Role of Procalcitonin in Predicting Dilating Vesicoureteral Reflux in Young Children Hospitalized With a First Febrile Urinary Tract Infection

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Objective: The aim of this article was to assess the usefulness of procalcitonin (PCT) as a marker for predicting dilating (grades III–V) vesicoureteral reflux (VUR) in young children with a first febrile urinary tract infection.

Methods: Children ≤2 years of age with a first febrile urinary tract infection were prospectively evaluated. Serum samples were tested for PCT at the time of admission to a tertiary hospital. All children underwent renal ultrasonography (US), ^{99m}Tc-dimercaptosuccinic acid renal scan, and voiding cystourethrography. The diagnostic characteristics of PCT test for acute pyelonephritis and dilating VUR were calculated.

Results: Of 272 children analyzed (168 boys and 104 girls; median age, 5 months), 169 (62.1%) had acute pyelonephritis. There was VUR demonstrated in 97 (35.7%), including 70 (25.7%) with dilating VUR. The median PCT value was significantly higher in children with VUR than in those without ($P < 0.001$). Using a PCT cutoff value of ≥1.0 ng/mL, the sensitivity and negative predictive value for predicting dilating VUR were 94.3% and 95.4%, respectively, for PCT, and 97.1% and 97.8%, respectively, for the combined PCT and US studies, whereas the positive and negative likelihood ratios were 2.03 and 0.107, respectively, for PCT, and 1.72 and 0.067, respectively, for the combined studies. By multivariate analysis, high PCT values and abnormalities on US were independent predictors of dilating VUR.

Conclusions: PCT is useful for diagnosing acute pyelonephritis and predicting dilating VUR in young children with a first febrile urinary tract infection. A voiding cystourethrography is indicated only in children with high PCT values (≥1.0 ng/mL) and/or abnormalities found on a US.

Key Words: acute pyelonephritis, procalcitonin, dilating vesicoureteral reflux, febrile urinary tract infection, young children

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Urinary tract infection (UTI) is one of the most common bacterial infections in febrile children younger than 2 years of age.[1] The association between UTI and congenital abnormalities can put children at a high risk for developing acute pyelonephritis (APN) and subsequent renal scarring.[1–3] Vesicoureteral reflux (VUR), the most common urologic abnormality, is found in 20–40% of children after febrile UTI.[4,5] Although its importance is being questioned,[6,7] recent studies show that the frequency of renal damage significantly increases with dilating VUR (grades III or higher).[8–10]

Voiding cystourethrography (VCUG) can reliably demonstrate the grade of VUR.[11] However, it is an invasive procedure that may cause catheter-induced infection and urethral trauma, as well as a high radiation burden on small children. The recent National Institute for Health and Clinical Excellence guidelines for children with a febrile UTI do not recommend VCUG in children >6 months of age,[12] which may delay the diagnosis of high-grade VUR. Renal ultrasonography (US) is known to be poorly sensitive to detect VUR; therefore, US findings should not be used to influence the decision to investigate young children with febrile UTI.[13,14] Several studies claim that ^{99m}Tc-dimercaptosuccinic acid (DMSA) renal scan can be used instead of VCUG because children with normal DMSA scans rarely have dilating VUR.[15–18] However, factors like availability, costs and risks of exposing patients to attendant radiation and sedation limit the widespread use of early DMSA renal scan.

Studies have shown that serum procalcitonin (PCT) is a reliable marker for differentiating APN from lower UTI in children.[19–22] It also can be used as a predictor of moderate-grade and high-grade VUR.[23,24] This prospective cohort study aimed to examine the diagnostic performance of PCT-based strategy for predicting the presence of dilating VUR in children ≤2 years of age who were hospitalized with a first febrile UTI.

PATIENTS AND METHODS

Patients and Study Design

This prospective cohort study evaluated children ≤2 years of age who were admitted to the pediatric ward of an urban tertiary referral center and academic teaching hospital for a first febrile UTI. The diagnosis of a first febrile UTI was based on the following: (1) fever with body temperature ≥38°C; (2) presence of pyuria, defined as ≥5 white blood cell (WBC) per high-power field and/or abnormal dipstick urinalysis (positive nitrite or leukocyte esterase tests); (3) positive urine culture, defined as any growth of a single bacterium in urine from a suprapubic bladder aspiration, or growth of a single microorganism ≥10^5 colony-forming units/mL collected from the midstream clean-void urine specimen or ≥5×10^4 colony-forming units/mL collected from a transurethral catheterized specimen[1]; (4) no previous history of UTI, kidney, bladder or urogenital disease; and (5) without any other coincidental infections.

All of the children were treated empirically with combined intravenous cefazolin (100 mg/kg/d) and gentamicin (7.5 mg/kg/d) for at least 3 days after admission. This regimen was later adjusted according to results of the bacterial-susceptibility tests for total treatment duration of 7–21 days. The hospital's institutional review board approved the study protocol, and the parents of all the participants provided informed consent.

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Assessment of Laboratory Markers

Serum and urine indices for laboratory investigations, including PCT, C-reactive protein (CRP), WBC count, urinalysis and urine and blood cultures were taken on admission and before the initiation of antibiotic treatment for all patients. Rapid and quantitative measurement of PCT values was done using enzyme-linked fluorescent assay in an automated instrument (VIDAS BRAHMS PCT, BRAHMS Diagnostica, Berlin, Germany) according to the manufacturer's instructions. Assay time was <20 minutes, and the results were routinely obtained within 2 hours after blood sample collection. The detection limit was 0.05 ng/mL, and PCT values ≥0.5 ng/mL were considered abnormal. The CRP values were measured by nephelometry (Dade Behring Marburg GmbH, Marburg, Germany) and values ≥2 mg/dL were considered abnormal. The WBC count was measured by an automated hematology analyzer (XE-2100, SYSMEX, Kobe, Japan).

Imaging Studies

All of the children underwent US to detect urinary tract abnormalities within the first 3 days of admission by an experienced pediatric nephrologist. All abnormal US findings considered related to VUR were recorded, including anteroposterior diameter of the renal pelvis ≥5 mm and/or any grade of dilatation of calyces or ureters; pelvic or ureteral wall thickening; absence of corticomedullary differentiation; irregular renal outline and signs of renal hypodysplasia (ie, small kidney, thinned or hyperechoic cortex); and duplicated renal collecting system.[25] The DMSA scan was performed within the first 5 days of admission to verify the presence of renal lesions. Planar images of both kidneys were performed in the supine position at 3–4 hours after an intravenous injection of DMSA in a dose of 2 MBq/kg (0.06 mCi/kg) body weight (minimum, 15 MBq [0.4 mCi]).[26] An abnormal acute DMSA scan suggesting APN was defined as the presence of focal or diffuse areas of decreased uptake with preservation of the renal contour.[6,26]

A VCUG was performed 1–3 weeks after diagnosis and control of the acute infection. The VUR was graded I–V according to the International Reflux Study in children.[27] Dilating VUR was defined as VUR grade III or higher.[15,17] Interpretations of the DMSA and VCUG were made by a single, experienced nuclear medicine physician and a single, experienced pediatric radiologist who were unaware of the patient's clinical and laboratory findings and were blinded to the study.

The assessment of diagnostic performance for predicting dilating VUR constituted PCT alone, US alone and the combined PCT and US studies, which was defined as a positive finding if either test was positive.

Statistical Analyses

Nonparametric data were assessed by the Mann-Whitney *U* test or the Kruskal-Wallis 1-way analysis of variance and expressed as medians and interquartile ranges (Q_1–Q_3), followed by the Dunn multiple comparison test for multiple groups. χ^2 test was used to compare group proportions with qualitative data. The receiver operating characteristic (ROC) curve analysis was performed to assess quantitative variables for diagnosing APN and for predicting dilating VUR. The diagnostic values of sensitivity, specificity, positive and negative predictive value and positive and negative likelihood ratios (LRs) were all calculated. Comparisons of area under curve (AUC) were conducted using the software package MedCalc (version 9.6.2.0, MedCalc Software, Mariakerke, Belgium).

A multivariate logistic regression model with stepwise procedure was used to identify the potential predictors of dilating VUR. The Hosmer-Lemeshow test was used to assess the model's goodness-of-fit. Results were expressed as odds ratio, 95% confidence interval (CI) and *P* value. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL).

RESULTS

Patients and Clinical Characteristics

In this 4.5-year study period, 322 consecutive children ≤2 years of age with a first febrile UTI were identified. Only children who completed all 3 diagnostic methods (PCT test, DMSA renal scan and VCUG) were enrolled. A final total of 272 children (84.5%) had complete data and were eligible for subsequent analyses. There were 168 (61.8%) boys and 104 (38.2%) girls, with a median age of 5.0 months (range, 0.5–24 months) and male-to-female ratio of 1.62:1.

Of the 272 children, 234 (86.0%) were younger than 1 year of age, including 152 (90.5%) boys and 82 (78.8%) girls, with male-to-female ratio of 1.85:1. There were 38 (14.0%) children aged 1–2 years, with male-to-female ratio of 0.73:1. The boys were significantly younger than the girls ($P < 0.001$). All of boys in the study were uncircumcised. The causative microorganism isolated was *Escherichia coli* in 232 children (85.3%), whereas 40 (14.7%) had other bacteria, including *Klebsiella*, *Proteus*, *Citrobacter*, *Pseudomonas* and *Enterococcus* spp.

Findings on DMSA

Acute DMSA renal scan was performed at a median of 4 days (range, 2–6 days) after admission. There were abnormal acute DMSA scans suggesting APN in 169 (62.1%) children (102 boys, 60.4%; 67 girls, 39.6%). The remaining 103 (37.9%; 66 boys, 64.1%; 65 girls, 35.9%) had normal acute DMSA scan suggesting lower UTI.

Findings on US and VCUG

Abnormal US findings thought to be associated with VUR were seen in 95 children (34.9%), including various grades of dilatation of an anteroposterior diameter and/or dilation of calyces or ureters in 67 children, duplex kidney in 4, unilateral renal agenesis in 3 and unilateral hypodysplastic kidney in 21. The presence of VUR grade by gender is summarized in Table 1 (maximum degree of reflux given if bilateral). Of the 272 children, VUR was diagnosed in 97 (35.7%). There was no difference in the incidence of VUR between boys and girls. Dilating VUR was present in 70 children (25.7%; 48 boys, 22 girls). Children with APN had significantly higher rates of VUR than those with lower UTI (46.2% versus 18.2%, $P < 0.001$). The rate of APN in children with VUR was also significantly higher than that in children without VUR (80.4% versus 52.0%, $P < 0.001$). There was a significant association between APN and the presence and severity of VUR ($P < 0.001$).

Diagnostic Performance of Laboratory Markers for Identifying APN

To differentiate APN from lower UTI in hospitalized children, the ROC curves were plotted by the sensitivity versus 1—specificity for different cutoff values of PCT, CRP and WBC count (Fig. 1). The AUC of the ROC was 0.948 (95% CI: 0.924–0.973) for PCT, 0.813 (95% CI: 0.763–0.863) for CRP and 0.720 (95% CI: 0.659–0.780) for WBC count. Comparing the 3 variables, the AUC of PCT was significantly higher than that of CRP ($P < 0.001$) and WBC count ($P < 0.001$). Thus, the PCT test had the best diagnostic performance for identifying APN in hospitalized children. The optimal cutoff value of PCT for distinguishing between APN and lower UTI was ≥1.0 ng/mL, with 87.6% sensitivity and 89.3% specificity.

TABLE 1. VUR Grade by Gender in the Study Subjects

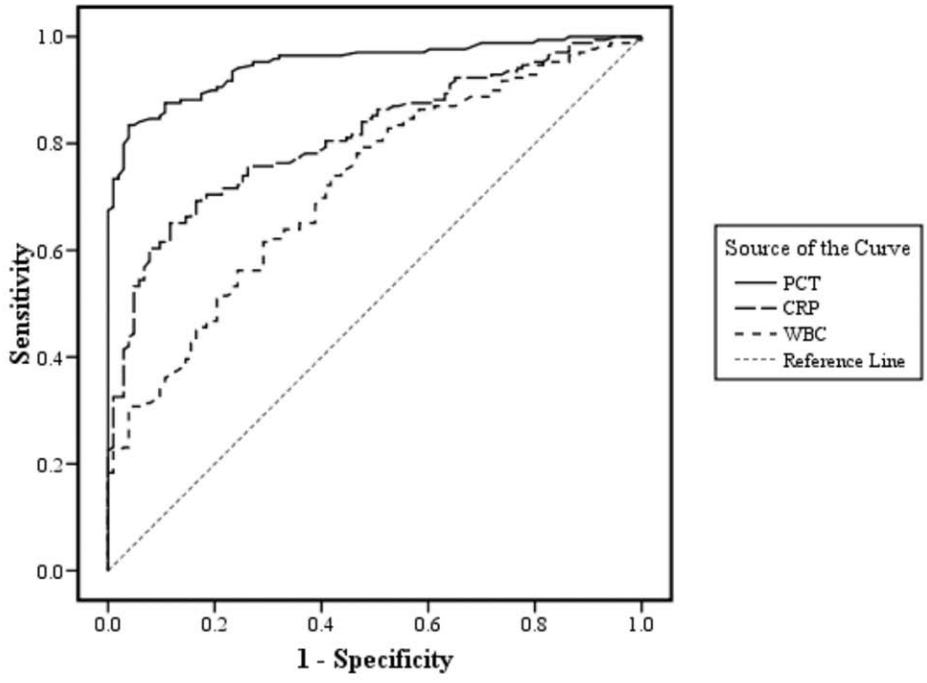
VUR Grade	All Patients (n = 272)	Boys (n = 168)	Girls (n = 104)	*P*
	n (%)	n (%)	n (%)	
No VUR	175 (64.3)	106 (63.1)	69 (66.3)	0.679*
VUR	97 (35.7)	62 (36.9)	35 (33.7)	
Grade I	3 (3.1)	2 (3.2)	1 (2.9)	
Grade II	24 (24.7)	12 (19.4)	12 (34.3)	0.193†
Grade III	28 (28.9)	14 (22.6)	14 (40.0)	
Grade IV	30 (30.9)	24 (38.7)	6 (17.1)	
Grade V	12 (12.4)	10 (16.1)	2 (5.7)	

*The difference in the rate of VUR between boys and girls.
†The difference in the rate of dilating VUR between boys and girls.

Diagnostic Performance of PCT, US and the Combined Studies for Predicting Dilating VUR

In the current study, the rate of APN in our children with VUR was 80.4%. Therefore, based on the optimal cutoff value of PCT for diagnosing APN in hospitalized children, a PCT value of 1.0 ng/mL was selected as the threshold for dichotomization for the subsequent analysis for predicting the presence of dilating VUR. The diagnostic performance of PCT alone, US alone and the combined PCT and US studies are shown in Table 2 and Figure 2. The AUC of ROC curve for PCT alone in predicting dilating VUR was 0.739 (95% CI: 0.679–0.799; $P < 0.001$). Of the 70 children with dilating VUR, only 4 (5.7%) with grade III had a PCT value <1.0 ng/mL. They would have been missed if PCT was the only screening test. The AUC of ROC curve of US for dilating VUR was 0.765 (95% CI: 0.697–0.833; $P < 0.001$). However, 18 of 70 (25.7%) children with dilating VUR had a normal US finding (grade III in 14, IV in 4). They would have been missed if US was the only screening test. The AUC of ROC curve for the combined PCT and US studies revealed an AUC of 0.704 (95% CI: 0.641–0.766; $P < 0.001$) for predicting dilating VUR. By using the 2 combined strategies, we could slightly increase the sensitivity for predicting dilating VUR in children without decreasing the negative predictive value (Table 2). Only 2 children with grade III VUR were not identified by the combined studies. Comparing the AUCs of PCT alone, US alone and the combined PCT and US studies, there were no statistical differences in AUCs of ROC between PCT alone, US alone and the combined studies (all $P > 0.05$).

The best cutoff value of the PCT test for the fewest possible misdiagnoses of dilating VUR is 1.0 ng/mL. The negative predictive values are high (96.4% and 97.8%) regardless of the tests (Table 2), indicating that approximately 3% of children with a low PCT value and normal US will be missed when they actually have dilating VUR. The negative LR of PCT test is 0.107, meaning that children without dilating VUR are about 9 times more likely to have a PCT value of <1.0 ng/mL compared with those with dilating VUR. It also indicates that the pretest probability (25.7%) for dilating VUR in this population decreases to approximately 3% posttest probability. This may make pediatricians decide not



Optimal cutoff value	AUC (95% CI)	*P*	Sensitivity (%)	Specificity (%)
PCT (≥1.0 ng/mL)	0.948 (0.924-0.973)	< 0.001	87.6	89.3
CRP (≥6.2 mg/dL)	0.813 (0.763-0.863)	< 0.001	70.4	81.6
WBC (≥16650/mm^3)	0.720 (0.659-0.780)	< 0.001	56.2	75.7

FIGURE 1. Comparison of ROC curves for PCT, CRP and WBC count to distinguish APN from lower UTI. The PCT was determined as the best index compared with CRP and WBC count (both $P < 0.001$).

TABLE 2. Diagnostic Performances of PCT Alone, US Alone and the Combined PCT and US Studies for Predicting Dilating VUR in Young Children With a First Febrile UTI

Variables	PCT (≥1.0 ng/mL)	US	Combined PCT and US
Sensitivity (%)	94.3	74.3	97.1
Specificity (%)	53.5	78.7	43.6
PPV (%)	41.3	54.7	37.4
NPV (%)	96.4	89.8	97.8
LR+	2.03	3.49	1.72
LR–	0.107	0.327	0.067*

*The value represented a good diagnostic ability (LR– <0.1).

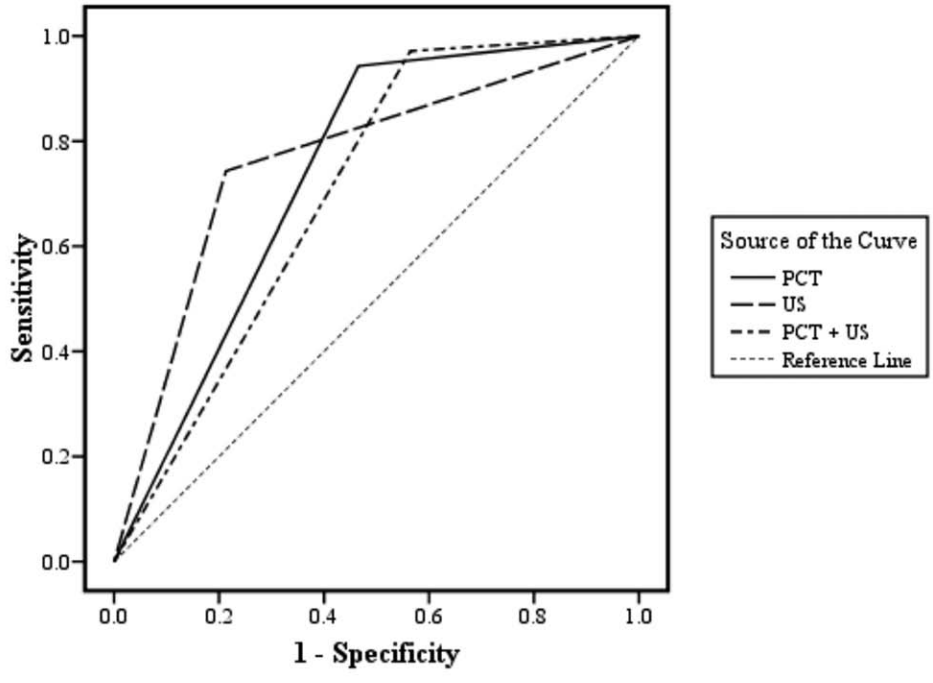
PPV indicates positive predictive value; NPV, negative predictive value; LR–, negative LR.

to recommend a VCUG. If VCUG is performed only in children with PCT value ≥1.0 ng/mL, approximately 112 of 272 (41.2%) VCUG procedures would have been avoided and only 4 children with grade III VUR would have been missed. In addition, if VCUG was performed only in children with a high PCT value or an abnormal US finding, 90 of 272 (33.1%) VCUG procedures would be omitted and only 2 children with grade III VUR would have been missed. No grade IV or grade V VUR was missed on the PCT-based strategy.

Relationship Between PCT Value and VUR

The median PCT value was significantly higher in children with VUR than in those without (3.29 [1.24–7.72] ng/mL versus 0.85 [0.43–4.33] ng/mL, $P < 0.001$; Fig. 3). The median PCT value increased significantly with VUR grade ($P < 0.001$, by Kruskal-Wallis test) and was significantly higher in children with dilating VUR than in those with grades I–II VUR and no VUR (both $P < 0.001$; Fig. 4). However, there was no significant difference in median PCT value in children with grades I–II VUR compared with those with no VUR. Using the PCT cutoff value of ≥1.0 ng/mL, the odds ratio between high PCT values and VUR was 4.366 (95% CI: 2.458–7.757; $P < 0.001$) for all VUR grades (Table 3). The strength of the association increased significantly as VUR grade increased, with the odds ratio rising from 0.780 for grades I–II VUR to 18.713 for dilating VUR.

Potential independent predictors of dilating VUR in hospitalized children with a first febrile UTI were assessed by multivariate logistic regression analysis. After adjusting for confounding factors, high PCT values and US abnormalities were retained as independent predictors in a binary logistic regression model (Table 4). The Hosmer-Lemeshow test was not statistically significant ($P = 0.722$), indicating a good fit. The accuracy of the model was 84.2%, signifying that 84.2% of children outcomes were correctly classified as dilating and low grade or no VUR. There was a 22-fold increase in risk of dilating VUR in children with PCT value ≥1.0 ng/mL compared with those with PCT value <1.0 ng/mL.



	AUC (95% CI)	*P*	Sensitivity (%)	Specificity (%)
PCT (≥1.0 ng/mL)	0.739 (0.679-0.799)	< 0.001	94.3	53.5
US	0.765 (0.697-0.833)	< 0.001	74.3	78.7
PCT + US	0.704 (0.641-0.766)	< 0.001	97.1	43.6

FIGURE 2. ROC curves for PCT alone, US alone and the combined PCT and US studies for predicting dilating VUR. Comparing the ROC curves, there were no statistical differences in the AUC between PCT alone, US alone and the combined PCT and US studies (all $P > 0.05$).

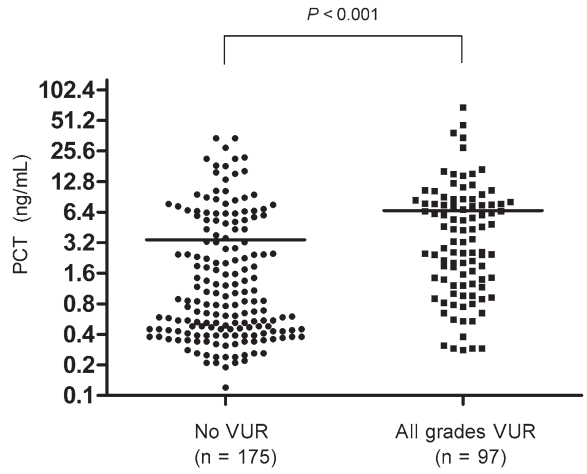


FIGURE 3. Scattergram shows PCT values in children with and without VUR. The horizontal lines denote median values.

DISCUSSION

This study consecutively enrolled hospitalized children ≤2 years of age with a first febrile UTI. The male predominance during the first year of life is the characteristic of the population in whom circumcision is not a common procedure, consistent with previous reports.[16,28] The rate of APN significantly increases with the presence and severity of VUR, similar to previous studies.[10,15,17,29] VUR as a risk factor for acquired renal scarring is directly related to its role as a risk for APN.[6] When VUR is present, approximately 80–90% children with febrile UTI have been found to have APN,[6,30] as was noted in the present study (80.4%). This indicates that VUR is an important risk factor, particularly for kidneys with grades III or higher VUR.[6,10,31] The frequency of renal damage significantly increases with grades III–V,[10,15,31] whereas there is no significant difference in the incidence of renal damage in kidneys with no or with grades I–II VUR.[32,33] The current study has focused on dilating VUR because the diagnosis of grades I–II VUR serves no further therapeutic purpose.[34,35]

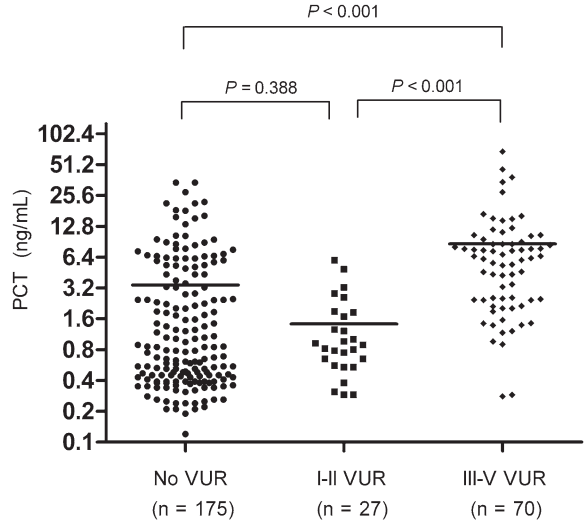


FIGURE 4. Scattergram shows PCT values in children without VUR, with grades I–II VUR and with grades III–V VUR. The horizontal lines denote median values.

TABLE 3. Association Between PCT Value and VUR Grade

VUR	PCT (ng/mL), n (%)		OR (95% CI)*	*P*
	<1.0	≥1.0		
No VUR (n = 175)	93 (53.1)	82 (46.9)		
All grade (n = 97)	20 (20.6)	77 (79.4)	4.366 (2.458–7.757)	<0.001
Grade I–II (n = 27)	16 (59.3)	11 (40.7)	0.780 (0.342–1.776)	0.699
Grade III–V (n = 70)	4 (5.7)	66 (94.3)	18.713 (6.535–53.585)	<0.001

*OR for VUR of children with high PCT values.
OR indicates odds ratio.

The association of PCT values with VUR in children with febrile UTI remains controversial.[19,20,22–24,36–38] This study shows a significant difference in PCT values between children with and without VUR, similar to available published data.[20,23,24,38] Previous studies have shown that elevated PCT values during the early phase of the disease is closely related to the onset of bacterial infection and correlate to disease severity.[39,40] The present findings support this assertion.

In clinical practice, finding a rapid, reliable test to differentiate APN from lower UTI in children and to provide a further therapeutic strategy is important. Recently, PCT has been shown to be a better marker than CRP in discriminating between a first febrile UTI with and without renal involvement.[19–22,36] The current data shows that using a PCT cutoff value of 1.0 ng/mL has the best performance for identifying children with APN. This study demonstrates that PCT is a reliable diagnostic marker that distinguishes between APN and lower UTI in young children, consistent with published data.[19–22,36]

This study shows that PCT value is a reliable diagnostic test for both APN and dilating VUR, suggesting that in cases where the PCT value in hospitalized children is <1.0 ng/mL, the possibility of renal lesions and the presence of dilating VUR is low. Thus, a low PCT value may be a sufficient screening test for the exclusion of APN and dilating VUR in children with a febrile UTI.

TABLE 4. Multivariate Logistic Regression Model Predicting Dilating VUR in the Study Children

Variables	Coefficient	Standard Error	Odds Ratio (95% CI)	*P*
Age, mo	0.147	0.543	1.158 (0.399–3.360)	0.787
≤12				
>12				
Gender	0.265	0.380	1.304 (0.619–2.748)	0.485
Boy				
Girl				
PCT, ng/mL	3.104	0.631	22.293 (6.478–76.714)	<0.001
<1.0				
≥1.0				
Finding on US	2.150	0.357	8.587 (4.262–17.300)	<0.001
Abnormal				
Normal				

For multivariate regression analysis, a binary logistic regression model with stepwise procedure was used.

The easy-to-perform PCT test has significant clinical implications. Therefore, it is reasonable to design a strategy not to search for VUR in children with low PCT value and normal US after their first febrile UTI, which not only prevents a sufficient number of unpleasant examinations but also reduces medical costs.

Previous published reports that focus on the study of PCT for predicting dilating VUR are rare, and all are from 1 cooperative group of multicenter cohort studies.[23,24,41,42] Their studies have shown that a PCT value ≥0.5 ng/mL has 83–92% sensitivity and 38–45% specificity, whereas PCT ≥1.0 ng/mL has 74% sensitivity and 57% specificity.[42] The results here are consistent with those of Leroy et al, indicating that a high PCT value is a reliable marker for predicting dilating VUR.[23,24,41,42] However, the current results have higher sensitivity (94.3%) and specificity (53.5%) and lower negative LR value compared with those of Leroy et al.[23,24,41,42] The differences may be attributed to the greater proportion of children with all grades of VUR (35.7% versus 25–26%) and dilating VUR (25.7% versus 9–12%) in this study compared with the studies by Leroy et al.[23,24,41,42] This may increase the sensitivity rate of predicting dilating VUR, with less false-negative cases.

This study has several strengths. Data were collected from a single center and involved prospectively and consecutively enrolled inpatient children during a 4.5-year period. Thus, this study has a consistent strategy in managing children with febrile UTI. To date, the prospective cohort study represents the largest case numbers of pediatric population in a single center on PCT studies. In contrast, the studies of Leroy et al are secondary analyses of retrospective, multicenter cohorts.[23,24,41,42] The current study presents the AUCs of ROC curves with comparison of statistical differences between AUCs of different diagnostic tests. This has not been addressed in previous studies. Moreover, a multivariate regression model was conducted to examine independent predictors for dilating VUR in children after a first febrile UTI.

This study also has some limitations. First, it only enrolled hospitalized children ≤2 years of age with a first febrile UTI, which may pose a selection bias because most patients with UTI are managed as outpatients. Second, children with afebrile UTI or with body temperature <38°C were all excluded. This may prevent further generalizations of the findings. Last, this study was strict and only enrolled subjects with a first UTI and not general cases. Because it is also limited to hospitalized children, the current findings may not be immediately generalized or extrapolated to outpatients with UTI.

In conclusion, the PCT test is a rapid, easily available and reliable marker for diagnosing APN and predicting the presence of dilating VUR among children with a first febrile UTI. It is simple yet effective, and its availability and noninvasiveness render it a valid diagnostic first-level choice in hospitalized children to facilitate clinical decision making and planning further therapeutic strategies, especially for children 2 years or younger with a first febrile UTI. A VCUG is indicated only in children with high PCT values (≥1.0 ng/mL) and/or abnormalities found on a US. These findings can help avoid VCUG procedure in children with low PCT values.

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