Clinical Value of Procalcitonin for Patients With Suspected Bloodstream Infection

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Key Words: Procalcitonin; Blood culture; Bloodstream infection; Renal function; C-reactive protein

DOI: 10.1309/AJCP4GV7ZFDTANGC

ABSTRACT

Objectives: *Procalcitonin (PCT) might be a useful marker to exclude bacteremia or to predict the severity of bacteremia and its outcome. However, most previous studies of PCT were limited to particular patient populations. In addition, reports about PCT levels in patients with renal dysfunction have been conflicting. We investigated the predictive value of PCT in an unselected population with suspected bloodstream infections and also assessed the relationship between PCT and renal function.*

Methods: *We retrospectively analyzed medical records of 1,331 patients (age ≥18 years) with suspected bloodstream infections who had concurrent biochemical data and blood culture results.*

Results: *The PCT level was significantly elevated in patients with positive blood cultures, and it showed a significant relation with survival in patients with bacteremia. The optimal cutoff value of PCT for predicting a positive blood culture showed an increase as the estimated glomerular filtration rate declined.*

Conclusion: *PCT can be a useful marker to exclude bacteremia and also to predict severe bacteremia, but renal function should be taken into account.*

Bloodstream infections such as bacteremia and sepsis are potentially life-threatening and thus require early diagnosis and prompt administration of antibiotics to reduce mortality related to multiple organ failure.[1,2] Because conventional clinical and laboratory parameters, such as fever, pulse rate, WBC count, and C-reactive protein (CRP), often lack sufficient sensitivity and specificity,[3] it can be difficult to distinguish between bloodstream infections and other diseases.[4,5] Blood culture is a specific method for detecting bloodstream infections, but the result is only available after 24 to 48 hours.[6] Therefore, empiric antibiotic therapy for suspected bloodstream infection usually has to be given for several days before the culture results are obtained. A rapid and reliable test to confirm or exclude the existence of bloodstream infection would thus be very useful when deciding on the need for antibiotics, and it could also have a considerable impact on medical costs.[7]

In 1993, Assicot et al[8] first observed a marked increase of the circulating procalcitonin (PCT) level in patients with sepsis and other clinically significant bacterial infections. Recent studies have demonstrated that PCT is a useful marker for excluding sepsis in the emergency department (ED), and elevation of PCT is an early independent predictor of all-cause mortality in the intensive care unit (ICU).[2,4] Several studies have indicated that PCT might be useful for predicting the severity of illness, the risk of serious adverse events, and the outcome in patients with community-acquired pneumonia (CAP) or pancreatitis.[9-11] However, these studies were limited to particular patient populations (patients in the ED and ICU, or those with CAP or pancreatitis).[1,2,4,9-11]

In addition, it has been reported that renal function influences the circulating PCT level.[12,13] Dahaba et al[14] suggested that the normal value of PCT may be up to 1.5 ng/mL in patients with end-stage renal failure. Amour et al[13] also reported that renal function had a marked influence on PCT levels in both noninfected and infected patients. Although elevation of PCT has previously been described in patients with chronic kidney disease (CKD), data about PCT levels in patients with CKD are conflicting.[15-18] In fact, little is known about the pathways for elimination of PCT. Because these reports suggest that the PCT level indicating bloodstream infection might be influenced by renal function, the diagnostic value of PCT could vary in different patient populations.

However, PCT has not yet been studied in a large patient population. Accordingly, we investigated the usefulness of PCT as both a diagnostic and prognostic marker for bacteremia in a large number of patients with suspected bloodstream infection. We also assessed the relationship between PCT and renal function.

Materials and Methods

Study Population and Medical Records

We retrospectively analyzed the medical records of 1,331 patients (aged ≥18 years) with suspected bloodstream infections who had concurrent biochemical data and blood culture results. They were treated from July 2010 to June 2012 at Japanese Red Cross Nagoya Daiichi Hospital (Nagoya, Japan), which is one of the major referral hospitals in Nagoya city with more than 800 beds and 31 clinical departments. For each patient, the age, sex, results of blood culture, biochemical data, and survival were recorded.

Laboratory Tests

Blood samples were obtained from each patient to determine the plasma PCT level, serum CRP level, serum creatinine level, and WBC count. The estimated glomerular filtration rate (eGFR) was calculated using the following equation as recommended by the Japanese Society of Nephrology[19]:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Scr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739 \text{ (if female)}$$

Blood samples for biochemical tests and blood culture were collected at the same time. Plasma PCT was measured with a Cobas e411 electrochemiluminescence immunoassay (Roche Diagnostics Japan, Tokyo, Japan). The lower limit of detection for this assay was 0.02 ng/mL. The reportable range of this assay (analytic measurement range and clinical reportable range) is between 0.02 and 100 ng/mL. According to the manufacturer's data on within-run reproducibility at approximately 0.5 ng/mL, mean value and coefficient of variants were 0.55 ng/mL and 1.1%, respectively. All assays were performed at a single laboratory. A JCA-BM2250 analyzer (Japan Electron Optics , Tokyo) was used to measure serum CRP (N-assay LA CRP-S D-type, Nittobo Medical, Tokyo, Japan) and serum creatinine (Pureauto S CRE-N, Sekisui Medical, Tokyo). A Coulter LH750 counter (Beckman Coulter, Tokyo, Japan) was used to determine the WBC count.

Blood Culture

Blood culture bottles were incubated under aerobic and anaerobic conditions in an automated BacT/ALERT 3D system (SYSMEX bioMérieux, Tokyo, Japan) until a positive result was obtained or for up to 7 days. A significant positive blood culture was defined as previously reported.[3,4,20,21] Microorganisms from positive blood cultures were further identified using standard laboratory methods.[22] In brief, a small volume of the blood culture sample was inoculated onto sheep blood agar, chocolate agar, or MacConkey agar plates. Then the plates were incubated at 35°C overnight in a 5% carbon dioxide incubator except for the MacConkey agar plates, which were incubated in normal air without carbon dioxide. Isolates were assessed after 24 and 48 hours and were characterized on the basis of colony morphology and Gram staining. Microorganisms were further identified using manual methods or the MicroScan WalkAway system (Siemens Healthcare Diagnostics Japan, Tokyo). If a blood culture yielded organisms commonly considered as blood culture contaminants (eg, coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species, or *Propionibacterium acnes*), the culture was considered to have been contaminated as defined in previous literature.[3,4,20,21] The time until a blood culture became positive (time to positivity [TTP]) was defined as the interval between the start of incubation and detection of growth by the automated blood culture system.

To assess the diagnostic value of PCT for bacteremia, blood cultures were classified into three groups—positive, negative, and contaminated cultures. Positive blood cultures were divided into four categories according to the microorganisms identified: Gram-positive bacteria, Gram-negative bacteria, fungi, and multiple bacteria. Cultures with contamination

DOI: 10.1309/AJCP4GV7ZFDTANGC

were considered "negative" for the purpose of determining the usefulness of PCT for diagnosis of bacteremia.

Outcome Measures

Survival from the date when the blood culture was obtained was investigated from the medical records. This study attempted to identify the optimum PCT value for predicting bacteremia and estimating the survival of patients with bloodstream infection. The relationship between PCT and renal function was also analyzed.

Statistical Analysis

Diagnostic accuracy was assessed by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver operating characteristic (ROC) curves were drawn and the area under each ROC curve (AUC) was calculated to assess the diagnostic value of PCT, CRP, and WBC count for discriminating bacteremia (ie, positive blood culture) from nonbacteremia (ie, negative or contaminated blood culture). Differences of the AUC were analyzed with the DeLong test,[23] while the correlation between PCT and TTP was assessed with the Spearman rank test.

Follow-up information for at least 30 days was compiled for all patients. If a patient had more than one positive blood culture within 30 days, only the first was considered for survival analysis. If a patient was unavailable for follow-up during the 30-day observation period, he/she was censored at the last follow-up. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was used to evaluate survival differences between groups.

Continuous variables are expressed as the mean ± standard deviation or median (95% confidence interval), unless otherwise stated. For the graphic display of PCT and CRP levels, logarithmic transformation of the data was performed. Nonparametric comparisons between two groups were done with the Mann-Whitney *U* test. For multigroup comparisons, Kruskal-Wallis nonparametric analysis of variance was performed, and the Mann-Whitney *U* test with Bonferroni correction was used for post hoc comparisons. All tests were two-tailed, and $P < .05$ was considered to indicate statistical significance except for the Mann-Whitney *U* test with Bonferroni correction ($P < .01$). All statistical analyses were performed with StatView 4.5 software (Abacus Concepts, Berkeley, CA) or modified *R* software (The R Foundation for Statistical Computing, Perugia, Italy).

Results

Subjects

A total of 1,331 patients with 1,874 sets of biochemical and blood culture data were included in this study. The median age of the patients was 67.9 years (range, 18-102 years) and 59.7% were male. The majority of the 1,874 blood samples were obtained in the ED (48%), followed by the Departments of Nephrology (13%), Hematology (10%), Gastroenterology (7%), and Gastroenterological Surgery (5%).

Results of Blood Culture

There were 297 positive blood cultures (15.8%). Blood culture detected Gram-positive bacteria, Gram-negative bacteria, fungi, and multiple bacteria in 81, 122, 13, and 16 cultures, respectively, and 65 culture samples were contaminated **Table 1**.

Comparison of Biochemical Data

The PCT, CRP, and WBC count of each group classified by the microorganisms identified are shown in **Figure 1** and **Table 2**. Compared with patients who had negative cultures, PCT was significantly elevated in patients whose blood cultures were positive for Gram-positive or Gram-negative bacteria, fungi, and multiple bacteria but not in patients with contaminated cultures. In addition, CRP was significantly higher in patients with Gram-positive and Gram-negative bacteria than in patients with a negative blood culture. However, the WBC count showed no significant difference among the groups.

Among 231 patients with positive blood cultures, PCT was significantly correlated with TTP ($R = -0.21$, $P < .001$, Spearman rank correlation) **Figure 2**. In contrast, there was no significant correlation between CRP or WBC count and TTP (data not shown).

Table 1
Microorganisms Isolated From Blood Culture

Microorganism	No. (%) of Isolates
Gram-positive bacteria	81 (27.3)
Staphylococcus aureus	35
Streptococcus pneumoniae	9
Streptococcus anginosus group	9
Streptococcus equisimilis	7
Enterococcus species	5
Other Gram-positive bacteria	16
Gram-negative bacteria	122 (41.1)
Escherichia coli	65
Klebsiella species	27
Pseudomonas aeruginosa	9
Gram-negative anaerobic bacteria	6
Other Gram-negative bacteria	15
Fungi	13 (4.4)
Candida albicans	7
Other yeast and fungi	6
Multiple bacteria	16 (5.4)
Contaminant bacteria	65 (21.9)
Coagulase-negative staphylococci	43
Bacillus species	16
Other contaminant bacteria	6

DOI: 10.1309/AJCP4GV7ZFDTANGC

Diagnostic Accuracy for Positive Blood Culture

The diagnostic accuracy of PCT, CRP, and WBC count for a positive blood culture is presented in **Table 3**. ROC curves of PCT, CRP, and WBC count for discriminating positive blood cultures are shown in **Figure 3**. The AUC for PCT was 0.753, and the optimal cutoff value of PCT for predicting a positive blood culture was 0.9 ng/mL. Using this cutoff value, the sensitivity, specificity, PPV, and NPV were

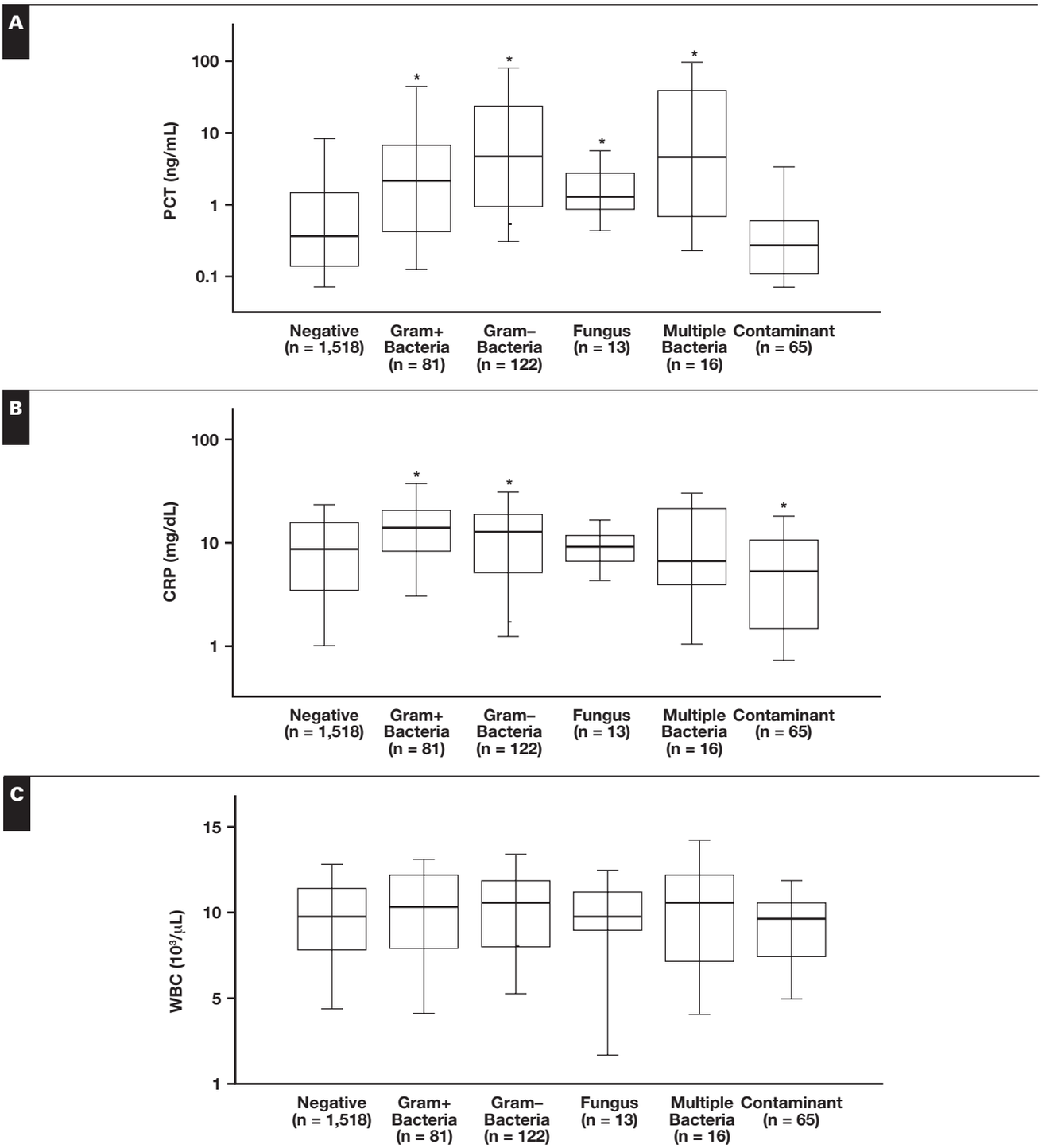


Figure 1 Procalcitonin (PCT) (**A**), C-reactive protein (CRP) (**B**), and WBC count (**C**) in patients stratified by blood culture results. Boxes represent the 25th to 75th percentiles, with horizontal lines and whiskers indicating the median value and range, respectively. *$P < .01$ vs negative.

DOI: 10.1309/AJCP4GV7ZFDTANGC

71.9%, 69.1%, 24.5%, and 94.6%, respectively. The best cutoff value for CRP was 12.5 mg/dL, at which it showed a sensitivity, specificity, PPV, NPV, and AUC of 66.1%, 50.4%, 17.6%, 90.3%, and 0.601, respectively. For the WBC count, the cutoff value was 12,000/μL (12.0 ×10^9/L), at which the sensitivity, specificity, PPV, NPV, and AUC was 67.4%, 46.3%, 16.9%, 90.0%, and 0.559, respectively. The AUC for PCT was significantly larger than that for CRP ($P < .001$) or the WBC count ($P < .001$). The sensitivity, specificity, PPV, and NPV of PCT for predicting a positive blood culture were all higher than those of CRP and the WBC count.

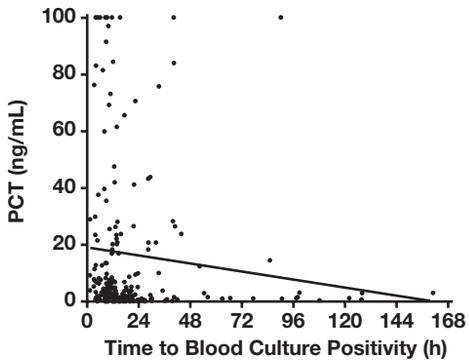


Figure 2 Correlation between procalcitonin (PCT) and the time to positivity (TTP) of blood cultures.

Prognostic Value of PCT in Patients With Positive Blood Cultures

Figure 4 shows the survival curves of patients with positive blood cultures stratified into three groups according to the PCT level. Patients with a high PCT level had a significantly lower survival rate than those with a low PCT level. The survival of patients in the lowest PCT tertile (<0.5 ng/mL) was significantly better than that of patients with a PCT

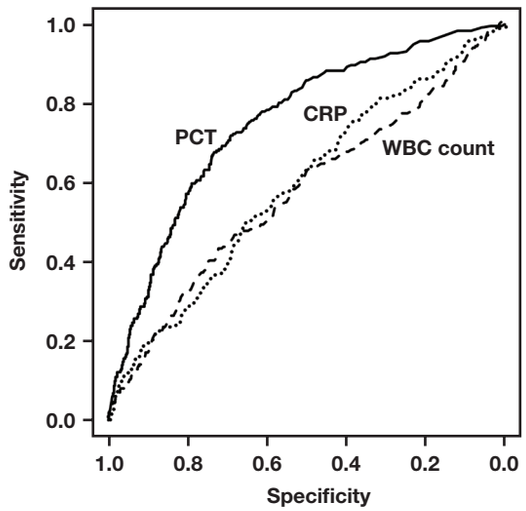


Figure 3 Receiver operating characteristic curves for procalcitonin (PCT), C-reactive protein (CRP), and WBC count as predictors of a positive blood culture.

Table 2
Comparison of Blood Biochemical Data of 1,874 Tests According to Blood Culture Results[a]

		Positive Blood Culture Results				
Biochemical Variable	**Negative Blood Culture Results (n = 1,578)**	**Gram+ Bacteria (n = 81)**	**Gram– Bacteria (n = 122)**	**Fungi (n = 13)**	**Multiple Bacteria (n = 16)**	**Contaminant (n = 65)**
PCT (ng/mL)	0.36 (0.32-0.40)	2.17 (1.30-3.35)[b]	4.59 (3.12-7.23)[b]	1.29 (0.87-2.64)[b]	5.21 (0.73-35.27)[b]	0.28 (0.19-0.41)
CRP (mg/dL)	8.4 (7.9-9.0)	14.0 (10.8-16.2)[b]	12.6 (8.6-13.5)[b]	9.2 (6.5-11.1)	6.6 (4.4-18.6)	5.1 (3.0-8.4)[b]
WBC (×10^3/μL [×10^9/L])	9.5 (9.1-9.8)	10.7 (9.6-12.8)	11.4 (9.9-12.9)	9.7 (8.3-12.8)	11.4 (5.2-15.4)	9.2 (7.4-10.5)

CRP, C-reactive protein; Gram +, Gram-positive bacteria; Gram –, Gram-negative bacteria; PCT, procalcitonin.
[a] Data are shown as median (95% confidence interval).
[b] $P < .01$ vs negative.

Table 3
Diagnostic Value for Positive Blood Culture of PCT, CRP, and WBC Count

Variable	PCT	CRP	WBC Count
Optimal cutoff value	0.9 ng/mL	12.5 mg/dL	12,000/μL (12.0 ×10^9/L)
Sensitivity (%)	71.9	66.1	67.4
Specificity (%)	69.1	50.4	46.3
Positive predictive value (%)	24.5	17.6	16.9
Negative predictive value (%)	94.6	90.3	90
Area under the ROC curve (95% confidence interval)	0.753 (0.720-0.786)	0.601 (0.562-0.641)	0.559 (0.517-0.601)

CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operating characteristic.

DOI: 10.1309/AJCP4GV7ZFDTANGC

level between 0.5 ng/mL and 2.0 ng/mL (P = .039) or those with a PCT level higher than 2.0 ng/mL (P = .003).

Influence of Renal Function on PCT

The correlation between PCT and eGFR in the 1,874 blood samples is shown in **Figure 5**. The PCT level was found to show a significant correlation with eGFR (R = –0.44, P < .001, Spearman rank correlation). Therefore, the cutoff value of PCT for predicting a positive blood culture was analyzed in relation to eGFR **Table 4**. The optimal cutoff value of PCT for predicting a positive blood culture increased along with the deterioration of renal function, with values of 0.37, 1.06, and 2.50 ng/mL for patients with an eGFR of 60 mL/min/1.73 m^2 or more, 30 to less than 60 mL/min/1.73 m^2, and less than 30 mL/min/1.73 m^2, respectively. The sensitivity of the adjusted PCT values for predicting a positive blood culture was higher than the sensitivity of the unadjusted PCT value for all patients (Tables 3 and 4).

Figure 6 shows survival curves stratified according to PCT for patients with a positive blood culture and normal renal function (eGFR ≥60 mL/min/1.73 m^2) or impaired renal function (eGFR <60 mL/min/1.73 m^2). The PCT values at which the survival difference was maximal were 1.3 and 4.0 ng/mL for patients with normal and impaired renal function, respectively. Patients with higher PCT

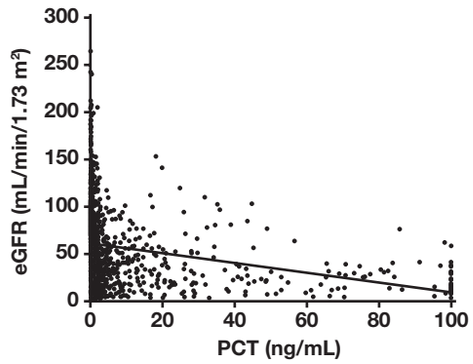
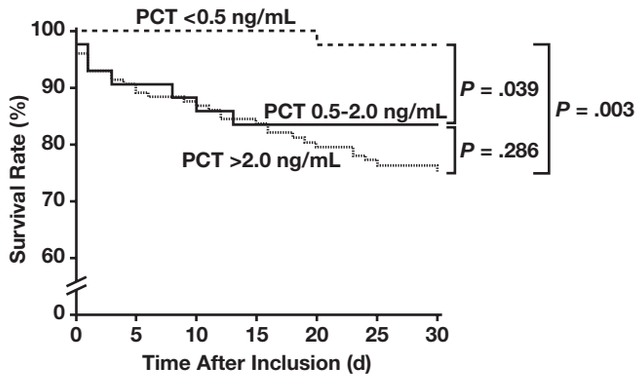


Figure 5 Correlation between procalcitonin (PCT) and estimated glomerular filtration rate (eGFR).



No. at risk							
PCT <0.5 ng/mL	46	46	44	44	44	43	43
PCT 0.5-2.0 ng/mL	43	39	37	35	35	35	35
PCT >2.0 ng/mL	130	116	112	106	100	93	92

Figure 4 Kaplan-Meier survival curves for patients with positive blood cultures stratified according to the procalcitonin (PCT) level.

Table 4
PCT for Predicting Positive Blood Culture According to Renal Function

	eGFR (mL/min/1.73 m^2)		
Variable	**≥60 (n = 836)**	**30-<60 (n = 481)**	**<30 (n = 497)**
Mean ± SD PCT (ng/mL)	1.7 ± 6.8	6.6 ± 17.5	12.6 ± 25.9
Optimal cutoff value	0.37	1.06	2.50
Sensitivity	77.5	81.7	72.2
Specificity	62.8	65.3	68.5
Positive predictive value	19.6	32.2	28.4
Negative predictive value	96.0	94.6	93.4
Area under the ROC curve (95% confidence interval)	0.733 (0.676-0.791)	0.768 (0.713-0.822)	0.746 (0.686-0.806)

eGFR, estimated glomerular filtration rate; PCT, procalcitonin; ROC, receiver operating characteristic; SD, standard deviation.

DOI: 10.1309/AJCP4GV7ZFDTANGC

values (≥1.3 ng/mL or ≥4.0 ng/mL) showed worse survival than those with lower PCT values in both the normal and impaired renal function groups.

Discussion

To our knowledge, this is the largest study so far to examine the clinical usefulness of PCT in an unselected patient population with suspected bloodstream infection managed at a single institution. We found that the PCT level was significantly higher in patients with a positive blood culture and that it was more useful for predicting bloodstream infection than CRP or WBC count. In addition, PCT was significantly correlated with TTP and survival in patients with positive blood cultures. Furthermore, PCT was significantly correlated with eGFR, and the optimum cutoff value of PCT for predicting a positive blood culture increased along with the deterioration of renal function.

Early assessment of bacteremia generally relies on a combination of clinical examination and laboratory tests, such as CRP and WBC. However, these parameters lack sufficient accuracy for early diagnosis of bacteremia[24]; there may not be an increase during the acute phase, or sometimes the increase may occur after the infection has already been controlled or even in the absence of infection.[2] We found that PCT was better at discriminating bloodstream infections than CRP or WBC count. In addition, PCT did not increase in patients with contaminated blood cultures, although our definition of contaminated blood culture may be controversial. Blood samples for culture are often collected under suboptimal conditions, resulting in frequent contamination by common skin flora.[25] For distinguishing contamination from true bloodstream infections, PCT was superior to both CRP and WBC count. Many studies have been performed to determine the cutoff value of PCT for predicting a positive blood culture, but the results have varied. Lorrot et al[26] reported a value of 2 ng/mL, while Ugarte et al[27] concluded that the best cutoff value was 0.6 ng/mL for adult patients in the ICU. In our study, when the cutoff value was less than 0.9 ng/mL, PCT showed a PPV of 24.5% and an NPV of 94.6% for positive blood cultures. Therefore, we propose that

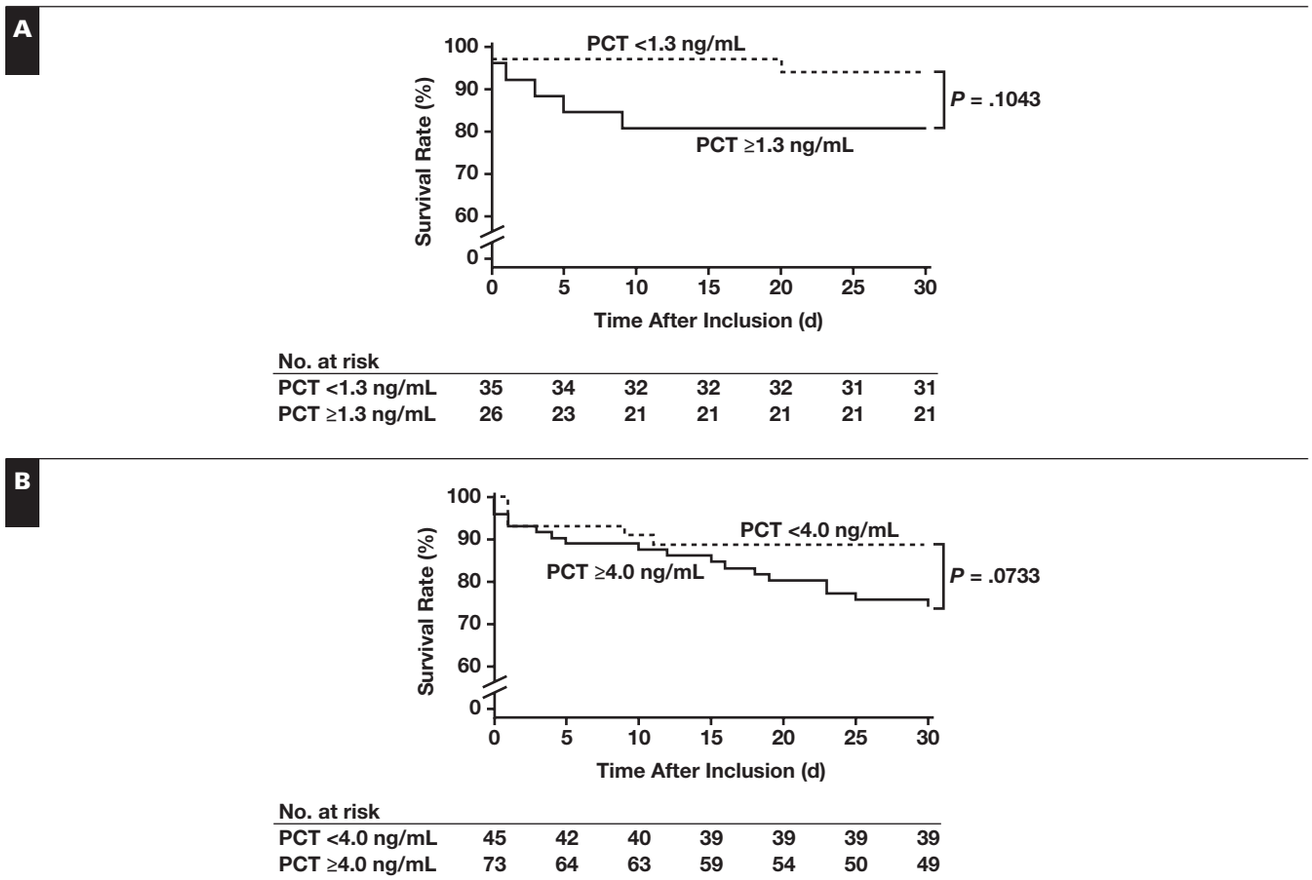


Figure 6 Kaplan-Meier survival curves for patients with positive blood cultures and normal (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2, **A**) or impaired (eGFR <60 mL/min/1.73 m^2, **B**) renal function.

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a PCT level lower than 0.9 ng/mL can be used as a marker to detect or exclude bacteremia in unselected adult patients with suspected bloodstream infection. However, PCT should be used in combination with clinical signs and other parameters because the NPV in our study was less than 100%.

Several studies have shown that a short TTP is associated with a significantly higher mortality rate in patients with *Staphylococcus aureus* bloodstream infection.[28,29] In the present study, PCT and TTP were significantly correlated, suggesting that PCT can be a prognostic factor for bacteremia. Some authors have provided convincing evidence that PCT is useful not only for detecting bacteremia but also for evaluating severity (predicting mortality) in patients with pneumonia.[9,10,30] Jensen et al[2] found that a high maximum PCT level and the daily changes of PCT were independent predictors of 90-day mortality in patients in the ICU. The CAPNETZ study reported a high prognostic value of PCT for predicting mortality in patients with CAP.[9] In contrast, the GenIMS cohort study only found moderate additional value of PCT compared with the pneumonia severity index and the CURB-65 score.[30] To the best of our knowledge, however, no previous study has reported the prognostic value of PCT for bacteremia in an unselected patient population from a single institution. Our results demonstrated that PCT was significantly correlated with the survival of patients who had positive blood cultures. Measurement of PCT can help physicians to safely withhold antibiotics in patients with suspected bloodstream infection or identify high-risk patients, which could have a major impact on clinical practice.[31] Because the assay time for PCT is only about 20 minutes,[32] its measurement may aid decision making, particularly in the ED.

Little is known about the elimination pathways of PCT, but renal function appears to influence the PCT level.[12] Our study revealed that the PCT level was significantly correlated with renal function, which is consistent with findings of a previous report.[13] The cause of PCT elevation in patients with renal dysfunction could be its impaired renal or hepatic elimination or increased production. Peripheral blood mononuclear cells release more PCT in patients with impaired renal function and those receiving renal replacement therapy.[33] In addition, patients with severe renal dysfunction often show evidence of a systemic inflammatory response, which leads to PCT production.[12] In the present study, the optimum cutoff value of PCT for predicting a positive blood culture increased in parallel with the decrease in eGFR. The sensitivity of PCT for predicting positive blood cultures was higher after adjusting for renal function than when the PCT value was calculated for all patients. Thus, renal function should be taken into account when using PCT to estimate the risk of bloodstream infection. In addition, the prognostic value of PCT for bacteremia differed between patients with normal and impaired renal function. The PCT level that predicts a positive blood culture or severe bacteremia seems to be higher in patients with renal dysfunction.

This study had some limitations. First, the administration of antibiotics before blood collection for culture was not investigated. Some patients might have received antibiotics, leading to negative blood culture results associated with high PCT levels, which would reduce the PPV of PCT for predicting positive blood cultures. Schuetz et al[34] reported that restricting the analysis to patients without antibiotic pretreatment did not significantly improve the prognostic performance of PCT. Second, the causes of death were not fully investigated. Some patients might have had terminal malignancy or major surgical complications, such as liver failure after hepatectomy, and the cause of death might not have been bacteremia in such patients. To assess the value of PCT for predicting severe bacteremia, it might be acceptable to consider sepsis-related mortality. However, several large clinical studies on PCT adopted all-cause mortality as a primary outcome.[9,10,35] Despite these limitations, the results of our study can be applied to various situations and patient populations because this study was conducted in a relatively large number of patients.

In conclusion, PCT is not only a useful marker to rule out bacteremia but also can predict severe bacteremia. Because PCT is significantly correlated with eGFR, renal function should be taken into account when using this parameter clinically.

This research was presented in part at the 59th National Congress of the Japanese Society of Laboratory Medicine; November 29 to December 2, 2012; Kyoto, Japan.

This work was supported in part by a grant-in-aid from the Policy-Based Medical Service Foundation.

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References

1. Nakamura A, Wada H, Ikejiri M, et al. Efficacy of procalcitonin in the early diagnosis of bacterial infections in a critical care unit. *Shock*. 2009;31:586-591.
2. Jensen JU, Heslet L, Jensen TH, et al. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med*. 2006;34:2596-2602.
3. Liaudat S, Dayer E, Praz G, et al. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. *Eur J Clin Microbiol Infect Dis*. 2001;20:524-527.
4. Riedel S, Melendez JH, An AT, et al. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol*. 2011;135:182-189.
5. Jaimes F, Arango C, Ruiz G, et al. Predicting bacteremia at the bedside. *Clin Infect Dis*. 2004;38:357-362.

DOI: 10.1309/AJCP4GV7ZFDTANGC

6. Christ-Crain M, Muller B. Procalcitonin in bacterial infections—hype, hope, more or less? *Swiss Med Wkly*. 2005;135:451-460.
7. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004;363:600-607.
8. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341:515-518.
9. Kruger S, Ewig S, Marre R, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J*. 2008;31:349-355.
10. Schuetz P, Suter-Widmer I, Chaudri A, et al. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J*. 2011;37:384-392.
11. Mofidi R, Suttie SA, Patil PV, et al. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. *Surgery*. 2009;146:72-81.
12. Meisner M, Lohs T, Huettemann E, et al. The plasma elimination rate and urinary secretion of procalcitonin in patients with normal and impaired renal function. *Eur J Anaesthesiol*. 2001;18:79-87.
13. Amour J, Birenbaum A, Langeron O, et al. Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery. *Crit Care Med*. 2008;36:1147-1154.
14. Dahaba AA, Rehak PH, List WF. Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. *Intensive Care Med*. 2003;29:579-583.
15. Sitter T, Schmidt M, Schneider S, et al. Differential diagnosis of bacterial infection and inflammatory response in kidney diseases using procalcitonin. *J Nephrol*. 2002;15:297-301.
16. Steinbach G, Bolke E, Grunert A, et al. Procalcitonin in patients with acute and chronic renal insufficiency. *Wien Klin Wochenschr*. 2004;116:849-853.
17. Ozturk R, Yilmaz GR, Bulut C, et al. Assessment of procalcitonin and other inflammatory markers in peritoneal dialysis-related peritonitis. *Turk J Med Sci*. 2010;40:199-206.
18. Lu XL, Xiao ZH, Yang MY, et al. Diagnostic value of serum procalcitonin in patients with chronic renal insufficiency: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2013;28:122-129.
19. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982-992.
20. Chirouze C, Schuhmacher H, Rabaud C, et al. Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. *Clin Infect Dis*. 2002;35:156-161.
21. Richter SS, Beekmann SE, Croco JL, et al. Minimizing the workup of blood culture contaminants: implementation and evaluation of a laboratory-based algorithm. *J Clin Microbiol*. 2002;40:2437-2444.
22. Jeong S, Park Y, Cho Y, et al. Diagnostic utilities of procalcitonin and C-reactive protein for the prediction of bacteremia determined by blood culture. *Clin Chim Acta*. 2012;413:1731-1736.
23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837-845.
24. Bates DW, Sands K, Miller E, et al, for the Academic Medical Center Consortium Sepsis Project Working Group. Predicting bacteremia in patients with sepsis syndrome. *J Infect Dis*. 1997;176:1538-1551.
25. Gander RM, Byrd L, DeCrescenzo M, et al. Impact of blood cultures drawn by phlebotomy on contamination rates and health care costs in a hospital emergency department. *J Clin Microbiol*. 2009;47:1021-1024.
26. Lorrot M, Moulin F, Coste J, et al. Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections. *Presse Med*. 2000;29:128-134.
27. Ugarte H, Silva E, Mercan D, et al. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med*. 1999;27:498-504.
28. Marra AR, Edmond MB, Forbes BA, et al. Time to blood culture positivity as a predictor of clinical outcome of *Staphylococcus aureus* bloodstream infection. *J Clin Microbiol*. 2006;44:1342-1346.
29. Sowden D, Anstey C, Faddy M. Blood culture time to positivity as a predictor of mortality in community acquired methicillin-susceptible *Staphylococcus aureus* bacteremia. *J Infect*. 2008;56:295-296.
30. Huang DT, Weissfeld LA, Kellum JA, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med*. 2008;52:48-58.e42.
31. Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. *JAMA*. 1995;273:117-123.
32. Meisner M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta*. 2002;323:17-29.
33. Herget-Rosenthal S, Klein T, Marggraf G, et al. Modulation and source of procalcitonin in reduced renal function and renal replacement therapy. *Scand J Immunol*. 2005;61:180-186.
34. Schuetz P, Zimmerli, W, Mueller, B. Another view on the prediction of outcomes in patients with community-acquired pneumonia. *Eur Respir J*. 2011;38:992-993.
35. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463-474.

DOI: 10.1309/AJCP4GV7ZFDTANGC

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