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REGULAR ARTICLE

Ultrasonography and C-reactive protein can predict the outcomes of voiding cystography after the first urinary tract infection

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Keywords
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ABSTRACT

Aim: This study evaluated whether sex, clinical variables, laboratory variables or ultrasonography predicted the presence of vesicoureteric reflux during the first episode of urinary tract infection in paediatric patients. We also aimed to define the criteria that indicated the need for voiding cystography testing.

Methods: We used voiding cystography to investigate 200 patients who experienced their first urinary tract infection at our institution between 2004 and 2013 and retrospectively analysed the data by reviewing their medical records.

Results: Sex ($p = 0.001$), peak blood C-reactive protein levels ($p < 0.001$), the duration of fever after antibiotic administration ($p = 0.007$) and the ultrasonography findings grade ($p < 0.001$) were significantly different between patients with and without vesicoureteric reflux. Grade IV–V ultrasonography findings and C-reactive protein levels of ≥80 mg/L predicted vesicoureteric reflux with a sensitivity, specificity and odds ratio of 47.8%, 87.8% and 6.59 (95% confidence interval = 3.26–13.33), respectively ($p < 0.001$).

Conclusion: Voiding cystography should be performed for patients with C-reactive protein levels of ≥80 mg/L and grade IV–V ultrasonography findings, but is not necessary in patients with C-reactive protein levels of <80 mg/L and grade I–III ultrasonography findings.

INTRODUCTION

Urinary tract infection (UTI) is one of the most frequent bacterial infections in children together with bacterial respiratory infections. The annual incidence of UTI in children <15 years old is 1.7 per 1000 in boys and 3.1 per 1000 in girls (1,2). Underlying diseases such as vesicoureteric reflux (VUR) also arise in some patients with UTI. VUR is an important risk factor for recurrent UTI, and recurrent UTI contributes to the development of renal scarring or deterioration in renal function. Recently, it has been considered that the damage occurring because of pyelonephritis is less severe than previously believed (3). It has also been suggested that antimicrobial prophylaxis for children with VUR is not so beneficial because antimicrobial prophylaxis reduces the risk of recurrent UTI, but not that of renal scarring, and increases the risk of microbial resistance (4–6). However, it is important for paediatricians to diagnose VUR at an early stage and perform adequate follow-up renal function studies to prevent the development of complications.

Whether we should perform voiding cystography (VCG) in all patients during the first episode of UTI is controversial, as VCG is an invasive procedure that requires catheterisation and exposure to X rays (7). In addition, VUR is present in only 25–40% of children with febrile UTI and is often of grade I or II severity (8,9). Predicting the presence of high-grade VUR using 99mTc-dimercaptosuccinic acid

Abbreviations
AFBN, Acute focal bacterial nephritis; CRP, C-reactive protein; DMSA, 99mTc-dimercaptosuccinic acid; ROC, Receiver operating characteristic; UTI, Urinary tract infection; VCG, Voiding cystography; VUR, Vesicoureteric reflux.

Key notes
- This study evaluated whether sex, clinical variables, laboratory variables or ultrasonography could predict the presence of vesicoureteric reflux (VUR) during the first episode of urinary tract infection (UTI).
- We found that ultrasonography findings and blood C-reactive protein (CRP) levels predicted the presence of VUR.
- Voiding cystography should be performed if the patient's CRP levels are ≥80 mg/L and there are grade IV–V ultrasonography findings.

(DMSA) scintigraphy is effective (10,11). However, in Japan, only patients with high-grade VUR diagnosed using VCG are likely to undergo DMSA scintigraphy, because VCG is easier to perform than DMSA scintigraphy, which can only be performed in a limited number of institutions. Therefore, it is often difficult to determine whether VCG should be performed during the first UTI in patients.

In this study, we aimed to evaluate whether sex, clinical variables, laboratory variables or ultrasonography could predict the presence of VUR in patients presenting with UTI for the first time and to define the criteria for performing VCG in these patients.

PATIENTS AND METHODS

We retrospectively studied the medical records of 286 patients with a median age of 5 months (range: 0.5–169 months) who presented with a UTI for the first time without other evidence of urologic disease and who were hospitalised in Kumamoto Regional Medical Center between January 2004 and December 2013. Clinical information, including age, sex, symptoms, present condition and medical history, medication use and family history were recorded on a standardised data form by the examining paediatricians at the patients' visits. We defined a UTI as a fever of ≥38°C and urine sediments containing white blood cell counts of ≥10 per high-power field (HPF) of spun fresh urine. Moreover, if urinary findings were normal, then patients with acute focal bacterial nephritis (AFBN) or renal abscess, identified as a defect of blood flow or poor blood flow into a kidney, identified by computed tomography and/or ultrasonography, were also included in the UTI patient group. In addition, this study included patients with positive urine cultures (n = 202), as well as patients with negative urine cultures (n = 74) and patients who did not undergo urine culture (n = 10) because antibiotics were administered before hospital admission. This study was approved by the ethical committee of Kumamoto Regional Medical Center.

A total of 286 patients presented with UTI for the first time and 200 (69.9%) of these underwent VCG. In 69 patients (34.5%) with a median age of 4 months (range: 1–122 months), we detected VUR and 131 patients (65.5%) with a median age of 5 months (range: 1–143 months) did not exhibit VUR. The presence or absence of VUR was determined by VCG and graded from I to V according to the International Reflux Study in Children guidelines (12). Patients who did not undergo VCG had a median age of 7 months (range: 0.5–169 months) and included 65 patients where VUR was considered absent on the basis of the first ultrasonography, 12 patients who displayed transient abnormal ultrasonography findings, four patients who did not undergo ultrasonography during the first episode of UTI, four patients who transferred to another institution for comprehensive examination and treatment because they developed AFBN, renal abscess, or an inherited disease of the urinary system and a patient whose parents did not provide consent for participation in this study. Fever was defined as a body temperature of ≥38°C, and we regarded bacteria detected by urine culture as the causative pathogens. The presence of bacteria on urine culture was confirmed in 48 patients who did not undergo VCG, and 66.7% (32/48) of these patients had *Escherichia coli* in their urine culture. Of these, 22 had ultrasonography grades I–II, eight had grades III–IV and two had grade V.

The blood white blood cell counts were measured using the XE-2100 multiitem automated haematology analyser (Sysmex), and blood C-reactive protein (CRP) levels were measured using an AU680 Chemistry Analyzer (Beckman Coulter Inc., Brea, California, USA). Urine, collected with a bag, was measured using the Versatile Urine Analysis System AUTION ELEVEN AE-4020 (Arkray). The presence of occult blood in urine was graded as follows: I, −; II, +−; III, 1+; IV, 2+; and V, 3+. Similarly, the presence of urine protein was scored as follows: I, −; II, +−; III, 1+; IV, 2+; and V, 3+. Urine was centrifuged at 500 × *g* for 5 min, and the urinary sediment was quantified visually. The urinary white blood cell count was scored as follows: 1–4/HPF, grade I; 5–9/HPF, grade II; 10–19/HPF, grade III; 20–29/HPF, grade IV; 30–49/HPF, grade V; 50–99/HPF, grade VI; and ≥100/HPF, grade VII. Abdominal ultrasonography findings were classified as follows: grade I if there were no abnormal findings, grade II in cases of mild pyelectasis, as grade III in cases of pyelectasis and dilation of the urinary tract, grade IV in cases of pyelectasis, dilation of the urinary tract and abnormal movement of the ureter resembling urine reflux in the urinary tract (Video S1) and grade V when grade ≥III hydronephrosis (13), hydroureter of ≥5 mm in diameter, or pathological features such as AFBN, renal abscess, or renal scarring were present. Ultrasonography findings were double-checked by two technicians.

Statistical analysis, as indicated in Table 1, was performed using a *t*-test, nonparametric test, or χ^2 test using SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). The independent predictive value of the investigated determinants for VUR was analysed by multivariate regression analysis using Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

This study included 200 children presenting with UTI for the first time and whose diagnosis of VUR was confirmed using VCG. The comparison of sex, clinical variables, laboratory variables and ultrasonography findings in patients with and without VUR showed the following.

In 69 patients with VUR of various grades, three had grade I, eight had grade II, 17 had grade III, 26 had grade IV and 15 had grade V. Because 20 of these patients had VUR on both sides, we regarded such patients as having high-grade VUR. Table 1 reports the characteristics of patients with and without VUR in this study, as well the maximum blood CRP levels during hospitalisation, peak blood white blood cell counts and the results of urine tests on admission. Sex ($p = 0.001$), peak blood CRP levels ($p < 0.001$), the duration of fever (days) after the administration of antibiotics

Table 1 General characteristics of patients with and without VUR

	VUR patients (n = 69)	Non-VUR patients (n = 131)	p value
Sex	Male: 52, Female: 17	Male: 65, Female: 66	p = 0.001**
Age (month)	Median 4 (Interquartile range: 2–31)	Median 5 (Interquartile range: 3–10)	p = 0.453
Blood WBC (WBC/μL)	19 500 ± 7500 (7500–47 400)	18 800 ± 6800 (4700–44 500)	p = 0.499
Blood CRP (mg/L)	101 ± 66 (5–350)	64 ± 52 (1–251)	p < 0.001**
Urine WBC	Median: V (I: 1, II: 4, III: 14, IV: 5, V: 12, VI: 11, VII: 22)	Median: V (I: 1, II: 1, III: 27, IV: 13, V: 27, VI: 26, VII: 36)	p = 0.908
Urine OB	Median: III (I: 10, II: 11, III: 20 IV: 14, V: 14)	Median: III (I: 32, II: 20, III: 24 IV: 29, V: 26)	p = 0.764
Urine TP	Median: III (I: 12, II: 16, III: 30, IV: 9, V: 1, VI: 1)	Median: II (I: 35, II: 32, III: 51, IV: 8, V: 5)	p = 0.694
Escherichia coli as the causative pathogen	66.7% (38/57)	74.0% (74/100)	p = 0.264
Fever duration (day) after the administration of antibiotics	Median: 2 (Interquartile range: 1–2)	Median: 1 (Interquartile range: 1–2)	p = 0.007**
US grade	Median: V (I: 1, II: 3, III: 7, IV: 19, V: 39)	Median: II (I: 25, II: 48, III: 17, IV: 28, V: 13)	p < 0.001**

US, Ultrasonography; WBC, White blood cell; OB, Occult blood; CRP, C-reactive protein; VUR, Vesicoureteric reflux.
**p value < 0.01.

(p = 0.007) and the presence of abdominal ultrasonography findings (p < 0.001) (Table 1) were significantly different between patients with and without VUR.

The patients with VUR who had abnormal ultrasonography findings comprised one patient with grade I, three with grade II, seven with grade III, 19 with grade IV and 39 patients with grade V findings. We found that nine patients with VUR and four patients without VUR developed AFBN. All patients with grade I–II urine white blood cell counts developed AFBN. Moreover, two patients without VUR developed renal abscess. The durations of fever after the administration of antibiotics in these patients were eight and 10 days, respectively. The presence of bacteria on urine culture was confirmed in 57 patients with VUR and 100 patients without VUR. Moreover, 66.7% of patients with VUR (38/57) and 74.0% of patients without VUR (74/100) had *Escherichia coli* in their urine culture.

We found that the grade of the ultrasonography findings and the peak blood CRP levels were significant factors when it came to predicting VUR. We determined the ultrasonography grade that most significantly differentiated patients with and without VUR. An abdominal ultrasonography grade of III or greater was present in 94% of patients with VUR (65/69) and 50% of patients without VUR (65/131) (Fig. 1). The area under the receiver operating characteristic (ROC) curve for ultrasonography grade was 0.837. The ultrasonography grade that most accurately discriminated subjects with and without VUR was grade IV, as it resulted in an ROC curve closest to the top left corner of the graph. Using the χ^2 test to compare ultrasonography grades IV–V, the sensitivity, specificity and odds ratio (OR) were 84.1%, 68.7% and 11.57% [95% confidence interval (CI): 5.5–24.3], respectively (p < 0.001).

Next, we evaluated peak blood CRP content, which was identified as the second-most discriminatory variable regarding the presence or absence of VUR. In 71% of patients with VUR (49/69) and 28% of patients without VUR (37/131), peak blood CRP levels were 80 mg/L or more (Fig. 2). The area under the ROC curve for peak blood CRP levels was 0.681. The CRP level closest to the top left corner of the ROC curve was 80.6 mg/L. A χ^2 test evaluating a CRP level of ≥80 mg/L for VUR-positive patients revealed a sensitivity, specificity and OR of 71.0%, 71.8% and 6.22 (95% CI: 3.27–11.86), respectively (p < 0.001). The sensitivity, specificity and OR for both ultrasonography grades IV–V and a CRP level ≥80 mg/L for VUR-positive patients were 47.8%, 87.8% and 6.59 (95% CI: 3.26–13.33), respectively (p < 0.001). If patients had either grade IV–V ultrasonography findings or a CRP level ≥80 mg/L, the sensitivity, specificity and OR were 92.8%, 51.9% and 6.59 (95% CI: 3.26–13.33), respectively (p < 0.001).

The study identified useful factors in predicting the outcome of VCG. The grade of ultrasonography findings, blood CRP levels and the duration of fever, which exhibited significant differences between the patient groups as shown in Table 1, were analysed in logistic regression analyses.

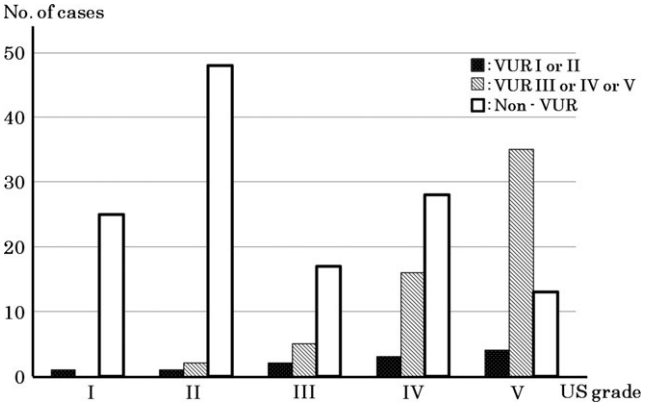

Figure 1 Ultrasonography grade of patients with and without VUR The echo grade was ≥3 in 94% (65/69) of patients with VUR. VUR, vesicoureteric reflux.

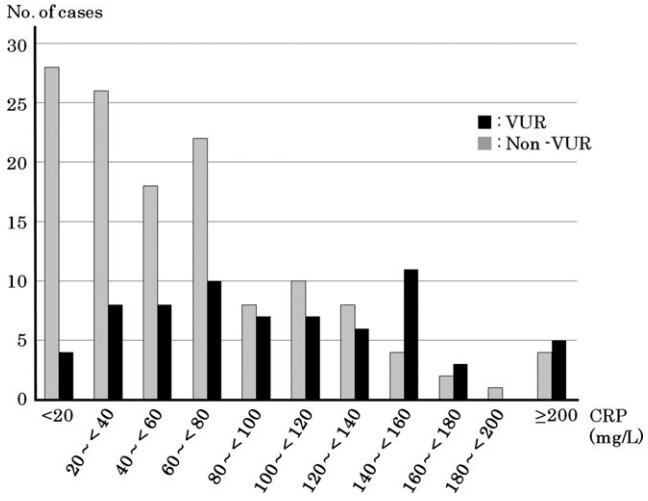

Figure 2 Maximum blood CRP level in patients with and without VUR 71% (49/69) of patients with VUR and 28% (37/131) of patients without VUR patients had a peak blood CRP level of ≥80 mg/L. VUR, vesicoureteric reflux; CRP, C-reactive protein.

When the value of x (i.e. the predictive probability of VUR) was 0.5 or more, the cut-off values for the grade of ultrasonography findings, blood CRP levels and the duration of fever were grade V, ≥133 mg/L, and ≥3 days, respectively (Table 2).

Moreover, we evaluated whether an additional parameter associated with the grade of ultrasonography findings could improve the ability to predict the development of VUR. Table 2 presents the results of these logistic regression analyses. The x value (x4–x6) expressed the expected probability of the presence of VUR. When the value of x was 0.5 or more, the cut-off values for the grade of ultrasonography findings and blood CRP levels were as follows: blood CRP levels ≥100 mg/L with grade IV ultrasonography findings and blood CRP levels ≥250 mg/L with grade III ultrasonography findings (Table 2).

The study also explored the effectiveness of age, sex, duration of fever, CRP levels and the grade of ultrasonography findings in predicting the outcome of VCG. We performed multivariable logistic regression analysis using the above variables and calculated the probability of positivity for VUR (Table 3). The significance of age and the duration of fever in predicting VUR in univariate analysis were not maintained. The grade of ultrasonography findings most accurately predicted positivity for VUR. When we considered a y value of ≥0.5 as indicating VUR positivity, the sensitivity, specificity, positive predictive value and negative predictive value were 77.6, 87.0, 75.4 and 88.4%, respectively. Grade IV ultrasonography findings and blood CRP levels of 80 mg/L produced a y value of ≥0.5.

DISCUSSION

As illustrated in Table 1, sex, the duration of fever, blood CRP levels and the grade of ultrasonography findings were identified as predictive risk factors for VUR. The most significant factor among these was the grade of ultrasonography findings. In previous retrospective reports, abnormal ultrasonography findings such as dilation of the ureter and pyelectasis were considered useful for predicting VUR (14–16), whereas other retrospective (17) and prospective (18–20) reports indicated that abdominal ultrasonography is of

Table 2 Results of logistic regression analysis

	p value	Odds ratio (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1. US grade	p < 0.001**	3.26 (2.32–4.58)	76.5	79.6	56.5	90.7
2. Blood CRP (mg/L)	p < 0.001**	1.13 (1.07–1.20)	61.1	71.0	31.9	89.2
3. Fever duration (days)	p < 0.001**	1.74 (1.29–2.42)	60.7	69.4	24.6	91.5
4. US grade and blood CRP	p < 0.001**	3.05 (2.16–4.31)	74.2	84.8	71.0	86.8
	p = 0.027*	1.08 (1.01–1.15)				
5. US grade and sex	p < 0.001**	3.13 (2.23–4.41)	67.1	86.6	76.8	79.8
	p = 0.067	2.06 (0.95–4.47)				
6. US grade and fever duration	p < 0.001**	3.09 (2.20–4.34)	75.5	80.0	58.0	89.9
	p = 0.107	1.38 (0.93–2.04)				

CRP, C-reactive protein; US, Ultrasonography; CI, Confidence interval, PPV, Positive predictive value, NPV, Negative predictive value.

1. $\log_e (x_1/1-x_1) = 1.1822 \times$ [US grade] − 4.8565.
2. $\log_e (x_2/1-x_2) = 0.01082 \times$ [Blood CRP] − 1.5175.
3. $\log_e (x_3/1-x_3) = 0.5674 \times$ [Fever duration] − 1.6044.
4. $\log_e (x_4/1-x_4) = 1.1163 \times$ [US grade] + $0.00761 \times$ [CRP] − 5.2319.
5. $\log_e (x_5/1-x_5) = 1.1431 \times$ [US grade] + $0.7236 \times$ [Sex] − 5.1758.
6. $\log_e (x_6/1-x_6) = 1.1279 \times$ [US grade] + $0.3208 \times$ [Fever duration] − 5.1977.

x value: the predictive probability of vesicoureteric reflux.

Points assigned to [US grade]: 1 point for grade I, 2 points for grade II, etc.

Points assigned to [Sex]: 0 points for female, 1 point for male.

Points assigned to [CRP] were the actual value of maximum blood CRP, and points assigned to [Fever duration] was the actual fever duration (days).

*p value < 0.05 and **p value < 0.01.

Table 3 Results of multivariate logistic regression analysis

	p value	Odds ratio (95% CI)
Age (month)	p = 0.175	0.99 (0.98–1.00)
Sex	p = 0.030*	2.60 (1.10–0.14)
Fever duration (days)	p = 0.351	1.24 (0.79–1.94)
CRP	p = 0.028*	1.09 (1.01–1.18)
US grade	p < 0.001**	2.91 (2.03–4.17)

CI, Confidence interval.
log (y/1−y) = −0.0092 × [Age] + 0.9553 × [Sex] + 0.2138 × [Fever duration] + 0.00875 × [CRP] + 1.068 × [US grade]−5.9493.
y value: the predictive probability of vesicoureteric reflux.
Points assigned to [Age] was the actual patient age (months).
*p value < 0.05 and **p value < 0.01.

little benefit for diagnosing VUR. Although the utility of ultrasonography findings in predicting VUR is controversial, the ultrasonography findings were extremely useful and important for predicting VUR in this retrospective study and all of the prior reports demonstrated the high specificity of ultrasonography for predicting high-grade VUR. As the subjects with grade III ultrasonography findings (ureteral dilation and pyelectasis) included many patients without VUR and the use of grade V ultrasonography findings (hydronephrosis, hydroureter or pathological features such as AFBN, renal abscess or renal scarring) as a diagnostic criterion was likely to exclude many patients with VUR, we determined that grade IV ultrasonography findings (ureteral dilation, pyelectasis and abnormal movement of the ureter resembling urine reflux in the urinary tract) could enhance the predictive value of ultrasonography for diagnosing VUR. All abdominal ultrasonography procedures were performed at our institute, and the ultrasonography findings were confirmed by two independent technicians. As a result, we believe that errors caused by technical differences were minimal in this study. Patients without VUR were found among all grades of ultrasonography findings, but the number of patients with VUR increased as the grade of ultrasonography findings increased (Fig. 1).

Just less than a third (30%) of the original study population (86/286) was excluded because the subjects did not undergo VCG. Of these, 65 had normal ultrasonography findings (grades I–II) and 12 had transient abnormalities in their ultrasonography findings (grades III–IV). The median CRP level in 65 patients with normal ultrasonography findings was 53.3 mg/L (interquartile range: 27.5–83.8 mg/L), and the median CRP level in 12 patients with transient ultrasonography abnormalities was 59.6 mg/L (interquartile range: 19.5–93.8 mg/L). Some of these 86 patients may have VUR, and there is likely to be bias concerning whether the patients underwent VCG. This study included only 11 children with low-grade VUR (grades I–II), compared to 58 children with high-grade VUR (grades III–V). Because the distribution of VUR grades in this study differed from those reported by Hoberman et al. (18) and the RIVUR trial (21), this distribution is likely to reflect a bias, but we clarified the records of 69 patients with VUR who were definitely diagnosed by VCG. Because this study was a retrospective study performed by investigating all medical records, and VUR grades were determined by each paediatrician who performed VCG, although we checked most of the images taken at the time of VCG, there was a limitation concerning the diagnostic accuracy. Moreover, retrospective or prospective studies of children with primary VUR (14–21) all differ in the demographics of the population studied. These studies had a variety of designs with differences in inclusion and exclusion criteria as well as in the numbers of patients, patient age, healthcare delivery systems, sociocultural characteristics and race and ethnic variables that can influence the obtained results, reducing the ability to generalise the findings to all populations. These venue and demographic differences may explain the disparate outcomes across studies.

There were significant differences in the duration of fever after antibiotic administration and blood CRP levels. Soylu et al. (22) reported CRP values of ≥50 mg/L and a fever of ≥38.5°C to be useful for predicting grade ≥III VUR. In our χ^2 test using blood CRP levels ≥80 mg/L and a duration of fever of ≥2 days, the sensitivity, specificity and OR were 36.2%, 82.9% and 2.76 (95% CI: 1.41–5.41), respectively (p = 0.003). Therefore, patients with blood CRP levels ≥80 mg/L and a duration of fever of ≥2 days are also likely to be VUR positive.

Klar et al. (23) reported that 50% (4/8) of patients with AFBN had VUR, and therefore, it is recommended that VCG be performed in patients with AFBN. In total, nine of the 13 patients with AFBN included in this study had VUR. Although there was no significant difference in the incidence of VUR according to the presence of AFBN because of the small number of patients with AFBN in this study (p = 0.166), AFBN can be considered a predictor of VUR.

As shown in Figures 1 and 2, it is likely to predict the presence or absence of VUR by classifying patients according to CRP levels and the grade of ultrasonography findings. In fact, for CRP levels ≥80 mg/L and grade IV–V ultrasonography findings, the specificity was high at 87.8%. Even in the logistic regression analysis of CRP levels and ultrasonography findings grade (Tables 2 and 3), both the sensitivity and specificity were high. Therefore, using these two factors in combination may prove useful. Because 84% of patients with VUR (58/69) in this study had high-grade VUR (grades III–V), patients presenting with their first episode of UTI are likely to have high-grade VUR when they display both CRP levels ≥80 mg/L and grade IV–V ultrasonography findings. Therefore, we recommend performing VCG in patients with CRP levels ≥80 mg/L and grade IV–V ultrasonography findings, whereas VCG can be avoided in patients with CRP levels <80 mg/L and grade ≤III ultrasonography findings. Only 7.2% (5/69) of patients with VUR patients had CRP levels <80 mg/L and grade ≤III ultrasonography findings, consisting of one, two, one and one patient with grades II, III, IV and V findings, respectively.

In this study, sex was also an important predictor of VUR, and multivariable logistic regression analysis identified male sex as a predictor of VUR. We analysed five variables,

namely age, sex, duration of fever, CRP levels and ultrasonography findings, in a step-down procedure. When we analysed these five variables together, the overall sensitivity and specificity were the highest, and these five variables better predicted VUR than the combination of sex, CRP levels and the grade of ultrasonography findings, which were also significant. In patients with either grade IV ultrasonography findings or CRP levels ≥80 mg/L, it would be useful to use the formula derived from our multivariable logistic regression analysis.

In conclusion, sex, fever duration, blood CRP levels and the grade of ultrasonography findings were useful predictors of VUR according to multivariable logistic regression analysis. Among these variables, the grade of ultrasonography findings was the most important factor for predicting VUR. VCG should be performed for paediatric patients with CRP levels ≥80 mg/L and with grade IV–V ultrasonography findings, whereas VCG can be avoided in patients with CRP levels <80 mg/L and grade <III ultrasonography findings. When either CRP levels are at least 80 mg/L or the ultrasonography grade is IV–V, the formula derived from our multivariable logistic regression analysis will be informative for predicting VUR.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Video S1 Abnormal movement of the ureter resembling urine reflux in the urinary tract.