4 and TSH concentrations have been associated with increased mortality in cases of sepsis and septic shock, with the decrease in T4 identified as the most significant predictor of mortality (8-10). Studies have also investigated the potential effects of TSH and THs on various components of the immune system (11). Circulating TH levels have been found to correlate positively with immunological reactivity, such as the preservation of lymphocyte subpopulations, in healthy individuals (12).

A recent study suggested potential associations between TSH, and THs and lymphopenia observed during coronavirus disease-2019 (COVID-19) infections. It was demonstrated that patients with severe lymphopenia had significantly lower levels of TSH, free T3, and free T4, and higher levels of inflammatory markers, findings which are comparable to those seen in bacterial sepsis (13).

However, the extent to which changes in TSH and TH concentrations are linked to components of the immune system in patients with mild, moderate, or severe infections remains unclear. Based on the existing literature, it is hypothesized that abnormal thyroid function may be associated with changes in the infection markers observed in these patients. To date, the relationship between thyroid function and inflammatory markers in both infectious and non-infectious conditions in children has not been thoroughly examined.

In this study, we aimed to evaluate whether infection markers in children presenting with acute infections could serve as predictors of clinical outcomes and to assess their relationship with thyroid function tests.

Materials and Methods

This study was approved by the Non-interventional Ethics Committee of University of Health Sciences Türkiye, University of Health Sciences Türkiye, İzmir City Hospital, in accordance with the Helsinki Declaration (decision no.: 2025/18, date: 13.02.2025).

Children under the age of 18 years who had previously presented to the pediatric outpatient clinics of Izmir City Hospital with acute infections and had blood tests performed were included in this study. All patients had their weight, height, and body mass index recorded and evaluated according to age and sex norms. Any findings suggestive of acute infection or thyroid disease identified during physical examination were documented.

In the study group, the following laboratory parameters were recorded from the patient files: inflammatory markers including C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR); complete blood count parameters including hemoglobin, white blood cell count, neutrophils, lymphocytes, platelets, eosinophils, monocytes, and mean platelet volume; biochemical parameters including glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, and albumin; and thyroid function tests including free T3, free T4, and TSH. If available, anti-thyroglobulin and anti-thyroid peroxidase antibody levels were also recorded in order to exclude chronic thyroiditis.

Infections such as acute sinusitis, otitis media, and pneumonia were grouped as severe infections compared to acute upper respiratory tract infections and gastroenteritis as they require higher doses and longer duration of antibiotics.

A control group consisting of children of similar age who had no diagnosis of acute infection and who had undergone

haematological and biochemical testing for other reasons was also evaluated. In this group, the relationship between thyroid function tests and laboratory parameters was analysed and compared to the study group. Additionally, this study aimed to assess whether these laboratory parameters could be used to predict infection severity, to determine in which clinical scenarios thyroid function tests might provide diagnostic utility, and to evaluate when they might lead to diagnostic uncertainty, especially in distinguishing thyroid disease from transient changes due to infection.

Following power analysis, it was determined that a minimum of 50 patients and 112 controls would be required. Those patients with chronic diseases such as chronic kidney disease, type 1 diabetes mellitus, or celiac disease; those with signs of chronic inflammation or diagnosed with chronic inflammatory conditions; patients using medications known to affect thyroid function tests or infection markers (e.g., antidepressants, anticonvulsants, anxiolytics); and those with incomplete data were excluded from this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0. The distribution of the data was assessed using the Kolmogorov-Shapiro test. Descriptive statistics are expressed as numbers, percentages, means, and standard deviations for normally distributed variables, and as medians with interquartile ranges (25^{th}-75^{th} percentiles) for non-normally distributed variables. The Student's t-test was used to compare normally distributed variables between groups, while the Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were analysed using the chi-square test. Pearson or Spearman correlation analysis was performed in order to evaluate associations between parameters, depending on the data distribution. One-Way analysis of variance (ANOVA) was used to compare the mean values of continuous variables between the groups. Additionally, Tukey's post-hoc test was used for pairwise comparisons between the groups if the initial value of ANOVA test was statistically significant. The sample size was calculated based on a power analysis with 80% power ($1-\beta=0.80$) and a significance level of 5% ($\alpha=0.05$), which are commonly accepted thresholds in behavioural sciences.

Results

A total of 162 children under the age of 18 years, who had previously presented to the pediatric outpatient clinics and had blood tests performed for various reasons, were included in this study. Fifty patients with a documented diagnosis of acute infection (mean age: 5.77±3.91 years; 54% female, n=27) were designated as the study group. Thirty-two patients had presented as acute upper respiratory tract infections, 4 patients as acute otitis media, 7 patients as acute gastroenteritis, 2 patients as acute sinusitis and 5 patients as acute pneumonia. A control group of 112 children from a similar age range (mean age: 6.65±4.73 years; 54.5% female) who had no diagnosis of acute infection at the time of evaluation was also included. Demographic data, anthropometric measurements (adjusted for age and sex), and laboratory findings for all of the participants are presented in Table I.

Overall, free T3 and TSH levels were significantly lower in the patient group when compared to the control group, while CRP, procalcitonin, and ESR values, as well as the CRP/lymphocyte ratio (CLR), neutrophil/lymphocyte ratio (NLR), and monocyte/neutrophil to lymphocyte ratio, were significantly higher in the patient group when compared to the controls. Except for body weight, no statistically significant differences were observed in any other patient characteristics between the groups.

Based on the clinical findings (persistent high fever, prolonged illness, need for antimicrobial therapy) and laboratory parameters (leukocytosis, elevated CRP, and procalcitonin), the patients were categorized into "severe disease" and "mild disease" groups. Comparisons of thyroid function tests and infection markers were made between the control group and the patients with mild and severe disease. The laboratory characteristics of these subgroups are presented in Table II. Levels of free T3, TSH, ESR, and CLR differed significantly between the severe and mild disease groups. CRP levels and monocyte/neutrophil to lymphocyte ratios showed significant differences both between the overall control and patient groups and also according to disease severity. Procalcitonin levels and NLRs did not significantly differ between the control group and the mild disease subgroup but were significantly elevated in the severe disease group when compared to both the mild disease and control groups.

A subgroup analysis was conducted in order to examine the relationship between significantly decreased T3 levels and hemogram as well as other infection markers within the study group. The median T3 level in the study group was 3.96±0.75, which was significantly lower when compared to the control group. Table III presents the correlation between T3 levels and infection parameters. A negative correlation was found between T3 levels and CRP, procalcitonin, neutrophil count, CLR, NLR, monocyte/lymphocyte ratio (MLR), and disease severity.

Table I. Baseline characteristics of the cohort

Parameter	All participants (n=162)	Control group (n=112)	Study group (n=50)	p value
Age (years)	6.38±4.50	6.65±4.73	5.77±3.91	0.25
Female, n (%)	88 (54.3)	61 (54.5)	27 (54)	0.956
Free T3 (pg/mL)	4.31±0.70	4.47±0.61	3.96±0.75	<0.001
Free T4 (ng/dL)	1.33±0.16	1.33±0.15	1.34±0.19	0.743
TSH (µIU/mL)	2.67±1.51	3.06±1.52	1.80±1.06	<0.001
Weight SDS*	0.37±0.80	0.23±0.83	0.51±0.76	0.077
Height SDS*	0.78±1.03	0.63±1.04	0.92±1.01	0.167
BMI SDS*	-0.14±0.70	-0.17±0.71	-0.11±0.71	0.685
CRP (mg/L)	8.97±18.25	1.10±1.23	16.52±22.91	<0.001
Lymphocytes (/mm^3)	3,758±1,952	3,466±1,460	3,976±2,241	0.181
Procalcitonin (ng/mL)	0.10±0.18	0.05±0.02	0.15±0.24	0.003
ESR (mm/h)	8.29±7.78	5.24±3.92	11.30±9.36	<0.001
CRP/lymphocyte ratio	0.00365±0.00805	0.00037±0.00048	0.00687±0.01035	<0.001
Neutrophil/lymphocyte ratio	1.62±1.70	1.10±0.55	2.18±2.17	0.001
Monocyte/lymphocyte ratio	0.25±0.17	0.18±0.09	0.31±0.21	<0.001

*Standard deviation scores adjusted for age and sex
T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone, SDS: Standard deviation score, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table II. Baseline laboratory findings of the groups

Parameters	General control (n=112)	Mild illness (n=39)	Severe illness (n=11)	p value
T3 (pg/mL)	4.47±0.61	3.99±0.80[a]	3.86±0.60[b]	<0.001[a], 0.012[b]
T4 (ng/dL)	1.33±0.15	1.34±0.19	1.35±0.19	>0.05
TSH (µIU/mL)	3.06±1.52	1.76±0.86[a]	1.96±1.63[b]	<0.001[a], 0.039[b]
CRP (mg/L)	1.10±1.23	12.26±19.88[a]	31.64±27.35[b,c]	0.003[a], <0.001[b], 0.001[c]
Lymphocyte (/mm^3)	3,466±1,460	3,893±2,164	4,273±2,586	>0.05
Procalcitonin(ng/mL)	0.05±0.02	0.12±0.16[a]	0.28±0.36[b,c]	>0.05[a], <0.001[b], 0.013[c]
Sedimentation rate (mm/h)	5.24±3.92	10.59±7.41[a]	14.22±15.31[b]	0.002[a], 0.002[b]
CRP/lymphocyte ratio	0.00037±0.00048	0.00599±0.01062[a]	0.00999±0.00909[b]	0.002[a], <0.001[b]
Neutrophil/lymphocyte ratio	1.10±0.55	1.88±1.84[a]	3.24±2.95[b,c]	>0.05[a], <0.001[b], 0.03[c]
Monocyte/lymphocyte ratio	0.18±0.09	0.28±0.17[a]	0.40±0.31[b,c]	0.004[a], 0.037[b], <0.001[c]

Data are presented as mean ± standard deviation, *p<0.05
[a]indicates a significant difference between mild illness and control groups
[b]indicates a significant difference between mild illness and severe illness groups
[c]indicates a significant difference between severe illness and control groups
T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone, CRP: C-reactive protein

Table III. Pearson correlation of clinical parameters with T3 levels

Parameters	Crude r	p value
CRP	-0.210	0.039
Procalcitonin	-0.239	0.018
Sedimentation rate	-0.193	0.063
Neutrophil	-0.243	0.016
Platelet	0.156	0.123
Lymphocyte	0.132	0.193
AST	0.108	0.287
ALT	0.084	0.408
Albumin	0.009	0.928
CRP/lymphocyte ratio	-0.242	0.017
Neutrophil/lymphocyte ratio	-0.288	0.004
Monocyte/lymphocyte ratio	-0.267	0.008
Disease severity	-0.326	<0.001

T3: Triiodothyronine, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Discussion

In our study, T3 and TSH levels were found to be significantly lower in the patient group compared to the control group, while CRP, procalcitonin, sedimentation rate, and the ratios of CLR, NLR, and MLR were significantly higher.

NTIS refers to alterations in thyroid function tests observed during starvation, malnutrition, acute and chronic illnesses, or surgical procedures, despite the absence of primary thyroid disease. Various thyroid dysfunction patterns may be observed depending on the severity and progression of the underlying illness. In less severe illnesses, low T3 levels with normal or elevated T4 levels and normal or low TSH levels are expected. In our study, the patient group exhibited significantly decreased T3 levels. In acute illnesses, particularly in critically ill patients, a rapid decline in T3 levels may occur, known as "low T3 syndrome" (5). Previous studies have reported the presence of low T3 syndrome in approximately 60-70% of critically ill patients admitted to ICUs (14-16). When our patient group was stratified into "severe" and "mild" illness categories, T3 and TSH levels were significantly lower in the severe illness subgroup.

There is evidence suggesting the development of central hypothyroidism during severe NTIs. In such cases, the diurnal rhythm of TSH is disrupted, although the TSH response to TRH remains intact. Additionally, decreased messenger ribonucleic acid expression involved in TRH synthesis within the hypothalamic paraventricular neurons has been demonstrated. These findings collectively indicate TRH deficiency in severe NTIS. Consistent with this, TSH levels in our patient group were significantly lower when compared to the controls. During the recovery phase, TSH levels typically rise and may exceed normal limits before a normalization of TSH is observed (17).

When the patient group was categorized into "severe illness" and "mild illness," T3, TSH, sedimentation rates, and CLR were found to be significantly different between severe and mild illness, while CRP levels and MLRs differed both between the overall control and patient groups and according to disease severity. Procalcitonin levels and NLRs did not show significant changes when compared to the controls in the mild illness group; however, in the severe illness, these markers were significantly elevated in comparison to both the mild illness and control groups.

In a study examining low T3 syndrome during COVID-19 infection, patients within the lowest tertile of T3 levels demonstrated higher CRP levels and lower average lymphocyte counts (18). Another study assessing the relationship between acute illness severity and NTIS found a positive correlation between disease severity and reverse T3 (rT3) levels, with higher rT3 values associated with severe disease (19). The same study also reported a negative correlation between disease severity and total T3 and T4 levels, while no statistically significant relationship was found with free T3 and T4 levels (19).

In our study, NLR did not significantly differ between the controls and the mild illness patients but was significantly higher in the severe illness group when compared to both the mild illness and control groups. NLR, defined as the ratio of absolute neutrophil count to absolute lymphocyte count, is an accessible, cost-effective, and easily calculated marker considered a valuable measure of systemic inflammation (20-23). It has been linked to various inflammatory and cardiovascular diseases, with elevated levels observed in conditions such as obesity, hypertension, diabetes mellitus, metabolic syndrome, and several cancers (20-26). Recent studies have also explored the prognostic role of NLR in COVID-19, showing promising results for its use as a biomarker (27-30). NLR has demonstrated strong correlations with adverse outcomes and potential utility as a risk stratification tool (27,31,32). A meta-analysis reported that NLR consistently had the highest predictive value across multiple parameters of severe COVID-19, including disease

severity, ICU admission, progression to acute respiratory distress syndrome, the need for mechanical ventilation, the length and cost of hospital stay, time to negative PCR, and mortality (20).

Recent studies have also highlighted the association of elevated CLR with adverse outcomes in certain clinical contexts. For example, a meta-analysis by Lagunas-Rangel (33) indicated that increased CLR reflects poor prognosis in COVID-19 patients. Furthermore, elevated CLR has been suggested as a prognostic indicator of poor outcomes in patients with malignancies (34-36). Specifically, Mungan et al. (35) found that CLR was more effective than CRP alone in predicting poor prognosis following colorectal surgery. Studies evaluating the role of CLR in predicting disease severity have shown significantly higher ratios in patients with severe illness, although CLR was less predictive compared to NLR (20). Consistent with these findings, our study also observed significantly elevated CLR levels in the severe illness group when compared to the mild illness group.

The MLR has also been found to be associated with morbidity in various infections, inflammatory conditions, certain cancers, and psychiatric disorders such as depression and schizophrenia, and has been reported as a useful prognostic indicator in some studies (37-41). In our study, MLR was significantly higher in the mild illness group compared to the controls and was significantly elevated in the severe illness group when compared to both the mild illness and control groups.

T3 levels, which were significantly decreased in our patient group, showed negative correlations with CRP, procalcitonin, neutrophil counts, CLR, NLR, MLR, and disease severity. A single-centre retrospective study including adult COVID-19 patients classified into moderate, severe, and critical groups demonstrated that dynamic changes in CLR were inversely correlated with disease severity (42). In a retrospective study involving 306 patients with ulcerative colitis, NLR was suggested as a non-invasive marker of disease activity (43). Another study investigating the prognostic role of NLR and MLR during acute exacerbations of chronic obstructive pulmonary disease (COPD) showed that these ratios were elevated in COPD patients when compared to healthy controls, further increased during exacerbations, positively correlated with CRP, and were associated with increased mortality (33). However, data on the correlation of these markers with thyroid function tests remain limited.

It is widely accepted that NTI is a physiological adaptive response during severe disease, which reduces basal metabolic rate in order to minimize caloric and protein expenditure. Whether to treat these alterations remains a matter of debate. The literature includes studies evaluating thyroid function tests during infectious and inflammatory states, demonstrating that thyroid functions can be affected during infections. Several adult studies have assessed correlations between infection markers and hematologic parameters, reporting associations with disease severity. In this study, we demonstrated, for the first time in children, a significant correlation between thyroid function and markers of infection/inflammation, which also varied according to disease severity.

Study Limitations

Our study had some limitations. Its relatively small sample size in the severe illness group and its retrospective design limited the ability to confirm diagnoses with viral swabs or cultures as direct evidence of infection. Nevertheless, this study's novelty lies in it being the first to investigate the relationship between inflammatory markers and thyroid function in pediatric infectious and non-infectious diseases, with significant results obtained.

Conclusion

In conclusion, this is the first study to examine the relationship between markers of inflammation and thyroid function in children with infectious and non-infectious conditions. Thyroid function correlates with infection/inflammation markers in pediatric patients presenting with acute infections, and these correlations can be used to predict disease prognosis according to severity.

Ethics

Ethics Committee Approval: This study was approved by the Non-interventional Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital, in accordance with the Helsinki Declaration (decision no.: 2025/18, date: 13.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., E.E., B.N.D., Concept: G.A., Design: G.A., B.N.D., Data Collection or Processing: S.O., B.A., Analysis or Interpretation: G.A., E.E., Literature Search: G.A., E.E., Writing: G.A., E.E.

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Original Article

The Relationship Between Social Media Use, Health Applications, and Metabolic Control in Young People with Type 1 Diabetes

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ABSTRACT

Aim: This research aimed to determine the characteristics of social media and mobile/web application usage in young people with type 1 diabetes (T1D) and to examine its effects on their metabolic control.

Materials and Methods: We enrolled 206 young people with T1D (aged 10-25 years) in this cross-sectional study. Face-to-face interviews were used to assess the relationships between their social media use, health practices, and metabolic control.

Results: The participants (55% girls) had a mean age of 13.33±4.40 years and a median diabetes duration of 4.83 years (interquartile range=7.31). The last 1-year average hemoglobin A1c (HbA1c) values were 8.02±1.39%. It was observed that HbA1c increased as daily phone usage time increased (r=0.18; p=0.01). The primary reason for internet use was accessing social media (73%). Other prevalent uses included watching movies (42%), alongside using health apps, playing games, and online shopping (each at 38%), and accessing education/information (37%). Blood sugar monitoring was the most frequently used application with 67 users (27.9%). It was followed by a pedometer (60 users; 25.0%) and carbohydrates counting (56 users; 23.3%). Less common applications included continuous glucose monitoring (26 users; 10.8%), care reminders (13 users; 5.4%), and pulse rate monitoring (9 users; 3.8%). The HbA1c values of those who used a blood sugar monitoring app were lower than those who did not use it (7.71±1.38; 8.23±1.36 p=0.01, respectively). Participants who used a pedometer app had a higher body mass index standard deviation score than non-users (0.53±1.11 vs. 0.32±0.99, respectively); however, this difference was not statistically significant (p=0.237).

Conclusion: Health applications may support diabetes management in young people with T1D, while excessive digital engagement may negatively impact metabolic outcomes.

Keywords: Type 1 diabetes, social media, health applications, young people

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Introduction

In recent years, digital technology has been involved in every aspect of life. Healthcare is one of the areas which uses digital technology most effectively and beneficially. Individuals can access health-related digital content without limitations of time and place. Smartphones provide faster access to digital content and have become an integral part of daily life (1). Internet usage is increasing day by day. Along with this increase, children and teens use the internet more. The pandemic increased the exposure of children and young people to digital screens, resulting in a surge in their use of mobile and web technology. Children and young people have easily adopted technology and new communication opportunities into their lives and education (2). This adaptation may be advantageous in type 1 diabetes (T1D) management to help young people develop self-management skills and behaviours (3). Numerous medical applications and internet options have emerged to meet the needs of individuals with T1D (4,5). When research on the use of digital technology, web, and mobile applications was examined, it was seen that there were studies on young people without chronic diseases. However, understanding the health consequences of the use of digital technology in chronic diseases is valuable in the development of new applications and web services. To date, there is insufficient information on the impact of smartphone apps and technology services, especially on whole-life conditions such as T1D. This research was conducted in order to determine the use of mobile, web, and communication technologies by young people aged 10 to 25 years with T1D and their effects on metabolic control.

Materials and Methods

Study Design

A descriptive cross-sectional survey was conducted with young people with T1D from June to August 2024. The survey incorporated closed questions about demographics and technology use. The survey was designed in a paper format and was filled out using a face-to-face interview technique under the observation of the researcher.

Ethics Approval

This study was approved by the Ege University Medical Research Ethics Committee (approval number: 24-9T/53, date: 05.09.2024). The aim of this study was explained to each participant, and written informed consent was obtained.

Inclusion Criteria

Inclusion criteria were as follows: being young (aged 10-25 years inclusive), having a diagnosis of T1D for at least 6 months, being able to read and understand Turkish, and being able to provide informed consent.

Survey Design

The survey consisted of 2 parts, with each part of the survey presented on a separate page. Part 1: Demographic information and technology access: including age, sex, educational background, age at diabetes diagnosis, mobile phone ownership, mobile phone and web usage time, the purpose of using the internet, and mobile phone and social media usage. Part 2: Using technology to manage diabetes and health: currently available apps and preferences for health apps.

Statistical Analysis

Data analysis was performed with a statistical package (SPSS Inc., version 25.0, Chicago, IL, USA). The normal distribution of data was assessed using the Shapiro-Wilk test with $p>0.05$ indicating a normal distribution. The survey data were analysed and summarized using descriptive quantitative analyses including means, standard deviations, and proportions. Correlation analysis was applied for the relationship between data. Only completed surveys were included in the analysis.

Results

This study examined the demographic data for 206 children and young people with T1D. Among the participants, 55% (n=107) were female, and people aged 10 to 15 years accounted for 47.6% (n=89). The most recent average hemoglobin A1c (HbA1c) value before this study was recorded as 8.12±1.47%. However, to minimize the impact of lifestyle and psychological factors which could affect treatment adherence and HbA1c, the average HbA1c value over the last year (8.03±1.39%) was also calculated. Table I shows the demographic characteristics, information about T1D, and physical findings. Out of the 206 study participants, only 35 did not have their own mobile phones. They were using their family's phone. In addition, 83% (n=171) of the children and young people had a smartphone, 64% (n=132) had their own computer, and 96% (n=198) had daily internet access. On average, participants spent 2.19±2.11 hours per day on mobile phones and spent 3.16±2.07 hours per day on the internet. As the age of the participants increased, the duration of internet

use increased (r=0.291; p=0.001). As the duration of internet use increased, the HbA1c value also increased (r=0.180; p=0.017). Regression analysis showed that age had no effect on HbA1c (R=0.124, R2=0.015, F=2.832, p=0.094). The study participants mainly used the internet to enter social media (73%). Other areas of use of the internet were watching movies (42%), playing games (38%), accessing education and information (37%), health applications (38%), as well as shopping online (38%). Regarding mobile health (mHealth) applications, the majority of participants reported using their smartphones and internet-based tools primarily for diabetes management apps (62%), followed by pedometers (25%), heart rate monitoring (3.8%), and reminder systems.

There was no effect of pedometer use on HbA1c, but it was observed that subjects with high body mass index (BMI) standard deviation score (SDS) used pedometers (pedometer user BMI SDS: 0.53±1.11; non-pedometer user BMI SDS: 0.32±0.99, p=0.237). The last HbA1c value and 1-year average HbA1c value of those who used any health application were found to be lower than those who did not use them (p=0.020; p=0.011, respectively). Likewise, both the 1-year average and the last HbA1c value of those using diabetes-related apps were found to be lower (p=0.047; p=0.024, respectively). Table II and Table III summarize the participants' mobile app and internet usage and their diabetes effects.

Table I. Demographic characteristics, information about type 1 diabetes and physical findings

	n	**%**
Sex		
Male Female	98 108	47.57 52.43
Age group (years)		
10-15 15-20 >20	89 74 24	47.59 39.57 12.83
Treatment		
CSII MDI	67 118	36.22 63.78
	Mean ± SD	**Median (IQR)**
Physical findings		
Weight SDS Height SDS BMI SDS	0.18±1.06 -0.36±1.06 0.38±1.03	0.21 (1.50) -0.43 (1.48) 0.50 (1.38)
Information about type 1 diabetes		
Diabetes duration (years) HbA1c (%) Mean HbA1c (%) in the past 1 year Total insulin (U/kg/d) Basal insulin (%) Bolus insulin (%)	5.81±4.64 8.12 ±1.47 8.03±1.39 0.83±0.32 42.79±11.63 57.17±11.63	4.83 (7.31) 8.0 (1.80) 7.90 (1.80) 0.81 (0.32) 41.13 (15.96) 58.82 (15.96)

SDS: Standard deviation score, IQR: Interquartile range, SD: Standard deviation, CSII: Continuous subcutaneous insulin infusion, MDI: Multiple daily injections, HbA1c: Hemoglobin A1c

Table II. Online applications used by young people with type 1 diabetes

Reason for internet usage	**%**	**Usage of mobile health applications**	**%**
Youtube and watching videos Accessing and listening to music Instagram, Facebook, X Watching movies Playing various games Access to education and information Shopping Health applications	77 53 50 42 38 37 22 33	Carbohydrate counting application Continuous glucose monitoring application Capillary blood sugar monitoring application Pedometer application Heart rate counting application Reminder application	23.3 10.8 27.9 25 3.8 5.4
Social media user	73	Diabetes application user	62

Table III. HbA1c values of young people with type 1 diabetes according to social media and health applications			
	Social media users	**Non-social media users**	**p-value**
HbA1c (%)	8.04±1.44	8.32±1.56	0.316
1-year average HbA1c (%)	7.96±1.33	8.19±1.54	0.262
	Health applications users	**Non-health applications users**	**p-value**
HbA1c (%)	7.87±1.57	8.40±1.30	0.020*
1-year average HbA1c (%)	7.77±1.43	8.31±1.29	0.011*
	Diabetes applications users	**Non-diabetes applications users**	**p-value**
HbA1c (%)	7.93±1.54	8.36±1.36	0.047*
1-year average HbA1c (%)	7.81±1.41	8.28±1.33	0.024*
*: p<0.05 HbA1c: Hemoglobin A1c			

Discussion

The use of social media and mHealth applications is quite common in young people with T1D (6). However, the mHealth applications, web services, and social media preferences of young people with T1D, their frequency of use, and their effects on metabolic control are unknown. This research was conducted in order to determine the usage characteristics of mobile and web applications in young people with T1D and to investigate their effects on metabolic control.

The multifunctional characteristics of smartphones and the internet allow multiple interventions, including knowledge and self-management skills enhancement. For this reason, smartphones and the internet are used at a high rate among adolescents and young people worldwide. According to the Center for Internet and Technology (2018), an estimated 95% of adolescents in the United States own a personal computer. A total of 45% of adolescents have stated that they use the internet constantly on their devices. In the United Kingdom, 62% of adolescents aged 12 to 15 years and in Australia, 94% of adolescents aged 16 to 17 years own a mobile phone (7). In our research, 64% of the children with T1D had a computer, 83% had a smartphone, and 96% had internet access every day. These results show that our participants were using their computers, the internet, and smartphones more than was reported in the worldwide data. This result makes the purpose of our research more important.

Especially, there is a need for alternative ways to support the diabetes management of young people with T1D. mHealth apps have the potential and power for the promotion of self-management in people with T1D (8). Today, more than 100,000 health-related applications are providing useful tools for those individuals who want them (9). Research has shown the positive effects of mHealth applications in diabetes management (4,10,11). One study which looked at 13 diabetes mobile apps found that they did work to lower HbA1c. The intervention group had an average 0.44% drop compared to the control group (12). Majeed-Ariss et al. (13) did a systematic review of the literature on the effectiveness of mobile apps designed to help teens manage their diabetes. They found that the average number of times blood glucose levels were checked each day went up by 50%, but HbA1c did not change significantly (13). In our study, we found that participants using mobile diabetes applications had lower HbA1c values than those using other applications. This result supports the literature.

However, mobile application and internet usage time is an important factor. While the internet usage time in the world is 5 hours 25 minutes/day, in our country, this rate was determined to be 7 hours 24 minutes/day (14). When participants were asked about the time they spent on the internet and phone, on average, they spent 2.19±2.11 hours per day on mobile phones and 3.16±2.07 hours per day on the internet. We observed an increase in the participants' internet usage time as their age increased. Increasing internet usage time resulted in an increase in HbA1c values. The increase in internet usage time may have caused the exercise time to decrease. However, we did not include exercise times in our study. It is one of our limitations.

Today's adolescents and young adults have grown-up in a technological age, embracing technology as a way to interact with others and education in social media (15). The role of social media (Facebook, Twitter, YouTube, blogs, and wikis) has expanded to diabetes education and management in youth. According to research, many

individuals are seeking social and emotional support on the Web (16). Malik et al. (6) stated in her research that adolescents with T1D expressed interest in the use of social media to support their diabetes management. Social media (Facebook, Instagram, music, and information videos) may be a more effective method for adolescents to communicate with their diabetes care team. In addition, social media may be a tool for adolescents to help each other (6). Petrovski et al. (17) found that social media usage allows people with T1D to gain diabetes knowledge and interact in their daily insulin adjustments. Patients with chronic diseases around the world use the internet to seek, meet, and interact with patients with similar problems (17).

In our research, participants used social media to listen to music (53%), watch videos (77%), and interact with their friends (50%). We found that adolescents and young people who used social media had lower HbA1c values than those who did not use it. Although the result was not statistically significant, it reflected the potential importance of social media for peer support and information sharing.

However, while acknowledging this potential of social media, we cannot ignore the real and serious risks inherent in these platforms' uncontrolled nature. Today's social media environment risks becoming a "wild west" for vulnerable groups, particularly adolescents (18,19). On these platforms, inappropriate eating behaviours and unhealthy "miracle" diets can be normalized, and even a serious chronic disease like T1D can be trivialized by entirely fraudulent and dangerous claims, such as promises of a cure without insulin (20). Inadequate oversight and age-specific restrictions allow misinformation to spread rapidly, distorting body image and negatively impacting young individuals prone to eating disorders (21). The diabetes team should support the use of mobile and internet applications, guiding patients toward reliable resources, while must focus on implementing regulatory oversight, fostering professional medical engagement, and enhancing media literacy. Social media can only transform into a constructive force once these conditions are met.

Study Limitations

This study has two main limitations. First, all data on phone usage and application preferences were based on self-report, which may introduce recall bias or social desirability bias. Second, the single-center design and relatively small sample size (n=206) limit the generalizability of the findings to all young people with T1D. The results may not be applicable to populations with different socio-cultural or economic backgrounds.

Conclusion

As a result, recognizing that adolescents and young adults with T1D are in need of support in diabetes management, mobile diabetes apps may offer a means to enhance collaboration with the care team in order to improve diabetes management and HbA1c outside of the clinical setting. Moreover, when used correctly, social media and the internet can provide benefits in diabetes management, peer support, and care. The diabetes team should support mobile/internet applications in order to enhance outcomes and improve diabetes education. Additionally, online education programs should be developed due to reasons such as the increasing prevalence of T1D, the insufficient number of health professionals, and difficulties in access.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval number: 24-9T/53, date: 05.09.2024).

Informed Consent: Written consent was obtained from the chidren and their parents.

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Footnotes

Authorship Contributions

Concept: G.D., Y.A.A., S.Ö., D.Ö.K., D.G., Design: Y.A.A., S.Ö., D.Ö.K., D.G., Data Collection or Processing: G.D., Analysis or Interpretation: G.D., Literature Search: G.D., Y.A.A., S.Ö., D.Ö.K., D.G., Writing: G.D., Y.A.A., S.Ö., D.Ö.K., D.G.

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Original Article

Validation of a Foreign Body Aspiration Scoring System in Critically Ill Children: Retrospective Analysis of Outcomes and Bronchoscopy

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ABSTRACT

Aim: Foreign body aspiration (FBA) is a common and potentially life-threatening emergency in pediatric patients. While bronchoscopy remains the gold standard for diagnosis, it carries procedural risks and may be unnecessary in a substantial number of cases. The Foreign Body Aspiration Score (FOBAS) was developed in order to improve diagnostic accuracy, but its utility in pediatric intensive care unit (PICU) settings has not been validated. This study aimed to externally validate the FOBAS system in a PICU population and assess its diagnostic performance and clinical applicability.

Materials and Methods: In this single-centre retrospective cohort study, 54 children aged 1 month to 18 years, admitted to a PICU with suspected FBA and undergoing bronchoscopy between 2015 and 2024, were analysed. Demographics, clinical findings, imaging, and FOBAS parameters were evaluated. The association between FOBAS scores and bronchoscopy results was statistically analysed.

Results: Of the 54 patients, 35 (64.8%) had a confirmed foreign body. The median FOBAS score was significantly higher in the positive group (7.0 vs. 3.0, $p<0.001$). Receiver operating characteristic analysis revealed excellent diagnostic performance (area under the curve: 0.910), with a cut-off of 6.5 providing 74.3% sensitivity and 88.5% specificity. Multivariate analysis identified foreign body exposure and total FOBAS score as independent predictors of positive bronchoscopy.

Conclusion: FOBAS demonstrates high diagnostic accuracy in critically ill children with suspected FBA and may reduce unnecessary bronchoscopies in the PICUs. A cut-off score of ≥6.5 effectively stratifies risk and supports clinical decision-making in intensive care settings.

Keywords: Foreign body aspiration, FOBAS score, pediatric intensive care unit, validation, bronchoscopy

Introduction

Foreign body aspiration (FBA) is a notable cause of childhood morbidity and mortality, with an incidence of around 1.4 per 100,000 person-years (1). Most cases occur in boys aged 1-3 years, linked to developmental factors such as oral exploration, poor chewing ability, and lack of coordination (2,3).

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Clinical presentations vary, and the classical triad (cough, wheezing, and reduced breath sounds) is seen in only a minority of cases (4). Typical symptoms such as cough, wheezing, respiratory distress, and fever may be present, yet the physical exam can be normal, making timely diagnosis difficult (5). Chest X-rays are often non-diagnostic with about half appearing normal (6). Common radiographic manifestations of FBA include unilateral air trapping, segmental or lobar atelectasis, and, less frequently, consolidation. Radiopaque objects are rare, as most aspirated materials are organic and not visible (7). Bronchoscopy remains the diagnostic and therapeutic gold standard, despite being invasive, requiring anaesthesia, and carrying complication risks. Its high false-negative rate (20-50%) also leads to unnecessary procedures and resource waste (8,9).

In order to address this, decision support tools have been introduced. Lee et al. (10) identified air trapping, unilateral decreased breath sounds, and witnessed choking as key predictors, while other models such as those by Özyüksel et al. (11), Fasseeh et al. (12), and Stafler et al. (13) have shown promise. The Foreign Body Aspiration Score (FOBAS), developed by Pozailov et al. (14), has demonstrated high sensitivity and specificity but lacks broad external validation.

Pediatric intensive care unit (PICU) patients may differ from other emergency populations due to comorbidities and more severe presentations, requiring tailored evaluation (15). Validating FOBAS in this setting is essential in order to reduce both missed diagnoses and unnecessary bronchoscopies. While timely diagnosis is vital for safety and resource use, delayed recognition increases complications (16). Thus, a reliable, PICU-specific scoring system is needed. This study aimed to externally validate FOBAS in PICU patients with suspected FBA and assess its diagnostic performance and clinical relevance.

Materials and Methods

This retrospective cohort study was conducted at a PICU, a nine-bed level III referral centre. We included all patients aged 1 month to 18 years admitted with suspected FBA between January, 2015 and December, 2024 who underwent bronchoscopy.

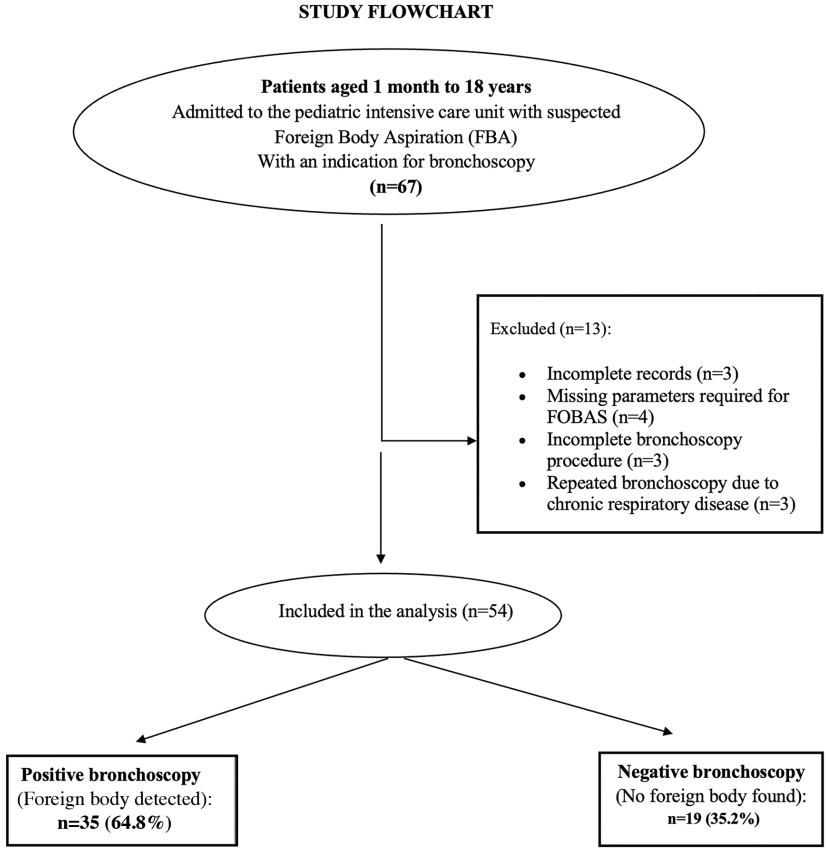

Figure 1. Study flowchart
FOBAS: Foreign Body Aspiration Score

The exclusion criteria were incomplete bronchoscopy, missing data required for FOBAS calculation, and repeated procedures due to chronic respiratory conditions (Figure 1). Of the 67 eligible patients, 54 met the criteria for analysis. Data were retrospectively collected from the electronic and archived medical records using a standardized form, covering demographics, comorbidities, aspiration history, clinical findings, vital signs, lab and imaging results, FOBAS parameters, bronchoscopy outcomes, complications, treatments, and follow-up.

FOBAS, developed and validated by Pozailov et al. (14), assigns a 0-10 score based on eight criteria: choking, exposure to a foreign object, sudden cough, absence of fever and rhinorrhoea, unilateral decreased breath sounds or wheezing, stridor, radiological findings, and radiopaque appearance. Risk levels are classified as low (1-3), moderate (4-6), or high (7-10). Each patient's score was calculated accordingly.

All bronchoscopies were performed under general anaesthesia, systematically examining the trachea and bronchi. Findings were recorded as positive (foreign body detected) or negative. Object characteristics and removal status were documented. Initial labs and chest X-rays were reviewed, along with intensive care unit/hospital stay durations, complications, and clinical outcomes.

Upon admission, all patients received blood tests [complete blood count, C-reactive protein (CRP), procalcitonin, biochemistry, blood gases] and posteroanterior chest radiographs, evaluated for signs of FBA (e.g., air trapping, atelectasis, consolidation, pneumothorax, mediastinal shift, radiopaque foreign body).

This study was approved by the Non-interventional Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (approval no.: 2025/0164, dated: 11.09.2025). Due to its retrospective nature, individual consent was waived. All data were anonymized and securely stored, in accordance with the Declaration of Helsinki (17).

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp.). The Shapiro-Wilk test assessed normality. Continuous variables are presented as mean ± standard deviation or median (interquartile range) and categorical data as frequencies and percentages. Group comparisons used independent samples t-test, Mann-Whitney U tests, chi-square or Fisher's exact tests as appropriate. Length of stay was analysed both as continuous and categorical data (>3 days in PICU, >7 days in hospital).

Diagnostic performance of FOBAS was evaluated with receiver operating characteristic (ROC) curve analysis and Youden's index in order to determine the optimal cut-off (18). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for total score, risk groups, and individual FOBAS items. In multivariate logistic regression, only variables with $p<0.005$ in univariate analysis were included, adhering to the "events per variable" rule (≥10 positive cases per variable) (19). The final model included foreign body exposure, total FOBAS score, sudden cough, and unilateral decreased breath sounds. All tests were two-tailed, with $p<0.05$ considered statistically significant. Reporting followed Standards for Reporting of Diagnostic Accuracy Studies (20) and Strengthening the Reporting of Observational Studies in Epidemiology (21) guidelines.

Results

Patient Characteristics

Among the 54 patients included, 35 (64.8%) had positive bronchoscopy findings and 19 (35.2%) had negative results. The mean age was 33.6±16.1 months ($p=0.101$), and 59.3% were male. Although body weight was higher in the negative group, the difference was not significant. In the analysis of comorbid conditions, developmental delay was observed in 0% of the control group compared to 21.1% in the negative bronchoscopy group ($p=0.012$). Additionally, gastroesophageal reflux was present in 17.1% of the control group versus 47.4% in the negative bronchoscopy group ($p=0.027$) (Table I). The mean age of the study cohort was 33.6±16.1 months. The mean ages for the groups with positive and negative bronchoscopy results were 31.5±16.4 months and 37.5±15.2 months, respectively, with no statistically significant difference observed ($p=0.101$). The majority of participants were aged between 6 and 48 months. Although individuals with positive bronchoscopy outcomes tended to be younger, the distribution of age groups did not differ significantly between the two groups ($p>0.05$).

Clinical, Laboratory, and Imaging Findings

Witnessed aspiration was significantly more frequent in the positive group (80.0% vs. 31.6%; $p=0.001$), as were sudden cough (82.9% vs. 42.1%; $p=0.006$), dyspnoea (74.3% vs. 42.1%; $p=0.041$), and unilateral decreased breath sounds (77.1% vs. 21.1%; $p<0.001$). Rhinorrhoea was more frequent in the negative group (36.8% vs. 8.6%; $p=0.023$). Chest X-rays showed more unilateral air trapping (45.7% vs. 10.5%; $p=0.020$) and more FBA-suggestive findings (77.1%

Table I. Patient characteristics, demographics, comorbidities, and medical history

Parameter	Total (n=54)	Positive bronchoscopy (n=35)	Negative bronchoscopy (n=19)	p-value
Age (months), mean ± SD	33.6±16.1	31.5±16.4	37.5±15.2	0.101
Age categories, n (%)				
6-24 months	20 (37.0)	16 (45.7)	4 (21.1)	0.155
25-48 months	22 (40.7)	13 (37.1)	9 (47.4)	0.574
>48 months	12 (22.2)	6 (17.1)	6 (31.6)	0.365
Sex, n (%)				
Male	32 (59.3)	20 (57.1)	12 (63.2)	0.667
Female	22 (40.7)	15 (42.9)	7 (36.8)	
Body weight (kg), mean ± SD	17.2±8.3	15.8±8.1	19.8±8.1	0.056
Height (cm), mean ± SD	84.8±8.0	84.1±7.4	86.1±9.0	0.517
Comorbidities and medical history, n (%)				
Asthma	4 (7.4)	3 (8.6)	1 (5.3)	>0.999
Cerebral palsy	4 (7.4)	1 (2.9)	3 (15.8)	0.119
Developmental delay	4 (7.4)	0 (0.0)	4 (21.1)	0.012
Gastroesophageal reflux	15 (27.8)	6 (17.1)	9 (47.4)	0.027
Any comorbidity	26 (48.1)	13 (37.1)	13 (68.4)	0.056

SD: Standard deviation

vs. 42.1%; p=0.023) in the positive group, while consolidation was more common in the negative group (42.1% vs. 14.3%; p=0.043) (Table II).

Laboratory values such as leukocyte count (12.5 vs. 9.9 $\times 10^3/\mu L$; p=0.047), CRP (p=0.007), and procalcitonin (p<0.001) were higher in the negative group. Positive cases had lower pO_2 levels (85.6 vs. 92.6 mmHg; p=0.011), and more frequently required mechanical ventilation (20.0% vs. 0%; p=0.044) and respiratory support (77.1% vs. 36.8%; p=0.008) (Table II).

Among the 35 confirmed FBA cases, 94.3% involved organic materials, most commonly peanuts (45.7%), sunflower seeds (20.0%), and walnuts (14.3%). The right main bronchus was the most frequent location (60.0%), followed by the left main bronchus (22.9%).

FOBAS Score Analysis

The median FOBAS score was higher in the positive group (7.0 vs. 3.0; p<0.001), with most positive cases in the high-risk category (74.3%) and over half of the negative cases in the low-risk category (57.9%; p<0.001). Significant predictors of positive bronchoscopy included foreign body exposure (p<0.001), sudden cough (p=0.002), absence of fever/rhinorrhoea (p=0.026), unilateral decreased breath sounds (p=0.002), and radiological findings (p=0.011) (Table III).

In univariate logistic regression, foreign body exposure (OR: 23.11), sudden cough (OR: 6.65), absence of fever/rhinorrhoea (OR: 3.74), unilateral decreased breath sounds (OR: 6.86), and suggestive radiology (OR: 4.64) were all significant. Each 1-point increase in FOBAS raised the likelihood of a positive bronchoscopy by 2.30 times (p<0.001). In multivariate analysis, only foreign body exposure (OR: 7.23; p=0.045) and total FOBAS score (OR: 2.07; p=0.015) remained independent predictors. Moderate-risk (OR: 33.6) and high-risk (OR: 243.8) categories were strongly associated with positive findings (Table IV).

Diagnostic Performance of FOBAS

ROC analysis showed excellent diagnostic accuracy for FOBAS, with an area under the curve (AUC) of 0.910 (95% CI: 0.860-0.960). The optimal cut-off was 6.5, yielding 74.3% sensitivity and 88.5% specificity. Positive and negative predictive values were 91.2% and 80.0%, respectively. The positive likelihood ratio was 7.1, and the negative likelihood ratio was 0.29. These results indicate that FOBAS is a reliable tool for identifying FBA, particularly at scores ≥6.5,

Table II. Clinical and laboratory data of foreign body aspiration cases

Parameter	Total (n=54)	Positive (n=35)	Negative (n=19)	p-value
Witnessed aspiration	34 (63.0)	28 (80.0)	6 (31.6)	0.001*
Time from aspiration to hospital admission (median, IQR, hours)	13.6 (5.5-29.6)	9.8 (5.1-22.0)	21.1 (9.3-35.0)	0.051
<24 hours	38 (70.4)	28 (80.0)	10 (52.6)	0.073
24-48 hours	13 (24.1)	6 (17.1)	7 (36.8)	0.181
2-8 days	2 (3.7)	1 (2.9)	1 (5.3)	1.000
>8 days	1 (1.9)	0 (0.0)	1 (5.3)	1.000
Clinical findings and physical examination				
Sudden cough	37 (68.5)	29 (82.9)	8 (42.1)	0.006*
Dyspnoea/shortness of breath	34 (63.0)	26 (74.3)	8 (42.1)	0.041*
Wheezing	40 (74.1)	24 (68.6)	16 (84.2)	0.331
Stridor	11 (20.4)	9 (25.7)	2 (10.5)	0.292
Cyanosis	10 (18.5)	8 (22.9)	2 (10.5)	0.465
Fever (≥38 °C)	17 (31.5)	9 (25.7)	8 (42.1)	0.351
Rhinorrhoea	10 (18.5)	3 (8.6)	7 (36.8)	0.023*
Unilateral decreased breath sounds	31 (57.4)	27 (77.1)	4 (21.1)	<0.001*
Unilateral wheezing	16 (29.6)	13 (37.1)	3 (15.8)	0.184
Rhonchi	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Rales	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Oxygen saturation (%)	96.2±2.6	96.2±2.4	96.2±3.0	0.731
Heart rate (beats/min)	120.7±16.1	123.2±16.0	116.2±15.7	0.142
Respiratory rate (breaths/min)	24.9±5.1	25.1±5.1	24.6±5.3	0.709
Systolic blood pressure (mmHg)	90.6±9.8	91.1±10.4	89.8±8.7	0.878
Chest X-ray findings				
Normal radiograph	13 (24.1)	6 (17.1)	7 (36.8)	0.181
Unilateral air trapping	18 (33.3)	16 (45.7)	2 (10.5)	0.020*
Atelectasis	22 (40.7)	15 (42.9)	7 (36.8)	0.889
Mediastinal shift	6 (11.1)	6 (17.1)	0 (0.0)	0.080
Pneumonia/consolidation	13 (24.1)	5 (14.3)	8 (42.1)	0.043*
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Radiopaque foreign body	6 (11.1)	6 (17.1)	0 (0.0)	0.080
Radiological findings suggestive of FBA	35 (64.8)	27 (77.1)	8 (42.1)	0.023*
Laboratory and microbiological findings				
Haemoglobin (g/dL)	12.0±1.6	12.0±1.6	12.1±1.7	0.664
Haematocrit (%)	36.1±4.8	35.9±4.7	36.3±5.2	0.657
White blood cell count ($\times 10^3/\mu L$)	10.8±3.9	9.9±3.2	12.5±4.5	0.047*
Neutrophil (%)	59.3±12.0	61.3±11.0	55.6±13.1	0.062
Platelet count ($\times 10^3/\mu L$)	333.8±83.4	344.7±81.7	313.9±84.8	0.145
CRP at admission (mg/L)	17.5 (5.1-31.5)	12.7 (3.8-24.1)	31.5 (14.8-50.3)	0.007*
Peak CRP (mg/L)	20.9 (6.2-37.8)	15.2 (4.6-28.8)	37.8 (17.8-60.4)	0.007*
Procalcitonin at admission (ng/mL)	0.3 (0.1-0.7)	0.2 (0.1-0.3)	1.1 (0.6-2.1)	<0.001*
Peak procalcitonin (ng/mL)	0.4 (0.2-0.9)	0.2 (0.1-0.4)	1.4 (0.8-2.7)	<0.001*

Table II. Continued

Parameter	Total (n=54)	Positive (n=35)	Negative (n=19)	p-value
pH at admission	7.40±0.04	7.40±0.05	7.40±0.04	0.841
pCO_2 at admission (mmHg)	40.69±4.98	41.02±5.10	40.09±4.82	0.538
pO_2 at admission (mmHg)	88.02±9.73	85.57±10.02	92.55±7.45	0.011*
HCO_3 at admission (mEq/L)	24.20±2.63	23.87±2.42	24.81±2.95	0.177
Lactate (mmol/L)	1.32±1.36	1.17±1.03	1.60 ±1.81	0.496
Treatment and respiratory support				
Antibiotic use	33 (61.1)	19 (54.3)	14 (73.7)	0.270
Steroid use	9 (16.7)	4 (11.4)	5 (26.3)	0.251
Bronchodilator use	35 (64.8)	19 (54.3)	16 (84.2)	0.057
Oxygen support	29 (53.7)	22 (62.9)	7 (36.8)	0.122
Mechanical ventilation	7 (13.0)	7 (20.0)	0 (0.0)	0.044*
Any respiratory support	34 (63.0)	27 (77.1)	7 (36.8)	0.008*
Complications				
Laryngospasm	4 (7.4)	2 (5.7)	2 (10.5)	0.607
Bronchospasm	5 (9.3)	4 (11.4)	1 (5.3)	0.646
Bleeding	2 (3.7)	1 (2.9)	1 (5.3)	1.000
Any early complication	11 (20.4)	7 (20.0)	4 (21.1)	1.000
Pneumonia	10 (18.5)	5 (14.3)	5 (26.3)	0.297
Atelectasis	6 (11.1)	3 (8.6)	3 (15.8)	0.653
Clinical outcomes and prognosis				
PICU length of stay (days)	2.5 (1.4-4.0)	2.5 (1.4-3.8)	2.7 (1.7-4.0)	0.550
PICU stay >3 days	20 (37.0)	12 (34.3)	8 (42.1)	0.785
Total hospital length of stay (days)	4.5 (2.6-6.6)	4.4 (2.8-6.5)	4.6 (2.7-6.9)	0.928
Mortality	3 (5.6)	3 (8.6)	0 (0.0)	0.544

Statistical significance: *p<0.05
Categorical variables are presented as n (%); continuous variables as mean ± standard deviation or median (IQR) as appropriate
IQR: Interquartile range, FBA: Foreign body aspiration, CRP: C-reactive protein, PICU: Pediatric intensive care unit

Table III. FOBAS analysis

Parameter	Total (n=54)	Positive (n=35)	Negative (n=19)	p-value
Choking episode	2 (0-2)	2 (0-2)	1 (0-2)	0.147
Foreign body exposure	1 (0-1)	1 (1-1)	0 (0-1)	<0.001
Sudden cough	1 (0-1)	1 (1-1)	0 (0-1)	0.002
Absence of fever/rhinorrhoea	1 (0-1)	1 (0-1)	0 (0-1)	0.026
Unilateral wheezing/decreased sounds	2 (0-2)	2 (2-2)	2 (0-2)	0.002
Stridor	0 (0-0)	0 (0-1)	0 (0-0)	0.194
Radiological findings	2 (0-2)	2 (2-2)	2 (0-2)	0.011
Radiopaque object	0 (0-0)	0 (0-0)	0 (0-0)	0.060
Total FOBAS (median, IQR)	7.0 (4.0-8.8)	7.0 (6.5-9.0)	3.0 (2.0-5.0)	<0.001
FOBAS risk category				
Low (1-3 points)	11 (20.4)	0 (0.0)	11 (100.0)	<0.001
Moderate (4-6)	15 (27.8)	9 (60.0)	6 (40.0)	
High (7-10)	28 (51.9)	26 (92.8)	2 (7.1)	

FOBAS: Foreign Body Aspiration Score, IQR: Interquartile range

Table IV. Logistic regression analysis of FOBAS parameters in relation to foreign body aspiration

FOBAS parameter	Positive group (n=35)	Negative group (n=19)	Univariable analysis			Multivariable analysis		
			OR	95% CI	p value	OR	95% CI	p-value
Individual FOBAS parameters								
Choking episode	25 (71.4%)	11 (57.9%)	1.82	0.56-5.85	0.481			
Foreign body exposure	32 (91.4%)	6 (31.6%)	23.11	5.01-106.57	**<0.001***	7.23	1.04-50.13	**0.045***
Sudden cough	29 (82.9%)	8 (42.1%)	6.65	1.87-23.56	**0.006***			
Absence of fever and rhinorrhoea	24 (68.6%)	7 (36.8%)	3.74	1.16-12.10	**0.050***			
Unilateral wheezing/ decreased breath sounds	28 (80.0%)	7 (36.8%)	6.86	1.97-23.86	**0.004***	1.02	0.33-3.15	0.968
Stridor	9 (25.7%)	2 (10.5%)	2.94	0.57-15.32	0.292			
Radiological findings	27 (77.1%)	8 (42.1%)	4.64	1.39-15.48	0.023*			
Radiopaque foreign body	6 (17.1%)	0 (0.0%)	8.59†	0.46-161.39	0.080			
FOBAS total score and risk categories								
FOBAS total score	8.9±4.2	3.7±2.1	2.30‡	2.28-2.33	**<0.001***	2.07‡	1.15-3.70	**0.015***
FOBAS risk categories								
Low risk (1-3 points)	0 (0.0%)	11 (100.0%)	1.00 (Ref)					
Moderate risk (4-8 points)	9 (60.0%)	6 (40.0%)	33.62	1.67-676.61	**<0.001***			
High risk (9+ points)	26 (92.9%)	2 (7.1%)	243.80	10.83-5489.80	**<0.001***			

Categorical variables are presented as n (%); continuous variables as mean ± standard deviation. Multivariable analysis included only variables with p<0.005 in univariable analysis, following the events per variable (EPV) rule
*: p<0.05, †: Odds ratio calculated using Haldane correction due to zero cell, ‡: Odds ratio per 1-point increase in FOBAS score
FOBAS: Foreign Body Aspiration Score, OR: Odds ratio, CI: Confidence interval

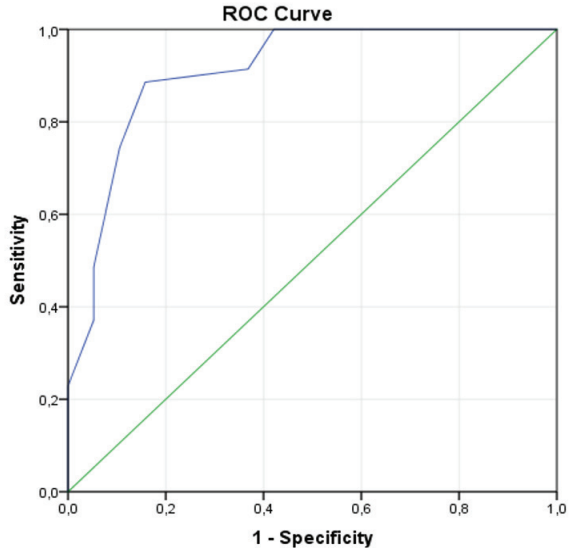

Figure 2. ROC curve demonstrating the diagnostic accuracy of the Foreign Body Aspiration Score for predicting positive bronchoscopy findings (AUC=0.910)
ROC: Receiver operating characteristic, AUC: Area under the curve

Table V. Diagnostic performance of FOBAS (ROC curve analysis)

Parameter	Value	95% CI
Area under the curve (AUC)	0.910	0.860–0.960
Optimal cut-off (Youden index)	6.5	
Sensitivity (%)	74.3	
Specificity (%)	88.5	
Positive predictive value (%)	91.2	
Negative predictive value (%)	80.0	
Positive likelihood ratio	7.1	
Negative likelihood ratio	0.29	

FOBAS: Foreign Body Aspiration Score, ROC: Receiver operating characteristic, CI: Confidence Interval

and may help reduce unnecessary bronchoscopies due to its strong positive predictive value (Table V, Figure 2).

Discussion

Our study presents the first external validation of FOBAS in patients admitted to a PICU for FBA. Our findings demonstrate that FOBAS shows strong diagnostic

performance in a PICU setting (AUC: 0.910), indicating its potential use not only in the general pediatric population but also as a reliable clinical decision support tool in critically ill children. To the best of our knowledge, this study represents the first external validation of the FOBAS specifically in critically ill pediatric patients, underscoring its potential to address a significant gap in clinical decision-making within the PICU setting.

The epidemiological findings of our study are consistent with the literature. A total of 94% of the detected foreign bodies were organic in nature, with peanuts and sunflower seeds being the most commonly identified objects. This ratio parallels the findings of Ding et al. (22) (93.5%) and aligns with the conclusions of Bajaj et al. (23), who reported that organic foreign bodies were associated with increased complication risks. Our findings are also important in demonstrating that regional dietary habits may influence the epidemiology of FBA.

PICU patients differ in many aspects from the general pediatric population. In our cohort, the rate of underlying diseases was 48.1%. Particularly, gastroesophageal reflux, cerebral palsy, and aspiration risks were more frequently observed in the negative bronchoscopy group. This indicates that symptoms mimicking FBA due to comorbidities can complicate the diagnostic process. It is clear that conditions such as neurological disorders and reflux make diagnosis more challenging and may affect the performance of FOBAS in these subgroups. As emphasized by Mîndru et al. (24), socio-demographic factors and comorbidities complicate the diagnostic process, thus making objective scoring systems even more critical in the PICU setting.

The literature indicates a lack of standardized and validated clinical algorithms for children presenting with suspected FBA, and most existing protocols are retrospective and limited in nature (25). Our study serves as the first external validation of FOBAS in a PICU cohort and demonstrates a higher predictive value with an AUC of 0.91. This suggests that FOBAS may be a reliable diagnostic tool not only in emergency department admissions but also in intensive care settings.

In the present study, exposure to a foreign body, sudden cough, absence of fever and rhinorrhoea, unilateral wheezing or decreased breath sounds, and radiological findings were all significantly associated with positive bronchoscopy findings. In contrast, choking episodes and stridor were not found to be statistically significant. In the original validation study (14), although stridor and absence of fever/rhinorrhoea did not reach statistical significance, they were included in the score for clinical reasons. Similarly, in our study, stridor was not significant, but absence of fever and rhinorrhoea was significantly associated with positive bronchoscopy. This discrepancy may be explained by the higher prevalence of infectious comorbidities in the PICU. Therefore, the contribution of FOBAS parameters may vary depending on patient characteristics, and absence of fever/rhinorrhoea may become a stronger predictor in the PICU.

Although many parameters showed significance in the univariate analysis, the CIs were wide. Multivariate analysis identified only a history of foreign body exposure and the total FOBAS score as independent predictors. This supports the observation reported in the original study: individual parameters are associated with various clinical situations and have limited discriminative power, whereas the total score offers a much more specific predictor. The high AUC (0.91) and specificity rate (88.5%) observed in our study demonstrate that FOBAS is a strong tool, especially in reducing unnecessary bronchoscopies in the PICU setting.

No FBA cases were identified in the low-risk group (1-3 points), indicating that bronchoscopy may be safely avoided in these patients. The FBA rate in the moderate-risk group (4-6 points) was 60% (n=9/15), which is higher than the original study's 36.6%. In the high-risk group (7-10 points), a positivity rate of 92.8% (n=26/28) was observed, which is largely consistent with the original study's 90%. These data indicate that FOBAS is effective in reducing unnecessary bronchoscopies in the low-risk group and in maintaining strong predictive values in the high-risk group within the PICU setting, while in the moderate-risk group, its performance may vary depending on the patient population.

The diagnostic performance of FOBAS was found to be similar to that reported in the original development study. While Pozailov et al. (14) prospective validation study reported an AUC of 0.89, our PICU cohort yielded an AUC of 0.910. This strong performance is also notable when compared to other scoring systems recently developed in pediatric critical care. Sautin et al. (26) highlighted that the time between suspected FBA and bronchoscopy impacts mortality and emphasized the importance of early diagnosis. Similarly, Zheng et al. (27) identified diagnostic challenges in developing countries through a global epidemiological study and noted the importance of standardized scoring systems in promoting healthcare equity.

In a study by Goodarzy et al. (28), the diagnostic value of chest CT in detecting FBA was assessed, emphasizing the limitations of conventional radiological methods. The CT

sensitivity was 89.2% and its specificity was 76.8%; when compared to FOBAS (sensitivity: 74.3%, specificity: 88.5%), FOBAS showed superior performance as a non-invasive method.

Lee et al. (10) reported C-statistics for current clinical prediction models ranging from 0.74 to 0.88; our findings exceeded the upper limit of this range. That same study identified air trapping (OR: 8.3), unilateral decreased breath sounds (OR: 4.8), and witnessed choking (OR: 3.1) as the strongest predictors of FBA. Similarly, in our cohort, unilateral breath sound reduction (77.1%) and witnessed aspiration (80%) were significantly higher in the positive bronchoscopy group. In a study by Yi et al. (29), a nomogram to predict major postoperative respiratory complications following rigid bronchoscopy was developed and reported an AUC of 0.847. This finding underlines the risks associated with bronchoscopy itself and emphasizes the importance of appropriate patient selection. The high negative predictive value (80%) of FOBAS allows for the safe postponement of bronchoscopy in low-risk patients, thereby reducing such risks.

Among the methodological strengths of our study are the external validation of FOBAS in a different patient population and the implementation of a comprehensive data collection process. The determination of the optimal cut-off value via ROC analysis and the evaluation of its association with clinical outcomes enhance the scientific value of this study. The shared multidisciplinary language provided by FOBAS suggests that it may serve as a practical tool which can facilitate decision-making processes among paediatricians, otolaryngologists, and anaesthesiologists.

However, our study also had several limitations. Due to its retrospective design, there is a risk of bias, and the single-centre experience may limit its generalizability. Although the sample size (54 patients) was adequate according to power analysis, validation in larger cohorts is still necessary. The PICU-specific characteristics of the patient selection (high pre-test probability, severe clinical presentations, coexisting comorbidities) may also have affected our results.

Our study supports the applicability of FOBAS in the PICU setting and presents one of the first datasets in this field. In the future, validation in larger, multicentre prospective studies will be essential in order to confirm these findings across broader populations. The development of a modified version tailored to PICU-specific factors (FOBAS-PICU), along with cost-effectiveness and long-term outcome analyses and integration with artificial intelligence, may further enhance its diagnostic power. Additionally, evaluation of its performance across different age groups and analysis of socioeconomic factors will contribute to its global applicability.

This study demonstrates that the FOBAS is a reliable and valid tool for predicting the presence of foreign bodies in children admitted to the PICU with suspected FBA. The high diagnostic accuracy, with an AUC of 0.910 and a cut-off score of 6.5 providing optimal sensitivity and specificity, supports its use as a clinical decision-making aid in critically ill pediatric patients. The FOBAS system may help reduce unnecessary bronchoscopies while minimizing the risk of missed diagnoses, thus improving both patient safety and resource utilization in intensive care settings. Further prospective, multicentre studies are warranted in order to confirm its utility across different PICU populations and clinical environments.

Study Limitations

Among the primary limitations of this study are its single-center and retrospective design, which may result in unavoidable record deficiencies and information bias. Additionally, the study's limited external validity is attributable to the patient profile specific to a tertiary-level PICU, and the relatively small subgroups contribute to wide CIs in multivariate analyses. Furthermore, the operator-dependent interpretation of bronchoscopy findings heightens the risk of observer variability, particularly in borderline cases. The retrospective nature of the study precludes the assessment of long-term outcomes, symptom recurrence, or cost-effectiveness. Consequently, prospective and multicenter studies are necessary to validate these findings.

Conclusion

The present study has established that FOBAS exhibits high diagnostic accuracy in pediatric patients admitted to the PICU with suspected FBA, and it may serve as a reliable decision-support tool for evaluating the necessity of bronchoscopy. The ability of FOBAS to deliver strong sensitivity and specificity, particularly at a threshold value of ≥6.5, the significant increase in positive bronchoscopy rates within the high-risk group, and its potential to minimize unnecessary interventions in the low-risk group, render the score an effective triage tool that could standardize clinical decision-making processes in intensive care practice. Despite variability observed in the moderate-risk group, the findings indicate that FOBAS is a valuable tool for predicting FBA in PICU patients and underscore the need for the score

to be validated through prospective studies across different centers and larger populations.

Ethics

Ethics Committee Approval: This study was approved by the Non-interventional Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (approval no.: 2025/0164, dated: 11.09.2025).

Informed Consent: Due to its retrospective nature, individual consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.D., A.A., S.A., Ç.U.D., Concept: M.D., A.A., Design: M.D., Ç.U.D., Data Collection or Processing: M.D., A.A., S.A., Analysis or Interpretation: M.D., AA., Literature Search: M.D., S.A., Writing: M.D., Ç.U.D.

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Case Report

Aggressive Ewing Sarcoma of the Mandible in a Child: A Case Report

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ABSTRACT

Ewing sarcoma is a highly aggressive malignant bone tumor which most commonly arises in the long bones and pelvis of adolescents and young adults. Craniofacial involvement, particularly of the mandible, is extremely rare and may mimic odontogenic or inflammatory lesions, leading to diagnostic delay. We report the case of a 14-year-old girl with histologically confirmed Ewing sarcoma of the left mandible. Clinical and initial radiological findings suggested an aggressive mandibular lesion with locoregional extension. For comprehensive baseline evaluation, an ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was performed. It demonstrated intense metabolic activity of the mandibular mass, consistent with high tumor aggressiveness, while excluding cervical, thoracic, abdominal, and skeletal metastases. This case underlines the crucial role of ^{18}F-FDG PET/CT not only in the initial staging of Ewing sarcoma but also in the differential diagnosis of atypical mandibular swellings in children and adolescents. By combining functional and anatomical data, PET/CT improves diagnostic confidence, guides therapeutic planning, and contributes to prognostic assessment in such uncommon presentations.

Keywords: Ewing sarcoma, mandible, child, FDG PET/CT

Introduction

Ewing sarcoma is a primary malignant bone neoplasm of uncertain origin which was first described by James Ewing in 1921 (1). It is a highly aggressive, small round blue cell tumor which typically arises from bone and, less frequently, from soft tissues (2). It represents approximately 10-15% of all primary bone malignancies in children and adolescents (3). The tumor most often involves the pelvis, femur, tibia, or humerus. Craniofacial localization is rare, accounting for only 1-4% of cases (4). Within the craniofacial skeleton, mandibular involvement is particularly uncommon, representing approximately 0.7% of all Ewing sarcoma sites (5), and it may easily be mistaken for odontogenic or inflammatory conditions. Such non-specific presentations

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often result in delayed diagnosis, which can adversely affect prognosis. Comprehensive and early imaging is therefore essential to establish the extent of the disease and guide multidisciplinary management, which usually combines neoadjuvant chemotherapy, surgery, and/or radiotherapy. In this context, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as a valuable diagnostic tool. In addition to its high sensitivity for detecting metabolically active lesions, it provides a whole-body overview which is crucial for differential diagnosis, initial staging, restaging, and response assessment. We report the case of a 14-year-old girl with mandibular Ewing sarcoma, an exceptionally rare presentation. This case underscores the importance of including Ewing sarcoma in the differential diagnosis of mandibular swellings in adolescents and highlights the pivotal role of ^{18}F-FDG PET/CT in both the diagnostic work-up and staging process. The aim of this report was to illustrate the diagnostic challenges posed by mandibular Ewing sarcoma and to emphasize the contribution of ^{18}F-FDG PET/CT in the staging and management of this rare localization.

Case Report

A 14-year-old girl presented with progressive swelling and pain localized on the left side of her face, which had been evolving over the prior few weeks. Clinical examination revealed a firm, tender mass in the left mandibular region. There were no signs of cervical lymphadenopathy, fever, weight loss, or other systemic symptoms. An initial contrast-enhanced CT scan revealed a large, destructive lesion of the left mandible associated with soft tissue invasion. Incidentally, a solitary 8 mm pulmonary nodule was also identified in the right upper lobe, raising concerns of possible metastatic spread. Histopathological analysis of a biopsy taken from the mandibular mass confirmed the diagnosis of Ewing sarcoma. Microscopically, the tumor consisted of small round blue cells with scant cytoplasm and hyperchromatic nuclei. Immunohistochemistry demonstrated diffuse membranous positivity for cluster of differentiation 99 and nuclear positivity for Friend leukemia virus integration 1. Markers for lymphoma (leukocyte-common antigen), rhabdomyosarcoma (desmin, myogenin), and carcinoma (cytokeratin) were negative, thereby supporting the diagnosis of Ewing sarcoma. In order to complete the initial staging and evaluate the extent of the disease, a whole-body ^{18}F-FDG PET/CT was performed. It demonstrated a markedly hypermetabolic mass involving both the horizontal body and ascending ramus of the left mandible (Figure 1). The lesion measured approximately 73×73 mm in axial dimensions and extended vertically over 111 mm. It exhibited a very high maximum

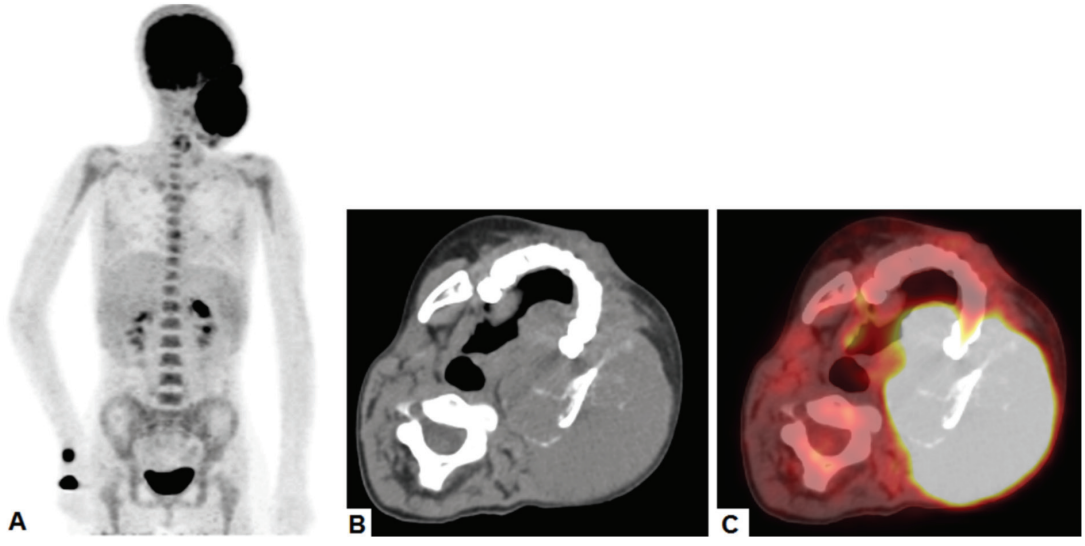

Figure 1. A: Maximum intensity projection image from the ^{18}F-FDG PET scan showing intense hypermetabolic activity in the left mandibular region, consistent with a large primary tumor, without evidence of distant metastatic uptake. **B:** Axial CT scan at the mandibular level revealing a large destructive mass involving the left mandibular body and ramus, with cortical bone lysis and extension into adjacent soft tissues. **C:** Axial fused ^{18}F-FDG PET/CT image demonstrating intense FDG uptake within the mandibular lesion (SUV_{max} 19.9), with a central photopenic area suggestive of necrosis and infiltration of surrounding tissues, including the left maxillary sinus and parapharyngeal space, showing intense hypermetabolic activity in the left mandibular region, consistent with a large primary tumor, without evidence of distant metastatic uptake.

^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value

standardized uptake value (SUV_{max}) of 19.9, reflecting intense metabolic activity. The tumor had a heterogeneous appearance with a central photopenic area suggestive of necrosis. It infiltrated the surrounding soft tissues, including the left maxillary sinus, the left parapharyngeal space, and extended anteriorly to the region of the external auditory canal. However, there was no involvement of the cranial vault. No abnormal FDG uptake was noted in cervical, supraclavicular, mediastinal, hilar, or abdominal lymph nodes. Importantly, the 8 mm pulmonary nodule identified on CT showed no FDG uptake, lowering the suspicion of metastatic disease. No other hypermetabolic foci were observed in the lungs. The liver, spleen, pancreas, adrenal glands, and gastrointestinal tract appeared metabolically unremarkable. Skeletal evaluation revealed no FDG-avid bone lesions suggestive of metastasis. A diffuse and mildly heterogeneous increase in bone marrow activity was noted in the spine, pelvis, and proximal long bones, with a peak SUV_{max} of 4.9 in the thoracic vertebrae. This pattern was interpreted as reactive bone marrow activation, commonly observed in pediatric patients or in the context of systemic inflammation. Overall, PET/CT confirmed the presence of an aggressive, metabolically active mandibular tumor with extensive local spread but no evidence of distant metastasis. These findings established the initial staging and supported the decision to begin curative-intent treatment. The patient subsequently received neoadjuvant chemotherapy according to the standard protocol, including vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. Despite the initiation of treatment, the disease progressed rapidly, and the patient's clinical condition deteriorated. She unfortunately died three months after the initial diagnosis.

Written informed consent was obtained from the patient's legal guardians for the publication of this case report and all accompanying clinical information. Assent was also obtained from the 14-year-old patient in accordance with ethical guidelines.

Discussion

Mandibular Ewing sarcoma is considered an exceptionally rare presentation within the spectrum of head and neck localizations, with only a limited number of case reports and small series described in the literature (2,4). This scarcity underlines the importance of detailed clinicopathological and imaging descriptions to guide both differential diagnosis and management. The non-specific clinical presentation often mimics odontogenic infections or benign jaw lesions, which may delay diagnosis and compromise prognosis. In our patient, the lesion was initially suggestive of an odontogenic process, emphasizing the need to include Ewing sarcoma in the differential diagnosis of mandibular swellings in adolescents. From a radiology and nuclear medicine perspective, ^{18}F-FDG PET/CT was pivotal. The intense metabolic activity and extensive local invasion it demonstrated were crucial findings which supported the diagnosis of a highly aggressive tumor rather than an odontogenic or inflammatory condition. As well as this diagnostic contribution, PET/CT provided a comprehensive baseline evaluation by excluding nodal, visceral, and skeletal metastases. Previous studies have shown that ^{18}F-FDG PET/CT can reveal additional metastatic sites not detected by conventional imaging in up to 21% of patients (6). Furthermore, its ability to quantify metabolic activity adds prognostic value by correlating with tumor aggressiveness and potential treatment response (7). The management of Ewing sarcoma is based on internationally established protocols, largely derived from cooperative group studies such as the Children's Oncology Group, the European Ewing Tumor Working Initiative of National Groups (EURO EWING), and the National Comprehensive Cancer Network (NCCN) guidelines. Current standards recommend a multimodal approach combining systemic multi-agent chemotherapy with local control by surgery and/or radiotherapy. First-line chemotherapy typically alternates vincristine, doxorubicin, and cyclophosphamide with ifosfamide and etoposide over 6-12 cycles (8), a regimen which has significantly improved survival compared to historical treatments. Surgical resection with negative margins remains the preferred option for local control whenever feasible, while radiotherapy is an effective alternative or adjunct in anatomically complex regions such as the head and neck (9). Modern radiotherapy modalities, including intensity-modulated radiotherapy and proton therapy, are recommended to optimize tumor targeting while limiting toxicity to surrounding critical structures, especially in children and adolescents (10). According to both NCCN and EURO EWING recommendations, management should be coordinated within a multidisciplinary team and ideally delivered in specialized sarcoma centers in order to maximize oncologic outcomes and preserve function. Recent advances are also exploring targeted and innovative therapies. Agents directed against molecular pathways such as the insulin-like growth factor 1 receptor and poly adenosine diphosphate-ribose polymerase inhibitors have shown encouraging activity in early trials (11). Immunotherapy approaches, including checkpoint inhibitors, are under investigation but are limited by the

typically low mutational burden of Ewing sarcoma (12). The prognosis of Ewing sarcoma is strongly influenced by the presence of metastases at diagnosis and by the tumor's histological response to chemotherapy. Patients with localized disease treated with intensive multimodal therapy achieve 5-year survival rates of approximately 70% (13). Nevertheless, mandibular involvement poses unique challenges related to anatomical complexity and the risk of delayed diagnosis, both of which may adversely affect outcomes. Histological response to neoadjuvant chemotherapy is also an important prognostic factor, correlating with long-term survival (14). Looking ahead, the future management of Ewing sarcoma is increasingly oriented toward personalized medicine. Genomic profiling may help identify actionable mutations and guide targeted therapies, moving beyond conventional cytotoxic regimens (15). Combination approaches incorporating chemotherapy with novel targeted agents or immunotherapy are currently under investigation and may enhance treatment responses (16). In parallel, advances in imaging, including PET tracers beyond FDG, and liquid biopsy technologies hold promise for earlier detection of residual or recurrent disease. Equally important are strategies to optimize functional and psychosocial rehabilitation, particularly for adolescent patients, in order to improve their quality of life after treatment. Overall, despite significant progress in multimodal therapy, the prognosis of mandibular Ewing sarcoma remains guarded, especially in those cases with delayed diagnosis or poor therapeutic response.

Conclusion

Mandibular Ewing sarcoma is an exceptionally rare and diagnostically challenging entity. ^{18}F-FDG PET/CT plays a pivotal role in its initial evaluation, not only by confirming the extent of locoregional disease and excluding distant metastases, but also by contributing to the differential diagnosis in adolescents presenting with atypical mandibular lesions. By providing comprehensive staging information, PET/CT helps guide therapeutic decisions and supports individualized, multidisciplinary management. Continued advances in imaging and treatment strategies hold the promise of improving outcomes in such uncommon and aggressive malignancies.

Ethics

Informed Consent: A written informed consent form was taken from the patient and family in order to publish this case.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.B., R.B., H.M., C.E.M, A.D., Concept: Y.B., A.D., Design: Y.B., A.D., Data Collection or Processing: Y.B., R.B., H.M., C.E.M., Analysis or Interpretation: Y.B., Literature Search: Y.B., Writing: Y.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

A Rare Pediatric Case of *Morganella morganii* Urinary Tract Infection with Hydronephrosis and Antimicrobial Resistance Challenges: A Case Report

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ABSTRACT

Morganella morganii (*M. morganii*) is a facultative anaerobic, gram-negative bacillus which uncommonly causes urinary tract infections in children. We report a rare pediatric case of *M. morganii*, highlighting the diagnostic and treatment challenges associated with this microorganism, its notable antimicrobial resistance profile, and the importance of antibiotic stewardship in guiding effective therapy.

Keywords: *Morganella morganii*, pediatric urinary tract infection, hydronephrosis, gram-negative bacilli, case report

Introduction

Morganella morganii (M. morganii) is a facultative anaerobic, gram-negative bacillus, non-lactose-fermenting, and urease-positive microbe. It belongs to the *Enterobacteriaceae* family, which is normally found in the gastrointestinal flora and is typically considered as an opportunistic pathogen (1). Although *M. morganii* has been more commonly associated with nosocomial infections in adults (2,3), community-acquired cases have also been reported (1,4).

There is limited data reporting on *M. morganii* infections, but studies across different countries have reflected the rarity of this microorganism in the general population and its exceptionally low incidence among pediatric patients. According to a study conducted in Australia from 2000 to 2019, only 709 cases of *M. morganii* were identified in the bloodstream, corresponding to an annual incidence of 9.2 cases per million population, with a median patient age of 75.2 years and also indicating an incidence of almost zero cases per million in children and adolescents. Among the 709 cases reported, only 97 (13.7%) cases were isolated from the renal system (4). Although that study specifically reported on *M. morganii* isolated from bloodstream infections, which does not directly apply to the patient described in this case study, it still serves as an indication of the organism's very low prevalence in the pediatric population.

Another study in Taiwan reviewed 82,861 patients over a 6-year period with gram-negative nosocomial infections, from which, *M. morganii* was isolated in only 1,219 cases (1.47%) (5).

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Between 2015 and 2017, a pediatric clinic in Türkiye conducted a retrospective study on a total of 2,866 cases of urinary tract infection (UTI) in children. *M. morganii* was isolated in the urine cultures of only 11 patients, revealing a prevalence of 0.38% among pediatric UTIs (1).

Given the limited epidemiological data available, the presence of *M. morganii* in the pediatric population remains both a diagnostic and therapeutic challenge, mainly due to its natural and acquired resistance to antibiotics. In this report, we describe a rare case of *M. morganii* pyelonephritis in an 11-year-old boy with newly diagnosed hydronephrosis, highlighting this pathogens potential to cause serious infection, particularly in medically complex children with communication barriers which may delay diagnosis and obscure the classic symptoms of UTI.

Case Report

An 11-year-old non-verbal, non-ambulatory male with cerebral palsy and developmental delay presented to the emergency department with a 3-day history of persistent fever (maximum temperature of 39.2 °C recorded at home) and irritability. One day prior to admission, he experienced five episodes of watery, non-bloody diarrhea and one episode of vomiting. His past medical history is significant extreme prematurity at 27 weeks' gestation, neonatal intensive care unit stay complicated by necrotizing enterocolitis requiring bowel surgery, and recurrent dental abscesses and infections. His immunizations were up to date, and his family history was unremarkable.

On physical examination, the patient appeared in mild discomfort but otherwise unremarkable. Laboratory workup revealed a low creatinine level of 0.7 mg/dL, a markedly elevated white blood cell (WBC) count of 28.8 $x10^3/\mu L$, and a high C-reactive protein (CRP) of 319 mg/L. Urinalysis was abnormal consistent with large leukocytes esterase and WBC, raising concerns for a UTI. Consequently, a urine sample was collected by catheter for culture. Blood cultures and respiratory viral panels were unremarkable. The patient was initially managed for urosepsis and started on empiric ceftriaxone.

On day 2, the urine culture grew gram-negative bacilli, later identified as *M. morganii*. A susceptibility test resulted in admission on day 3 and also revealed resistance to ampicillin–sulbactam, nitrofurantoin, and trimethoprim–sulfamethoxazole, with retained susceptibility to ciprofloxacin, levofloxacin, and meropenem. Upon consultation with the infectious diseases department, ceftriaxone was discontinued, and the patient was transitioned to intravenous levofloxacin. Despite improvement of the inflammatory markers, WBC count and CRP, and a negative repeat urine culture, the patient's fever persisted until day 13 of admission, which required continuation of intravenous levofloxacin for a total of 21 days.

Following the guidelines for UTI management in pediatrics, a retroperitoneal ultrasound was performed on day 4 of admission, which revealed dilation of the right renal pelvis and calyces (Figure 1 area between red x) with mild thinning of the right kidney's cortex (Figure 1 green arrow), indicating severe right hydronephrosis consistent with ureteropelvic junction (UPJ) obstruction. A mercaptoacetyltriglycine (MAG-3) scan showed significant delayed excretion on the right side, and a subsequent voiding cystourethrogram confirmed vesicoureteral reflux (Figure 2 a red arrow). Pediatric urology recommended ureteral stent placement to relieve the obstruction and facilitate urine drainage, but the procedure was deferred until the patient was no longer febrile. Two days after the stent placement (Figure 2b red arrow), an ultrasound revealed mildly improved hydronephrosis with a decrease in the right kidney's length from 13 cm to 11.5 cm.

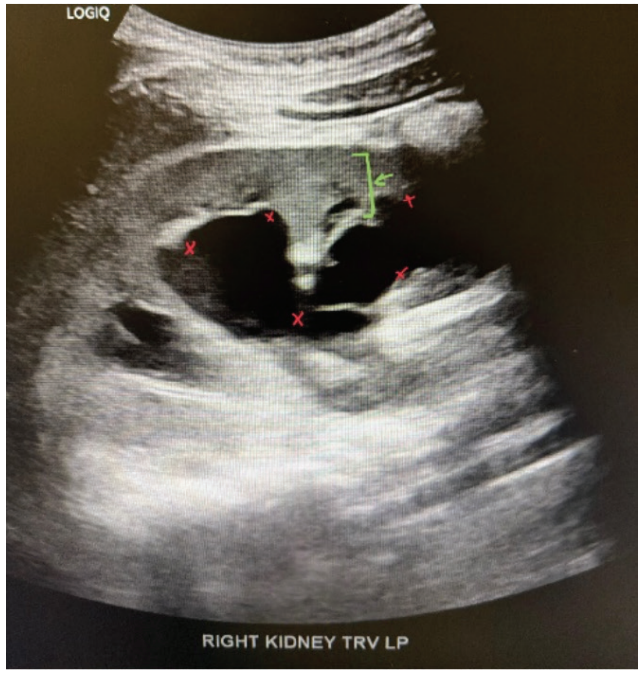

Figure 1. Retroperitoneal ultrasound demonstrating right-sided hydronephrosis. Retroperitoneal ultrasound showing severe right-sided hydronephrosis due to ureteropelvic junction obstruction, with marked dilatation of the renal pelvis and calyces (red x) and cortical thinning (green arrow)
TRV: Transverse, LP: Lower pole

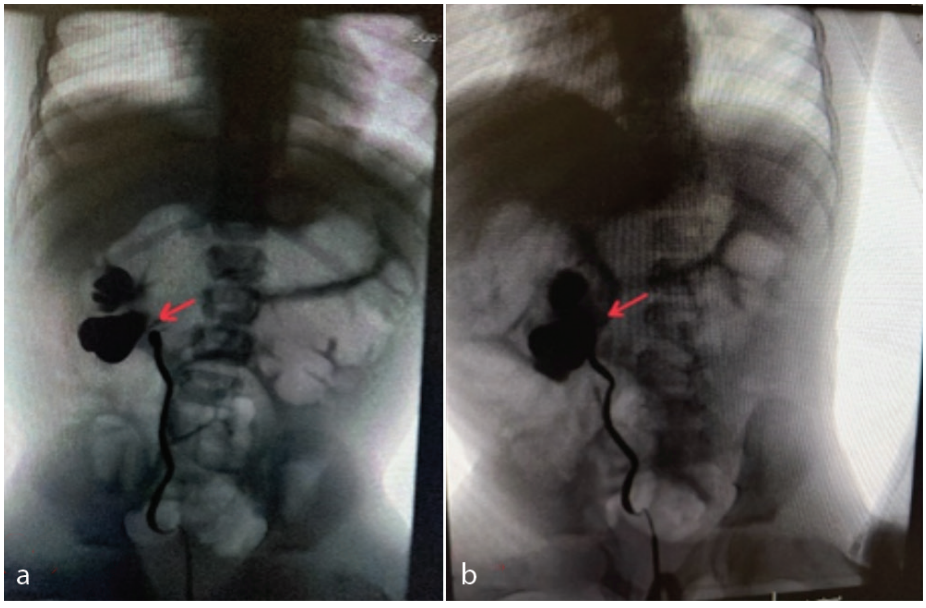

Figure 2. Voiding cystourethrogram (VCUG) images of the right kidney and ureter before and after double-J stent placement **(a)** VCUG prior to stent placement showing right-sided vesicoureteral reflux and proximal ureteropelvic junction (UPJ) obstruction (red arrow). **(b)** VCUG after double J stent placement showing relief of the obstruction at the right proximal UPJ

According to the patient's mother, this was his first known UTI. However, given his non-verbal status and the absence of typical symptoms such as dysuria, it was difficult to determine whether previous UTIs had gone undetected. A review of his medical records revealed two pelvic ultrasounds were performed two and 10 years earlier, both documenting normal renal anatomies.

Three months later, the stent was removed and a follow-up ultrasound revealed persistent severe right hydronephrosis with further shrinking in renal length to 8.9 cm. Despite the progressive decrease in renal measurements, a subsequent MAG-3 scan showed persistent delayed excretion and partial UPJ obstruction, suggesting chronic obstructive injury and cortical atrophy.

Discussion

One of the major challenges faced in managing *M. morganii* infections lies in its extensive antimicrobial resistance profile. Similar to other pathogens belonging to the *Enterobacteriaceae* family known collectively as the *Enterobacter, Serratia, Citrobacter, Providencia, Morganella (ESCPM)* group, *M. morganii* possesses an inducible chromosomal AmpC β-lactamase gene encoding the enzyme responsible for hydrolysis of many β-lactam antibiotics upon exposure (3,6). This mechanism confers natural resistance to penicillin, ampicillin, ampicillin/sulbactam, oxacillin, first- and second-generation cephalosporins, and narrow-spectrum β-lactam/β-lactamase inhibitor combinations (7). In addition, resistance to agents such as tetracyclines, tigecycline, polymyxins, and nitrofurantoin has been well-documented, further limiting empirical treatment options (8).

In many cases, *M. morganii* has been shown to retain susceptibility to third- and fourth-generation cephalosporins. Yet, clinical studies have suggested that treatment with these agents may result in a rapid emergence of resistance (6). A study by Mizrahi et al. (6) focused on the role of third-generation cephalosporins in inducing or selecting resistance among certain *Enterobacteriaceae* species. Their study demonstrated that the resistance developed is primarily attributable to the induction of AmpC β-lactamases enzymes, which exhibit stronger induction properties compared to those in other cephalosporins (6). This phenomenon explains why third- and fourth-generation cephalosporins are often ineffective against *ESCPM* organisms, which aligns with the lack of clinical improvement observed in our patient during the first three days of hospitalization.

Meanwhile, carbapenems, aztreonam, aminoglycosides, and chloramphenicol generally demonstrate good *in vitro* activity. However, reports of multidrug-resistant *M. morganii* strains emphasize the need for careful antimicrobial use and close monitoring (9). With the variability in resistance and

the risk of new resistant strains developing, susceptibility testing is vital in order to guide appropriate antimicrobial therapy.

A recent study by Tasanapak et al. (10) reviewed the geographic prevalence of fluoroquinolone resistance in *M. morganii* from 1998 to 2024. Their study reported a rise in resistance from 2% between 1993-1997 to 30% between 2013-2024. The highest resistance rates were in Africa (55%), followed by South America (36%), Asia (35%), and North America (11%). The rapid increase in resistance was mainly attributed to plasmid-mediated resistance mechanisms, which protect DNA gyrase and topoisomerase IV, encode drug-modifying enzymes, and sometimes promote efflux pumping, thereby reducing fluoroquinolone efficacy. Despite limitations such as regional variations in antibiotic use, their study provided valuable insights into global resistance trends (10).

Aside from the challenges posed by *M. morganii*'s drug resistance, the presence of right-sided hydronephrosis in our patient raised concerns about the chronicity of urinary tract involvement. Although imaging carried out two and 10 years earlier demonstrated normal renal anatomy, the development of hydronephrosis and mild cortical thinning in the current study indicated an underlying chronic or congenital obstruction rather than a purely acute process. The absence of renal congenital malformations, along with the exclusion of extrinsic crossing vessels on imaging, supported the diagnosis of congenital UPJ obstruction. Since the blockage may have been partial or subclinical initially, the current infection and inflammation likely contributed to symptomatic presentation and may have exacerbated the obstruction.

In pediatric patients, particularly those with limited communication abilities, early identification of pathogens with unusual resistance patterns is crucial. Prompt initiation of targeted therapy based on culture and sensitivity results has been shown to markedly prevent complications such as persistent infection, renal damage, progression to sepsis, and even death (3,4). This case serves as a reminder to consider less common organisms such as *M. morganii* in pediatric UTIs and highlights the importance of timely imaging, appropriate antimicrobial selection, and continuous microbiological monitoring.

Ethics

Informed Consent: This case report was a retrospective descriptive observation describing a single patient. Written informed consent from the patient's guardian could not be obtained. All identifying information has been removed to protect confidentiality.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.G., V.E., Concept: Y.A., V.E., Design: Y.A., Data Collection or Processing: Y.A., Analysis or Interpretation: Y.A., K.G., V.E., Literature Search: Y.A., Writing: Y.A.

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Case Report

First Reported Case of Bacillus Calmette–Guérin Associated Mastitis in an Immunocompetent Infant: A Rare Complication of Vaccination

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ABSTRACT

Mastitis beyond the neonatal period is an uncommon condition in children, with *Staphylococcus aureus* being the most frequently implicated pathogen. However, mastitis due to *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) has not been previously reported. Herein, we present the first case of mastitis following a BCG vaccination in a 6-month-old immunocompetent infant.

Keywords: Bacillus Calmette-Guérin, *Mycobacterium bovis*, mastitis

Introduction

The Bacillus Calmette-Guérin (BCG) vaccine, derived from an attenuated strain of *Mycobacterium bovis (M. bovis),* has been in use for over a century (first administered to humans in 1921) and it remains the only widely used vaccine for tuberculosis (TB) prevention (1). It is one of the most broadly administered vaccines globally, with more than 100 million newborns receiving BCG each year as part of infant immunization programs (2). Multiple BCG vaccine strains (e.g., Danish 1331, Tokyo, Moscow) are employed worldwide, all of which are live attenuated *M. bovis* preparations with comparable efficacy (1). In general, BCG has a strong safety profile in immunocompetent infants. Expected local reactions include a small papule at the injection site which may ulcerate and heal with a scar, often accompanied by mild regional lymphadenopathy (1,3). More significant adverse events are rare. Severe or disseminated BCG infections occur in approximately 1 to 15 per 10 million vaccinees, predominantly among individuals with underlying immunodeficiencies (1). Intermediate complications such as osteitis have been reported at rates ranging from 0.01 to 30 per million doses (1). Among immunocompetent children, the most frequently observed complications are localized, including suppurative regional lymphadenitis or, less commonly, cold abscess formation at the vaccination site. Overall, the incidence of BCG-related adverse events remains well below 1% in most published series (1). Nevertheless, isolated case reports have documented that even immunocompetent hosts can occasionally develop atypical, localized infections caused by the attenuated vaccine strain, such as abscesses or granulomatous lesions in tissues distant from the inoculation site (1).

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The breast has not previously been described as a site of BCG-related infection. Mastitis is uncommon in children and, beyond the neonatal period, typically occurs in those aged 8 years or older. Most cases are caused by *Staphylococcus aureus*, and less frequently by other pathogens such as group A *Streptococcus*, and gram-negative bacilli (4). Mycobacterial infection, particularly with an attenuated vaccine strain, has not been recognized as a cause of mastitis in immunocompetent children. We conducted a literature search (PubMed and Google Scholar, up to October 2025) using the terms "BCG vaccine," "*M. bovis* BCG," "mastitis," and "breast abscess," and found no previously published cases of BCG-related mastitis. Herein, we describe what appears to be the first documented case of mastitis caused by *M. bovis* BCG (Moscow strain) following a routine BCG vaccination in an otherwise healthy 6-month-old infant. This rare presentation expands the known spectrum of BCG vaccine complications and highlights the importance of considering atypical mycobacterial infections in unusual pediatric presentations.

Case Report

A previously healthy 6-month-old girl presented with swelling and erythema of the left breast. There was no history of trauma or local skin infection. She had received the BCG vaccine at 2 months of age. A typical local reaction developed with small ulceration and healed spontaneously without lymphadenitis. On physical examination, a fluctuant, erythematous swelling was noted on the left breast (Figure 1), and an erythematous nodule was observed at the BCG vaccination site. No lymphadenopathy was observed. Laboratory tests revealed a white blood cell count of 12×10^9/L with 55% neutrophils, a C-reactive protein level of 10 mg/L, and an erythrocyte sedimentation rate of 18 mm/h. Ultrasonographic evaluation showed features suggestive of a breast abscess. Empirical intravenous ampicillin/sulbactam (200 mg/kg/day) therapy was initiated; however, there was no clinical improvement. Therefore, the patient underwent incision and drainage. Gram stain revealed no microorganisms, and routine bacterial cultures were negative. Despite drainage and antibiotic therapy, swelling persisted, and a draining fistula subsequently developed at the incision site. Consequently, a pus sample was submitted for mycobacterial culture and polymerase chain reaction (PCR) testing. Reverse-transcription PCR detected the *Mycobacterium tuberculosis* complex (MTBC) in two consecutive samples. Deoxyribonucleic acid amplification from the abscess material was performed using a commercial multiplex real-time PCR assay targeting the IS6110, 16S ribosomal ribonucleic acid, and *rpoB* regions specific to the MTBC. In order to further differentiate the strain, RD1 and RD9 deletion analysis was used, confirming *M. bovis* BCG. Spoligotyping subsequently identified the isolate as the Moscow sub-strain. Culture of the drained pus yielded slow-growing acid-fast bacilli on Löwenstein-Jensen medium after four weeks, consistent with BCG. Drug susceptibility testing was not formally performed; however, intrinsic resistance to pyrazinamide was inferred based on the classification of the organism as *M. bovis* BCG. The patient was treated with isoniazid (10 mg/kg/day) and rifampin (15 mg/kg/day) for 6 months as an outpatient and recovered without complications. A summary of the chronological sequence of clinical events is provided in Figure 2. Follow-up immunological evaluations, including lymphocyte subsets, mitogen-induced lymphoproliferation, dihydrorhodamine assay, and flow cytometry for interleukin-12Rβ1 and interferon-gamma-γ (IFN-γ) expression, were all within normal limits. Serologic testing for human immunodeficiency virus was negative.

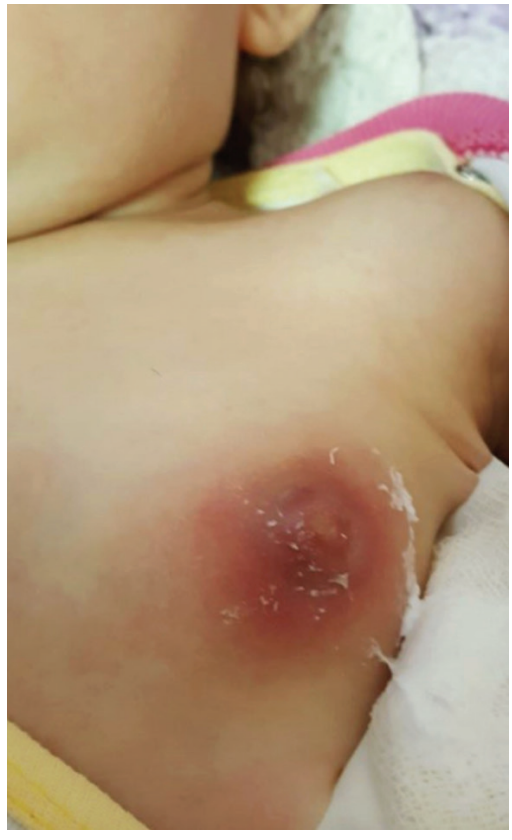

Figure 1. Erythematous, fluctuant swelling on the left breast, consistent with a localized abscess

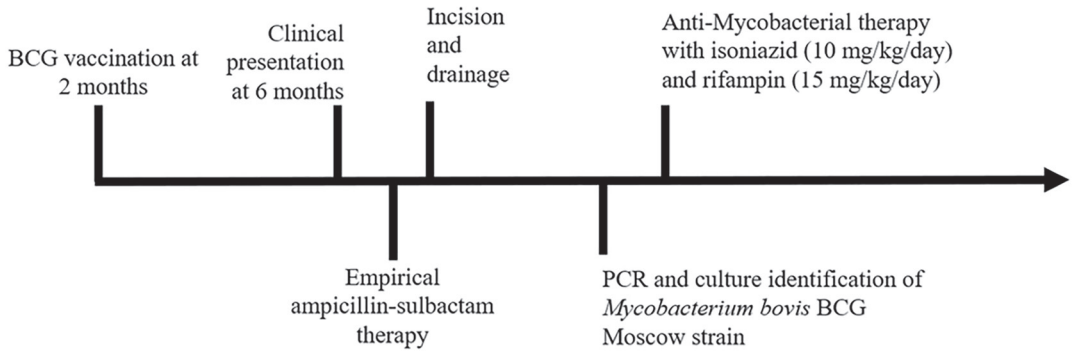

Figure 2. Clinical timeline summarizing the main events in the patient's course
BCG: Bacillus Calmette-Guérin, PCR: Polymerase chain reaction

Discussion

The BCG vaccine remains a cornerstone of TB prevention in infants worldwide, due to its proven efficacy in reducing severe pediatric TB (e.g., miliary TB and TB meningitis) (5). It is generally considered a safe vaccine; in healthy individuals, the vast majority of adverse reactions are limited to mild local effects (1,3). However, as a live attenuated mycobacterium, BCG is capable of causing disease under certain circumstances. Known adverse events range from injection site abscesses and suppurative lymphadenitis to osteomyelitis and disseminated infection (1). The most serious complications, such as disseminated BCGosis, are exceedingly rare and occur almost exclusively in immunocompromised patients with impaired cell-mediated immunity (1).

Severe BCG-related complications are rarely observed in immunocompetent children. Nevertheless, sporadic reports have documented localized infections in otherwise healthy infants, suggesting that even vaccines considered safe can occasionally lead to atypical manifestations. Among these, chest wall and cutaneous abscesses attributable to BCG have been reported in immunocompetent children, occurring at sites distant from the vaccination site (6,7). However, mastitis as a complication of BCG vaccination has not been previously reported.

BCG vaccine complications are most commonly observed within the first six months after vaccination, but cases have been reported as late as 12 months post-vaccination (8). The optimal management of these complications remains uncertain. Disseminated disease occurs only exceptionally and is observed primarily in immunocompromised children (8,9). In our patient, the breast abscess developed approximately 4 months after BCG, which is within the typical timeframe for vaccine complications. In terms of clinical features, the published cases, similar to ours typically involved a localized swelling or abscess with minimal systemic symptoms. For instance, an infant in a Korean case had a tender, erythematous subcutaneous mass on the chest wall but no fever or constitutional signs (10). Similarly, our patient's mastitis manifested as a localized breast abscess without systemic illness. In all such cases, routine bacterial cultures of abscess fluids were negative, prompting further investigation for mycobacterial etiology, as was the case here.

Our patient's presentation aligns with other published reports of distant-site BCG infections in immunocompetent children. For example, Polat and Belen (6) described a cold abscess of the chest wall with rib destruction attributed to hematogenous spread of the BCG strain. Okazaki et al. (7) reported a cutaneous TB granuloma at a distant body site, confirmed by multiplex PCR to be the BCG vaccine strain. Lee et al. (10) also documented a BCG-induced anterior chest wall abscess without dissemination, emerging seven months post-vaccination.

The pathogenesis of BCG-related complications is not completely understood. In our case, direct lymphatic spread from the vaccination site may have contributed to the development of mastitis. Alternatively, local inoculation at a site of minor trauma or microabrasion cannot be entirely excluded. The presence of an erythematous nodule at the vaccination site concomitant with breast involvement suggests a potential link through contiguous or lymphatic spread. Regardless of the exact route, the temporal association between vaccination and breast abscess formation, coupled with the identification of the BCG Moscow strain from the abscess, indicates a causal link.

Management of BCG-related complications remains challenging. While incision and drainage are often performed for abscesses, they may not be sufficient in cases

of mycobacterial infections, and antimicrobial therapy is usually required (8,11). Our patient did not respond to routine antibiotics, which is consistent with the intrinsic resistance of *M. bovis* to several antimicrobial agents, including pyrazinamide. The persistent drainage and lack of clinical improvement prompted further testing, ultimately confirming mycobacterial infection. Once identified, targeted therapy is essential. Anti-tuberculous pharmacotherapy is the cornerstone of treatment. In previous reports, favorable outcomes have been achieved with anti-mycobacterial regimens (11). Our patient responded well to a six-month course of isoniazid and rifampin, mirroring successful treatment protocols in the literature (9,10). Reported cases have generally been managed with a combination of surgical and medical therapy. Surgical intervention (incision and drainage or excisional surgery) is often performed to remove abscess collections or obtain diagnostic material (8); however, surgery alone does not eradicate the infection. When conventional antibiotics fail to resolve presumed pyogenic abscesses, especially in recently vaccinated infants, clinicians should maintain a high index of suspicion for BCG-related disease, even if the child is immunocompetent. The favorable response to a combination of isoniazid and rifampin underlines the importance of early consideration of mycobacterial etiology in non-resolving mastitis cases.

In addition, evaluation for underlying immunodeficiency is critical, since disseminated or unusual manifestations of BCG infection are strongly associated with primary immunodeficiencies affecting the interleukin-12/IFN-γ axis or chronic granulomatous disease (12). In our patient, the comprehensive immunological work-up was normal, supporting the interpretation that this was a sporadic, localized complication in an otherwise healthy infant. This finding parallels other reports in which no immune abnormalities were detected despite the presence of BCG complications (6,7). By contrast, when BCG causes disseminated disease, it is typically in the context of conditions such as severe combined immunodeficiency, chronic granulomatous disease, or genetic defects in IFN-γ signaling. The absence of any immune disorder in our patient reinforces the interpretation that her mastitis was a chance, localized complication of the BCG vaccination rather than a marker of undiagnosed systemic susceptibility.

To the best of our knowledge, this is the first reported case of BCG-induced mastitis in an otherwise healthy infant. Previous reports have described complications such as lymphadenitis, osteomyelitis, and distant-site abscesses, but none have documented breast involvement (6,13). Our case broadens the understanding of BCG-associated clinical presentations and highlights the capacity of *M. bovis* BCG to infect diverse tissues under specific conditions. Fortunately, similar to other localized BCG infections, mastitis responded well to timely diagnosis and appropriate treatment. For healthcare providers, recognizing the atypical presentations of BCG complications is essential, particularly when standard therapies fail. This case adds breast mastitis as a novel clinical manifestation to the existing spectrum of BCG-related adverse effects.

Conclusion

Our case expands the clinical spectrum of BCG-related complications and highlights mastitis as a rare but potential complication in immunocompetent infants. Clinicians should maintain a high index of suspicion for atypical presentations of BCG infection, particularly in cases of mastitis unresponsive to conventional therapy in order to ensure timely and effective management.

Ethics

Informed Consent: Informed consent has been obtained from parents for incorporating the patient details into the manuscript.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.P., Concept: N.A.Ü., M.P., Design: M.P., Data Collection or Processing: N.A.Ü., M.P., Analysis or Interpretation: N.A.Ü., M.P., Literature Search: N.A.Ü., M.P., Writing: N.A.Ü., M.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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