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PREDICTORS OF RENAL SCARRING FOLLOWING FIRST FEBRILE URINARY TRACT INFECTION IN CHILDREN: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Objective: Renal scarring is a serious long-term complication of febrile urinary tract infection (UTI) in children and may predispose affected individuals to hypertension, proteinuria, and chronic kidney disease. Early identification of children at high risk is essential for timely intervention and prevention of permanent renal damage. This study aimed to identify clinical, laboratory, microbiological, and radiological predictors of renal scarring following the first episode of febrile UTI in children.
Study Design and Duration of Study: A prospective cohort study. Lady Reading Hospital from June 2023 to May 2024.
Method: A total of 172 children aged 2 months to 12 years with a first documented febrile UTI completed six months of follow-up. Demographic, clinical, laboratory, microbiological, and imaging findings were recorded. Renal scarring was assessed using follow-up dimercaptosuccinic acid (DMSA) scintigraphy performed six months after the acute infection. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of renal scarring.
Results: Renal scarring developed in 39 children (22.7%). Children with renal scarring had significantly longer fever duration before antibiotic initiation, higher C-reactive protein levels, more frequent abnormal renal ultrasonography, acute DMSA abnormalities, and high-grade vesicoureteral reflux (all $p<0.05$). Multivariable analysis demonstrated that delayed antibiotic therapy beyond 48 hours (adjusted odds ratio [aOR] 3.41, 95% CI: 1.52–7.67), elevated C-reactive protein (aOR 1.18 per 10 mg/L increase, 95% CI: 1.06–1.31), abnormal renal ultrasonography (aOR 2.96, 95% CI: 1.24–7.05), acute DMSA abnormalities (aOR 5.82, 95% CI: 2.11–16.08), and high-grade vesicoureteral reflux (aOR 6.47, 95% CI: 2.18–19.21) were independent predictors of renal scarring.
Conclusion: Permanent renal scarring occurred in nearly one-quarter of children after their first febrile UTI. Early diagnosis, prompt antimicrobial treatment, and risk-based imaging may facilitate early identification of high-risk children and reduce long-term renal morbidity.

KEYWORDS: Febrile Urinary Tract Infection, Renal Scarring, Children, Dimercaptosuccinic Acid Scintigraphy, Vesicoureteral Reflux.

1.INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections affecting children and represents a major cause of pediatric morbidity worldwide [1,2]. Approximately 7–8% of girls and 2% of boys experience at least one UTI during childhood, with the highest incidence occurring during infancy and the first few years of life [3,4]. Febrile UTI is generally considered a marker of upper urinary tract involvement and acute pyelonephritis, a condition that may lead to permanent renal parenchymal injury if diagnosis and treatment are delayed [5,6]. Despite considerable advances in antimicrobial therapy and diagnostic imaging, renal scarring remains a clinically significant complication because of its association with hypertension, proteinuria, reduced renal function, and chronic kidney disease (CKD) later in life. Early recognition of children at increased risk of renal scarring is therefore essential for preventing long-term renal morbidity and improving

clinical outcomes [7,8].
The pathogenesis of renal scarring involves a complex interaction between bacterial virulence factors and the host inflammatory response [9, 10]. During acute pyelonephritis, inflammatory cell infiltration, cytokine release, oxidative stress, and ischemic injury contribute to tubular destruction, interstitial fibrosis, and irreversible cortical damage [11,12]. The extent of renal injury is influenced by multiple host-, microbial-, and treatment-related factors. Delayed initiation of antibiotic therapy permits prolonged bacterial proliferation and sustained inflammation, thereby increasing the likelihood of permanent renal cortical damage. Likewise, congenital urinary tract abnormalities, particularly vesicoureteral reflux (VUR), facilitate the retrograde flow of infected urine into the renal parenchyma, predisposing children to recurrent pyelonephritis and progressive renal injury [13, 14, 15].
Several clinical, laboratory, microbiological, and radiological factors have been investigated as potential predictors of renal scarring following the first febrile UTI [16, 17, 18]. Younger age, prolonged fever before antibiotic administration, elevated inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), leukocytosis, bacteremia, and recurrent febrile infections have all been associated with an increased risk of permanent renal damage. In addition, infections caused by antimicrobial-resistant organisms and delayed clinical presentation may further increase the severity of renal parenchymal involvement [19]. Imaging findings also play an important role in risk prediction, as abnormal renal ultrasonography, acute cortical defects detected on dimercaptosuccinic acid (DMSA) scintigraphy, and high-grade VUR have consistently been associated with subsequent renal scar formation [20, 21, 22]. However, the strength of these associations varies among studies because of differences in patient characteristics, imaging protocols, follow-up duration, and diagnostic criteria. Consequently, no universally accepted prediction model is currently available to accurately identify children at the greatest risk of developing renal scars after their first febrile UTI [23, 24].
Radiological evaluation is an essential component of the assessment of children with febrile UTI [25, 26]. Renal and bladder ultrasonography is widely used as the initial imaging modality to identify structural abnormalities of the urinary tract [27, 28, 29]. DMSA renal scintigraphy remains the gold standard for detecting acute pyelonephritis and permanent renal cortical scarring because of its high sensitivity for cortical involvement. Voiding cystourethrography (VCUG) is selectively recommended to diagnose VUR in children with recurrent infections or abnormal imaging findings. Recent international guidelines advocate a selective and risk-based imaging strategy to minimize unnecessary radiation exposure and invasive procedures while ensuring appropriate evaluation of high-risk children.
The burden of pediatric UTI is particularly substantial in low- and middle-income countries, where delayed healthcare access, inappropriate antibiotic use, increasing antimicrobial resistance, and limited diagnostic facilities may adversely affect patient outcomes. In Pakistan, febrile UTI remains a frequent cause of pediatric hospital admissions; however, prospective evidence regarding predictors of renal scarring is limited. Most published studies have been conducted in high-income countries, limiting the generalizability of their findings to local populations with different epidemiological characteristics, healthcare resources, and antimicrobial resistance patterns. Identifying predictors of renal scarring following a first febrile UTI could facilitate early risk stratification, optimize imaging strategies, guide follow-up protocols, and reduce the risk of long-term renal complications. Therefore, the present prospective cohort study was conducted to identify the clinical, laboratory, microbiological, and radiological predictors of renal scarring following the first episode of febrile UTI in children treated at Lady Reading Hospital. The findings of this study may contribute to evidence-based clinical decision-making and support the development of targeted management strategies for children at increased risk of permanent renal injury.

2.METHODOLOGY

2.1 Design of the Study
This prospective cohort study was conducted in the Department of Pediatrics at Lady Reading Hospital over a 12-month period, from June 2023 to May 2024. The study was designed to identify clinical, laboratory, microbiological, and radiological predictors associated with the development of renal scarring following the first episode of febrile urinary tract infection (UTI) in children. Ethical approval was obtained from the Institutional Review Board of Lady Reading Hospital before the commencement of the study, and written informed consent was obtained from the parents or legal guardians of all enrolled participants.

2.2 Sample
Children aged 2 months to 12 years presenting with their first documented febrile UTI were consecutively recruited using a non-probability consecutive sampling technique. Febrile UTI was defined as the presence of a documented body temperature of ≥38.0°C accompanied by significant bacteriuria confirmed on urine culture. Urine specimens were collected using age-appropriate sterile techniques, including midstream clean-catch urine in toilet-trained children and catheterization or suprapubic aspiration in younger children when clinically indicated. Significant bacteriuria was defined as the growth of a single pathogenic organism at concentrations consistent with established pediatric diagnostic criteria

2.3 Exclusion Criteria
Children with a previous history of UTI, known congenital anomalies of the kidney and urinary tract, vesicoureteral reflux diagnosed before enrollment, chronic kidney disease, neurogenic bladder, immunodeficiency disorders, previous renal surgery, or incomplete follow-up investigations were excluded from the study.

2.4 Procedure

At enrollment, demographic characteristics, including age and sex, were recorded along with relevant clinical information such as duration of fever before presentation, peak recorded temperature, urinary symptoms, previous antibiotic exposure, hydration status, family history of urinary tract abnormalities, and associated comorbidities. Physical examination findings were documented systematically. Laboratory investigations included complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, blood urea nitrogen, urinalysis, urine microscopy, urine culture with antimicrobial susceptibility testing, and blood culture where clinically indicated. Microbiological identification and antimicrobial susceptibility testing were performed according to standard laboratory protocols.

Radiological evaluation followed a standardized imaging protocol. Renal and bladder ultrasonography was performed during the acute illness or within two weeks of diagnosis to identify structural abnormalities. A dimercaptosuccinic acid (DMSA) renal cortical scintigraphy scan was performed during the acute phase, preferably within 5–7 days of diagnosis, to detect acute pyelonephritis. A repeat DMSA scan was obtained six months after the initial infection to evaluate for permanent renal cortical scarring. Renal scarring was defined as persistent focal or diffuse cortical photon defects with associated cortical thinning or loss of renal contour on follow-up DMSA imaging. A voiding cystourethrogram (VCUG) was performed selectively in children with abnormal ultrasonographic findings, recurrent febrile infections during follow-up, or abnormal acute DMSA findings suggestive of high-grade urinary tract involvement, in accordance with contemporary pediatric imaging recommendations. Vesicoureteral reflux was graded using the International Reflux Study classification.

Participants were followed prospectively for six months after the initial infection. Compliance with antimicrobial therapy, recurrence of febrile UTIs, hospitalization, and additional clinical events were documented during scheduled follow-up visits. The primary outcome was the presence of renal scarring on the follow-up DMSA scan. Potential predictor variables evaluated included age, sex, duration of fever before initiation of antibiotic therapy, inflammatory markers (CRP, ESR, leukocyte count), infecting organism, antimicrobial resistance pattern, bacteremia, ultrasonographic abnormalities, acute DMSA findings, vesicoureteral reflux, and length of hospital stay.

Data were entered into and analyzed using the IBM SPSS Statistics. Continuous variables were assessed for normality using the Shapiro–Wilk test and summarized as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between children with and without renal scarring were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Variables demonstrating a p-value <0.20 in univariate analyses or considered clinically relevant based on previous evidence were entered into a multivariable logistic regression model to identify independent predictors of renal scarring. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated. Model fitness was assessed using the Hosmer–Lemeshow goodness-of-fit test, and multicollinearity was evaluated using variance inflation factors. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

3. RESULTS

A total of 186 children presenting with their first episode of febrile urinary tract infection (UTI) were initially assessed for eligibility during the study period. Fourteen patients were excluded due to incomplete follow-up (n = 8), previous undocumented UTI identified during record review (n = 3), congenital renal anomalies diagnosed after enrollment (n = 2), or incomplete imaging investigations (n = 1). Consequently, 172 children completed the study and were included in the final analysis.

The mean age of the study population was 3.8 ± 2.6 years (range: 2 months–12 years), with children younger than 5 years comprising the majority (69.8%). There were 98 females (57.0%) and 74 males (43.0%). Follow-up DMSA scintigraphy performed six months after the initial infection demonstrated renal scarring in 39 children (22.7%), whereas 133 children (77.3%) showed complete resolution of renal cortical defects.

Table 1: Baseline demographic and clinical characteristics of the study population (n = 172)

Variable	Overall (n = 172)
Age (years), mean ± SD	3.8 ± 2.6
Age <5 years, n (%)	120 (69.8)
Female, n (%)	98 (57.0)
Male, n (%)	74 (43.0)
Fever duration before antibiotics >48 hours, n (%)	61 (35.5)
Peak temperature ≥39°C, n (%)	82 (47.7)
Previous antibiotic use before admission, n (%)	34 (19.8)
Hospital stay >5 days, n (%)	47 (27.3)
Positive blood culture, n (%)	14 (8.1)
Renal scarring on follow-up DMSA, n (%)	39 (22.7)

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comprising the majority (69.8%). There were 98 females (57.0%) and 74 males (43.0%). Follow-up DMSA scintigraphy performed six months after the initial infection demonstrated renal scarring in 39 children (22.7%), whereas 133 children (77.3%) showed complete resolution of renal cortical defects. Urine culture identified Escherichia coli as the predominant uropathogen in 136 patients (79.1%), followed by Klebsiella pneumoniae (11.6%), Proteus mirabilis (4.7%), Enterococcus faecalis (2.9%), and other organisms (1.7%). Extended-spectrum β-lactamase (ESBL)-producing organisms were isolated in 28 children (16.3%).

Renal ultrasonography demonstrated abnormalities in 44 children (25.6%), while acute DMSA scintigraphy revealed cortical involvement suggestive of acute pyelonephritis in 69 patients (40.1%). Vesicoureteral reflux (VUR), evaluated in children meeting imaging criteria, was identified in 31 patients (18.0%), including 18 (10.5%) with high-grade (Grade III–V) reflux.

Children who subsequently developed renal scarring were significantly younger, had a longer duration of fever before antibiotic initiation, higher inflammatory marker levels, more frequent ultrasonographic abnormalities, positive acute DMSA findings, and a higher prevalence of high-grade VUR than children without renal scarring.

Table 2: Comparison between children with and without renal scarring

Variable	Renal scarring (n = 39)	No renal scarring (n = 133)	p-value
Age (years), mean ± SD	2.7 ± 1.9	4.2 ± 2.7	0.003
Female, n (%)	24 (61.5)	74 (55.6)	0.512
Fever >48 hours before treatment, n (%)	26 (66.7)	35 (26.3)	<0.001
CRP (mg/L), mean ± SD	82.6 ± 28.4	51.7 ± 20.9	<0.001
Leukocyte count (×10⁹/L), mean ± SD	16.9 ± 3.8	13.8 ± 3.2	<0.001
ESBL-positive organism, n (%)	12 (30.8)	16 (12.0)	0.006
Abnormal renal ultrasound, n (%)	21 (53.8)	23 (17.3)	<0.001
Acute DMSA abnormality, n (%)	34 (87.2)	35 (26.3)	<0.001
High-grade VUR, n (%)	14 (35.9)	4 (3.0)	<0.001
Hospital stay >5 days, n (%)	20 (51.3)	27 (20.3)	<0.001

Univariate logistic regression demonstrated significant associations between renal scarring and younger age, delayed initiation of antibiotics (>48 hours), elevated CRP, abnormal renal ultrasonography, acute DMSA abnormalities, ESBL-producing organisms, prolonged hospitalization, and high-grade vesicoureteral reflux.

After adjustment for potential confounders in the multivariable logistic regression model, delayed initiation of antibiotic therapy, abnormal acute DMSA findings, high-grade vesicoureteral reflux, elevated CRP concentration, and abnormal renal ultrasonography remained independent predictors of renal scarring.

Table 3: Multivariable logistic regression analysis of predictors of renal scarring

Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age <5 years	1.58	0.71–3.52	0.258
Fever >48 hours before antibiotics	3.41	1.52–7.67	0.003
CRP (per 10 mg/L increase)	1.18	1.06–1.31	0.002
ESBL-positive organism	1.89	0.82–4.37	0.135
Abnormal renal ultrasound	2.96	1.24–7.05	0.015
Acute DMSA abnormality	5.82	2.11–16.08	<0.001
High-grade vesicoureteral reflux	6.47	2.18–19.21	<0.001
Hospital stay >5 days	1.53	0.69–3.42	0.295

The final multivariable model demonstrated good calibration (Hosmer–Lemeshow test, p = 0.71) and acceptable discrimination, correctly classifying 84.3% of study participants. Acute DMSA abnormalities and high-grade vesicoureteral reflux were the strongest independent predictors of permanent renal scarring, followed by delayed initiation of antibiotic therapy, elevated CRP levels, and abnormal renal ultrasonography. Neither sex, prolonged hospitalization, nor infection with ESBL-producing organisms remained statistically significant after adjustment for confounding variables.

4. DISCUSSION

This prospective cohort study evaluated predictors of renal scarring following the first episode of febrile urinary tract infection (UTI) in children and demonstrated that approximately one in five children developed permanent renal cortical scars on follow-up DMSA scintigraphy. The incidence of renal scarring observed in the present study (22.7%) is consistent with previously published pediatric cohorts reporting rates ranging from 15% to 30% after a first febrile UTI, although reported estimates vary according to patient age, imaging protocols, follow-up duration, and the prevalence of vesicoureteral reflux (VUR) [7, 16]. These findings emphasize that permanent renal injury remains a clinically important consequence of febrile UTI despite advances in antimicrobial therapy and diagnostic imaging.

One of the most important findings of this study was the independent association between delayed initiation of antibiotic therapy and subsequent renal scarring. Children who received antimicrobial treatment more than 48 hours after fever onset had more than a threefold increased risk of developing permanent renal cortical damage. This observation supports the concept that prolonged bacterial replication and sustained inflammatory responses within the renal parenchyma increase

the likelihood of irreversible tissue injury. These findings are consistent with those of Horsager et al. and Shaikh et al., who also reported delayed initiation of antimicrobial therapy as an important predictor of permanent renal scarring [13, 15]. These findings reinforce current pediatric recommendations advocating prompt recognition and early antimicrobial treatment of febrile UTIs, particularly in younger children in whom clinical symptoms are often nonspecific.

Acute DMSA abnormalities emerged as the strongest imaging predictor of renal scarring in the multivariable analysis. Nearly nine out of ten children who eventually developed renal scars demonstrated cortical defects during the acute phase of infection. This finding is biologically plausible because DMSA scintigraphy directly reflects renal cortical inflammation and functional impairment during acute pyelonephritis. Persistent inflammatory injury may subsequently progress to fibrosis and permanent cortical loss. These findings agree with those reported by Vali et al. and Kosmeri et al., who identified acute DMSA abnormalities as one of the strongest predictors of subsequent renal scar formation. [20, 22]. Therefore, acute cortical involvement identified by DMSA imaging may serve as an important risk stratification tool for selecting children who require closer clinical surveillance.

High-grade vesicoureteral reflux (Grade III–V) was another independent predictor of renal scarring and demonstrated the highest adjusted odds ratio among anatomical risk factors. VUR facilitates retrograde transport of infected urine into the renal collecting system, increasing intrarenal pressure and promoting recurrent bacterial exposure to renal tissue. Although the relationship between VUR and renal scarring remains debated, particularly for low-grade reflux, our findings are consistent with evidence indicating that high-grade reflux substantially increases the risk of permanent renal injury. These results support current imaging strategies that prioritize evaluation for VUR in children with abnormal renal ultrasonography, recurrent infections, or significant cortical abnormalities rather than universal cystographic screening.

Elevated C-reactive protein (CRP) independently predicted renal scarring even after adjustment for other clinical variables. CRP is an acute-phase reactant reflecting the magnitude of systemic inflammation and has previously been associated with upper urinary tract involvement [18, 23]. Higher inflammatory marker concentrations likely indicate more extensive renal parenchymal infection and a greater inflammatory cascade leading to tissue fibrosis. Although leukocytosis was associated with renal scarring in univariate analysis, it lost statistical significance after multivariable adjustment, suggesting that CRP may provide a more robust measure of disease severity in children presenting with febrile UTI.

Abnormal renal ultrasonography also remained independently associated with permanent renal scarring. Structural abnormalities detected on ultrasonography may reflect congenital urinary tract anomalies, hydronephrosis, or renal enlargement secondary to acute infection, each of which may predispose children to more severe renal involvement. However, ultrasonography alone demonstrated limited sensitivity compared with DMSA scintigraphy for identifying children who subsequently developed cortical scars. This finding supports previous evidence that ultrasonography should be considered a complementary imaging modality rather than a replacement for functional renal imaging in high-risk patients [25, 26].

Interestingly, younger age was associated with renal scarring in univariate comparisons but was no longer an independent predictor after adjustment for imaging findings, inflammatory markers, and treatment delay. Previous investigations have reported conflicting results regarding the influence of age on scar formation. Younger children may possess greater susceptibility because of renal immaturity and delayed recognition of infection, yet age itself may function primarily as a surrogate for disease severity and diagnostic delay rather than an independent biological determinant. Similarly, infection caused by extended-spectrum β-lactamase-producing organisms demonstrated an increased crude risk but lost significance in the adjusted model, suggesting that antimicrobial resistance contributes indirectly through delayed effective therapy rather than directly causing renal injury.

The findings of this study have important clinical implications. Identification of children at increased risk for renal scarring permits individualized follow-up strategies, optimization of imaging protocols, and earlier nephrology referral where appropriate. Children presenting with prolonged fever before treatment, elevated inflammatory markers, abnormal renal ultrasonography, acute cortical defects on DMSA scintigraphy, or high-grade VUR should be considered high-risk and monitored closely for long-term renal sequelae, including hypertension, proteinuria, and progressive decline in renal function. Risk-based management may improve resource utilization while minimizing unnecessary invasive investigations in children with uncomplicated infections.

Several limitations should be considered when interpreting these findings. First, this was a single-center study conducted at a tertiary referral hospital, which may limit the generalizability of the results to community healthcare settings or populations with different disease characteristics. Second, the sample size, although adequate to identify significant predictors, may have limited statistical power for evaluating less common microbiological or anatomical risk factors. Third, selective performance of voiding cystourethrography according to clinical indications may have resulted in underestimation of low-grade vesicoureteral reflux. Fourth, the follow-up period was limited to six months, and longer observation may identify additional late renal changes or recurrent infections that contribute to scar progression. Finally, residual confounding from unmeasured variables, including genetic susceptibility, host immune responses, and bacterial virulence factors, cannot be excluded.

Despite these limitations, this study possesses several strengths. The prospective cohort design minimized recall bias, standardized imaging protocols ensured consistent assessment of renal outcomes, and comprehensive evaluation of demographic, clinical, microbiological, laboratory, and radiological variables enabled robust multivariable risk modeling. These methodological strengths enhance the validity of the findings and contribute clinically relevant evidence regarding predictors of renal scarring following first febrile UTI in children.

In conclusion, permanent renal scarring developed in nearly one-quarter of children following a first febrile UTI. Delayed initiation of antibiotic therapy, elevated CRP concentration, abnormal renal ultrasonography, acute DMSA cortical

abnormalities, and high-grade vesicoureteral reflux were identified as independent predictors of renal scarring. Early diagnosis, prompt antimicrobial treatment, and targeted imaging of high-risk children may reduce long-term renal morbidity and facilitate timely intervention for those at greatest risk of chronic kidney complications. Future multicenter studies with larger cohorts and longer follow-up are warranted to validate these findings and develop evidence-based prediction models for individualized pediatric UTI management.

5 . CONCLUSION

This prospective cohort study demonstrated that permanent renal scarring developed in nearly one-quarter of children following their first episode of febrile urinary tract infection, highlighting the persistent burden of renal complications despite contemporary management. Delayed initiation of antibiotic therapy, elevated C-reactive protein levels, abnormal renal ultrasonography, acute cortical abnormalities detected on DMSA scintigraphy, and high-grade vesicoureteral reflux were identified as independent predictors of renal scar formation. Among these, acute DMSA abnormalities and high-grade vesicoureteral reflux showed the strongest associations with permanent renal injury. These findings support the implementation of early diagnosis, prompt antimicrobial treatment, and targeted imaging strategies to identify children at increased risk for long-term renal sequelae. A risk-stratified approach may improve clinical decision-making, optimize follow-up, and reduce unnecessary investigations. Future multicenter studies with larger populations and extended follow-up are warranted to validate these predictors and develop reliable clinical prediction models for pediatric febrile urinary tract infections.

AI Use Disclosure

ChatGPT (OpenAI) was used exclusively for English language editing and improvement of grammar, readability, and manuscript presentation. All scientific content, study design, data analysis, interpretation of results, and conclusions were developed, verified, and approved by the authors.

Author Contributions

Conceptualization: Dr. Izhar Ali, Associate Prof. Dr. Asif
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Writing – Original Draft: Dr. Izhar Ali
Writing – Review & Editing: All authors critically reviewed, revised, and approved the final version of the manuscript.

Informed Consent

Informed consent was obtained from the parents or legal guardians of all children included in this study.

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Conflict of Interest

The authors declare that they have no competing interests.

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