〈Regular Article〉

The diagnostic accuracy of biomarkers for the prediction of bacteremia in patients with suspected infection: a prospective observational study

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ABSTRACT Rapid recognition of bacteremia is important for critical care, especially in patients with suspected bloodstream infections. Procalcitonin and presepsin are widely used biomarkers in point-of care medical testing for identifying infectious diseases and sepsis; however, the diagnostic accuracy for the prediction of bacteremia is not well established. Therefore, this study aimed to evaluate the diagnostic accuracy of procalcitonin and presepsin for the prediction of bacteremia in patients with suspected bacteremia. We performed a prospective observational study at our hospital. A total of 210 patients (307 samples) who had been admitted from December 2014 through September 2016 with a suspected infection were included. Presepsin and procalcitonin were tested simultaneously with blood cultures and routine laboratory tests. One hundred and four blood samples were obtained at the emergency room (ER). Others were obtained during hospital admission. Blood cultures were positive in 34 samples; 25 samples were obtained in the ER. Presepsin and procalcitonin levels were significantly higher in patients with positive blood cultures than in those with negative blood cultures (1028.5 pg/mL vs. 485.0 pg/mL, $P < 0.001$ and 4.53 ng/mL vs. 0.33 ng/mL, $P < 0.001$, respectively). For predicting bacteremia, receiver operating characteristic curve analysis for presepsin showed an area under the curve (AUC) of 0.718 and negative predictive value (NPV) of 95%. The analysis for procalcitonin showed an AUC of 0.778 and NPV of 94.8%. C-reactive protein tests and the quick Sequential Organ Failure Assessment score in the ER failed to be useful tools for predicting bacteremia. Based on our results, procalcitonin and presepsin showed good diagnostic accuracy and NPV for predicting bacteremia among patients with suspected infection. Therefore, these biomarkers may be useful for ruling out bacteremia in patients with suspected infection.

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Key words：Bacteremia, Procalcitonin, Presepsin, Early diagnosis, Diagnostic test

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INTRODUCTION

In 1914, Budelmann[1] defined sepsis as septicemia, a disease resulting from the infiltration of microorganisms into the bloodstream. Subsequent medical advances have resulted in significant changes to this definition, and the 2012 Surviving Sepsis Campaign Guidelines described this condition as "probable (documented or suspected) infection and signs of systemic inflammation"[2]. In February 2016, the new Sepsis-3 definition resulted in the disease being limited to patients with severe sepsis[3]. As proposed by Budelmann[1], the infiltration of a microorganism into the bloodstream is now termed bacteremia and is no longer a prerequisite for diagnosing sepsis due to the poor sensitivity of blood culture[3]. However, some serious infectious diseases, such as primary bacteremia, infective endocarditis, or catheter-related blood stream infections, are difficult to diagnose with only physical examinations; these are all diagnosed with a positive blood culture. Patients with such underlying conditions may benefit from early diagnosis of bacteremia. Additionally, it has been reported that in ICU patients, bacteremia is a risk factor for increased mortality and prolonged ICU stay[4]. In this setting, rapid diagnosis of not only sepsis but also bacteremia is important. However, several days are needed to obtain the blood culture result.

Some novel technologies including DNA analysis may be used to help predict blood culture results[5]. However, DNA analysis is expensive and complicated; therefore, it is difficult to implement it in a clinical setting.

Biomarkers such as C-reactive protein (CRP), presepsin (PSEP), and procalcitonin (PCT) are available in clinical settings for speedy and easy point-of-care testing. Specifically, PCT is a widely recognized biomarker of sepsis[3].

PSEP (a subtype of soluble CD14) is a glycoprotein with a molecular weight of approximately 13 kDa. High PSEP blood levels are thought to be observed in sepsis patients. PSEP is thought to appear in the blood when stimulation by an infection leads to shedding of CD14 from the cell membrane[6].

PSEP levels rise 12 hours to several days earlier than PCT levels, and it has been reported in burn patients[7]. The ability of PCT to predict blood culture positivity has been examined in some specific disease such as febrile neutropenia[8–10]. However, few studies have been conducted on the diagnostic ability of PSEP for bacteremia. Therefore, this study aimed to determine the ability of two promising biomarkers, namely PSEP and PCT, to predict bacteremia in patients suspected of having bacteremia.

SUBJECTS AND METHODS

Inclusion and exclusion criteria

Our study comprised patients who had been hospitalized in the Advanced Critical Care Center at Kawasaki Medical School Hospital in Okayama, Japan, from December 2014 through September 2016 and had been performed blood cultures due to suspected bacteremia upon admission or during hospitalization. Only patients who had a negative follow-up blood culture were excluded. This study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Kawasaki Medical School (approval no: 1926-2). At the time of admission, all patients were provided with an advanced explanation regarding this study; written consent was obtained from each patient.

Study design and data collection

Blood culture samples obtained from patients with suspected bacteremia in the ER, intensive care unit, or ward were included in this single-center, prospective, observational study. Each sample was included in our study from a single time-point or

independent episode. Patients who had multiple independent episodes of suspected bacteremia were separately enrolled. Whether a blood culture examination should be conducted for each patient depended on the clinical decision of the attending physician. Therefore, this study protocol had no effect on the decision regarding whether to perform a blood culture. In addition to general blood test including white blood cell count assessment, patient characteristics, diagnosis of admission, vital signs, suspected site of infection and biomarkers (CRP, PSEP, and PCT) were measured at the same time the blood culture was performed. Medical care was provided as normal, based upon the judgment of each patient's attending physician. The primary outcome of this study was to evaluate the diagnostic accuracy of biomarkers (PSEP and PCT) for bacteremia at the time of clinical physician suspected bacteremia. In addition, we assessed the outcomes associated with the blood culture.

Blood Culture

Ethanol containing 1% chlorhexidine gluconate was generally used for routine disinfection. A solution containing 10% povidone iodine was used as an alternative when the routine disinfectant was contraindicated. For all patients, two sets of blood samples were collected from different sites (for each set, a ≥ 16 mL blood sample was dispensed into an aerobic and anaerobic bottle) and submitted for blood culture testing. We used BD ™ Bactec ™ Media: Plus Aerobic/F blood culture bottles (Nippon Becton Dickinson Company, Ltd., Tokyo, Japan). Results were assessed after culturing the samples for 7 days. Among the positive blood culture results, those deemed clearly contaminated, based on culture results and the patient's clinical course, were excluded.

Psep

Point-of-care PSEP measurement was performed using a PATHFAST immunoanalyzer (LSI Medience Corporation, Tokyo, Japan) immediately after whole blood (collected along with the blood culture testing) was collected in an EDTA blood collection tube. The assay detects PSEP levels of 20-20,000 pg/mL, with a cut off value of 500 ng/L for sepsis diagnosis. Hematocrit correction was performed for all samples.

Pct

Serum PCT was measured using an electrochemiluminescence immunoassay (SRL, Inc, Tokyo, Japan). The lower limit of measurement was 0.02 ng/mL, and the normal range was < 0.05 ng/mL. The threshold for diagnosing bacterial sepsis was ≥ 0.5 ng/mL.

Statistical Analysis

Sample size was calculated to achieve a power of $1-\beta$ of 0.90, area under the curve (AUC) of 0.70, α value of 0.05, and kappa (blood culture negative/blood culture positive) coefficient of 9. Under these assumptions, the sample size was estimated at 232. Because the primary outcome of this study was the diagnostic accuracy of biomarkers for bacteremia from blood culture samples, which is not affected by clinical characteristics of patients, we analyzed each sample from each event as independent data. Results are presented as actual values for categories and as percentages and medians (first quartile to third quartile). All results were divided into two groups: blood culture-positive and blood culture-negative groups. False-positive blood culture results were judged according to the clinical course and detected pathogen, and the data were added to the blood culture-negative group. When performing an inter-group analysis, the Mann-Whitney U-test (two-tailed) was used for non-normally distributed data. When investigating ratios, Pearson's chi-squared test or Fisher's exact test was used. Missing values were left as they were without imputation. Receiver

Table 1. Patient characteristics

Patients (n = 210)		Laboratory data, median (IQR)	
Age (years) at admission, median (IQR)	70.5 (50-80)	White blood cell count (/ μL)	10,940 (8,110–13,920)
Sex, n (male %)	134 (63.8)	Hematocrit (%)	31.05 (27.3–37.1)
Consecutive samples (n = 307)		Creatinine (mg/dL)	0.66 (0.48–1.10)
Age (years) at admission, median (IQR)	71 (50–80)	C-reactive protein (mg/dL)	8.83 (4.26–15.95)
Sex, n (male %)	204 (67.1)	Suspected site of infection, n (%)	
Diagnosis on admission, n (%)		Lung	126 (41.4)
Trauma	176 (57.3)	Abdomen	19 (6.3)
Infectious disease	83 (27.0)	Urinary tract	42 (13.8)
Others	48 (15.6)	Blood infection/endocardium/catheter/implant device	11 (3.6)
Obtained in the ER, n (%)	104 (33.9)	Central nerve	10 (3.3)
qSOFA score, n		Osteoarticular	6 (2.0)
0	18	Skin	29 (9.5)
1	41	Wound	37 (12.2)
2	38	Other	27 (8.9)
3	7		
Vital signs, median (IQR)			
Body temperature (degree Celsius)	38.5 (34.4–39.0)		
Heart rate (beats/min)	96 (80–110)		
Systolic blood pressure (mmHg)	128 (109–149)		
Respiratory rate (breaths /min)	21 (17–27)		

IQR, interquartile range; ER, emergency room; qSOFA, quick Sequential Organ Failure Assessment

operating characteristic (ROC) curve analysis was used to test diagnostic capability, and Youden's index was used to determine associated cut-off values. We also calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the determined cut-off values. Statistical analysis was performed using SPSS statistical package 25.0 (IBM), and a P-value < 0.05 was considered statistically significant.

RESULTS

Blood cultures were performed for 210 patients upon admission or while hospitalized during the study period (median age, 70.5 years; interquartile range [IQR], 50-80; males, 134; females, 76). A total of 153 patients had undergone sample collection for blood culture multiple times for completely unrelated episodes. Therefore, we investigated 307 consecutive samples. The most common source of infection suspected during blood culture collection was pneumonia (126 samples), followed by urinary tract infection (42 samples) and wound infection (37 samples) (Table 1).

Table 2 shows the clinical data for blood culture-positive and blood culture-negative groups in comparison with the expected infection sources. There were 35 blood-culture positive specimens; 25 were obtained during outpatient care at the ER. Only 1 sample obtained during admission was determined to be a false positive (0.3%) because of the detected pathogen (Bacillus species) and the patient's clinical course. Therefore, it was included in blood culture-negative group. As a result, 34 blood culture-positive specimens were included in analysis. Positive blood culture samples were reported in 12 (26.7%) of the 45 patients with a qSOFA score of $\geq$ 2 points and 13 (22.0%) of 59 patients with a qSOFA score of only 0 or 1 ($P = 0.647$). Heart rate, hematocrit, and serum creatinine and C-reactive protein (CRP) levels were significantly high in the blood culture-positive group. Gram-positive bacteria were isolated from 19 samples, gram-negative bacteria from 12, and multiple bacteria were detected in 3 samples (Table 3).

Table 2. Comparisons between blood culture-positive and blood culture-negative groups

Variable	Negative (n = 273)	Positive (n = 34)	P-value	Missing
Age (years) at admission, median (IQR)	71 (50–80.5)	70 (40–80)		
Sex, n (male, %)	183 (67.0%)	21 (61.8%)	P = 0.5661	
Obtained in the ER, n (%)	79 (28.9%)	25 (73.5%)	P < 0.0001	
qSOFA score (n=104), n				
0	13	5	P = 0.173	
1	33	8		
2	30	8		
3	3	4		
Vital signs, median (IQR)				
Body temperature (degree Celsius)	38.6 (37.4–39.0)	38.3 (37.4–39.3)	P = 0.748	
Heart rate (breaths/min)	94 (79–108)	105 (89–120)	P = 0.004	
Systolic blood pressure (mmHg)	129 (112–149)	116 (93–154)	P = 0.069	
Respiratory rate (breaths/min)	20 (17–26)	22.5 (17–33)	P = 0.309	
Laboratory data, median (IQR)				
White blood cell count (/ μL)	10,950 (8,155–13,905)	10,750 (7,727.5–14,905)	P = 0.826	
Hematocrit (%)	31.3 (27.25–36.15)	34.5 (28.9–40.1)	P = 0.033	
Serum creatinine (mg/dL)	0.64 (0.47–0.99)	1.13 (0.54–2.29)	P = 0.005	4
C-reactive protein (mg/dL)	8.32 (4.00–14.76)	14.39 (6.09–22.09)	P = 0.011	
Suspected site of infection, n (%)				
Lung	122 (44.7)	4 (1.5)	P = 0.0002	
Abdomen	16 (5.9)	3 (1.1)	P = 0.4528	
Urinary tract	31 (11.4)	11 (4.0)	P = 0.0024	
Blood infection/endocardium/catheter/implant device	11 (4.0)	0 (0)	P = 0.6178	
Central nerve	10 (3.7)	0(0)	P = 0.6091	
Osteoarticular	2 (0.7)	4 (1.5)	P = 0.0016	
Skin	21 (7.7)	8 (2.9)	P = 0.0078	
Wound	35 (12.8)	2 (0.7)	P = 0.3994	
Other	25 (9.2)	2 (0.7)	P = 0.7513	
Procalcitonin (ng/mL), median (IQR)	0.33 (0.12–1.15)	4.53 (0.61–28.73)	P < 0.001	
Presepsin (pg/mL), median (IQR)	485.0 (242.5–929.0)	1028.5 (585.8–1,898.8)	P < 0.001	

ER, emergency room; qSOFA, quick Sequential Organ Failure Assessment; IQR, interquartile range

Table 3. Organisms from positive blood cultures

Organisms	No.
Gram positive	19
Staphylococcus aureus	7
Streptococcus spp.	5
CNS	3
Enterococcus spp.	2
Peptostreptococcus spp.	1
Corynebacterium spp.	1
Gram negative	12
Escherichia coli	9
Edwardsiella tarda	1
Enterobacter cloacae	1
Bacteroides fragilis	1
Polymicrobial infections	3

CNS: coagulase-negative staphylococci

Both presepsin and procalcitonin levels were significantly higher in blood culture-positive patients than in blood culture-negative samples (1028.5 pg/mL vs. 485.0 pg/mL, P < 0.001 and 4.53 ng/mL vs. 0.33 ng/mL, P < 0.001, respectively) (Fig. 1A and 1B). ROC analysis was performed to investigate the accuracy of PSEP and PCT in predicting bacteremia. Results indicated the following: AUC of 0.778 (95% CI 0.696-0.860, P < 0.001) for PCT and an AUC of

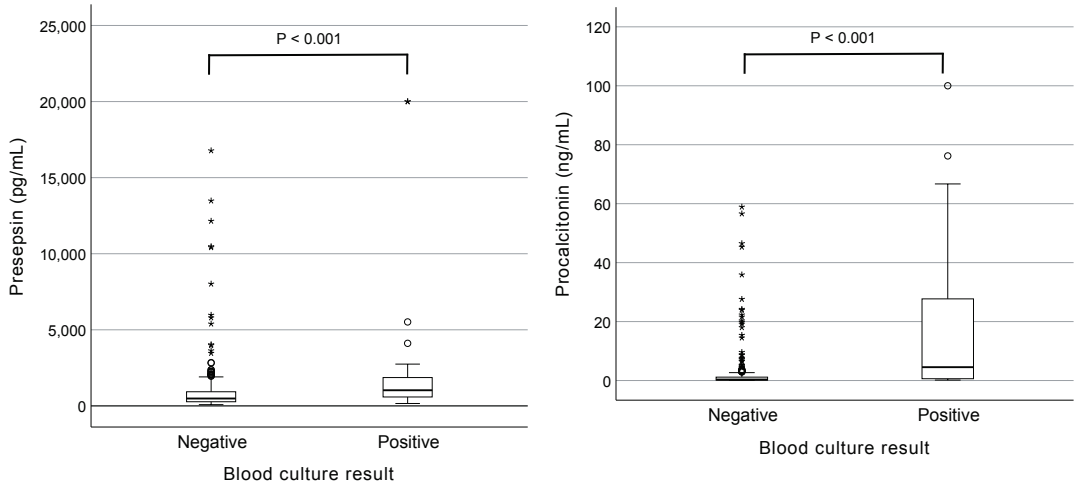

Fig. 1. Distribution of presepsin (A) and procalcitonin (B) relative to blood culture results.

0.718 (95% CI 0.634－0.803, P < 0.001) for PSEP (Fig. 2 and Table 4). Thus, no significant differences between PSEP and PCT were noted in the AUC results (P = 0.2373). Investigation of CRP levels indicated an AUC of 0.634 (95% CI 0.523－0.745, P < 0.009).

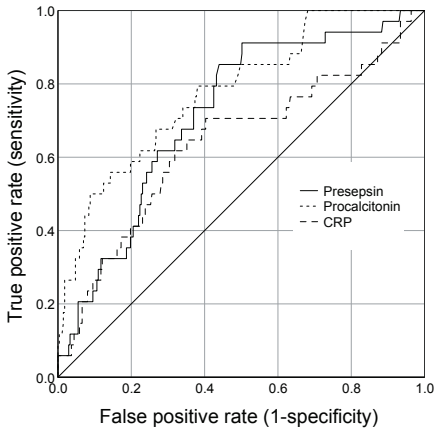

Fig. 2. ROC analysis for blood culture-positive results for presepsin, procalcitonin, and C-reactive protein.

DISCUSSION

In this prospective observational study, PCT and PSEP showed good diagnostic accuracy and NPV for predicting bacteremia among patients with suspected bacteremia in the clinical setting. However, the results for CRP in this study (AUC 0.634) did not indicate its superiority over PSEP or PCT for predicting bacteremia.

While many studies have investigated the role of biomarkers such as PCT[11, 12], PSEP[11], and interleukin 6 (IL-6)[13] for the early diagnosis of sepsis, few studies have examined the use of biomarkers, particularly PSEP, for the early diagnosis of bacteremia. In a study targeting patients with sepsis who had been diagnosed in an emergency outpatient setting and treated according to the SIRS criteria, Leli *et al.*[14] reported PCT levels of 23.7 ng/mL (6.9－101) in the blood culture-positive group and 0.34 ng/mL (0.05－2.1)

Table 4. Diagnostic accuracy of biomarkers for the prediction of bacteremia

	AUC	95% CI	P-value	Cut-off	Sensitivity	Specificity	PPV	NPV
Procalcitonin	0.778	0.695–0.861	<0.001	1.045	0.676	0.733	0.240	0.948
Presepsin	0.718	0.633–0.804	<0.001	654	0.735	0.630	0.198	0.950
CRP	0.634	0.523–0.745	0.009	12.475	0.618	0.679	0.194	0.934

CRP, C-reactive protein; PPV, positive predictive value; NPV, negative predictive value.

in the blood culture-negative group, with an AUC of 0.876. Congruently, PSEP levels were 1,290 pg/mL (1,005－2,041) in the positive group and 659 pg/mL (381－979) in the negative group, with an AUC of 0.788. However, this study only targeted SIRS patients, who are no longer used in clinical settings. Additionally, as patients without SIRS can develop bacteremia, the patient group targeted in that study for measuring PSEP to make an early diagnosis of bacteremia may be inappropriate.

Many studies have reported the usefulness of PCT in the early diagnosis of sepsis[11－13] and bacteremia[15, 16]. Jeong *et al*.[16] reported an AUC of 0.86 for the diagnostic precision of PCT for bacteremia with a cut-off value of 0.99 (ng/mL), which is similar to the results of our study that indicated an AUC of 0.778 and cut-off value of 1.045 (ng/mL).

Our study considered patients who had undergone blood culture collection as patients suspected of infection and bacteremia. Churpek *et al*. suggested that sepsis specific early warning scores such as SOFA, SIRS score, and qSOFA were not significantly different among patients who had undergone some form of culture collection due to suspected infection, those who had undergone blood culture collection, and those who were administered antibacterial agents[17]. Therefore, the results of our investigation for patients with suspected infection who had undergone blood culture collection are clinically useful. We indicated that the blood culture positivity rate was 11.1%, whereas previously reported positivity rates for blood culture samples in studies targeting sepsis patients were 17% for patients with sepsis, 25%－38% for patients with severe sepsis, and 69% for patients with septic shock[18, 19]. Additionally, the false-positive rate in the present study was 0.3%, which is appropriate considering the anticipated false-positive rate[20]. In view of this, our targeting of patients with suspected infection and bacteremia appears to have largely been in line with standard clinical assessments on eligibility for blood culture testing.

When the cut-off values determined in the present study were used, the NPV for both PCT and PSEP was good, at approximately 95%. It has been reported that 5.2% of patients administered antibacterial agents for a severe infection in the ICU did not actually have a bacterial infection[21]. The additional use of biomarkers for such patients may help reduce the unnecessary use of broad-spectrum antimicrobials.

This study had several limitations. First, we analyzed the use of general blood culture results for determining bacteremia as the outcome investigated in this study. Blood culture testing has been reported to have low sensitivity for determining bacteremia. Therefore, our results are likely to include a certain percentage of false negatives. In the future, methods such as real-time PCR could be implemented to avoid false-negative results.

Second, the sepsis-3 definition was published during the study period. Therefore, in many patients, the results of coagulation tests were not available, making it impossible to include SOFA scores for all patients. However, as the patients in this study were suspected of having an infection, we believe that the results were not greatly affected without the SOFA score evaluation.

Finally, this finding may have been influenced by the higher levels of PSEP observed even without the presence of infection in renal dysfunction and dialysis patients[22], indicating that false-positive results may frequently be seen in these patients.

In conclusion, both PSEP and PCT demonstrated good predictive ability for bacteremia in patients suspected of infection. Using the cut-off values determined in our analysis, we achieved a clinically useful NPV. PSEP and PCT may be useful for ruling out bacteremia.

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DECLARATIONS OF INTEREST

none.

REFERENCES

1）Budelmann G: Hugo Schottmüller, 1867-1936. The problem of sepsis. Internist. 10: 92-101, 1969

2）Dellinger RP, Levy MM, Rhodes A, *et al.*: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39: 165-228, 2013

3）Rhodes A, Evans LE, Alhazzani W, *et al.*: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 43: 304-377, 2017

4）Brooks D, Smith A, Young D, Fulton R, Booth MG: Mortality in intensive care: The impact of bacteremia and the utility of systemic inflammatory response syndrome. Am J Infect Control 44: 1291-1295, 2016

5）Peker N, Couto N, Sinha B, Rossen JW: Diagnosis of bloodstream infections from positive blood cultures and directly from blood samples: recent developments in molecular approaches. Clin Microbiol Infect 24: 944-955, 2018

6）Zhang X, Liu D, Liu YN, Wang R, Xie LX: The accuracy of presepsin (sCD14-ST) for the diagnosis of sepsis in adults: a meta-analysis. Crit Care 19: 323, 2015

7）Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S: Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. J Infect Chemother 17: 764-769, 2011

8）Giamarellou H, Giamarellos-Bourboulis EJ, Repoussis P, *et al.*: Potential use of procalcitonin as a diagnostic criterion in febrile neutropenia: experience from a multicentre study. Clin Microbiol Infect 10: 628-633, 2004.

9）Koivula I, Hämäläinen S, Jantunen E, Pulkki k, Kuittinen T, Nousiainen T, Juutilainen A: Elevated procalcitonin predicts Gram-negative sepsis in haematological patients with febrile neutropenia. Scand J Infect Dis 43: 471-478, 2011

10）Vänskä M, Koivula I, Jantunen E, Hämäläinen S, Purhonen AK, Pulkki K, Juutilainen A: IL-10 combined with procalcitonin improves early prediction of complications of febrile neutropenia in hematological patients. Cytokine 60: 787-792, 2012

11）Hall KK, Lyman JA: Updated review of blood culture contamination. Clin Microbiol Rev 19: 788-802, 2006

12）Wacker C, Prkno A, Brunkhorst FM, Schlattmann P: Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 13: 426-435, 2013

13）Hou T, Huang D, Zeng R, Ye Z, Zhang Y: Accuracy of serum interleukin (IL)-6 in sepsis diagnosis: a systematic review and meta-analysis. Int J Clin Exp Med 8: 15238-15245, 2015

14）Leli C, Ferranti M, Marrano U, Al Dhahab ZS, Bozza S, Cenci E, Mencacci A: Diagnostic accuracy of presepsin (sCD14-ST) and procalcitonin for prediction of bacteraemia and bacterial DNAaemia in patients with suspected sepsis. J Med Microbiol 65: 713-719, 2016

15）Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB: The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect 21: 474-481, 2015

16）Jeong S, Park Y, Cho Y, Kim HS: Diagnostic utilities of procalcitonin and C-reactive protein for the prediction of bacteremia determined by blood culture. Clin Chim Acta 413: 1731-1736, 2012

17）Churpek MM, Snyder A, Sokol S, Pettit NN, Edelson DP: Investigating the Impact of Different Suspicion of Infection Criteria on the Accuracy of Quick Sepsis-Related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores. Crit Care Med 45: 1805-1812, 2017

18）Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: The natural history of the systemic inflammatory response syndrome (SIRS). A

prospective study. JAMA 273: 117-123, 1995

19) Bates DW, Sands K, Miller E, *et al.*: Predicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consoritium Sepsisi Project Working Group. J Infect Dis 176: 1538-1551, 1997

20) Wu CC, Lan HM, Han ST, Chaou CH, Yeh CF, Liu SH, Li CH, Blaney GN 3rd, Liu ZY, Chem KF: Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. Ann Intensive Care 7: 91, 2017

21) Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C: Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 31: 2742-2751, 2003

22) Nakamura Y, Ishikura H, Nishida T, Kawano Y, Yuge R, Ichiki R, Murai A: Usefulness of presepsin in the diagnosis of sepsis in patients with or without acute kidney injury. BMC Anesthesiol 14: 88, 2014