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Validation of presepsin measurement for mortality prediction of sepsis: a preliminary study

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Background: Sepsis and septic shock remain the leading causes of death in critically ill patients worldwide. Various biomarkers are available to determine the prognosis and therapeutic effects of sepsis. In this study, we investigated the effectiveness of presepsin as a sepsis biomarker.

Methods: Patients admitted to the intensive care unit with major or minor diagnosis of sepsis were categorized into survival and non-survival groups. The white blood cell count and serum C-reactive protein, procalcitonin, and presepsin levels were measured in all patients.

Results: The study included 40 patients (survival group, 32; non-survival group, 8; mortality rate, 20%). The maximum serum presepsin levels measured during intensive care unit admission were significantly higher in the non-survival group (median [interquartile range]: 4,205.5 pg/ml [1,155.8–10,094.0] vs. 741.5 pg/ml [520.0–1,317.5], P<0.05). No statistically significant intergroup differences were observed in the maximum, minimum, and mean values of the white blood cell count, as well as serum C-reactive protein, and procalcitonin levels. Based on the receiver operating characteristic curve, the area under the curve for presepsin as a predictor of sepsis mortality was 0.764. At a cut-off value of 1,898.5 pg/ml, the sensitivity and specificity of presepsin for prediction of sepsis-induced mortality were 75.0% and 87.5%, respectively.

Conclusions: Early diagnosis of sepsis and prediction of sepsis-induced mortality are important for prompt initiation of treatment. Presepsin may serve as an effective biomarker for prediction of sepsis-induced mortality and for evaluation of treatment effectiveness.

Key Words: biomarkers; mortality; presepsin; sepsis; septic shock

Original Article

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INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite the availability of the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 [2], sepsis and septic shock remain major causes of death in critically ill patients; more than 1.7 million adults were diagnosed with sepsis annually in the United States, with 270,000 sepsis-induced deaths [3].

Various biomarkers are available for evaluation of the prognosis and therapeutic effects

of sepsis. The white blood cell (WBC) count is the most common laboratory investigation performed for diagnosis and treatment of sepsis. However, the WBC count is not a specific indicator of sepsis [4], and other advanced biomarkers are also used as sepsis predictors. Procalcitonin (PCT) and C-reactive protein (CRP) are representative biomarkers used to treat sepsis. According to the Surviving Sepsis Campaign Guidelines 2021, PCT is more useful as a prognostic biomarker of sepsis, although its diagnostic potential may be limited [2]. A study has reported that PCT was shown to be superior to serum CRP levels and the WBC count as a prognostic indicator of sepsis [5]. In contrast, another study reported that based on the area under the curve (AUC) for PCT, this biomarker was not useful for prognostic evaluation of sepsis [6]. Pro-inflammatory cytokines released during the acute phase of sepsis have been investigated as potential diagnostic and prognostic biomarkers of sepsis [7-9]. Studies have investigated the role of interleukin (IL)-6 and IL-8 as representative cytokines associated with sepsis [7,10]. However, previous studies have reported that the cytokines used as diagnostic and prognostic indicators of sepsis are not significant [9].

Presepsin (sCD14-ST) was introduced in 2004 and is used as a diagnostic and prognostic sepsis biomarker [11]. Previous studies have reported significantly increased serum presepsin levels in patients with sepsis and septic shock and that these levels were associated with sepsis severity [12,13]. Notably, serum presepsin levels tend to increase in patients with coronary artery disease, liver cirrhosis, heart failure, and hyperglycemia, even in the absence of sepsis [14]. Therefore, the Surviving Sepsis Campaign Guidelines 2021 do not mention the usefulness of presepsin as a sepsis biomarker. In this study, we investigated the role of biomarkers, particularly presepsin as diagnostic and prognostic indicators of infection and sepsis in patients admitted to the intensive care unit (ICU) with various diseases.

KEY MESSAGES

- Sepsis and septic shock are the leading causes of death in critically ill patients.
- Procalcitonin, presepsin, and lactate are some of the biomarkers available for diagnosis of sepsis and prediction of sepsis-induced mortality.
- Serum presepsin levels may serve as an effective biomarker for prediction of sepsis-induced mortality.

MATERIALS AND METHODS

Research Ethics

The study was approved by the Institutional Review Board of Ewha Womans University Seoul Hospital (No. SEUMC 2022-01-020) and waived the informed consents due to the retrospective study.

Patients, Data Collection and Study Design

The study included patients admitted to the ICU with a major or minor diagnosis of sepsis between March and May 2021. The diagnosis of sepsis followed the "Sepsis-3" diagnostic criteria. Patients who consented to do-not-resuscitate order or to discontinue life-sustaining treatment were excluded from the study. First of all, the following demographic and clinical data were recorded from patients who meet inclusion criteria: sex, age, body mass index (BMI), diagnosis, mortality rate, length of ICU stay, ICU mortality, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, duration of mechanical ventilation, use of continuous renal replacement therapy (CRRT), and the norepinephrine infusion rate. The following laboratory tests were performed during ICU admission: the WBC count, neutrophil count (%), serum CRP, lactate, PCT, and presepsin levels. The period of data collection for laboratory tests is from the date of inclusion criteria to the date of discharge from the ICU.

Measurement of Presepsin Levels

We measured presepsin levels along with PCT levels in patients diagnosed with sepsis by the "Sepsis-3" diagnostic criteria. From the first day of admission to the ICU, presepsin levels were measured simultaneously with PCT. Afterwards, when the intensivist determined that re-measurement of PCT levels was necessary, presepsin was also measured. A chemiluminescence enzyme immunoassay was performed using magnetic particles to measure presepsin levels.

Statistical Analysis

We performed intergroup comparison of the variables included in this study. Categorical variables were analyzed using the chi-squared test. Numeric variables, such as age, BMI, length of ICU stay, the APACHE II and SOFA scores, duration of mechanical ventilation, and the norepinephrine infusion rate were expressed as median (interquartile range) and were analyzed using the Mann-Whitney U-test. Results of individ-

ual laboratory tests for each patient were expressed as maximum, minimum, and mean values and were analyzed using the Mann-Whitney U-test. With regard to laboratory tests, we created a receiver operating characteristic (ROC) curve to determine the optimal indicator for mortality prediction. The optimal cut-off value for mortality was selected as the point at which the sum of sensitivity and specificity was highest. All statistical analyses were performed using the IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The figure was created using CorelDRAW 2019 (Corel Corp., Ottawa, Canada).

RESULTS

Patient Characteristics

This study was performed between March and May 2021 and included 40 patients categorized into the survival group (32 patients) and non-survival group (8 patients; mortality rate, 20%). Mechanical ventilation was used in 27 patients (survival group, 19; non-survival group, 8). CRRT was used only in four patients in the non-survival group. No statistically significant intergroup difference was observed in the APACHE II score, SOFA score, length of ICU stays, and norepinephrine infusion rates. Table 1 shows patient characteristics.

Laboratory Findings and Accuracy of Mortality Prediction

The maximum serum presepsin levels measured during ICU admission were significantly higher in the non-survival than in the survival group (median [interquartile range]: 4,205.5 pg/ml [1,155.8–10,094.0]) vs. 741.5 pg/ml [520.0–1,317.5], P<0.05). Additionally, the maximum, minimum, and mean PCT values were higher in the non-survival group; however, the difference was statistically nonsignificant. The maximum, minimum, and mean serum CRP levels were higher in the survival group, although the difference was statistically nonsignificant (Table 2). The maximum serum presepsin level was significantly higher in the non-survival group, and notably, only this difference was statistically significant.

Figure 1 shows the ROC curves for sepsis-induced mortality prediction. The AUCs calculated from the ROC curves were 0.764 for presepsin and 0.744 for the WBC count (P<0.05). The AUC for lactate was 0.700, although this value was statistically nonsignificant (P=0.105). At a cut-off value of 1,898.5 pg/ml, sensitivity and specificity of serum presepsin for sepsis-induced mortality prediction were 75.0% and 87.5%, respectively.

Table 1. Patients' clinical characteristics in survival and non-survival groups

Characteristics	Survival group (n=32)	Non-survival group (n=8)	P-value
Age (yr)	80.5 (65.25–88.75)	73.5 (62.75–82.00)	0.434
Sex (male:female)	15:17	5:3	0.625
BMI (kg/m^2)	22.2 (19.70–25.33)	22.7 (21.85–28.31)	0.325
APACHE II score	26.0 (21.25–34.75)	26.5 (25.25–31.25)	0.955
SOFA score	6.0 (3.25–9.00)	8.5 (5.00–11.50)	0.174
ICU stay period (day)	6.5 (2.00–20.50)	22.5 (17.50–71.25)	0.008
Mechanical ventilator (n=27)	19 (70.4)	8 (29.6)	0.037
Mechanical ventilator period	7 (2.0–33.0)	19.5 (13.75–68.25)	0.031
CRRT (n=4)	0	4	0.001
Norepinephrine infusion rate (μg/kg/min)	0.01 (0.00–0.10)	0.03 (0.00–0.25)	0.804
Disease classification			0.205
Gastrointestinal system	9 (28.1)	1 (12.5)	
Musculoskeletal system	7 (21.9)	0	
Septic shock	5 (15.6)	2 (25)	
Cardiopulmonary system	4 (12.5)	3 (37.5)	
Cerebrovascular system	4 (12.5)	0	
Malignancy	2 (6.3)	2 (25)	
Sepsis	1 (3.1)	0	

Values are presented as median (interquartile range) or number (%).
BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; CRRT: continuous renal replacement therapy.

Table 2. Comparison of the maximum, minimum, and mean values of laboratory parameters between survival and non-survival groups

Variable	Survival group (n=32)	Non-survival group (n=8)	P-value
Maximum presepsin level (pg/ml)	741.5 (520.0–1,317.5)	4,205.5 (1,155.8–10,094.0)	0.014
Minimum presepsin level (pg/ml)	532.5 (362.5–781.5)	2,143.5 (662.0–4,559.5)	0.030
Average presepsin level (pg/ml)	649.0 (403.5–825.2)	3,668.8 (938.0–7,339.8)	0.023
Maximum PCT level (μg/L)	0.885 (0.745–1.688)	1.165 (0.685–10.165)	0.960
Minimum PCT level (μg/L)	0.675 (0.170–0.885)	0.605 (0.498–0.783)	0.855
Average PCT level (μg/L)	0.778 (0.507–1.214)	0.838 (0.633–5.364)	0.539
Maximum WBC count ($\times10^3$/μl)	12.630 (9.290–16.080)	16.270 (10.420–18.045)	0.184
Minimum WBC count ($\times10^3$/μl)	9.070 (6.260–10.870)	8.555 (6.155–14.568)	0.959
Average WBC count ($\times10^3$/μl)	10.997 (8.950–13.310)	11.655 (8.022–17.145)	0.505
Maximum CRP level (mg/dl)	10.945 (5.498–14.873)	7.050 (4.483–17.310)	0.332
Minimum CRP level (mg/dl)	3.510 (1.793–10.095)	3.680 (2.458–7.338)	0.847
Average CRP level (mg/dl)	7.625 (4.615–12.248)	6.053 (3.428–10.827)	0.562
Maximum lactate level (mg/dl)	12.10 (8.88–18.03)	34.20 (9.90–80.30)	0.118
Minimum lactate level (mg/dl)	8.65 (6.60–12.23)	34.20 (6.70–50.70)	0.118
Average lactate level (mg/dl)	11.05 (8.18–14.63)	34.20 (8.78–62.75)	0.138

Values are presented as median (interquartile range).
PCT: procalcitonin; WBC: white blood cell; CRP: C-reactive protein.

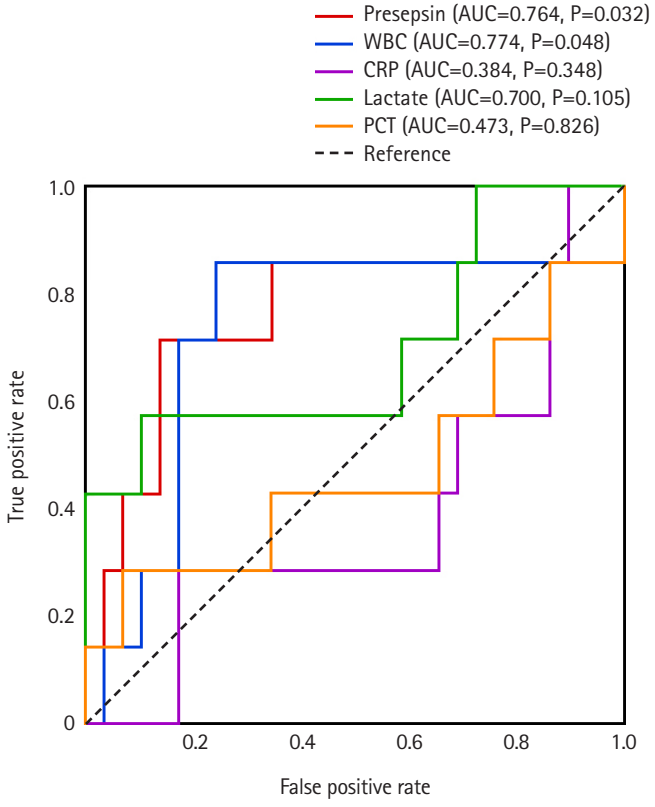

Figure 1. The receiver operating characteristic curve for maximum serum levels of biomarkers for sepsis-induced mortality prediction. The cut-off value of presepsin for sepsis-induced mortality prediction is 1,898.5 pg/ml (sensitivity, 75.0%; specificity, 87.5%). AUC: area under the curve; WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin.

DISCUSSION

Presepsin is a soluble N-terminal fragment of the differentiated marker protein cluster of differentiation 14 (CD14), which is released into the circulation during monocyte activation after the host cells recognize lipopolysaccharide (LPS) produced by an infectious agent. CD14, a 55 kDa glycoprotein, is expressed on monocytes and macrophage membranes and is released into the circulation as soluble CD14, which induces a Toll-like receptor 4-specific inflammatory response that mediates the response to LPS released by an infectious agent [12,15]. Inflammation triggers PCT production via direct pathways that are activated by LPS or other toxic metabolites released by microorganisms and indirect pathways that are activated secondary to the action of inflammatory mediators such as IL-6 and tumor necrosis factor-α [16]. CRP (an acute-phase protein of hepatic origin) production is increased in response to IL-6 secretion by macrophages and T cells during inflammation [17]. Therefore, various mechanisms underlie the release of different biomarkers; we attempted to identify the optimal biomarker for sepsis.

In this study, the mortality rate in patients with sepsis and septic shock was 20%, which was similar to findings reported by previous studies. We observed that serum presepsin levels were strongly associated with mortality in critically ill patients. Among the biomarkers commonly used in the management of critically ill patients, particularly in those with sepsis, serum

presepsin is shown to be superior to serum PCT (which is recommended by the Surviving Sepsis Campaign Guidelines 2021 as a sepsis biomarker) [2].

Many studies have reported the effectiveness and usefulness of presepsin measurement in patients with sepsis. Masson et al. [6] observed that the serum presepsin level on the day of admission to the ICU was significantly higher in non-survivors than in survivors, and this value was associated with the 28-day mortality rate. However, other studies have reported that measurement of serum PCT, CRP, and presepsin was of moderate diagnostic value in patients with sepsis. Therefore, owing to lack of consistent evidence to support its usefulness, presepsin is currently not included in the guidelines [18]. Early diagnosis followed by prompt and appropriate treatment of sepsis is essential immediately after diagnosis as recommended by the Surviving Sepsis Campaign Treatment Bundle [19]. According to the most recent update to the Surviving Sepsis Campaign Guidelines 2021, the level of evidence for the use of PCT for diagnosis of sepsis is weak [2]. According to the guidelines, evaluation of serum PCT levels and clinical symptoms should not take precedence over evaluation of clinical symptoms alone for decision-making regarding initiation of antibiotics, and PCT estimation is recommended to guide antibiotic discontinuation.

In this study, serum lactate levels were not significantly associated with sepsis-induced mortality, although several studies have reported an association between serum lactate levels and sepsis-induced mortality [20]. The Surviving Sepsis Campaign Guidelines 2021 currently recommend the use of serum lactate as a useful aid for evaluation of patients with sepsis. Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection [1], is associated with a broad range of diagnostic criteria owing to the multifactorial etiology of this condition. Broad diagnostic criteria can be considered to have a high incidence. Most patients require critical care management owing to the high mortality rate of sepsis. The ICU is a limited and critical resource; therefore, diagnosis of sepsis and sepsis-induced mortality prediction are important. However, biomarkers that are strongly associated with sepsis or septic shock are currently unavailable. Therefore, much research has focused on the high diagnostic value of presepsin, and several studies have reported its usefulness as a sepsis biomarker [6,11,12,14,21]. In this study, we observed that presepsin showed high accuracy for sepsis-induced mortality prediction. Although the Surviving Sepsis Campaign Guidelines 2021 do not currently discuss the utility of presepsin as a sepsis biomarker, further research is warranted to gain a deeper understanding of the effectiveness of this agent.

Following are the limitations of this study: (1) The design of this single-center small-scale study is a drawback that cannot be ignored. Therefore, we plan further studies with multi centers and larger sample numbers. Through this, we will confirm whether presepsin has important value in the treatment of sepsis patients. (2) Compared with estimation of the WBC count and serum lactate and CRP measurements, we did not frequently measure serum presepsin and PCT levels. (3) We did not consider the specific infection profile detected in each patient. The infection profile may be classified into fungal, viral, and bacterial infections; bacterial infections are further categorized into Gram-negative and Gram-positive bacterial infections. PCT levels were significantly higher in patients with gram-negative bacterial infections than in those with Gram-positive or fungal infections [22]. In contrast, serum presepsin levels were significantly higher in Gram-negative and Gram-positive bacterial and fungal infections [23]. Neither presepsin nor PCT is a specific biomarker for viral infections [24,25]. We intend to perform a multicenter large-scale study to validate the usefulness of presepsin measurement in sepsis. In conclusion, presepsin may be potentially useful as a predictor of sepsis-induced mortality and to evaluate the effectiveness of treatment.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: KSH. Data curation: SMB, SHC. Formal analysis: SMB. Methodology: all authors. Project administration: SMB. Visualization: SMB. Writing–original draft: SMB, KSH. Writing–review & editing: all authors.

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