

A study of the effectiveness of using the serum procalcitonin level as a predictive test for bacteremia in acute pyelonephritis

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Objectives: Serum procalcitonin (PCT) is a specific biomarker that rises after bacterial infection, and levels of PCT are known to correlate with the severity and mortality of patients with pneumonia and sepsis. However, the usefulness of PCT levels in acute pyelonephritis is unknown. This study aimed to evaluate the effectiveness of using the PCT level as a predictive test for bacteremia in acute pyelonephritis.

Methods: Between January 2012 and June 2013, 140 patients diagnosed with acute pyelonephritis were admitted to Haeundae Paik Hospital. Serum PCT, C-reactive protein (CRP), and white blood cell (WBC) levels at pre- and post- treatment were measured. Blood and urine cultures were obtained from all patients. The levels of PCT, CRP, and WBCs were each compared between the blood culture-positive and blood culture-negative groups to assess their effectiveness in predicting bacteremia.

Results: Pre-treatment PCT level was 0.77 ng/mL (95% CI: 0.42-1.60 ng/mL) in the blood culture-negative group and 4.89 ng/mL (95% CI: 2.88-9.04 ng/mL) in the blood culture-positive group, and the increase between the two groups was statistically significant. The area under the receiver operating characteristic curve of PCT level for prediction of bacteremia was 0.728. A cut-off value of 1.23 ng/mL indicated a sensitivity of 79.0 % and specificity of 60.0 % for PCT level.

Conclusions: Serum PCT level is a useful predictive test for bacteremia in acute pyelonephritis. Through the early detection of bacteremia, serum PCT level can help estimate the prognosis and predict complications such as sepsis.

Key Words: Bacteremia, Procalcitonin, Pyelonephritis

Acute pyelonephritis, which is the most common upper urinary tract infection, exhibits a varied clinical course and is usually accompanied by

bacteremia. Bacteremia correlates with a poor prognosis and a high occurrence of complications, such as renal abscess and sepsis. Therefore, the

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early detection of bacteremia is clinically important. To date, blood culture is the most basic and important method for diagnosing bacteremia: however, early detection is difficult because blood culture results are not available for at least 24 to 48 hours. Also, false positives may occur from culture contamination, and blood culture sensitivity is reduced after the administration of antibiotics.¹

Thus, existing diagnostic tests for bacteremia are insufficient and early diagnosis and treatment of bacteremia is limited. Many methods for early prediction of bacteremia have been developed, such as measuring or detecting bacterial genes and antigens in the blood and measuring substances that the body produces in reaction to bacterial infection. However, because of cost and complexity these methods are often difficult to apply clinically. Among them, serum procalcitonin (PCT) level, which increases in response to bacterial infection, is expected to be useful in the diagnosis and treatment of infectious diseases.

PCT is a calcitonin precursor consisting of 116 amino acids. PCT is usually secreted by the thyroid gland, and trace amounts of it can be measured in the blood. However, expression of the *CALC1* gene, which produces PCT, is rapidly increased by stimulation of inflammatory cytokines in infectious conditions, such as pneumonia and urinary tract infection. PCT is rapidly secreted into the blood from the thyroid gland, spleen, liver, and kidney.^{2,3} In previous studies, PCT level has been shown to predict the severity and prognosis of disease.⁴ Moreover, PCT is a useful biomarker

to distinguish bacterial from viral infections because the PCT level is not elevated in viral infections.⁵ The purpose of this study was to evaluate the diagnostic value of the PCT level for predicting bacteremia in patients with acute pyelonephritis.

MATERIALS AND METHODS

Study subjects

This case-control, retrospective, observational study was performed at a single tertiary hospital and was approved by the Institutional Review Board at our institution. From our hospital database, we recruited 320 patients with the diagnosis of uncomplicated or complicated associated with an underlying condition that increases the risk of failure of therapy including diabetes, hospital acquired infection, renal failure, urinary tract obstruction, presence of an indwelling urethral catheter, functional or anatomic abnormality of the urinary tract, renal transplantation or immunosuppression etc. acute pyelonephritis who were admitted to the Department of Internal medicine, Haeundae Paik Hospital, between January 2012 and June 2013. We then reviewed the medical records and laboratory findings of these patients. Inclusion criteria for the patients with acute pyelonephritis were 1) age at least 18 years; 2) presence of clinical features, such as acute onset of fever $> 38^{\circ}\text{C}$, flank pain, and dysuria; and 3) radiologic studies compatible with pyeloneph-

ritis localized hypodense lesions due to ischemia induced by marked neutrophilic infiltration and edema on contrast enhanced computed tomography or abnormal echogenicity of the renal parenchyma - focal/segmental hypoechoic regions or mass like change on renal ultrasound used in patients for whom exposure to contrast or radiation is undesirable. Key exclusion criteria were presence of 1) other acute infections, 2) malignancies, or 3) hematologic diseases. We ultimately analyzed the data of 140 patients who met all 3 inclusion criteria and had positive urine cultures.

Study methods

A urine culture and two sets of blood cultures were performed at admission. Blood samples were also tested for complete blood count, chemistry, PCT, and C-reactive protein (CRP); samples were obtained both initially (D1) and post-treatment (D3-7).

Blood cultures were collected in two sets of bottles and were incubated under aerobic and anaerobic conditions in an automatic machine (BacT/Alert 3D system, bioMérieux, Inc., Durham, NC, USA) for 5 days. The single isolation of coagulase-negative staphylococci or *Corynebacterium* species in blood was considered as contamination. Significant bacteremia was defined as isolation of a known pathogen in at least one culture. PCT concentrations (Low risk of severe sepsis: < 0.5 ng/mL) were measured using an electrical chemiluminescence assay (cobas e 411, Roche Diagnostics, Indianapolis, IN, USA), and the

measuring range was 0.05–200 ng/mL. CRP concentrations were quantitatively measured using an immunoturbidometric assay (Hitachi 7600 chemistry analyzer, Tokyo, Japan), and the measuring range was 0.03–350 mg/dL. To identify the usefulness of the PCT level as a predictor of bacteremia, we compared PCT levels between bacteremic and non-bacteremic patients. To investigate the superiority of PCT level to CRP level for predicting bacteremia, CRP and PCT levels were compared between blood culture-positive and blood culture-negative groups.

Statistical analysis

Clinical variables were compared in bacteremic vs. non-bacteremic patients. We analyzed categorical clinical variables using Fisher's exact test or the chi-square test and numerical values using Student's t-test or the Mann-Whitney U-test. Receiver operating characteristic (ROC) curves were plotted for each biomarker, and the area under the ROC curve (AUC) and 95% confidence interval (CI) for the respective biomarkers were compared by a non-parametric method. The cut-off value that maximized the sum of sensitivity and specificity (Youden Index) was calculated for each variable; and sensitivity, specificity, positive predictive values, and negative predictive values were calculated for each cut-off value of PCT and CRP. All statistical tests were performed using MedCalc 12.0 (MedCalc Software, Mariakerke, Belgium). For all calculations, p-values < 0.05 were considered statistically significant. All data

were expressed as median (range) and mean \pm standard deviation.

RESULTS

A total of 320 patients were reviewed, and 140 patients satisfied all inclusion and exclusion criteria for this study. Of these, 126 patients (91%) were women and 13 (9%) were men. The mean age was 67.1 years (range: 21-91 years). Of the 140 patients, 63 (45%) had bacteremia confirmed by positive blood culture, and 77 (55%) did not have bacteremia. Baseline demographic and clinical characteristics are shown in Table 1. The predominant causative microorganism confirmed by urine culture including polymicrobial infection was *Escherichia coli* (108/140, 77%), followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterococcus* species, *Citrobacter freundii*, and *Staphylococcus aureus* (Table 2). *Escherichia coli* (35/46, 76.1%) was also the major causative microorganism identified in urine culture in diabetic patients (Table 3). Among the pathogens, 12 were extended-spectrum β -lactamase-producing *Escherichia coli*. Pretreatment PCT level was 0.77 ng/mL (95% CI: 0.42-1.60 ng/mL) in the blood culture negative group and 4.89 ng/mL (95% CI: 2.88-9.04 ng/mL) in the blood culture-positive group. The level of PCT in the blood culture-positive group increased to a statistically significant degree. The level of CRP in the bacteremic group also increased significantly

as compared with the non-bacteremic group (Table 4).

On the basis of positive correlations between PCT level and bacteremia, an ROC curve analysis was performed. The AUC of the PCT level was 0.728, and a cut-off value of 1.23 ng/mL indicated a sensitivity of 79.0% and specificity of 60.0% for PCT.

The levels of PCT and CRP in the bacteremic group were significantly higher than in the non-bacteremic group. We analyzed the ROC curve to evaluate the utility of PCT and CRP levels for diagnosing bacteremia. The AUC of the PCT level before treatment was 0.728, and the AUC of the CRP level before treatment was 0.614 (Fig. 1). In addition, the platelet level before treatment was significantly lower in the bacteremic group than in the non-bacteremic group. The levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly higher in the bacteremic group than in the non-bacteremic group although they were within the normal range in both groups.

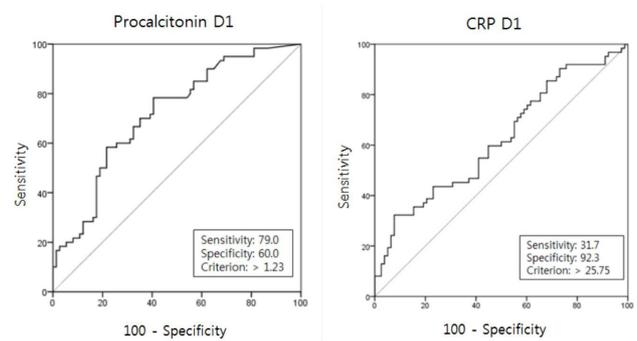


Fig. 1. ROC curves of procalcitonin, C-reactive protein for prediction of bacteremia Procal, procalcitonin: CRP, C-reactive protein: ROC, receiver operating characteristic

Table 1. Baseline characteristics and laboratory data of patients presenting with acute pyelonephritis

	Blood culture positive (N = 63)	Blood culture negative (N = 77)	P-value
Sex (F:M)	54:9 (85.7%)	73:4 (94.8%)	0.115
Age (years)	64.7 ± 14.7	60.4 ± 17.7	0.126
Mortality (= N)	3 (4.7%)	3 (3.8%)	1.000
Diabetes melitus (= N)	29 (46.8%)	24 (30.7%)	0.103
Creatinine (mg/dL)	1.2 (0.5–4.7)	1.0 (0.6–9.8)	0.058
Platelet (10 ⁹ /L)	181.9 ± 76.9	210.2 ± 73.3	0.027
Hemoglobin (mg/dL)	11.6 ± 1.7	11.7 ± 1.6	0.724
WBC (D1), 10 ³ /μL	13,040 (11,605–14,347)	11,550 (10,469–13,250)	0.341
PCT (D1), mg/dL	4.89 (2.88–9.14)	0.77 (0.42–1.60)	0.001
CRP (D1), mg/dL	17.9 (15.20–20.60)	13.4 (11.50–15.30)	0.049
AST, IU/L	30.0 (9.0–319.0)	23.0 (6.0–225.0)	0.0168
ALT, IU/L	21.0 (9.0–241.0)	16.0 (2.0–210.0)	0.0414

Continuous values are presented as median (range) or mean ± standard deviation WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; AST, aspartate transferase; ALT, alanine transferase.

Table 2. Type of microorganisms isolated from urine cultures and blood cultures

Microorganisms	Urine culture (= N)	Blood culture (= N)
<i>Escherichia coli</i>	108 (77.1%)	57 (89.1%)
<i>Klebsiella pneumoniae</i>	7 (5.0%)	2 (3.1%)
<i>Proteus mirabilis</i>	7 (5.0%)	3 (4.7%)
<i>Pseudomonas aeruginosa</i>	5 (3.6%)	0 (0%)
<i>Enterococcus</i> species	4 (2.9%)	1 (1.6%)
<i>Staphylococcus aureus</i>	3 (2.1%)	1 (1.6%)
<i>Citrobacter freundii</i>	1 (0.7%)	0 (0%)
<i>Acinetobacter baumannii</i>	1 (0.7%)	0 (0%)
<i>Candida</i> species	1 (0.7%)	0 (0%)
Unidentified Gram-negative organism	3 (2.1%)	0 (0%)
Total	140 (100%)	64 (100%)

Table 3. Type of microorganisms isolated from urine cultures and blood cultures in diabetes mellitus patients

Microorganisms	Urine culture (= N)	Blood culture (= N)
<i>Escherichia coli</i>	35 (76.1%)	22 (88.0%)
<i>Klebsiella pneumoniae</i>	2 (4.3%)	2 (8.0%)
<i>Proteus mirabilis</i>	2 (4.3%)	1 (4.0%)
<i>Pseudomonas aeruginosa</i>	1 (2.2%)	0 (0%)
<i>Enterococcus</i> species	3 (6.5%)	0 (0%)
<i>Staphylococcus aureus</i>	1 (2.2%)	0 (0%)
<i>Acinetobacter baumannii</i>	1 (2.2%)	0 (0%)
Unidentified Gram-negative organism	1 (2.2%)	0 (0%)
Total	46 (100%)	25 (100%)

Table 4. Correlation of biomarkers and bacteremia in acute pyelonephritis patients

	Blood culture positive (N = 63)	Blood culture positive (N = 77)	P-value
PCT (D1), ng/dL	4.89 (2.88–9.14)	0.77 (0.42–1.60)	0.009
PCT (D3–7), ng/dL	4.14 (2.38–5.22)	0.32 (0.15–0.87)	0.008
CRP (D1), mg/dL	17.9 (15.20–20.60)	13.4 (11.50–15.30)	0.042
CRP (D3–7), mg/dL	9.41 (7.83–11.7)	5.74 (4.40–8.78)	0.047
WBC (D1), 10 ³ /μL	13,040 (11,605–14347)	11,550 (10,469–13,250)	0.341
WBC (D3–7), 10 ³ /μL	9,090 (9,897–10,387)	7,330 (6,269–7,783)	0.043

Continuous values are presented as median (range).

PCT, procalcitonin; WBC, white blood cell count; CRP, C-reactive protein; 95% CI, 95% confidence interval.

DISCUSSION

Early detection of bacteremia is important in patients with acute pyelonephritis. Recently, there has been increasing interest in the use of PCT as complementary marker in the diagnosis of bacteremia.⁶ PCT is considered a useful marker for rapid differential diagnosis of bacterial

sepsis.⁷ PCT is a product response to bacterial infection in the human body.

In a previous study, after injection of extracted endotoxin from *Escherichia coli*, the PCT level rapidly started increasing in 2–4 hours, reached a peak in 6–12 hours, and maintained a blood concentration in 12–24 hours.⁸ On the other hand, the CRP level started increasing after 12 hours and reached its peak after 30 hours. Because the

concentration of PCT increases faster than that of CRP in the systemic inflammatory response to bacterial infection, PCT has the merit of facilitating early diagnosis of infection. Also, the concentration of PCT is known to correlate with the severity and course of the disease (e.g., sepsis, pneumonia).^{9,10} PCT is a useful marker in the differential diagnosis of urinary tract infection and evaluation of the severity of kidney injury in children. Our study confirms that PCT is also more useful marker than CRP in prediction of bacteremia in adults with acute pyelonephritis. Although we did not analyze prognosis or treatment failure in relation to PCT levels in this study, repeating the PCT level during treatment is helpful to assess treatment response and failure.¹¹⁻¹³ Proper clinical application of PCT levels might decrease unnecessary use of antibiotics and side effects, such as antibiotic resistance.^{14,15}

We observed that platelet count in the bacteremic group was significantly lower than in the non-bacteremic group. Platelet count is a useful marker for the diagnosis of bacteremia in patients with acute pyelonephritis, and several studies have shown that patients with bacteremia have low platelet counts.^{16,17} In patients with bacteremia, the low platelet count is due to multiple etiologies, including accelerated platelet destruction by a nonimmunologic mechanism, increased platelet consumption, suppression of platelet production in the bone marrow, drugs, and disseminated intravascular coagulation.¹⁸

Although the average AST/ALT levels in our

study were within the normal range, they were significantly higher in the bacteremic group than in the non-bacteremic group. Abnormal liver function tests occur in over 10% of patients with sepsis.¹⁹ The cause of this is not clearly known. It appears that complex factors are associated with abnormal liver function tests in patients with sepsis; possible causes include ischemic injury due to decreased hepatic perfusion (e.g., from cardiogenic shock) and hepatocyte injury due to an inflammatory response to cytokines such as interleukin-6 and tumor necrosis factor- α .

In prior studies, cut-off values of PCT using an electrochemiluminescence immunoassay method—the same method used in this study—to identify sepsis were 0.28–3.3 ng/mL.^{20,21} The various cut-off values of PCT in prior studies were due to different characteristics of patient groups or disease groups. Follow-up measurement of PCT levels during treatment may predict clinical improvement. Also, because the PCT level can be normal in a very early stage of disease, follow-up measurement of PCT level is helpful to definitively exclude bacterial infection. Furthermore, because PCT levels increase with severe trauma, surgery, burns, and cardiogenic shock,^{22,23} their interpretation should be made with reference to clinical signs and overall examination.

Our study was potentially biased because of its design as a retrospective analysis in a single center. Also, female patients predominated in the study because of the nature of urinary tract infection. Thus, some limitations exist regarding

generalization of our results, and additional investigations should be performed.

In conclusion, PCT is a useful marker for the early prediction of bacteremia (i.e., before blood culture results are available) in patients with acute pyelonephritis. Proper clinical application of PCT levels might be helpful for deciding on the administration of antibiotics and their optimal duration of use. It might also simplify examination in patients with urinary tract infection, including acute pyelonephritis. However, more research is needed in the future to confirm these findings.

KEY MESSAGE

1. Serum procalcitonin (PCT) level is a useful predictive test for bacteremia in acute pyelonephritis.

2. Through the early detection of bacteremia, serum PCT level can help estimate the prognosis and predict complications such as sepsis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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