Author's response to reviews

Title: Procalcitonin and C-reaction protein in urinary infection position diagnosis

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Procalcitonin and C-reaction protein in urinary infection position diagnosis

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Abstract

Background

Urinary infections are a common type of pediatric disease whose treatment and prognosis are closely correlated with infection location. Common clinical manifestations and laboratory test are not enough for acute pyelonephritis and lower urinary tract infection differentiation. The aim of this study was to explore a diagnostic method for upper and lower urine tract infection differentiation.

Methods

The diagnostic values of procalcitonin (PCT) and c-reaction protein (CRP) were analyzed using the ROC curve method for upper and lower urine tract infection differentiation. PCT was determined using chemiluminescent immunoassay.

Results

The PCT and CRP values in children with acute pyelonephritis were significantly higher than those in children with lower urine tract infection (3.90 ± 3.51 ng/ml and 68.17 ± 39.42 mg/l vs. 0.48 ± 0.39 ng/ml and 21.39 ±14.92 mg/l). The PCT values were correlated with renal involvement degrees, whereas the CRP values did not bear such a significant correlation. PCT had sensitivity of 90.47% and specificity of 88% in predicting nephropathia, whereas CRP had sensitivity of 85.71% and specificity of 48%.

Conclusions

Although both PCT and CRP can be used for upper an lower urine tract infection differentiation, PCT has higher sensitivity and specificity in predicting
pyelonephritis than CRP. PCT is better than CRP. PCT values are also correlated with renal involvement degrees.

**Keywords**

Urinary tract infections, acute pyelonephritis, receiver operating characteristic curve, procalcitonin

**Introduction**

Urinary infections are a common type of pediatric disease whose treatment and prognosis are closely correlated with infection location. Common clinical manifestations and laboratory indices are not enough for acute pyelonephritis and lower urinary tract infection differentiation. For infants and children, the differentiation becomes more difficult. However, despite the difficulty, their differentiation is very necessary, as pyelonephritis poses a risk of renal parenchyma involvement which can lead to renal scar formation, or even high blood pressure and end stage renal failure in adults [1-4]. Retrospective analysis of 52 patients with neodevelopment or progressive renal scars by Smellie et al. revealed 50 of them had a medical history of urinary infection diagnosis or treatment delay [5]. Therefore, to seek a technically easy and practical method for upper and lower urinary tract infection differentiation is urgent.

Nowadays, $^{99m}$Tc-DMSA scintigraphy is a commonly-adopted method for diagnosing
severity degrees of renal involvement, as well as pyelonephritis. However, this method is costly; even more, it is radioactive to sick children [6,7]. Procalcitonin (PCT) is a type of hormonal activity-free calcitonin precursor protein. PCT can serve as an early diagnosis index of serious bacterial infections and septicaemia; meanwhile, it is correlated with the severity of bacterial infections [8-10]. However, studies on PCT in urinary tract infections are rare. The efficacy of a PCT-based diagnostic test can be comprehensively assessed based on the sensitivity (Se) and specificity (Sp) of receiver operating characteristic (ROC) curves, with the areas under the curves reflecting the diagnostic value of the test [11,12].

In the current study, to explore the diagnostic value of PCT in differentiating upper and lower urinary tract infections, the serum PCT level was determined and compared with c-reactive protein (CRP) and peripheral blood leucocyte count; the outcomes were then analyzed using the ROC method.

**Materials and methods**

**Clinical data**

A total of 46 children with urinary infection who received treatment between December 1999 and April 2002 were enrolled. Among the patients, 18 were males and 28 were females. Their ages ranged from 2 months to 14 years: 6 males and 2 females were < 1 year old, 7 males and 11 females were between 1 year old and 3 years old, and 5 males and 15 females were ≥ 3 years old. 38 patients had primary
urinary infection, and 8 had recurrent infection. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Qilu Hospital of Shan Dong University. Written informed consent was obtained from all parent or guardian of participants.

Their courses of disease ranged from three days to one year. They did not receive antibiotic treatment within half a month before hospitalization. 40 patients had body temperatures between 38.5 °C and 40.0 °C, 28 presented urinary tract infection symptoms such as frequent micturition, urgent micturition, odynuria, and crying while urinating, 12 had lumbago and percussion pain on kidney region, 4 had macroscopic hematuria, 8 patients, 6 of whom were less than 2 years old, presented non-specific signs and symptoms such as emesis, diarrhea, abdominal pain, poor spirit and appetite, icterus, and irritability. All patients had white blood cell (WBC) count > 10/HP, 12 had red blood cell > 5/HP, and 11 had urine protein between + and ++, according to urine routine examination. Urine culture outcomes of all patients were positive. Acute pyelonephritis was confirmed using radioactive nuclide $^{99m}$Tc-DMSA scanning.

Diagnostic criteria were based on literature [13]: Acute pyelonephritis is indicated when there are radioactive renal parenchyma distributional sparse or loss areas accompanied with swelling or a normal kidney profile, and renal scar formation is diagnosed when the kidney volume decreases (manifested by cortex attenuation, renal morphologic abnormality, or profile shrinkage) with wedge-shaped defects. Renal
involvement was graded as follows: Renal injury < 25% was considered mild, that between 25% and 50% was considered moderate, and that > 50% was considered serious.

**Experimental methods**

The patients were divided into the acute pyelonephritis and lower urinary tract infection groups. PCT was determined using chemiluminescent immunoassay, and CRP was scored using nephrometry scoring.

**Statistical analysis**

All data were presented as means ± standard error (\( \bar{x} \pm s \)). T-tests were performed to compare the means between groups. Cut points were selected and then graded according to normal, basically normal, suspectable, basically abnormal, and abnormal classifications. Se and Sp of each point were calculated. Taking Se as the ordinate which represented true positive rate and (1-Sp) as the abscissa which represented false positive rate, ROC curves were drawn by the SPSS10.0 software for the calculation of area under curve and standard errors. Values of different indices were also compared.

**Results**

**Radioactive nuclide scanning**

21 out of the 46 patients were diagnosed with acute pyelonephritis. Among these patients, 1 presented renal scar formation, and 2 presented vesico-ureteral reflux.
PCT and CRP

The serum PCT and CRP levels of the acute pyelonephritis group were significantly higher than those of the lower urine tract infection group (3.90 ± 3.51 ng/ml and 68.17 ± 39.42 mg/l vs. 0.48 ± 0.39 ng/ml and 21.39 ±14.92 mg/l; \( P < 0.01 \); (Table 1). Correlation analysis demonstrated that PCT and CRP were in a significant positive correlation with a correlation coefficient of 0.729 \( (P < 0.01) \).

Curve analysis

As Figure 1 shown, the areas under the PCT, CRP, and WBC curves were 0.958, 0.858, and 0.588, respectively. Group comparison analysis showed that there was no significant difference between the areas under the PCT and CRP curves \( (P > 0.05) \), whereas the areas under these curves were significantly larger than that under the WBC curve \( (P < 0.01) \). These results indicate that PCT and CRP are highly accurate in diagnosing acute pyelonephritis.

Diagnostic values

The diagnostic values of PCT, CRP, and WBC were 1.0 ng/ml, 20 mg/l, 15000 /mm³, respectively. The sensitivity and specificity of PCT in predicting nephropathia were 90.47% and 88%, and those of CRP were 85.71% and 48%. PCT had the highest sensitivity and specificity in diagnosing acute pyelonephritis among the three. The results are summarized in Table 2.
Renal involvement degrees

The PCT level in children with serious renal involvement (8.60 ± 2.80 ng/ml) was noticeably higher than that in children with mild and moderate renal involvement (2.02 ± 1.24 ng/ml; \( P < 0.01 \)), whereas the WBC counts and serum CRP levels among children with different renal involvement degrees did not show significant differences (\( P > 0.05 \)). These results indicate that the higher a PCT value is, the more serious the renal involvement degree will be. The results are summarized in Table 3.

PCT and CRP outcome analysis

The pre- and post-treatment PCT levels were 3.90 ± 3.51 ng/ml and 1.78 ± 2.07 ng/ml, respectively, and the pre- and post-treatment CRP levels were 68.17 ± 39.42 mg/l and 26.13 ± 15.14 mg/l; great differences in PCT and CRP were observed before and after treatment (\( P < 0.05 \)). Follow-up DMSA scanning at 6 months after treatment showed that 15 children completely recovered, 3 got great improvement, 2 got a little improvement, 1 did not have noticeably improvement (he had had renal scars accompanied with vesico-ureteral reflux before the hospitalization), and all patients had no new scars; the serum PCT levels (> 10 ng/ml) in 3 patients before treatment were still higher than 5 ng/ml after treatment.

Discussion
Urinary infections are a common type of pediatric disease whose treatment and prognosis are closely associated with infection position. As differentiating acute pyelonephritis from lower urine tract infection is difficult based on common clinical manifestations and laboratory indices, an easier and more practical method is very necessary. Although $^{99m}$Tc-DMSA scintigraphy is a commonly-adopted method for the diagnosis of renal involvement degrees and pyelonephritis nowadays, it is costly as well as radioactive to children [6,7].

PCT is a kind of hormonal activity-free calcitonin precursor protein. Studies have proved that PCT can serve as an early diagnosis index of bacterial infections and septicaemia, and that it is also correlated with the severity of bacterial infections, thus possessing a prognosis-predicting value [14-16]. PCT has a half life period of 25-30 h in serum. It is highly stable in blood samples (no matter in whole blood, blood plasma, or serum), which does not degrade and is easily determinable [17]. Normally, PCT does not increase when local bacterial infection occurs unless it is accompanied with systemic inflammatory reactions [16,18,19]. To date, studies on the correlation between PCT and urinary infections have only been rarely seen in literature. Therefore, in the present study, the PCT and CRP levels in 46 children with urinary infection were determined. The results show that the average PCT and CRP levels of children with acute pyelonephritis were greatly higher than those of children with lower urine tract infection ($P < 0.01$); in contrast, peripheral blood WBC counts did not show significance in predicting renal involvement.
Sensitivity and specificity are two basic indices in assessing diagnostic values. ROC curves do not fix classification boundary values, which allow the existence of transition states. They enable users to combine their expertise to weigh the influences of missed diagnosis and misdiagnosis and to select a more suitable cut point as the diagnostic reference value. Furthermore, ROC curves incorporate sensitivity and specificity into whole and present them graphically. A ROC curve which is more convex and closer to the top left corner indicates a higher diagnostic value. This feature endows ROC curves with visibility for the sake of comparisons among different indices. Moreover, the area under a curve can be used for diagnostic accuracy assessment. According to John, < 0.5 of the area under a curve indicates no diagnostic value, 0.5-0.7 tells a low degree of accuracy, 0.7-0.9 demonstrates a certain degree of accuracy, and > 0.9 represents a high degree of accuracy. In this study, the results show that the areas under the PCT, CRP, and WBC curves were 0.958, 0.858, and 0.588, respectively, and the group analysis shows that the areas under both PCT and CRP curves displayed significant differences compared with that under the WBC curve. These results indicate that both PCT and CRP can serve as laboratory indices for acute pyelonephritis diagnosis, but that PCT has a higher diagnostic value. The ROC curves in this study illustrate the same findings.

In addition, this study shows that PCR and CRP have a significant correlation with
a Pearson’s correlation coefficient of 0.729 ($P < 0.01$). Although CRP also has a diagnostic value for acute pyelonephritis diagnosis, its sensitivity, specificity, and accuracy are low. The sensitivity and specificity of CRP, PCT, and WBC are related a real positive patient’s threshold determination. Based on the results in this study, 1 ng/ml PCT can be taken as the reference value, as PCT has sensitivity of 90.47%, specificity of 88%, accuracy of 89%, a positive predictive value of 87%, and a negative predictive value of 95% in predicting acute pyelonephritis.

This study also shows that the PCT and CRP levels after treatment significantly decreased compared with those before treatment ($P < 0.05$). This result indicates that both PCT and CRP can be taken for pathogenesis and curative effect observation. The serum PCT value in children with serious renal involvement was significantly higher than those with mild and moderate involvement. This finding indicates that the higher a PCT value is, the more serious renal involvement will be; therefore, PCT can be applied in predicting renal involvement. Although the CRP value in children with serious renal involvement was higher than those in children with mild and moderate renal involvement, no significant difference was observed.

To sum up, serum PCT determination is an easy and cheap method for acute pyelonephritis diagnosis, and it only needs a small amount of blood. Furthermore, PCT is highly stable in serum, and the whole PCT determination process only takes 2 h. In addition, PCT determination can also be used for the observation of
curative effect and follow-up pathogenetic condition sequelae, prognostic judgement, and renal involvement degree prediction. Because of these merits, serum PCT determination is worthy to populate clinically.

**Competing interests**

I declare that we have no financial competing interests.

**Authors’ Contributions**

Rui-Ying Xu participated in the design of the study, statistical analysis and drafting the manuscript. Hua-Wei Liu helped to carry out the immunoassays and data analysis. Ji-Ling Liu helped collecting blood samples. Jun-Hua Dong has given medical instruction.

**Acknowledgements**

We thank Xiang-Dong Jian who provided medical writing services and technical help.

**References**


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renal scarring after urinary infection in childhood. *BMJ* 1990, **300**:840-844.


Table 1 Comparisons of the laboratory outcomes between groups (\(\overline{x} \pm s\))

<table>
<thead>
<tr>
<th>Group</th>
<th>PCT ((\rho/\text{ng} \cdot \text{ml}^{-1}))</th>
<th>CRP ((\rho/\text{mg} \cdot \text{L}^{-1}))</th>
<th>WBC number ((/\text{mm}^{3}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower urine tract infection</td>
<td>0.48 ± 0.39</td>
<td>21.39 ± 14.92</td>
<td>14068 ± 6870</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>3.90 ± 3.51</td>
<td>68.17 ± 39.42</td>
<td>15882 ± 7350</td>
</tr>
<tr>
<td>(p) value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Table 2 Comparisons of the diagnostic values of PCR, CRP, and WBC for acute pyelonephritis (%)

<table>
<thead>
<tr>
<th>Index</th>
<th>Diagnostic reference value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>1 ng/ml</td>
<td>90.47</td>
<td>88</td>
<td>89</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>CRP</td>
<td>20 mg/l</td>
<td>85.71</td>
<td>48</td>
<td>86.9</td>
<td>58</td>
<td>80</td>
</tr>
<tr>
<td>WBC</td>
<td>15000 /mm³</td>
<td>57</td>
<td>44</td>
<td>71</td>
<td>46</td>
<td>55</td>
</tr>
</tbody>
</table>
Table 3 Correlations between laboratory outcomes and renal involvement degrees

<table>
<thead>
<tr>
<th>Index</th>
<th>Mild and moderate degrees (n = 15; DMSA scanning)</th>
<th>Serious degree (n = 6; DMSA scanning)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ρ/ng·ml⁻¹)</td>
<td>2.02 ± 1.24</td>
<td>8.60 ± 2.80</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CRP (ρ/mg·l⁻¹)</td>
<td>62.0 ± 42.83</td>
<td>82.02 ± 28.56</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>WBC (cells/mm³)</td>
<td>14990 ± 2611</td>
<td>15980 ± 3220</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Figure Legend

Figure 1 Comparison of the ROC curves of PCT, CRP and WBC.