Procalcitonin Is a Marker of Gram-Negative Bacteremia in Patients With Sepsis

Shun Yuan Guo, MD, Yin Zhou, MD, Qing Feng Hu, PhD, Jiong Yao, PhD and Hong Wang, MD

Abstract: *Background:* Prediction of the species of pathogen among patients with sepsis within hours would be helpful in accelerating proper treatment. As a potential method of shortening the time to identification, this study considered the usefulness of measuring procalcitonin (PCT) to predict blood culture (BC) results. *Methods:* The authors retrospectively analyzed the data of patients with a diagnosis of sepsis in their hospital from December 2012 to December 2013. The authors analyzed all diagnostic episodes consisting of BC and PCT concentration. The diagnostic performance of PCT to predict gram-negative bacteremia was tested using a receiver operative characteristic curve. Logistic regression was constructed using the presence of gram-negative bacteria as the dependent variable. *Results:* A total of 262 diagnostic episodes met the inclusion criteria. According to BC classifications, a significantly higher value of PCT was observed in bloodstream infections caused by gram-negative bacteria (26.7 ng/mL, 0.09–188.3) than that in bloodstream infections caused by gram-positive bacteria (0.84 ng/mL, 0.05–18.79) or *Candida* spp. (1.12 ng/mL, 0.07–49.68). A cutoff value of $\geq$3.39 ng/mL for PCT showed a sensitivity of 80%, a specificity of 71%, a positive predictive value of 35%, a negative predictive value of 91% and an area under the curve of 0.73 for gram-negative bacteremia identification by BC. Among the 122 diagnostic episodes with positive BC results, a cutoff value of $\geq$6.47 ng/mL for PCT yielded a sensitivity of 74%, a specificity of 81%, a positive predictive value of 82%, a negative predictive value of 75% and an area under the curve of 0.81 for gram-negative bacteremia identification. *Conclusions:* PCT may represent a useful tool for differentiating gram-positive from gram-negative bloodstream infection with a significantly higher PCT level indicating gram-negative bacteremia.

Key Indexing Terms: Procalcitonin; Sepsis; Bacteremia; C-reactive protein. [Am J Med Sci 2015;349(6):499–504.]

Sepsis is among the most common causes of death in hospitalized patients. Despite improvements in antimicrobial therapy, it is still associated with high mortality.[1] In cases where sepsis is suspected, timely and adequate clinical decision making is required. A delay in starting adequate antibiotic treatment is an independent predictor of high mortality.[2,3] Empirical antimicrobial therapy should be started upon suspicion of sepsis before blood culture results become available.

However, in one third of sepsis patients, the causative pathogens cannot be identified.[4]

Because of concerns regarding the potential for a β-lactam–resistant gram-positive coccal infection, such as methicillin-resistant *Staphylococcus aureus* infection, patients with suspected severe sepsis require empiric combination antimicrobial therapy with specific activity against gram-positive cocci and agents with efficacy against gram-negative bacteria.[5] This is especially true if the patient is known to have acquired sepsis in the hospital. However, the need for combination antimicrobial therapy covering gram-positive cocci has long been debated.[6] Given the significant negative impact of the broad use of anti-positive cocci antimicrobials, such as the emergence of vancomycin-resistant enterococci,[7] better targeting of their use is needed. If the infectious pathogen could be quickly identified by laboratory tests within an hour, it will allow a more timely and accurate clinical decision and more appropriate empirical antibiotic therapy.

Procalcitonin (PCT) is the prohormone of calcitonin and is synthesized by the C cells in the thyroid gland. It is produced ubiquitously in response to endotoxin or to mediators released in response to bacterial infections.[8] As such, it has become the mostly widely used biomarker in the management of sepsis around the world. PCT has the highest sensitivity and specificity for predicting systemic bacterial inflammation; moreover, high PCT concentrations have a positive predictive value for severe sepsis and septic shock and distinguish between viral and bacterial infections.[9–11] The levels of PCT correlate with the severity of bacterial infection and bacterial load. PCT may assist in decisions about the initiation and/or duration of antibiotic therapy (antibiotic stewardship).[12] Moreover, pieces of studies have described the correlation between PCT concentration and identification of specific bacterial species,[13,14] but the results needs to be validated. The aim of this study was to investigate whether serum PCT level could be used as an early surrogate marker for bacterial species-level detection by blood culture (BC) in septic patients. In addition, the authors investigated the predictive value of serum PCT level compared with standard clinical inflammatory biomarkers such as white blood cell (WBC) count, C-reactive protein (CRP) and platelet (PLT) count and prediction rules.

METHODS

Patients and Definitions

This was a retrospective observational clinical study and was approved by the Ethics Committee of Zhejiang Provincial People's Hospital. The written informed consent was given by participant. The authors reviewed the clinical records of all patients with a diagnosis of sepsis or septic shock from December 2012 to December 2013 and registered those in agreement with the diagnostic protocol consisting of a blood culture and measurement of serum PCT. The authors excluded the diagnostic episodes done on patients with missing tests and those not completed with an 8-hour time interval. Clinical and microbiologic data were obtained from the comprehensive electronic medical

```
┌─────────────────────┐
│ 280 sepsis patients │
└─────────────────────┘
           │
           ▼
┌─────────────────────┐
│     Diagnostic      │
│  episodes analyzed  │
│       n = 292       │
└─────────────────────┘
           │
   ┌───────┴───────────────────┐
   ▼                           ▼
┌──────────────────┐  ┌──────────────────────────────┐
│ Diagnostic       │  │ Diagnostic episodes excluded  │
│ episodes included│  │ n = 30                        │
│ n = 262          │  │ No BC or BC not within 12 h   │
│ (from 202        │  │ (n = 10)                      │
│ patients)        │  │ No PCT (n = 15)               │
│                  │  │ PCT not within 12 h (n=5)     │
└──────────────────┘  └──────────────────────────────┘
```
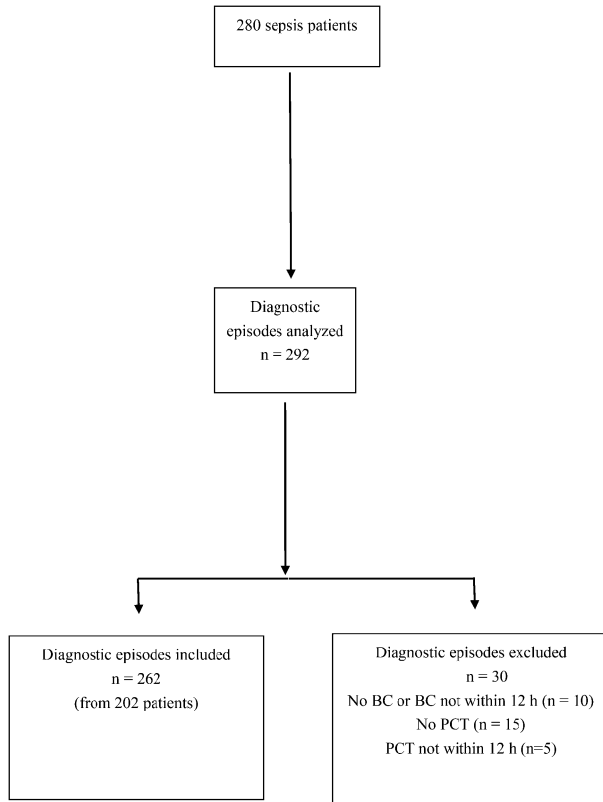
FIGURE 1. Study flow chart. BC, blood culture; PCT, procalcitonin.

record. For each complete diagnostic episode, the testing physicians collected all patient information using a standardized data collection form.

Demographic factors and comorbid illnesses, including age, sex, diabetes mellitus, renal failure and malignancy were evaluated. The 1st available physical examination findings were collected; including altered mental status, pulse rate, respiratory rate, blood pressure and body temperature. Laboratory tests included PCT level, CRP level, WBC count, PLT count, blood urea nitrogen, arterial pH, arterial lactic acid, oxygen saturation with the fraction of inspired oxygen and Sequential Organ Failure Assessment score. When inclusion criteria were met more than once for a single patient during the intensive care unit admission (ie, new bloodstream infection [BSI] documented by blood culture), the authors considered this event a new diagnostic episode for data analysis. In the hospital, a set of 2 blood specimens is drawn from each patient for BC, according to the guidelines of the Infectious Diseases Society of America. According to the results of each microbiological test, diagnostic episodes were classified into 6 groups: gram-positive bacterial infection, gram-negative bacterial infection, mixed infection-1 (gram-positive bacterial and gram-negative bacterial infection), mixed infection-2 (bacterial infection and *Candida* spp. infection), *Candida* infection and negative.

Measurements

Serum PCT concentration was measured by chemiluminescent enzyme immunoassay using Modular E170 (Roche Diagnostics, Mannheim, Germany). Serum CRP concentrations were measured by luminescent oxygen channeling immunoassay using Immage 800 (Beckman Coulter, Brea, CA). WBC and PLT counts

TABLE 1. Laboratory and infection source by diagnosis

	Gram-negative bacteremia	Gram-positive bacteremia	Mixed-1	Negative	Candida	Mixed-2	Total	P
Diagnostic episodes	65	36	7	140	11	3	262	
Age (n ± SD)	67.8 ± 17.1	64.8 ± 15.1	66.4 ± 11.9	65.9 ± 15.5	63.6 ± 21.4	66.1 ± 15.9	66.1 ± 15.9	0.81
Male sex, n (%)	48 (73.8)	21 (58.3)	5 (71.4)	95 (67.9)	8 (72.7)	3 (100)	180 (68.7)	0.49
PCT (range), ng/mL	26.7 (0.09–188.3)	0.84 (0.05–18.8)	1.5 (0.21–12.4)	3.82 (0.02–172)	1.12 (0.07–49.7)	19.8 (10.9–39)	4.30 (0.02–188.3)	0.001
WBC (range) × 10^9	12.6 (1.85–45.5)	10.9 (1.77–23.1)	9.5 (3.3–12.2)	13.02 (0.26–38.7)	13.2 (4.46–35.3)	5.84 (2.58–22.26)	12.4 (0.26–45.24)	0.27
CRP (range), ng/mL	145.2 (11–288)	126.5 (1.44–288)	117.6 (83.2–163.6)	165 (17.5–314)	117 (0.6–341)	148 (108–168)	154.7 (0.6–341)	0.04
PLT (range) × 10^{12}	117 (8–389)	142.5 (11–467)	189 (25–314)	138.3 (3–532)	94 (15–311)	96 (54–303)	137 (3–532)	0.78
Lactic acid (range), mmol	2.24 (0.6–27)	1.6 (0.6–8.4)	1.5 (1.2–1.8)	2.14 (0.6–18)	1.8 (1.2–4.1)	2.5 (2.2–3.5)	2.1 (0.6–27)	0.02
SOFA, n (range)	6 (0–16)	4 (0–13)	3 (0–16)	3 (2–15)	2 (0–11)	10 (10–13)	4 (0–16)	0.06
Severe sepsis, n (%)	32 (49.2)	14 (38.9)	3 (42.9)	53 (37.9)	4 (36.4)	3 (3/3)	153 (41.6)	0.24
Surgical, n (%)	11 (17%)	3 (8.6%)	2 (2/7)	24 (17%)	3 (3/11)	2 (2/3)	44 (16.8%)	0.01
Sepsis shock, n (%)	24 (36.9)	8 (22.2)	3 (28.6)	39 (27.9)	2 (18.2)	2 (66.7)	77 (29.4)	0.32

CRP, C-reactive protein; PLT platelet count; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count.

TABLE 2. C-reactive protein and procalcitonin levels in different cohorts according to blood culture results

Bacterial species	CRP (μg/mL)	P	PCT (ng/mL)	P
Acinetobacter (n = 5)	198 (30–262)	0.2	16.6 (0.37–132)	<0.0001
Escherichia (n = 13)	128 (11–128)		29.9 (1.14–180)	
Klebsiella (n = 21)	171 (15–278)		48.17 (0.9–188.3)	
Enterobacter (n = 20)	156.8 (20–230)		16.8 (0.1–94)	
Pseudomonas (n = 4)	198 (30–262)		16.6 (0.37–137)	
Enterococcus (n = 7)	63.3 (20–188)		0.26 (0.5–2.8)	
Staphylococcus (n = 24)	148.2 (37–288)		0.8 (0.77–8.8)	
Streptococcus (n = 2)	112.5 (13–212)		2.4 (0.3–4.5)	
Candida (n = 11)	135.4 (0.6–341)		2.9 (0.7–49.7)	
Corynebacterium (n = 3)	73.8 (1.4–128)		3.9 (0.6–18.7)	

CRP, C-reactive protein; PCT, procalcitonin.

were performed using the Cell-Dyn Sapphire (Abbott Diagnostics Division, Santa Clara, CA). Blood culture was performed using an automated system (BACTEC 9050; Becton-Dickinson, San Jose, CA). Positive blood cultures were examined following standard procedures. In cases where only 1 set of coagulase-negative staphylococcus was detected, the authors considered it to be contamination and judged the results as "negative."

Statistical Analysis

Variables distribution was analyzed by D'Agostino-Pearson's test. For variables with normal distribution, the authors calculate and reported mean and standard deviation. Variables without a normal distribution were expressed as median and ranges. Categorical variables were compared using the χ^2 test. The Kruskal–Wallis test was used to analyze the effect of a classification factor on ordinal data when the distribution of the sample was not normal. The diagnostic performance of PCT was evaluated using a receiver operating characteristic curve. The cutoff value of PCT to predict gram-negative bacteremia was selected considering the sum of the highest sensitivity and specificity. Logistic regression analysis was performed to determine the independent factors associated with the presence of gram-negative bacteremia. A value of $P < 0.05$ was considered

statistically significant. Statistical analysis was performed using SPSS for Windows (version 11.5; SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

A total of 280 patients with sepsis were selected for the analysis accounting for a total of 292 diagnostic episodes. Of these, 262 met the inclusion criteria (Figure 1). One hundred two episodes were from the intensive care unit, 137 were from internal medicine, 45 from infectious disease, 16 from gastro-enterology, 24 from respirology, 23 from neurology, 10 from immunology, 12 from nephrology and 7 from oncohematology.

BC detected 108 BSI caused by bacteria (65 gram-negative, 36 gram-positive, 7 mix-1, 11 *Candida* spp., 3 [mix-2] and 140 negative). Laboratory data and characteristics of all diagnostic episodes are shown in Table 1. In infections demonstrated by BC, a higher percentage was gram-negative BSI. PCT values are shown in Table 2. Considering BC results, a significantly higher PCT value was observed in gram-negative BSI (26.7 ng/mL, 0.09–188.3) than gram-positive BSI (0.84 ng/mL, 0.05–18.79) or in *Candida* spp. BSI (1.12 ng/mL, 0.07–49.68, $P < 0.001$) (Figure 2).

Independent Risk Factors Associated With Gram-Negative Bacteremia Among Patients With Sepsis

Univariate and multivariate logistic regression analyses were performed for the principal study sample to examine PCT, CRP, PLT and lactic acid levels and WBC count as potential independent predictors of gram-negative BSI. As described in Table 3, PCT and CRP were independent factors predicting gram-negative BSI among all episodes. However, among the subgroup with a positive BC result, PCT was the only predictor of gram-negative BSI even after adjustments (Table 4).

Performance of Procalcitonin Values in Predicting Gram-Negative Bloodstream Infection

Among all episodes, the area under the receiver operating characteristic curve (AUROC) of PCT to identify gram-negative bacteremia was 0.73 (95% confidence interval [CI], 0.66–0.81, $P < 0.001$). A cutoff value of 3.39 ng/mL for PCT showed a sensitivity of 80%, a specificity of 71%, a positive predictive value (PPV) of 35%, a negative predictive value (NPV) of 91% and a diagnostic accuracy of 0.60. For comparison, the AUROC of CRP to identify gram-negative bacteremia was 0.46 (95% CI, 0.46–0.67, $P = 0.31$) (Figure 3). However,
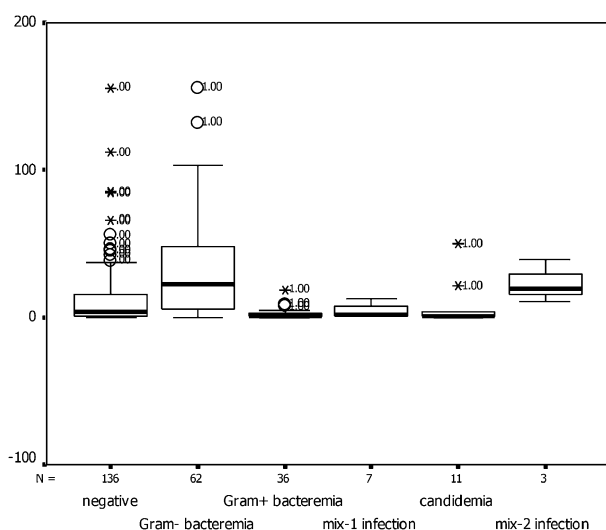

FIGURE 2. Box-plot distribution of procalcitonin values according to blood culture classification.

TABLE 3. Univariate and multivariate regression analysis of gram-negative BSI in all episodes

Variable	Crude OR, n (range)	*P*	Adjusted OR, n (range)	*P*
Age	1.0 (0.99–1.02)	0.32	1.0 (0.98–1.03)	0.62
Male sex	0.72 (0.38–1.35)	0.3	0.66 (0.31–1.39)	0.27
WBC	1.03 (0.99–1.06)	0.13	1.04 (0.99–1.08)	0.1
PLT	0.99 (0.99–1.00)	0.18	1.0 (0.99–1.0)	0.68
CRP	0.99 (0.99–1.0)	0.23	0.99 (0.99–1.0)	0.04
PCT	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Lactic acid	1.11 (0.99–1.24)	0.07	1.03 (0.91–1.16)	0.62

CRP, C-reactive protein; OR, odds ratio; PCT, procalcitonin; PLT, platelet count; WBC, white blood cell count.

among the 122 diagnostic episodes with positive BC results, a higher percentage of subsequent diagnostic episodes (53.3%) was encountered in gram-negative BSI ($P < 0.001$). Median of CRP and PCT in different cohorts and comparison of measured values are included in Table 2. Significantly, higher PCT levels were founds in patients with *Escherichia*, *Klebsiella* and *Acinetobacter* as determined by BC. *Candida*, *Enterococcus* and *Staphylococcus* were linked with mild PCT elevation. Moreover, among episodes with positive results of BC, the AUROC of PCT to identify gram-negative bacteremia was 0.81 (95% CI, 0.74–0.89, $P < 0.001$) (Figure 4). A cutoff value of 6.47 ng/mL for PCT showed a sensitivity of 74%, a specificity of 81%, a PPV of 82%, a NPV of 75% and a diagnostic accuracy of 0.79 (Table 3).

DISCUSSION

In this study, the authors assessed the relationship between PCT levels and the blood culture results in patients with sepsis. The results show that PCT and CRP levels independently predicted gram-negative BSI among sepsis episodes. However, PCT had a higher AUROC for predicting gram-negative bacteremia than did CRP. Furthermore, the authors identified a cutoff value for PCT with a high NPV (0.91) to rule out the presence of gram-negative bacterial species. The finding of a significantly higher PCT level in gram-negative BSI than in gram-positive BSI and fungal BSI is consistent with previous reports.[13,14] The high NPV of PCT for detection of gram-negative bacteria through BC may represent a useful tool to exclude the presence of gram-negative BSI and guide the empirical antimicrobial therapy regimens in critically ill patients; this has the advantage of reducing costs and optimizing treatment. Thus, measurement of PCT is a useful tool in differentiating *Candida* spp. and gram-positive BSI from gram-negative BSI.

In this study, gram-negative BSI was more prevalent in patients with positive BC results (gram-negative in 53% of cases and gram-positive in 29.5% of cases). Fungal infection was identified in only 5.7% of individuals. *Staphylococci* were identified as the most frequent causal pathogen, followed by *Klebsiella* and *Enterobacter*; this is consistent with prior observations. In general, *staphylococci* and gram-negative rods from the *Enterobacteriaceae* family are the most common causative agents of sepsis.[14,15] The highest PCT values were present in patients with *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas* spp. as determined using BC. In contrast, *Candida* spp., *Streptococcus* and *Enterococcus* were associated with mildly elevated PCT regardless of disease severity. This may be explained by the recognition of sepsis as a complex immune response to different pathogens. In vitro studies have clearly described the difference of gram-negative, gram-positive and fungal agents in the initiation of inflammatory cascades,[12,16] during which lipopolysaccharide patterns of gram-negative bacteria may activate neutrophils through the Toll-like receptor (TLR)-4, whereas lipoteichoic acid from gram-positive bacteria act through TLR-2.[16] TLR activation triggers inflammatory cascades leading to synthesis of proinflammatory cytokines and acute phase proteins.

Gram-negative infections probably increase tumor necrosis factor alpha production more than do gram-positive infections, and differences have also been found in plasma levels of interleukin (IL)-1, IL-6, IL-10 and IL-8.[16] That gram-negative bacteremia induces a greater inflammatory response than gram-positive bacteremia may help explain the higher PCT levels in gram-negative bacteremia. In addition, in BSI due to gram-negative and *Candida* spp., PCT was higher than that in BSI caused only by fungal or negative BSI but was lower than that in gram-negative bacteremia. This finding may be explained by the recognition of sepsis as a complex immune response to pathogens with an early hyperinflammatory response followed by an impaired immunity and anti-inflammatory phase. Due to this susceptibility, a secondary nosocomial infection such as *Candida* spp. infection may occur.[17] Thus, measuring PCT levels in the case of a mixed infection is important because a growing number of critically ill patients in immunoparalysis are prone to fungal infection and prompt administration of antifungal therapy is pivotal to reduce mortality.[9]

TABLE 4. Univariate and multivariate regression analysis of PCT for gram-negative bloodstream infection in episodes with positive blood culture results

Predictor (ng/mL)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
PCT (0–3)	0.10 (0.05–0.24)	<0.001	0.11 (0.05–0.27)	<0.001
PCT (3–6)	0.35 (0.09–1.41)	0.12	0.29 (0.07–1.24)	0.09
PCT (≥6)	10.9 (4.65–26.63)	<0.001	10.3 (10.3–24.7)	<0.001

CI, confidence interval; OR, odds ratio; PCT, procalcitonin.
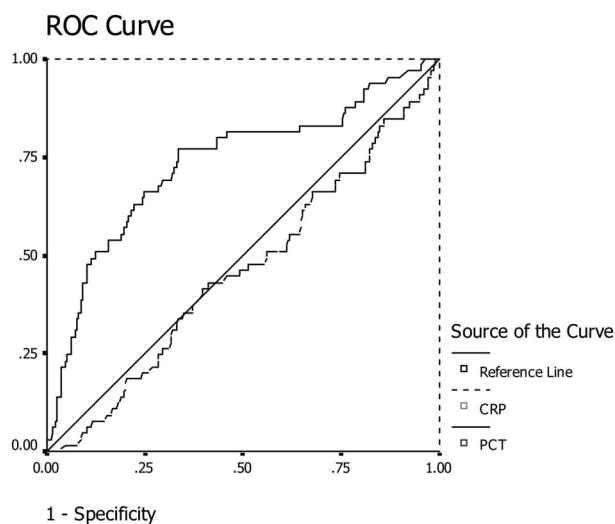
ROC Curve

FIGURE 3. Receiver operator characteristic curves (ROC) of procalcitonin (PCT) and C-reactive protein (CRP) for predicting gram-negative bacteremia confirmed by blood culture in all sepsis episodes.

BC reflects the current gold standard for detection of BSI. The practical value of BC in diagnosis of sepsis, however, is limited by the delayed results and because positive blood cultures are found in only approximately 30% of patients.[18,19] This study shows that PCT concentration, along with CRP, was a potential independent predictive factor of gram-negative BSI as identified using BC among all patients with sepsis. The AUROC for PCT was 0.73, which was significantly higher than that for CRP (0.46, *P* = 0.001). Sensitivity of 80% and
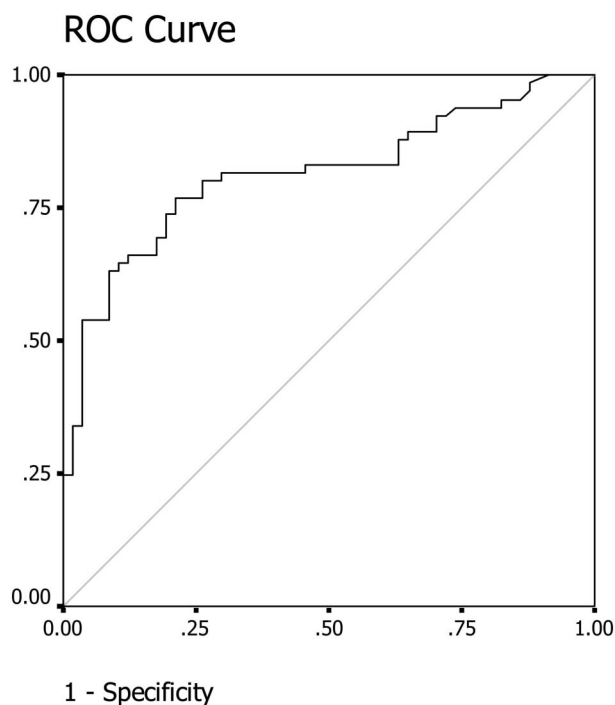
ROC Curve

FIGURE 4. Receiver operator characteristic curve (ROC) of procalcitonin for predicting gram-negative bacteremia confirmed by blood culture.

specificity of 71% were achieved with a PCT cutoff value of 3.39 ng/mL. Similar conclusions have been reported by Charles et al.[20] Moreover, according to the patients with positive BC results, the AUROC of PCT in diagnosis of gram-negative bacteremia was 0.81. A cutoff value of 6.47 ng/mL for PCT showed a sensitivity of 74%, a specificity of 81% and a PPV of 82%. For comparison, CRP levels did not significantly differ among patients with gram-negative bacterial septicemia, gram-positive bacteremia and fungal BSI. Hence, PCT levels could serve as a simple utility for confirmation or exclusion of gram-negative BSI in patients with sepsis. A significantly higher PCT level was a marker of gram-negative bacteremia. Thus, the authors could improve the diagnostic effect combine PCT with other markers such as WBC, CRP and IL-6.

Some limitations of this study need to be considered. First, this study is a retrospective design and had a low number of infections with *Candida* spp., reflecting the low prevalence of fungal BSI. Second, the patient populations in this study are selected, and the gram-negative bacteremia was twice as prevalent as in this study as gram-positive bacteremia, which may indicate some selection bias. It may originate from the characteristic epidemiology of pathogens causing BSI in the authors' general ICU with a high admission rate of surgical patients. This setting leads to the high prevalence of gram-negative pathogens in this population as responsible for BSI. However, previous studies found that gram-negative bacteria is the major pathogen in sepsis.[19] Another limitation is that the diagnostic performance of PCT was investigated only in conjunction with BC results and did not use other identification methods, such as real-time polymerase chain reaction (PCR), which may have increased the number of positive results.[21] However, the PCR technique as diagnostic tool for septicemia may preclude potential contamination with clinically insignificant pathogenic DNA.[22] Moreover, PCR-based molecular techniques require technical skills and equipment that may not readily be available.

In conclusion, a higher PCT level was found in patients with a gram-negative BSI than in those with gram-positive BSI. Thus, PCT may represent a useful tool for differentiating gram-positive from gram-negative BSI with a significantly higher PCT level indicating gram-negative bacteremia. Measurement of serum PCT may be adopted as a component of a diagnostic strategy to guide empirical antimicrobial therapy regimens in sepsis patients.

REFERENCES

1. **Vincent JL, Marshall J, Silva E, et al; EPIC II Group of Investigators.** International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323–9.

2. **Dillinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup.** Surviving sepsis campaign: international guideline for management of severe sepsis and sepsis shock, 2012. Crit Care Med 2013;41:580–637.

3. **Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators.** Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2009;34:344–53.

4. **Bone RC, Fisher CJ Jr, Clemmer TP, et al.** Sepsis syndrome: a valid clinical entity. Methylprednisolone severe sepsis study group. Crit Care Med 1989;17:389–93.

5. **Cunha BA.** Antibiotic selection in CCU. In: Cunha BA, editor. Infectious Disease in Critical Care Medicine, 2nd ed. New York: Informa Healthcare; 2007.

6. **Ambrose PG, Owens RC, Quintiliani R, et al.** Antibiotic use in the critical care unit. Crit Care Clin 1998;8:283–308.

7. **Thomas PL, Drusano G, Zasawski E, et al.** Vancomycin exposure in patients with methicillin-resistant staphylococcus aureus bloodstream how much is enough? Clin Infect Dis 2014;59:666–75.

8. **Christ-Grain M, Muller B.** Procalcitonin in bacterial infection—hype, hope, more or less? Swiss Med Wkly 2005;135:451–60.

9. **Wacker C, Prkno A, Brunkhorst FM, et al.** Procalcitonin as a diagnostic marker for sepsis: a system review and meta-analysis. Lancet Infect Dis 2013;12:70323–7.

10. **Balcl C, Sungurtekin H, Gurses E, et al.** Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. Crit Care 2003;23:85.

11. **Tang BM, Eslick GD, Graig JC, et al.** Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 2007;7:210–7.

12. **Konrad R, Michael B, Niels CR, et al.** New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev 2012;25:609–34.

13. **Bateman BT, Schmidt U, Berman MF, et al.** Temporal trends in the epidemiology of severe postoperative sepsis after elective surgery: a large, nationwide sample. Anesthesiology 2010;112:917–25.

14. **Brodska H, Malickova K, Adamkova V, et al.** Significantly higher procalcitonin levels could differentiate gram-negative sepsis from Gram-positive and fungal sepsis. Clin Exp Med 2013;3:165–70.

15. **Gao H, Evans TW, Finney SJ.** Bench-to bedside review: sepsis, severe sepsis and sepsis shock—does the nature of the infecting organism matter? Crit Care 2008;12:213–21.

16. **Marshall JC, Foster D, Vincent JL, et al; MEDIC Study.** Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J Infect Dis 2004;190:527–34.

17. **Cortegiani A, Russotto V, Montalto F, et al.** Procalcitonin as a marker of candida species detection by blood culture and polymerase chain reaction in septic patients. BMC Anesthesiol 2014;14:1–9.

18. **Boomer JS, To K, Chang KC, et al.** Immunosuppression in patients who died of sepsis and multiple organ failure. JAMA 2011;306:2594–603.

19. **Arai T, Kumasaka K, Nagata K, et al.** Prediction of blood culture results by measuring procalcitonin levels and other inflammatory biomarkers. Am J Emerg Med 2014;32:330–3.

20. **Charles PE, Ladoir S, Aho S, et al.** Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis 2008;8:38–42.

21. **Chang SS, Hsieh WH, Liu TS, et al.** Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis—a system review and meta-analysis. PLoS One 2013;8:E62323.

22. **Diekes C, Ehrenstein B, Siebig S, et al.** Clinical impact of commercially available multiple PCR system for rapid detection of pathogens in patients with presumed sepsis. BMC Infect Dis 2009;9:126–34.