

Risk Factors for Recurrent Febrile Urinary Tract Infection in Children with Vesicoureteral Reflux

 Bahriye Uzun Kenan^{1*},  Asiye Gültekin Soylu¹,  Tülin Güngör¹,  Evrim Kargın Çakıcı¹,  Aysun Çaltık Yılmaz¹

¹ Department of Pediatric Nephrology, Ankara Etlik City Hospital, Ankara, Türkiye

*Correspondence: Bahriye Uzun Kenan; buzunkenan@gmail.com

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Abstract

Aim: Recurrent febrile urinary tract infection (UTI) in children with vesicoureteral reflux (VUR) is associated with renal scarring and long-term morbidity. This retrospective cohort study aimed to identify clinical and imaging factors associated with recurrent febrile UTI in children with VUR. **Materials and Methods:** We retrospectively reviewed 100 children diagnosed with VUR at the Pediatric Nephrology Clinic of Ankara Etlik City Hospital between January 2023 and May 2026. Recurrent febrile UTI was defined as two or more febrile UTI episodes during follow-up. Patients were divided into two groups based on recurrent febrile UTI status, and demographic characteristics, VUR grade, febrile UTI history, DMSA scintigraphy findings, laboratory results, and treatment data were compared. Factors associated with recurrent febrile UTI were evaluated by logistic regression analysis. **Results:** The median age at diagnosis was 36.5 months (3.25–81.0), and 35 patients (35%) experienced recurrent febrile UTI. High-grade VUR ($p=0.038$), bilateral involvement ($p=0.045$), and DMSA scarring ($p=0.012$) were significantly associated with recurrence; age, age at diagnosis, age at first UTI, and prophylaxis duration were also significantly higher in the recurrent-febrile-UTI group (all $p<0.05$). In the multivariable model, high-grade VUR (OR=3.28; 95% CI 1.09–9.85; $p=0.034$), bilaterality (OR=3.05; 95% CI 1.07–8.73; $p=0.037$), and CAP duration (OR=1.11; 95% CI 1.01–1.22; $p=0.022$) remained statistically associated with recurrent febrile UTI (Hosmer–Lemeshow $p=0.858$). **Conclusion:** High-grade and bilateral VUR were independently associated with recurrent febrile UTI. Longer CAP duration was also associated with recurrence; however, because CAP duration was determined during follow-up and may reflect clinical risk and prior breakthrough infections, this association should not be interpreted as causal. Patients with high-grade and bilateral VUR may benefit from closer follow-up and individualized management.

Keywords: Child; Urinary Tract Infections; Vesico-Ureteral Reflux

1. Introduction

Vesicoureteral reflux (VUR) is one of the most common urinary tract anomalies in childhood and is associated with recurrent febrile urinary tract infection (UTI), renal scarring, and long-term loss of renal function^{1,2}. Recurrent febrile UTI is clinically important

because repeated upper UTI may contribute to renal parenchymal injury and may identify children at greater risk of adverse long-term renal outcomes. The clinical course of VUR is highly heterogeneous; while spontaneous resolution is observed in some patients, others develop recurrent infections and progressive renal damage. Therefore, identifying children at increased risk of recurrent febrile UTI is important for individualized surveillance, prophylactic strategies, and timely consideration of further intervention.

Numerous clinical and imaging parameters have been reported to influence the development of recurrent UTI, including high-grade VUR, bilateral reflux, a history of febrile UTI at presentation, renal scarring, hydronephrosis, and the characteristics of the causative microorganism^{2,3,4}. However, the relative contribution of these factors varies across studies, and it is not always possible to determine which patients are truly at high risk of infection recurrence.

The current EAU/ESPU guideline recommends an individualized, risk-based approach to VUR management, emphasizing the importance of recognizing and treating bladder–bowel dysfunction⁵. Similarly, the RIVUR study showed that continuous antibiotic prophylaxis reduces the risk of recurrent UTI, although this benefit is not uniform across all patients⁶. In addition, long-term results from the International Reflux Study in Children demonstrated that the natural course of VUR depends not only on reflux grade but also on various other clinical characteristics⁷. These findings suggest that evaluating multiple clinical parameters together, rather than relying on a single variable, may be more useful for determining infection risk.

Studies evaluating independent risk factors for the development of recurrent febrile UTI in Turkish pediatric VUR populations are limited. The aim of this retrospective cohort study was to identify clinical and imaging factors independently associated with recurrent febrile UTI in children diagnosed with VUR, thereby supporting risk-stratified follow-up and management.

2. Materials and Methods

We retrospectively reviewed data from 100 children diagnosed with VUR at the Pediatric Nephrology Clinic of Ankara Etlik City Hospital between January 2023 and May 2026. Patients with secondary VUR, neurogenic bladder, posterior urethral valves, ureteral duplication, or other structural or functional urinary tract abnormalities that could independently predispose to recurrent UTI were excluded. Recurrent febrile UTI was defined as two or more febrile UTI episodes during follow-up. Patients were divided into two groups based on recurrent febrile UTI status, and demographic characteristics, VUR grade, febrile UTI history, DMSA scintigraphy findings, laboratory results, and treatment data were compared. Independent predictors of recurrent febrile UTI were evaluated by logistic regression analysis. Febrile UTI was defined as a body temperature of $\geq 38^{\circ}\text{C}$ together with pyuria (increased leukocytes on urine microscopy) and growth of a single uropathogen at $\geq 50,000$ CFU/mL in a catheter-obtained urine specimen.⁸

The follow-up period was defined as the interval between the date of VUR diagnosis and the date of the last documented clinic visit. Recurrent febrile UTI events occurring at any time within this follow-up interval were included in the analysis.

Data were analyzed using SPSS version 23.0 statistical software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages. The normality of continuous variables was assessed visually (histograms and probability plots) and analytically (Kolmogorov–Smirnov/Shapiro–Wilk tests). Continuous variables that did not follow a normal distribution were presented as median (interquartile range, IQR). The Mann–Whitney U test was used to compare non-normally distributed continuous variables between the two groups, and the chi-square test was used to compare categorical variables. Candidate variables considered for regression included VUR grade, laterality,

DMSA scarring, age, age at diagnosis, age at first UTI, and CAP duration. Variables significant in univariable logistic regression were subsequently entered into the multivariable logistic regression model using the Enter method. Model fit was assessed using the Hosmer–Lemeshow test. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF), with VIF >5 considered indicative of significant multicollinearity. A p-value <0.05 was considered statistically significant.

Ethics approval: This study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-562, Date: 14.07.2026), and was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

The median age at diagnosis of the 100 patients included was 36.5 months (3.25–81.0). A single episode of febrile UTI was observed in 65 patients (65%), while 35 patients (35%) met the definition of recurrent febrile UTI (Table 1).

Table 1. Comparison of demographic and clinical characteristics between patients with a single febrile UTI episode and those with recurrent febrile UTI

Demographic and Clinical Characteristics		Single (n=65)	Recurrent (n=35)	p
Gender	Female	31 (59.6)	21 (40.4)	0.334
	Male	34 (70.8)	14 (29.2)	
VUR Grade	Low	34 (77.3)	10 (22.7)	0.038
	High	31 (55.4)	25 (44.6)	
Laterality	Unilateral	41 (74.5)	14 (25.5)	0.045
	Bilateral	24 (53.3)	21 (46.7)	
Mode of diagnosis	UTI	35 (59.3)	24 (40.7)	0.128
	Prenatal	10 (90.9)	1 (9.1)	
	Incidental	20 (66.7)	10 (33.3)	
UTI pathogen	E. coli	49 (64.5)	27 (35.5)	>0.999
	Others	16 (66.7)	8 (33.3)	
CAP	Present	52 (60.5)	34 (39.5)	0.018
	Absent	13 (92.9)	1 (7.1)	
USG	Normal	20 (57.1)	15 (42.9)	0.051
	Hydronephrosis	33 (78.6)	9 (21.4)	
	Ureteral dilation	4 (80.0)	1 (20.0)	
	Ureteral dilation+Hydronephrosis	2 (28.6)	5 (71.4)	
	Other	6 (54.5)	5 (45.5)	
DMSA scar	Yes	19 (48.7)	20 (51.3)	0.012
	No	46 (75.4)	15 (24.6)	

Values are n (%). Yates-corrected chi-square test or Fisher's exact test was used, as appropriate. UTI, urinary tract infection; VUR, vesicoureteral reflux; CAP, continuous antibiotic prophylaxis; USG, ultrasonography; DMSA, dimercaptosuccinic acid.

Among continuous variables, age (median 79.0 vs 39.0 months; $p=0.007$), age at diagnosis (58.0 vs 20.0 months; $p=0.013$), and age at first UTI (21.0 vs 2.0 months; $p=0.001$) were significantly higher in patients with recurrent febrile UTI (Table 2).

The median duration of antibiotic prophylaxis was 6 months (2–11). There was no significant difference between groups in sex distribution ($p=0.334$). The distribution of

VUR grade was significantly associated with recurrent febrile UTI ($p=0.011$). When VUR grades were classified as low (grade 1–3) and high (grade 4–5), the difference remained significant ($p=0.038$). Recurrent febrile UTI was observed in 44.6% of patients with high-grade VUR, compared with 22.7% of those with low-grade VUR (Table 1).

No significant association was found between causative microorganism (*E. coli* versus other pathogens) and low- versus high-grade VUR (high-grade VUR rate 60.5% in the *E. coli* group versus 41.7% in the other-pathogen group; $\chi^2=2.633$, $df=1$, $p=0.105$).

Laterality also emerged as a significant determinant ($p=0.045$); recurrent febrile UTI was observed in 46.7% of patients with bilateral VUR, compared with 25.5% of unilateral cases (Table 1).

Recurrent febrile UTI was observed in 51.3% of patients with DMSA scarring, compared with 24.6% of those without scarring ($p=0.012$). Among patients with scarring, 41% had low-grade and 59% had high-grade VUR, but this distribution did not differ significantly from that of patients without scarring ($p=0.785$). CAP duration was significantly longer in the recurrent-febrile-UTI group (8.0 vs 6.0 months; $p=0.019$). No significant differences were found between groups in follow-up duration, creatinine, or estimated glomerular filtration rate (eGFR) (Table 2).

Table 2. Comparison of continuous variables between patients with a single febrile UTI episode and those with recurrent febrile UTI

Variable	Single (n=65)	Recurrent (n=35)	P
Age (months)	39.0 (15.0–99.5)	79.0 (42.0–103.0)	0.007
Age at diagnosis (months)	20.0 (3.0–56.5)	58.0 (27.0–92.0)	0.013
Follow-up duration (months)	12.0 (6.0–23.5)	14.0 (6.0–27.0)	0.403
Age at first UTI (months)	2.0 (0.0–34.0)	21.0 (4.0–38.0)	0.001
CAP duration (months)	6.0 (1.0–8.5)	8.0 (4.0–16.0)	0.019
Creatinine (mg/dL)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.899
eGFR (mL/min/1.73 m ²)	101.0 (73.0–113.5)	99.0 (90.0–122.0)	0.446

Values are median (IQR). Mann-Whitney U test was used for all comparisons. UTI, urinary tract infection; CAP, continuous antibiotic prophylaxis; eGFR, estimated glomerular filtration rate.

On multivariable logistic regression analysis, high-grade VUR (OR=3.28; 95% CI 1.09–9.85; $p=0.034$), bilateral involvement (OR=3.05; 95% CI 1.07–8.73; $p=0.037$), and CAP duration (OR=1.11; 95% CI 1.01–1.22; $p=0.022$) remained statistically associated with recurrent febrile UTI. DMSA scarring, age, and age at diagnosis, although significant on univariable analysis, lost significance in the multivariable model ($p=0.602$, $p=0.361$, and $p=0.082$, respectively). Model fit was good (Hosmer–Lemeshow $p=0.858$) (Table 3). Given the retrospective design and the time-dependent nature of CAP exposure, the CAP-duration association should not be interpreted as evidence that longer prophylaxis causes recurrence.

Table 3. Univariable and multivariable logistic regression analysis of independent predictors of recurrent febrile UTI

Variable	Univariable OR (95% CI)	<i>p</i>	Multivariable OR (95% CI)	<i>p</i>
VUR grade (High vs Low)	2.74 (1.13–6.61)	0.025	3.28 (1.09–9.85)	0.034

Variable	Univariable OR (95% CI)	<i>p</i>	Multivariable OR (95% CI)	<i>p</i>
Laterality (Bilateral vs Unilateral)	2.56 (1.10–5.95)	0.029	3.05 (1.07–8.73)	0.037
DMSA scarring (Present vs Absent)	3.22 (1.37–7.60)	0.007	1.35 (0.43–4.22)	0.602
Age	1.009 (1.001–1.017)	0.037	0.98 (0.94–1.01)	0.361
Age at diagnosis	1.01 (1.001–1.019)	0.023	1.03 (0.99–1.07)	0.082
Age at first UTI	1.004 (0.99–1.01)	0.570	–	–
CAP duration	1.08 (1.02–1.15)	0.007	1.11 (1.01–1.22)	0.022

OR, odds ratio; CI, confidence interval; VUR, vesicoureteral reflux; DMSA, dimercaptosuccinic acid; UTI, urinary tract infection; CAP, continuous antibiotic prophylaxis. Hosmer-Lemeshow test $p=0.858$ for the multivariable model. Reference categories: VUR grade – Low; Laterality – Unilateral; DMSA scarring – Absent.

4. Discussion

The relative contribution of variables such as reflux grade, laterality, DMSA scarring, and prophylaxis duration in predicting recurrent UTI in children with vesicoureteral reflux (VUR) remains debated in the literature⁹. In a secondary analysis of the RIVUR study, Keren et al.⁴ showed that bladder–bowel dysfunction and baseline DMSA scarring also increase the risk of recurrent UTI independent of VUR grade, indicating that a single variable is insufficient for risk prediction.

In our study, high-grade and bilateral VUR were identified as independent predictors of recurrent febrile UTI, consistent with the findings of Dias et al.¹⁰ and with the meta-analytic breakthrough-UTI risk score derived by Fang et al. from 24 cohort studies ($n=3,264$)¹¹, in which high-grade and bilateral reflux were similarly among the retained predictors. Similarly, in the multicenter prediction model by Ismail et al.¹², the initial grade of reflux was the primary determinant of postoperative UTI risk, while mild VUR recurrence detected after surgery did not independently increase risk. This finding supports the notion that the initial grade of reflux carries prognostic value independent of subsequent radiological course, consistent with the direction of our results.

In our cohort, median age and age at diagnosis were higher in patients with recurrent febrile UTI. However, follow-up duration did not differ significantly between groups; therefore, these age-related associations should not be interpreted as evidence that recurrence risk simply accumulates with longer follow-up. They may instead reflect differences in patient characteristics or clinical trajectories that cannot be fully resolved in this retrospective dataset.

No significant difference was found between groups by sex. Although this finding does not fully align with Dias et al.¹⁰, who identified female sex as an independent predictor of recurrent UTI, it is consistent with Bratslavsky et al.¹³, who evaluated an infant cohort with a negative radiographic evaluation and similarly found no statistically significant association between sex and recurrence, with only a non-significant trend toward higher risk in girls. The inconsistency of sex as a risk factor across the literature suggests that its effect may weaken once evaluated independently of underlying anatomical/functional factors.

No significant difference was found between groups regarding causative microorganism (*E. coli* versus other pathogens). In the 446-patient cohort of Choi et al.¹⁴, both the rate of recurrent febrile UTI and the rate of non-*E. coli* infection were significantly higher in the high-grade VUR group compared with other groups (recurrent UTI: $p<0.001$; non-*E. coli* infection: $p=0.001$). The predominance of *E. coli* in our cohort and the absence of a

separate subgroup analysis by VUR grade may have limited the power to detect this association.

The association between ultrasonographic (USG) finding type and recurrent febrile UTI approached but did not reach statistical significance; this borderline result may reflect limited sample size and could reach significance in a larger series.

The role of reflux grade in determining infection recurrence can be explained physiopathologically by more pronounced insufficiency of the ureterovesical junction in high-grade and bilateral involvement, which facilitates retrograde passage of infected urine to the upper urinary tract, and by the larger surface area exposed to reflux in bilateral disease. Although endpoints differ, most studies in the literature — including those of Dias et al.¹⁰ and Fang et al.¹¹, and, with respect to reflux grade, Ismail et al.¹² — similarly identify the grade and extent of reflux as the strongest clinical indicator, supporting the importance of closer follow-up, individualized prophylaxis, and, when indicated, early surgical evaluation in this patient group. Consistent with this, Al Qahtani et al.¹⁵, in a cohort limited to patients with primary bilateral high-grade VUR, showed that this subgroup carries a higher need for surgical intervention and a higher long-term risk of progression to chronic kidney disease, supporting the notion that bilateral and high-grade involvement together confer a stronger clinical risk profile than either alone.

CAP duration remained statistically associated with recurrent febrile UTI in the multivariable model, and median prophylaxis duration was longer in the recurrent-febrile-UTI group. The direction of this association should be interpreted cautiously. CAP duration is a time-dependent exposure determined during follow-up and may itself be influenced by prior breakthrough infections, disease severity, and clinician decision-making. Thus, the observed association is vulnerable to confounding by indication and reverse causality: clinicians may continue CAP longer in children already perceived to be at higher risk or after recurrent infection has occurred. In the PREDICT trial, Morello et al.¹⁶ demonstrated a modest but significant benefit of prophylaxis in preventing the first UTI in infants with grade III–V VUR. Accordingly, our CAP-duration finding should be regarded as an association and a potential marker of underlying clinical risk rather than as evidence that longer prophylaxis increases the risk of recurrent infection.

Renal scarring detected on DMSA scintigraphy was significantly associated with recurrent febrile UTI in the univariable analysis but lost significance in the multivariable model, a pattern often interpreted in the literature as confounding through VUR grade. However, cross-tabulation analysis in our cohort weakens this classic explanation: among patients with scarring, 41% had low-grade and 59% had high-grade VUR, a distribution not significantly different from that of patients without scarring. This suggests that the loss of significance for scarring may be attributable more to limited sample power than to classic confounding by VUR grade. Because DMSA scans were performed according to standard protocol 4–6 months after the first febrile UTI episode, once acute inflammation had resolved, the scarring detected likely preceded subsequent episodes; however, our retrospective design does not allow us to determine whether scarring was a cause or a consequence of recurrence. Patients with scarring may represent a high-risk subgroup warranting closer follow-up independent of causality.

4.1. Limitations

The main limitations of our study are its retrospective, single-center design and relatively small sample size ($n=100$), which limit the generalizability of the findings. Only 35 recurrent febrile UTI events were observed; this relatively small number of outcome events limits the statistical power and stability of the multivariable logistic regression model and may have contributed to the relatively wide confidence intervals. In addition, CAP duration was determined during follow-up and is therefore a time-dependent

exposure that may have been influenced by prior infections, disease severity, and clinician decision-making. Consequently, the observed association between CAP duration and recurrence is susceptible to confounding by indication and reverse causality and should not be interpreted causally. The predominance of *Escherichia coli* (76%) among causative microorganisms also precluded adequately powered subgroup analyses for other pathogens. In addition, bladder–bowel dysfunction, a recognized risk factor for recurrent UTI, could not be systematically evaluated because of the retrospective design. Larger, multicenter, prospective studies with time-to-event approaches are needed to confirm these associations.

5. Conclusion

High-grade VUR and bilateral involvement were independently associated with recurrent febrile UTI in children with VUR. CAP duration was also associated with recurrence in the multivariable model, but its time-dependent nature and susceptibility to confounding by indication and reverse causality preclude interpretation as an independent causal risk factor. Closer follow-up and individualized management should be considered, particularly for patients with high-grade and bilateral reflux.

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Informed Consent: Informed consent was obtained from the parents/legal guardians of all patients included in this retrospective study, in accordance with institutional policy. This study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-562).

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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