IJKD KIDNEY DISEASES

Risk Factors for High-Grade Vesicoureteral Reflux in Children Two Years or Younger with Febrile Urinary Tract Infections

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Keywords. Pediatrics; Urinary tract infection; Vesicoureteral reflux; Risk factors

Original Paper

Introduction. High-grade vesicoureteral reflux (VUR) in infants with febrile urinary tract infections is linked to a heightened risk of renal scarring. Identifying risk factors for high-grade vesicoureteral reflux could enable more selective use of voiding cystourethrography, thereby reducing unnecessary invasive procedures. This study aimed to determine the independent risk factors of high-grade vesicoureteral reflux in children ≤ two years with febrile urinary tract infections.

Methods. According to the defined sample size, a total of 223 children aged two years or younger were referred to the nephrology clinic of Dr.Sheikh children's hospital affiliated to Mashhad University of Medical Sciences from March 2006 to August 2023, meeting the inclusion criteria. Participants who underwent both kidney ultrasound and voiding cystourethrography (VCUG) were included in the analysis. Univariable and multivariable logistic regression tests were utilized to identify independent risk factors of high-grade VUR.

Results. Of 223 children included in the study, 180 were girls (80.7%). The median age at the presentation was 8.5 months. High-grade vesicoureteral reflux was identified in 23.8%. The univariable analysis revealed that male sex, abnormal renal ultrasound, hydronephrosis, prenatal hydronephrosis, and infections with non-E.coli as potential risk factors. In the multivariable analysis, male sex (OR = 4.41, $P < .001$), abnormal renal ultrasound (OR = 3.35, $P < .001$), hydronephrosis (OR = 5.69, $P < .001$), and prenatal hydronephrosis (OR = 6.31, $P = .004$) were confirmed independent risk factors .

Conclusion. Male sex, abnormal kidney ultrasound, hydronephrosis, and prenatal hydronephrosis are independent risk factors of high-grade vesicoureteral reflux in children aged ≤2 years with febrile urinary tract infections.

IJKD 2026;20:224-33
www.ijkd.org

INTRODUCTION

Recurrent urinary tract infections (UTIs) in infants and young children pose significant clinical challenges due to their potential for long-term renal complications, including renal scarring, hypertension, and chronic kidney disease (CKD). These infections negatively impact growth, cognitive development, and quality of life, as well.[1,2] Infants under two years are particularly at risk due to their immature renal function and high rates of congenital anomalies of the kidney and urinary tract (CAKUT).[3,4] Therefore, early identification of high-risk infants is essential for optimal follow-up and prevention of complications. Identifying children

at risk for recurrence begin with the first febrile UTI.[5] Factors such as hydronephrosis, oliguria, and neonatal sepsis may suggest renal abnormalities that increase UTI susceptibility.[6] Approximately 25% of infants with antenatal hydronephrosis (ANH) are later diagnosed with vesicoureteral reflux (VUR) or other anomalies. Combining prenatal findings with imaging and microbiological data can enhance risk assessment and reduce unnecessary voiding cystourethrography (VCUG).[7,8] Current guidelines, including the 2022 NICE Guidelines, suggest VCUG for infants ≤2 months after a first febrile UTI and for older children only after a second febrile UTI or in the presence of renal ultrasound abnormalities.[9] The current study aims to identify risk factors for high-grade VUR in children ≤ two years by evaluating the predictive value of the first renal ultrasound along with non-imaging factors like pathogen type, gender, and prenatal history. By combining clinical, microbiological, and imaging data, we intend to develop a risk factor evaluation that improves early detection, optimizes follow-up strategies, and minimizes unnecessary diagnostics.

MATERIALS AND METHODS

Study design and participants

This retrospective study was conducted at the Nephrology Clinic of a Dr.Sheikh children's hospital affiliated to Mashhad University of Medical Sciences from March 2006 to August 2023. The study was funded by a research grant from Mashhad University of Medical Sciences (grant number # 4010095). The institutional ethics committee approved the study (ethic code: IR.MUMS.MEDICAL.REC.1401.226). The eligible participants were children aged two years or younger who presented with febrile UTIs and underwent kidney ultrasound (US) and VCUG tests. Patients whose clinical, laboratory or imaging data were not completely recorded were excluded from the study. We recommended VCUG routinely for every children ≤2 years following the first febrile UTI wih normal or abnormal kidney US. Patients who were referrd to the nephrology clinic following recurrent febrile UTIs also underwent a VCUG examination. Urine samples were collected using a urinary bag. A febrile UTI was diagnosed based on the presence of fever (temperature ≥38.5 °C), pyuria (a white blood cell count ≥5 cells/high power field (HPF) in urinary sediment, and a positive urine culture (growth of a single uropathogen with a ≥100,000 colony forming units/ml (CFU/mL)).

Patient data were extracted from medical records using a structured checklist that included demographic, clinical, imaging, microbiological, and recurrence-related variables. Kidney US findings were categorized as normal or abnormal, with abnormalities defined as hydronephrosis (anteroposterior diameter of renal pelvis ≥ 5 mm), ureteral dilatation (ureteral diameter ≥4 mm), decreased kidney size (adjusted for the age), or renal cortical scarring, and decreased renal cortical thickness. VCUG results were also classified as normal or abnormal, with abnormalities expressed as VUR or posterior urethral valves (PUV). Microbiological data included information on the causative uropathogen, which was classified as E. coli and non-E. coli. Recurrence febrile UTIs were defined as having ≥2 episodes of febrile UTI during follow-up. Antenatal hydronephrosis (ANH) referred to hydronephrosis firstly detected on antenatal screening US examinations . The primary outcomes of the study were the presence of VUR (categorized into grades I-V based on findings on VCUG) and high-grade (severe) VUR (grades IV–V) (1) . Patient confidentiality was strictly maintained, and all data were anonymized prior to analysis.

$$n = \frac{z^2_{(1-\frac{\alpha}{2})} P(1-P)}{d^2}$$

Sample size calculation

The required sample size was estimated based on an anticipated prevalence of VUR of 30% among infants with febrile UTIs, as reported in a study by Chang *et al.*[10] To account for a margin of error of 30% (D = 0.3p) and potential loss to follow-up, the final calculated sample size was determined to be 130 patients. The value of P was set at 0.3. The following formula was used to calculate the sample size:

However, since our study was not an interventional one, accessing a larger sample size and including a higher number of patients did not lead to an increased budget. A total of 223 patients were enrolled in the study. Furthermore, having a number of patients that exceeds the calculated sample size improved the strength our study. Sampling began retroactively in December 2023.

Statistical Analysis

Descriptive statistics were employed to summarize the clinical, demographic, and paraclinical characteristics of the patients. Continuous variables, such as age and the time from symptom onset to diagnosis, were reported as mean ± standard deviation (SD) and median, while categorical variables, including gender and underlying conditions, were presented as frequencies and percentages. The normality of variables was assessed using the one-sample kolmogorov-smirnov test. Chi square, Fisher exact and Mann-Whitney U test were used for data analysis. A multivariable logistic regression was conducted to identify risk factors for high-grade VUR (Grades IV–V), adjusting for potential confounders. Variables with a *P*-value < .2 in the univariate analysis were included in the regression model. Odds ratios (OR) with 95% confidence intervals (CIs) were reported, and statistical significance was determined at p value 0.05. An Odd ratio > 1 accompanies with a *P*-value < .05 considered as risk factor.

RESULTS

Baseline characteristics

A total of 223 children aged two years or younger were referred to the nephrology clinic between March 2006 and August 2023. Tables 1 to 3 present a summary of the demographic characteristics, clinical presentations, bacterial etiologies of UTIs, and indications of assessments for VUR in the study population. Escherichia coli was the predominant pathogen, detected in 175 cases (78.5%), followed by Klebsiella pneumoniae (9.9%), Enterobacter species (2.7%), and Proteus mirabilis (2.2%). In six cases (2.7%), the pathogenic organism was not documented.

Normal kidney ultrasound was observed in 144 patients (64.6%), The most common abnormal finding was hydronephrosis, observed in 67 cases (30%). Unilateral hydronephrosis was identified in 39 cases (17.5%), while bilateral hydronephrosis was found in 28 cases (12.5%). Additionally, ureteral dilation (hydroureter) was present in 15 cases (6.7%).

At the initial kidney US, unilateral reduced kidney size and renal scarring were confirmed in four cases (1.8%). Bladder wall thickening was the most commonly reported abnormal finding in bladder ultrasounds, occurring in 18 patients (8.1%). Overall, 91.5% of the patients (n = 204) had normal bladder ultrasounds. A few cases of the study population had congenital structural abnormalities in urogenital or gastrointestinal systems. Specifically, there were three cases (1.3%)

Table 1. Baseline characteristics of the patients enrolled in the study (n = 223)

Variable	Number (%)
Female	180 (80.7)
Male	43 (19.3)
Age at first febrile UTIs[a] (months)	Range 1-24; median :8.5; IQR[b]: 4-12
Fever at the first presentation	219 (98.2)
Irritability	87 (39)
Vomiting	39 (17.5)
Poor Feeding	28 (12.6)
Foul-smelling urine	17 (7.6)
Normal findings on physical examinations	209 (93.7)
Labial Adhesions	6 (2.7)
Palpable Bladder	4 (1.8)
Myelomeningocele	3 (1.3)
Hypospadias	1 (0.5)
Labial Adhesions	14 (6.3)
Negative family history of UTI	123 (55.1)
Positive family history of UTI	58 (26)
Family history of UTIs was Unknown	42 (18.9)
Circumcision status (males only, n = 43)	
Circumcised	13 (30.2)
Uncircumcised	10 (23.2)
Non-recorded	20 (46.5)

[a]Urinary tract infections; [b]Interquartile range

Table 2. The reasons for performing VCUG in study population

Reasons for performing VCUG[a]	Number (%)
Recurrent febrile UTIs[b]	94 (42.2)
Hydronephrosis[c] in ultrasound	42 (18.8)
Antenatal hydronephrosis[d]	11 (4.9)
Ureteral dilatation[e] in ultrasound	6 (2.7)
Kidney size reduction in ultrasound	4 (1.8)
Renal scarring in ultrasound	4 (1.8)
Sibling of a patient with VUR[f]	4 (1.8)
Renal dysfunction	4 (1.8)
Imperforate anus	3 (1.3)
Decreased renal cortical thickness in ultrasound	1 (0.4)
UPJO[g]	2 (0.9)
Multicystic dysplastic kidney	1 (0.4)

The main reason for performing VCUG in all patients was febrile UTI. This Table represents extra indications for recommending VCUG examination. [a]Voiding cystourethrogram; [b]Urinary tract infections; [c]An anterior posterior renal pelvis diameter ≥5 mm; [d]Hydronephrosis firstly detected on antenatal ultrasound examination; [e]An ureteral diameter ≥ 4mm; [f]Vesicoureteral reflux; [g]Ureteropelvic junction obstruction.

Table 3. The etiologies of urinary tract infections in our participants

Urinary Pathogen	Number (%)
Escherichia coli	175 (78.5)
Klebsiella pneumoniae	22 (9.9)
Enterobacter cloacae	6 (2.7)
Proteus mirabilis	5 (2.2)
Enterococcus faecalis	4 (1.8)
Citrobacter species	3 (1.4)
Group B Streptococcus	1 (0.4)
Pseudomonas aeruginosa	1 (0.4)
Not recorded[a]	6 (2.7)
Total	223 (100)

[a]The names of the pathogens were not recorded in the medical files.

of imperforated anus, along with two cases (0.9% each) of PUV and ureteropelvic junction obstruction (UPJO). Additionally, one patient (0.4% each) noted to have multicystic dysplastic kidney, horseshoe kidney, hypospadias, and epispadias.

Vesicoureteral reflux was identified in 172 (77.1%) patients. In total, there were 88 cases (39.5%) with bilateral VUR, while 84 patients (37.7%) had unilateral VUR. High-grade VUR, classified as grades IV–V, was observed in 53 patients (23.8%), including bilateral high-grade VUR in 13 patients (5.8%). Out of 446 kidney ureter units (KUUs), 260 (58.3%) were affected by VUR of which 66 refluxing KUUs (25.4%) had high-grade VUR. Figure 1 presents the frequency of VUR grades I-V among the 260 refluxing KUUs.

Numerous variables, including gender, US findings, and bacterial etiology of UTIs, were analyzed to identify any associations with high-grade VUR (Table 4). As shown in Table 4, male gender, hydronephrosis, abnormal kidney ultrasounds, and a history of antenatal hydronephrosis (ANH) were significantly correlated with high-grade VUR ($P < .05$ for all). Patients with high-grade VUR experienced their first febrile UTIs at a median age of 7 months (interquartile range [IQR], 2-11 months). In contrast, those without high-grade VUR had their first febrile UTIs at a median age of 9 months (IQR, 5-12 months) ($P = .69$). Although patients with high-grade VUR were younger at the time of their first febrile UTIs, the age at this first occurrence did not correlate with the presence of high-grade VUR.

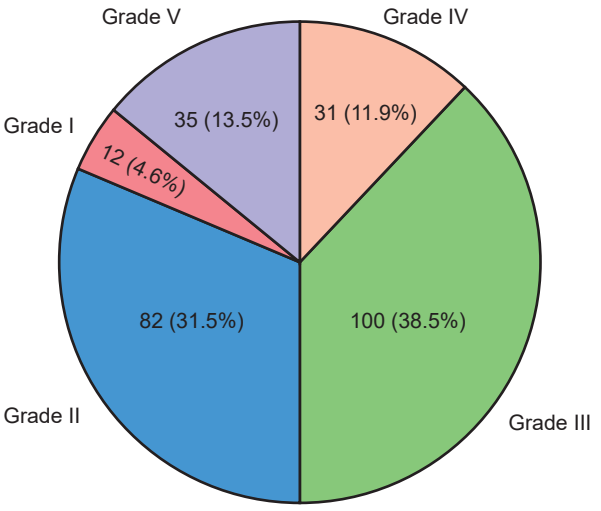

Figure 1. The frequency of VUR grading in 260 refluxing kidney ureter units .

In twelve patients (5.4%), parents were uncertain about the number of UTI episodes their child had experienced. Excluding these cases, recurrence status and imaging findings were grouped in 211 patients into the following categories:

1. Single UTI with a normal Kidney US (n = 118; 55.9%)
2. Single UTI with an abnormal Kidney US (n = 29;13.8%)
3. Recurrent UTIs with a normal Kidney US (n = 49; 23.2%)
4. Recurrent UTIs with an abnormal Kidney US (n = 15;7.1%)

The frequency of VUR in groups 1-4 was 78.8%(n = 93), 96.6%(n = 28), 67.3%(n = 33), and 73.3%(n = 11), respectively. The frequency of high-grade VUR was 25.1% (n = 53). The frequency of high-grade VUR was compared between the groups. High-grade VUR was observed in 48.3% of patients with a single UTI and an abnormal kidney US, and 19.5% of the cases with a single UTI and normal kidney US. In patients with recurrent UTIs, high-grade VUR was observed in 22.5% of cases with normal kidney US, and 33.3% of those with abnormal kidney US. High-grade VUR was significantly more prevalent in patients with a single UTI and an abnormal kidney US ($P = .012$; Table 5).

The frequency of high-grade VUR in relation to hydronephrosis, absence of hydronephrosis, and normal and abnormal kidney US findings was 50.7%, 12.2%, 11.8%, and 45.5%, respectively (Table 4). When considering the presence of hydronephrosis, abnormal kidney US findings, and recurrent versus single episodes of APN, the highest frequency of high-grade VUR was found

Table 4. Comparison of gender, clinical characteristics, ultrasound findings, and bacterial etiologies of UTIs concerning the presence of high-grade VUR

Variable	high-grade VUR[a]	No high-grade VUR	Number (%)	*P*
Female gender	32 (17.8)	148 (82.2)	180 (100)	< .001*
Male gender	21 (48.9)	22 (51.1)	43 (100)	
Hydronephrosis	34 (50.7)	33 (49.3)	67 (100)	< .001*
No hydronephrosis	19 (12.2)	137 (87.8)	156 (100)	
Dilated ureter[b]	3 (50)	3 (50)	6 (100)	.148**
Normal ureteral diameters	50 (23)	167 (77)	217 (100)	
Renal scar[b]	0 (0)	4 (100)	4 (100)	.575**
No renal scar	53 (24.2)	166 (75.8)	219 (100)	
Decreased kidneys sizes[b]	2 (50)	2 (50)	4 (100)	.24**
Normal kidneys sizes	51 (23.3)	168 (76.7)	219 (100)	
Normal kidney ultrasound	17 (11.8)	127 (88.2)	144 (100)	< .001*
Abnormal kidney ultrasound	36 (45.5)	43 (54.5)	79 (100)	
Normal bladder US findings	47 (23)	157 (77)	204 (100)	.403*
Abnormal bladder US findings	6 (31.6)	13 (68.4)	19 (100)	
Infections with E-coli species[c]	39 (22.3)	136 (77.7)	175 (100)	.338*
Infections with non-E-coli species	12 (28.6)	30 (71.4)	42 (100)	
No history of VUR in sibling	51 (23.3)	168 (76.7)	219 (100)	0.24**
History of VUR in sibling	2 (50)	2 (50)	4 (100)	
Single episodes of APN[d,e]	37 (25.2)	110 (74.8)	147 (100)	0.979*
Recurrent APN	16 (25)	48 (75)	64 (100)	
Positive history of ANH[f]	7 (63.6)	4 (36.4)	11 (100)	0.005**
No history of ANH	46 (21.7)	166 (78.3)	212 (100)	
Total cases (%)	53 (23.8)	170 (76.2)	223 (100)	

[a]Vesicoureteral reflux grades IV &V; *Chi square test; [b]On ultrasound examinations; **Fisher exact test; [c]In six patients, the uropathogens responsible for UTIs were not recorded in medical file, and only the colony count > 10^5 of a single pathogen was reported; [d]Acute pyelonephritis; [e]In 12 patients, the parents were unsure about the number of UTI episodes their child had experienced; [f]Antenatal hydronephrosis.

Table 5. Comparing the frequency of high-grade VUR considering kidney ultrasound findings and recurrence of urinary tract infections

Patients' group	With high-grade VUR[a] N (%)	Without high-grade VUR N (%)	Total cases N (%)	*P**
Group 1[b]	23 (19.5)	95 (80.5)	118 (100)	0.012
Group 2[c]	14 (48.3)	15 (51.7)	29 (100)	
Group 3[d]	11 (22.5)	38 (77.5)	49 (100)	
Group 4[e]	5 (33.3)	10 (66.7)	15 (100)	
Total cases (%)	53 (25.1)	158 (74.9)	211[f]	

[a]Vesicoureteral reflux; *chi square test; [b]Single UTI with a normal kidney US; [c]Single UTI with an abnormal kidney US; [d]Recurrent UTIs with a normal kidney US; [e]Recurrent UTIs with an abnormal kidney US; [f]Twelve patients' parents were unsure about the number of UTI episodes their child had experienced.

in patients with hydronephrosis (50.7%), while the lowest was seen in those with normal kidney ultrasounds (11.8%).

Univariable and multivariable analysis of risk factors for high-grade VUR

Table 6 presents the logistic regression analysis of risk factors associated with high-grade VUR. In this preliminary analysis, males were significantly more likely to have high-grade VUR compared to females (48.9% vs. 17.8%, $P < .001$). High-grade VUR was also more prevalent in patients with abnormal renal ultrasound findings (43.5% vs.11.8%, $P < .001$), hydronephrosis (50.7% vs. 12.2%, $P < .001$), and ANH (63.6% vs. 21.7%, $P = .005$).

In contrast, the presence of non-E.coli infections was not significantly associated with high-grade VUR ($P = .338$). Table 6 also includes the multivariable logistic regression analysis, which adjusts for potential confounders in order to determine the independent predictors of high-grade VUR. After adjustment, male sex remained a significant risk factor (OR = 4.41, 95% CI: 2.17–8.97, $P < .001$). Abnormal renal ultrasound findings

Table 6. Risk evaluation of high-grade VUR by logistic regression model

Variable	OR[a]	95% CI[b] (lower-upper)	*P**
Male gender	3.44 *	1.17 – 10.16	.025
Abnormal kidney ultrasound	6.25 *	3.19 – 12.25	.001
Hydronephrosis	3.36 *	1.42 – 7.93	.005
Hydroureter	0.101*	0.029 – 0.397	.001
E. coli infection	1.12 *	0.49 – 2.53	.782
Prenatal hydronephrosis	3.08 *	0.38 – 24.70	.280
Variable	**OR**	**95% CI (lower-upper)**	***P*******
Male sex	4.41**	2.17 – 8.97	< .001
Abnormal renal ultrasound	3.35**	1.67 – 6.75	< .001
Hydronephrosis	5.69**	2.47 – 13.12	< .001
Prenatal hydronephrosis	6.31**	1.77 – 22.51	.004
Non-E. coli infection	1.39**	0.65 – 2.97	.338

[a]odd ratio; [b]Confident interval; *Univariate logistic regression; **Multivariate logistic regression

were strongly associated with high-grade VUR (OR = 6.25, 95% CI: 3.19–12.25, $P < .001$), as were hydronephrosis (OR = 5.69, 95% CI: 2.47–13.12, $P < .001$) and ANH (OR = 6.31, 95% CI: 1.77–22.51, $P = .004$). However, non-E.coli infections was not identified as an independent risk factor (OR = 1.39, 95% CI: 0.65–2.97, $P = .338$).

DISCUSSION

The current study involved children aged two years and younger with a history of febrile UTIs. Univariable analysis initially identified male sex, abnormal renal US results, hydronephrosis, ANH, and non-E.coli infections as potential risk factors. However, after adjusting for confounding variables in multivariable analysis, non-E.coli infections were no longer independently associated with high-grade VUR, whereas male sex, abnormal renal US results, hydronephrosis, and ANH remained significant predictors. These findings reinforce the importance of early risk stratification in children with febrile UTIs, allowing for a more selective approach to VCUG testing.The American Academy of pediatrics guideline recommends VCUG after the first febrile UTI in infants aged 2-24 months if kidney US reveals hydronephrosis, scarring, or other findings suggestive of high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances.[11] Based on our three previous studies, we recommend VCUG be carried out routinely for infants 2-24 months with the first episode of febrile UTI even if the kidney US was normal.

One of our studies in children presented with UTI showed a high prevalence rate for VUR (46.9% of girls and 48.9% of boys).[12] In another investigation, we found prevalence rates of 56.64%, 48.2% for VUR in children presented with UTI in the first and second years of their life, respectively.[13] The indications for performing VCUG in this study were different and included some cases with lower UTI (non-febrile UTI) such as those with abnormal kidney US or recurrent cystitis.

Additionally, another study in childhood UTI demonstrated that kidney US is a effective screening tool, however, if used as the sole screening approach, approximately two-thirds of VUR and one-third of high-grade VUR cases would remain undiagnosed.[14] In infants aged 2-24 months with febrile UTI, a prevalence of 30-40% for VUR has been observed.[15] Performing VCUG selectively rather than routinely, may overestimate VUR frequency in our series (reported at 77.1%, notably higher than typical literature ranges of 30–40%). However, a group of patients underwent a VCUG examination following recurrent UTIs since they were referred to the nephrology clinic following recurrent UTIs. The prevalence of VUR in our participants was about twice that reported by Downs *et al.*[15] Differences in methodology may be responsible for the different results. They did not recommend VCUG in patients with the first febrile UTI and normal kidney US.

Our participants consisted of a heterogenous group of infants with febrile UTI, A total of 52.9% of our cases (n = 118) underwent VCUG following the first febrile UTI, despite normal kidney US findings (group 1). The frequency of VUR in this group of patients was 78.8% (n = 93). An underlying condition that can be associated with

VUR was observed in 11 out of 93 cases (11.8%). Seven cases had a history of ANH that VUR was found in six . Three patients were diagnosed with imperforated anus, and VUR was detected in all . In addition, VUR was found in one patient who was sibling of a child with a diagnosis of VUR. .High-grade VUR was found in four of these eleven patients (36.4%). Excluding these 10 cases with a diagnosis of VUR, 83 cases in group 1 (70.3%) had no underlying disease or condition that can be associated with VUR. It means that 48.2% of total VUR population (83 out of 172 patients), and 19 out of 53 cases with high-grade VUR (35.8%) had a single episode of febrile UTI + normal kidney US with no underlying disease or condition that can be associated with VUR.

It indicated that using kidney US as the only screening method in individuals with single episode of febrile UTI, can result in a miss VUR in about 48% and high-grade VUR in approximately 36% of the cases.

A study in patients under 19 years diagnosed with UTI revealed a male predominance in those under 12 months, with the male to female ratio 5.3:1 for ages 0 to 2 months, 2.1:1 for ages 3 to 5 months; and 1.6:1 for ages 6 to 11 months. From 12 months and above, there was female predominance; with the female to male ratio of 1.9:1 up to 4 years old.[16] The gender distribution in our cases was completely different from the mentioned study. In our study, there was a slightly male predominance only in age 0-2 months (male to female ratio 1.05: 1. After age 2 months, there was a female predominance with a female to male ratio of 3.6:1 in 3-5 months, 6: 1 in 6-11 months and 9.7:1 in age 12 months and above. The high proportion of females in our study (80.7%) contrasts with expected demographics in this age group and may reflect referral patterns or regional factors, warranting cautious generalization.

Infections with non-E.coli species are significantly more prevalent in patients with neurogenic bladder dysfunction rather than those with urological abnormalities.[17] Congenital anomalies of the kidneys and the urinary tract (CAKUT) and lower urinary tract dysfunction (LUTD) seem to be significant risk factors for UTIs in children.[18] Hydronephrosis occurs in 10-20% of initial febrile UTI cases and is closely associated with VUR, which is present in 30-40% of these cases.[19] Renal US is the recommended first-line imaging technique for febrile UTIs due to its non-invasive nature and wide accessibility. However, its limited sensitivity in detecting high-grade VUR indicates that additional diagnostic tools may be necessary in specific situations.[20,21] While VUR has traditionally been regarded as a primary cause of recurrent UTIs, not all recurrent infections are dependent on it.[20,22] In our study, the prevalence of VUR was 77.1%, with high-grade VUR at 23.8%. These findings are consistent with previous research, although variations may arise from differences in study populations and methodologies.[23,24] A study involving Taiwanese children with their first UTI showed that the prevalence of VUR was particularly high among infants aged one year or younger, further supporting our findings that younger children are at increased risk.[10]

Up to 80% of low-grade VUR cases resolve spontaneously,[25] highlighting the need for multifactorial risk stratification models that consider clinical, microbiological, and imaging predictors rather than relying solely on VUR status.[26] Our findings reinforce the established link between hydronephrosis and VUR, a connection that has been well-documented in recent studies.[27] We build on previous findings by emphasizing ANH as an independent predictor, which underscores the importance of early postnatal imaging and monitoring. This supports recommendations to incorporate prenatal ultrasound findings into postnatal UTI management strategies.[28] The relationship between infections with non-E.coli pathogens and the severity of VUR has been a subject of debate. While some studies report a significant correlation,[29] our findings are consistent with earlier research showing that while infections with non-E.coli pathogens are often associated with high-grade VUR in univariable analyses, they do not remain significant predictors in adjusted models.[30,31] This implies that the apparent connection between pathogen type and high-grade VUR may be confounded by underlying urological anomalies rather than representing an independent risk factor.

Additionally, the higher prevalence of high-grade VUR in male infants (48.9%) compared to females (17.8%) can likely be attributed to differences in urinary tract development during fetal phase. Male infants may experience delayed maturation of the vesicoureteral junction, which predisposes them to higher grades of reflux and an increased risk of renal scarring.[32] Hydronephrosis, identified as

a key risk factor in our study, can lead to urinary stasis and altered voiding dynamics, ultimately causing long-term complications such as renal scarring and impaired renal function.[1,33] Previous studies have linked breakthrough UTIs and renal function impairment to an increased risk of developing new renal scarring. Our findings highlight the importance of early identification of hydronephrosis, as it may be a modifiable risk factor that can help to prevent long-term renal injury.

Identifying hydronephrosis, both prenatally and postnatally, allows for proactive monitoring of high-risk children, potentially facilitating earlier intervention and enhanced therapeutic care. Consistent with previous research,[32] our findings demonstrated an association between high-grade VUR and male gender. Unlike many prior studies, we employed both univariable and multivariable analyses to differentiate between persistent associations and those that lost significance after adjustment. Our results align with earlier studies that established hydronephrosis as an independent predictor of VUR after controlling for confounding factors.[34]

Our study reinforces this evidence by showing that both prenatal and postnatal hydronephrosis are independent risk factors, underscoring the significance of prenatal ultrasound findings in early risk stratification. The literature has debated the association between non-E.coli infections and high-grade VUR. While some studies noted a significant correlation in unadjusted analyses, multivariable models often indicated that this association weakened when structural abnormalities were considered.[35,36] Our findings suggest that the apparent link between pathogen type and high-grade VUR may be confounded by underlying urological anomalies, rather than being an independent risk factor. We further confirm that hydronephrosis, prenatally, postnatally, and male sex are independent predictors of high-grade VUR through multivariable analysis. These results underscore the importance of adjusting for confounding factors; relying solely on univariable associations may overestimate the significance of certain risk factors and lead to unnecessary interventions.

Our results emphasize the importance of renal ultrasonography as a first-line screening tool for febrile UTIs. While ultrasonography cannot definitively diagnose VUR, it can detect hydronephrosis, renal asymmetry, and other structural abnormalities. This non-invasive method serves to identify high-risk infants who may require further evaluation with VCUG. We propose a selective VCUG approach for children with prenatally diagnosed hydronephrosis, renal abnormalities, or those who are male, suggesting they undergo early VCUG evaluation.

LIMITATIONS OF THE STUDY

This study provides valuable insights into the risk evaluatiom of high-grade VUR in children ≤ 2 years with febrile UTIs. The large sample size, comprehensive imaging and microbiological data, enhance the reliability of our findings. The use of both univariable and multivariable regression analysis allowed us first to identify multiple potential risk factors and then determine which remained significant independent predictors after adjusting for confounders. However, retrospective design, a possibility of selection bias since VCUG was not performed in all cases of febrile UTIs, and a single-center study that may cause the findings not be generalizable to all populations are the main limitations of the study that be considered . In addition, a low sample size in a group with recurrent UTIs and an abnormal Kidney US (group 4) may affect the analysis.

CONCLUSION

Male sex, abnormal renal ultrasound findings, hydronephrosis, and ANH were identified as independent predictors of high-grade VUR in children aged two years or younger with febrile UTIs. These findings support a selective approach to performing VCUG, ensuring that high-risk children receive early evaluation while minimizing unnecessary procedures in low-risk cases. The strong association between ANH and high-grade VUR highlights the importance of integrating both prenatal and postnatal imaging data into clinical decision-making. Future research should focus on risk factors of high-grade VUR in prospective and multicenter studies, considering factors that may cause selection bias, and assessing long-term renal outcomes.

AUTHOR CONTRIBUTIONS

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Received November 2025
Revised May 2026
Accepted July 2026