



# 24개월 미만 열 환자에서 혈청 크레아티닌, C-반응단백질, 백혈구의 요로감염 예측 성적

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## Performances of serum creatinine, C-reactive protein and white blood cell to predict urinary tract infection in febrile children younger than 24 months of age

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**Purpose:** Differentiation of urinary tract infection (UTI) from viral infection is a critical challenge in febrile children in emergency departments (EDs). This study aimed to assess the predicting performances of creatinine, C-reactive protein (CRP), and white blood cell (WBC) for predicting UTI in the children.

**Methods:** This study was a retrospective analysis of a prospectively enrolled cohort of febrile children who presented to our children's hospital ED from August 2016 through February 2018. We included previously healthy, febrile ( $\geq 38^\circ\text{C}$ ) children younger than 24 months whose urine cultures were obtained. Accuracy of creatinine, CRP, and WBC were assessed by optimal cutoffs, which were calculated using receiver operating characteristic curves.

**Results:** Among the total 33,013 children to the ED, 7,847 (23.8%) febrile children were registered to the fever registry. Finally, 506 children were included, and UTI was diagnosed in 127 (25.1%). The areas under the curve of creatinine, CRP, and WBC to predict UTI were 0.41 (95% confidence interval [CI], 0.35-0.46), 0.71 (95% CI, 0.66-0.77), and 0.66 (95% CI, 0.60-0.72), respectively. The cutoffs were 0.26 mg/dL for creatinine, 2.3 mg/dL for CRP, and  $14.4 \times 10^3$  cells/ $\mu\text{L}$  for WBC. Creatinine showed worse performance than the other variables. The application of creatinine added to the other variables led to an increase only in the sensitivity, but at the expense of a lower specificity, positive predictive value, and negative predictive value.

**Conclusion:** Serum creatinine showed a poor performance in predicting UTI in the febrile young children. Since a single biomarker can neither rule in nor rule out UTI in the children, the prediction of UTI can be achieved by the interpretation of both clinical and laboratory findings.

**Key words:** Child; C-Reactive Protein; Creatinine; Fever; Leukocytes; Urinary Tract Infections

Received: Mar 20, 2020

Revised: May 21, 2020

Accepted: May 26, 2020

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## Introduction

Fever is the most common chief complaint in children visiting emergency departments (EDs)<sup>1)</sup>. Even after history taking and physical examination, 20% of such patients are classified as fever without

source (FWS)<sup>2)</sup>. With the introduction of heptavalent pneumococcal conjugate vaccine (PCV), the incidence of serious bacterial infection (SBI) among children with FWS has significantly declined<sup>3)</sup>.

Urinary tract infection (UTI) is the most common SBI among young children with FWS<sup>4-6)</sup>, and young children with UTI who develop pyelonephritis are put at the long-term sequelae of hypertension and renal failure<sup>5,7,8)</sup>. Classic signs of UTI are usually not present in young children, instead fever being the most common symptom<sup>9)</sup>. A different potential source of fever, such as otitis media, cannot rule out UTI<sup>4,10)</sup>. Combined with the time-consuming task of obtaining clean urine specimens for culture, a reliable laboratory marker for predicting UTI would be of utmost value.

While many studies have reported white blood cell (WBC), absolute neutrophil count, and C-reactive protein (CRP) as surrogates for SBI<sup>11,12)</sup>, little has been verified for markers for UTI in the post-PCV era. A study has reported CRP to be superior to WBC in predicting confirmed bacterial infections, including *Escherichia coli* UTI<sup>13)</sup>. CRP has also been reported to be useful in predicting bacteremic UTI in children<sup>14-16)</sup>.

An increase in serum creatinine concentration is a marker of acute kidney injury (AKI). AKI following severe UTI or dehydration may lead to the elevation of serum creatinine<sup>17)</sup>. However, there have been no reports about the relationship between the UTI diagnosed at EDs and serum creatinine level. Several reports have proposed creatinine as a novel marker for predicting bacteremic UTI, especially in young infants<sup>18,19)</sup>. Further validation, however, is yet to be conducted. Accuracy of creatinine in predicting UTI itself is also yet unclear. Thus, this study was conducted to assess the performances of serum creatinine, CRP, and WBC for predicting UTI in febrile children.

## Methods

### 1. Study design, setting, and population

This was a retrospective analysis of a prospectively enrolled cohort of febrile children who presented to Seoul National University Hospital pediatric ED from August 2016 through February 2018. Our hospital is a large, urban, tertiary care, academic children's hospital with an annual ED volume of more than 20,000 children encounters. This cohort registry (Fever Registry) included children aged 5 years or younger who visited the ED within 24 hours from the onset of fever ( $\geq 38.0^{\circ}\text{C}$ ). Among all children registered in the registry, children aged 24 months or younger were enrolled whose urine cultures were obtained. Those with missing values of creatinine, CRP or WBC were excluded. We also excluded children who had major comorbidities (e.g., congenital urinary tract malformations, immunodeficiency or congenital heart disease), who returned to the ED within 1 week from the prior visits, and who had SBIs other than UTI. The study protocol was approved by the Institutional Review Board (IRB no. 2001-155-1099), and written informed consent was waived due to a retrospective design.

### 2. Data collection

Data from the registry included age and sex, comorbidities, temperature, heart rate, respiratory rate, history of antibiotics use in the 3 days preceding the visit, onset of fever, vaccination history, mental status, and severity of clinical manifestations. The manifestations included levels of feeding, activity, and urination on a degree of 0 (well) to 3 (poor), which were defined by the authors. A degree of clinical manifestation was determined by the caregivers' answers to the questions about percentage of feeding, activity, and urination compared with normal state (0 = 75%–100%, 1 = 50%–75%, 2 = 25%–50%, 3 = 0%–25%). Laboratory findings included serum creatinine, CRP, and WBC, blood culture, urinalysis, urine culture, and cerebrospinal fluid profile and

culture, and findings of chest radiograph. Hospitalized children were followed-up until discharge, and the final diagnoses were obtained.

### 3. Outcomes

Accuracy of serum creatinine, CRP, and WBC in predicting UTI was the primary outcome. UTI was defined as the growth of a single urinary tract pathogen of at least 50,000 colony forming units/mL on a transurethral catheterized specimen.

### 4. Statistical analysis

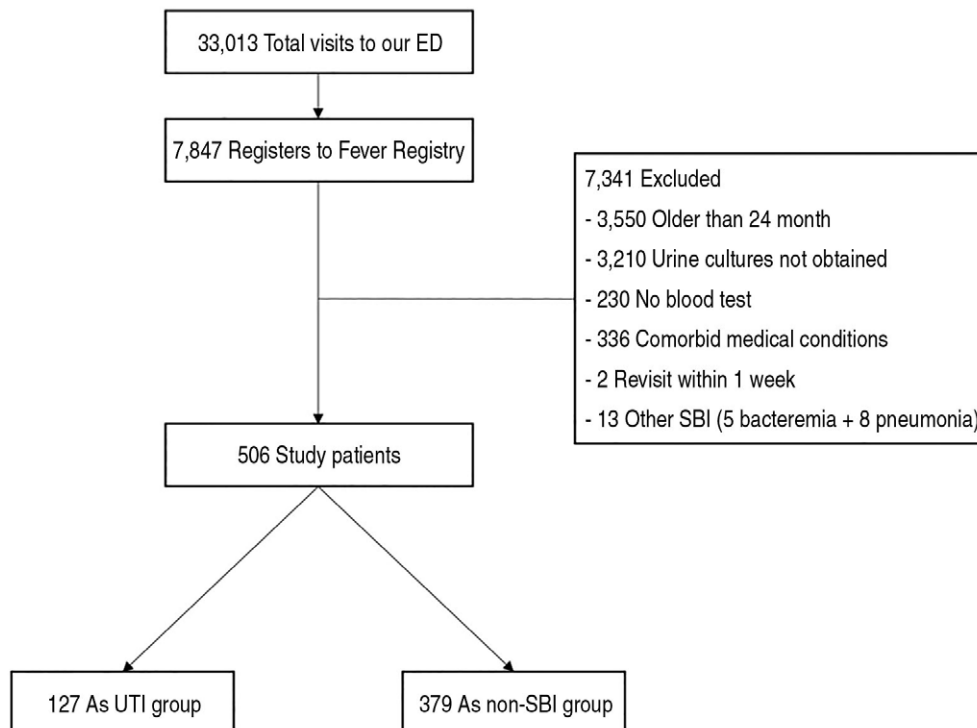
The children were divided into the 2 groups according to diagnosis as UTI or non-SBI. Continuous variables were presented as medians with interquartile ranges, then compared by the Mann-Whitney U test. Categorical ones were compared by Fisher's exact test. Receiver operating characteristic curves for predicting UTI were plotted for each laboratory marker. The optimal cutoffs for each marker were

calculated based on the curves as the Youden method. For each marker's optimal cutoffs, we reported sensitivity, specificity, positive and negative predictive values, and likelihood ratios with 95% confidence intervals (CIs). All statistical analyses were performed using STATA ver. 16.1 (StataCorp, College Station, TX). The level of statistical significance was defined as a  $P < 0.05$ .

## Results

### 1. Study population

During the study period, a total of 33,013 children visited the ED. Among the total visits, 7,847 (23.8%) febrile children aged 5 years or younger were registered to the Fever Registry. Of the 581 patients younger than 24 months whose urine culture was obtained, 506 met the inclusion criteria (Fig. 1). Among the 506 children, 127 (25.1%) had UTI, and the other 379 (74.9%) were classified as



**Fig. 1.** Flow diagram of the study population.

ED: emergency department, SBI: serious bacterial infection, UTI: urinary tract infection.

**Table 1.** Clinical characteristics of the study population

Characteristic	UTI (N = 127)	Non-SBI (N = 379)	P value
Age, mo	5 (3-7)	8 (2-15)	0.001
Boys	76 (59.8)	169 (44.6)	0.004
Initial vital signs			
Temp, °C	38.4 (37.6-39.1)	38.3 (37.7-38.9)	0.510
Heart rate, /min	167 (148-179)	166 (148-182)	0.696
Respiratory rate, /min	38 (32-44)	38 (32-44)	0.721
Fever duration, h	24 (7-48)	24 (6-72)	0.075
Clinical scores*			
Feeding	0 (0-1.5)	1 (0-2)	0.142
Activity	0 (0-1)	0 (0-1)	0.311
Urination	0 (0-0)	0 (0-1)	0.010
Hospitalization	108 (85.0)	124 (32.7)	< 0.001

Values are expressed as median (interquartile range) or number (%).

\*0 = well, 1 = mild decrease, 2 = moderate decrease, 3 = poor.

UTI: urinary tract infection, SBI: serious bacterial infection.

**Table 2.** Pathogens in the children with UTI

Pathogen	UTI without bacteremia (N = 122)	UTI with bacteremia (N = 5)
<i>Escherichia coli</i>	104 (85.3)	5 (100.0)
<i>Klebsiella pneumoniae</i>	10 (8.2)	0 (0)
<i>Pseudomonas aeruginosa</i>	2 (1.6)	0 (0)
<i>Klebsiella oxytoca</i>	2 (1.6)	0 (0)
<i>Citrobacter koseri</i>	1 (0.8)	0 (0)
<i>Enterobacter cloacae</i>	1 (0.8)	0 (0)
<i>Enterococcus faecalis</i>	1 (0.8)	0 (0)
<i>Proteus mirabilis</i>	1 (0.8)	0 (0)

Values are expressed as number (%).

UTI: urinary tract infection.

having non-SBI. Comparison of clinical characteristics between the 2 groups were summarized in Table 1. The children of the UTI group were significantly younger than the counterparts. Boys were more likely to have UTI. We found no significant difference with regards to temperature, heart rate, and respiratory rate. After the ED treatment, the children with UTI were more likely hospitalized than the counterparts.

## 2. Pathogens causing UTI

Pathogens isolated from the urine are listed in Table 2. *E. coli* was the most common pathogen

(85.3%). All 5 children with bacteremic UTI had the bacterium as the pathogen.

## 3. Accuracy of creatinine, CRP, and WBC in identifying children with UTI

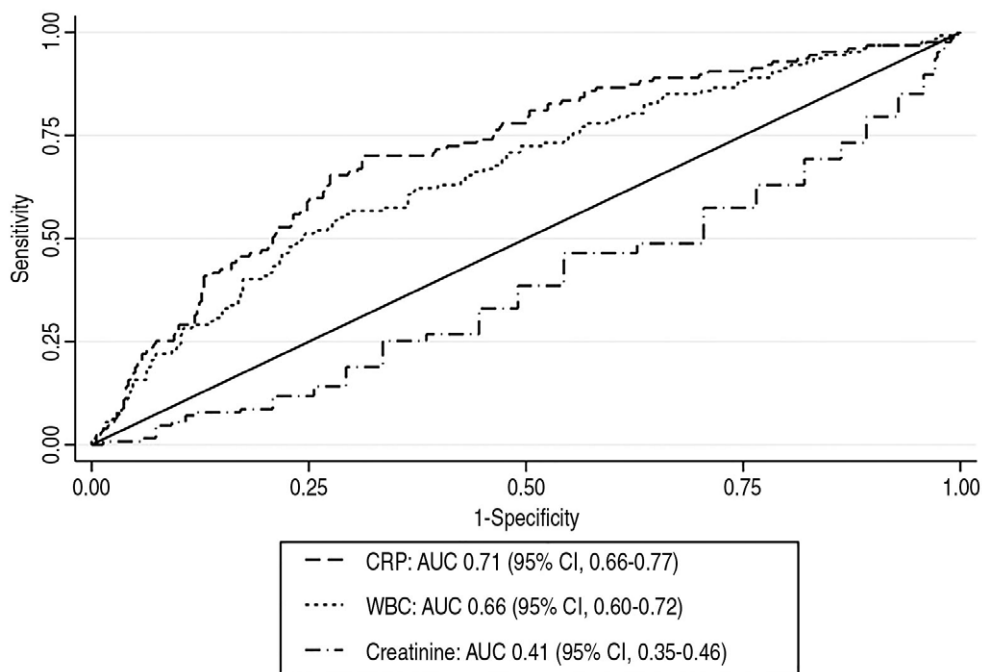
The children of the UTI group had lower creatinine concentration, higher WBC counts and CRP concentration than those of the non-SBI group (Table 3). The receiver operating characteristic curves for creatinine, CRP, and WBC are shown in Fig. 2. The areas under the curve for creatinine, CRP, and WBC were 0.41 (95% CI, 0.35–0.46), 0.71 (95% CI, 0.66–0.77), and 0.66 (95% CI, 0.60–0.72), respectively. The optimal cutoffs were 0.26 mg/dL for creatinine, 2.3 mg/dL for CRP, and  $14.4 \times 10^3$  cells/ $\mu$ L for WBC. The test characteristics of creatinine, CRP, and WBC at optimal cutoffs are presented in Table 4. CRP showed the highest overall predictive values with a positive and a negative likelihood ratios of 2.3 (95% CI, 1.9–2.7) and 0.4 (95% CI, 0.3–0.6), respectively. Creatinine showed poor performances than did WBC and CRP. The application of creatinine added to the other 2 tests led to an increase only in the sensitivity, but at the expense of a lower specificity, and positive and negative predictive values.

**Table 3.** Comparison of creatinine, CRP, and WBC between the children with and without UTI

Parameter	Median (IQR)		P value*	Mean ± SD		Difference (95% CI)
	UTI (N = 127)	Non-SBI (N = 379)		UTI (N = 127)	Non-SBI (N = 379)	
Creatinine, mg/dL	0.2 (0.2-0.3)	0.3 (0.2-0.3)	0.001	0.25 ± 0.06	0.27 ± 0.08	-0.02 (-0.04 to -0.01)
CRP, mg/dL	3.7 (1.4-8.1)	1.1 (0.4-2.9)	<0.001	5.4 ± 5.2	2.6 ± 3.8	2.9 (2.0 to 3.7)
WBC, × 10 <sup>3</sup> cells/μL	15.5 (10.6-19.6)	11.3 (8.0-15.3)	<0.001	15.4 ± 6.3	12.1 ± 5.5	3.4 (2.2 to 4.5)

\* P value for Wilcoxon rank sum test.

CRP: C-reactive protein, WBC: white blood cell, UTI: urinary tract infection, IQR: interquartile range, SD: standard deviation, CI: confidence interval, SBI: serious bacterial infection.



**Fig. 2.** AUCs for creatinine, CRP, and WBC to predict urinary tract infection. CRP: C-reactive protein, AUC: area under the curve, CI: confidence interval, WBC: white blood cell.

## Discussion

In this study, serum creatinine had the poorest accuracy in distinguishing UTI from non-SBI in the febrile children younger than 24 months. However, we found associations of higher levels of CRP and WBC with UTI in the children. While such changes are not definitive for final diagnosis, the elevations could be useful for predicting UTI. This is in line with a former study that reported increases in CRP and WBC levels in Finnish children with confirmed *E. coli* UTI<sup>14</sup>. Our finding

confirms this association based on a population of children in the post-PCV era. In addition, we investigated novel cutoffs for CRP and WBC from the population.

To our best knowledge, the association between serum creatinine and UTI has not been previously reported. Several authors have found elevated creatinine concentration to be predictive of bacteremia in children with febrile UTI<sup>18,19</sup>. From our study population, creatinine showed a poor performance to predict UTI as well. However, we reported a possible contribution to sensitivity to the prediction.

**Table 4.** Test characteristics of creatinine, CRP, and WBC in predicting UTI

Parameter	% (95% CI)		Likelihood ratio (95% CI)			
	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Creatinine $\geq$ 0.26 mg/dL*	46.5 (37.6-55.5)	45.6 (40.6-50.8)	22.3 (17.4-28.8)	71.8 (65.6-77.4)	0.9 (0.7-1.1)	1.2 (1.0-1.4)
CRP $\geq$ 2.3 mg/dL*	70.1 (61.3-77.9)	68.9 (63.9-73.5)	43.0 (36.2-50.0)	87.3 (83.0-90.8)	2.3 (1.9-2.7)	0.4 (0.3-0.6)
WBC $\geq$ $14.3 \times 10^3$ cells/ $\mu$ L*	56.7 (47.6-65.5)	70.2 (65.3-74.7)	38.9 (31.9-46.3)	82.9 (78.3-86.8)	1.9 (1.5-2.4)	0.6 (0.5-0.8)
WBC $\geq$ 14.3 or CRP $\geq$ 2.3 mg/dL	81.1 (73.2-87.5)	54.4 (49.2-59.4)	37.3 (31.6-43.3)	89.6 (84.9-93.2)	1.8 (1.6-2.0)	0.3 (0.2-0.5)
WBC $\geq$ 14.3, CRP $\geq$ 2.3 or creatinine $\geq$ 0.26 mg/dL	88.2 (81.3-93.2)	26.1 (21.8-30.9)	28.6 (24.1-33.3)	86.8 (79.2-92.4)	1.2 (1.1-1.3)	0.5 (0.3-0.7)

\* Estimated optimal cutoff point by the Youden method.

CRP: C-reactive protein, WBC: white blood cell, UTI: urinary tract infection, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio.

Significant elevations of serum creatinine are not apparent until 24–48 hours after the initiation of insult<sup>17</sup>. Therefore, the initial result of serum creatinine measured in EDs might be inappropriate to predict AKI induced by UTI despite the presence of relevant renal injury.

The low bacteremia rate in the children with UTI (3.9%) suggests a low feasibility of investigation on association between bacteremia and creatinine. Instead, we focused on the possible association of UTI with creatinine. Contrary to elevated creatinine concentration being predictive of bacteremic UTI<sup>18,19</sup>, creatinine was not increased in the children with UTI than those with non-SBI. While creatinine concentration was minimally lower for those with UTI, this might be due to the younger median age of the UTI group<sup>20</sup>. The elevated creatinine in bacteremic UTI has been attributed to renal hypoperfusion secondary to a high infectious burden<sup>18</sup>. This was especially true for young infants in the first weeks of their life whose renal perfusion accounts for only 10% of the cardiac output<sup>21</sup>. This statement could not be validated by our study for the following reasons. First, the bacterial load for UTI patients was not high, as is shown by the low rate of bacteremia. Second, sub-analysis for very young infants was not conducted.

Our study had several limitations. First, it was a single-center study. As our hospital is a tertiary center located in the capital city of Korea, the features of the study population may not be readily generalizable. To enhance generalizability, we excluded all children with severe or rare underlying diseases affecting laboratory findings. Another limitation came from the retrospective design. Although the Fever Registry was a prospectively collected dataset, some parameters were unavailable, especially in the children with non-SBI. Lastly, our study included children younger than 24 months. For a more age group-specific analysis, a multi-center study may be needed to support our findings.

In conclusion, serum creatinine showed a poor performance to diagnose UTI in previously healthy febrile young children compared with CRP and WBC

count. Since a single biomarker can neither rule in nor rule out UTI in febrile children, prediction of UTI can be achieved by interpretation of both clinical and laboratory findings.

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## Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

## Acknowledgements

No funding source relevant to this article was reported.