Diagnostic and prognostic value of presepsin in non-infectious organ failure, sepsis, and septic shock: a prospective observational study using Sepsis-3

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Abstract

We investigated the diagnostic and prognostic value of presepsin among patients with organ failure in the emergency department. This prospective observational study included 420 patients divided into three groups: non-infectious organ failure (n = 142), sepsis (n = 141), and septic shock (n = 137). Optimal cut-off values of presepsin to discriminate between the three groups were evaluated using receiver operating characteristic curve analysis. We extracted the optimal cut-off value of presepsin to predict mortality associated with sepsis and septic shock and performed Kaplan–Meier survival curve analysis according to the cut-off value. Presepsin levels were significantly higher in sepsis than in non-infectious organ failure ($p < 0.001$) and significantly higher in septic shock than in sepsis ($p = 0.002$). The optimal cut-off value for presepsin to discriminate between sepsis and non-infectious organ failure was 582 pg/mL ($p < 0.001$) and to discriminate between sepsis and septic shock was 1285 pg/mL ($p < 0.001$). The optimal cut-off value for presepsin for predicting 30-day mortality was 821 pg/mL ($p = 0.005$) in septic patients. Patients with higher presepsin levels (≥ 821 pg/mL) had significantly higher mortality rates than patients with lower presepsin levels (< 821 pg/mL) (log-rank test; $p = 0.004$). Presepsin levels could effectively differentiate sepsis from non-infectious organ failure and help clinicians identify sepsis patients with poor prognosis.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. Despite advances in management, sepsis is the leading cause of mortality in critically ill patients[2,3]. According to the Surviving Sepsis Campaign (SSC) guidelines, early diagnosis of sepsis and therapeutic interventions are essential to improve survival outcomes[2,4,5]. Although the third international consensus definitions for sepsis and septic shock (Sepsis-3) have been published[1,6], no single gold standard diagnostic method for sepsis has been identified. Blood cultures can determine the presence of bacteremia, but it usually takes a few days to obtain microbiological results and yields false negative results in many cases. Thus, various novel biomarkers to determine the presence of infection have been evaluated, and some markers, such as C-reactive protein (CRP) and procalcitonin (PCT), are widely used in clinical settings[7,8]. Although PCT is known to have higher specificity for bacterial infection than CRP and other traditional markers, its level may also be elevated in conditions without infection[7,9]. PCT also appears to have limited capacity to predict mortality associated with sepsis[10].

The soluble cluster of differentiation 14 subtype, presepsin, was reported to have diagnostic and prognostic capacity in septic patients in some studies performed according to the previous Sepsis-2 definitions[11–13]. Other studies using a systematic review and meta-analysis showed that the diagnostic accuracy of presepsin in detecting infection was similar to that of PCT, and both biomarkers were useful for the early diagnosis of sepsis[14,15]. A recent study using Sepsis-3 reported that presepsin and PCT were superior to CRP and lactate in discriminating sepsis and septic shock from systemic inflammatory response syndrome (SIRS) without infection[16]. Another study using the Sepsis-3 definition also showed

that presepsin could effectively discriminate sepsis without shock from non-septic patients with an increase in sepsis-related organ failure assessment (SOFA) score of ≥ 2 [17].

However, to the best of our knowledge, there has been no study on the diagnostic and prognostic value of presepsin, including patients with organ failure in the emergency department (ED), according to the latest Sepsis-3 definitions. Therefore, we aimed to investigate the diagnostic value of presepsin levels in patients with non-infectious organ failure, sepsis, and septic shock, as well as the prognostic value of presepsin levels in patients with sepsis and septic shock.

Results

Study population and baseline characteristics. During the study period, 517 patients with positive qSOFA scores upon presentation to the ED were screened using the i-SMS (Fig. 1). Among them, 97 patients were excluded due to refusal to participate (n = 54), increase in SOFA score of < 2 (n = 31), admission for trauma care (n = 7), or unknown outcomes (loss to follow-up) (n = 5). The final study population comprised 420 patients. Of these patients, 142 had non-infectious organ failure, 141 had sepsis, and 137 had septic shock. A flowchart of the study population is shown in Fig. 1. The baseline characteristics of the study population are presented in Table 1. Patients with sepsis and septic shock were older than those with non-infectious organ failure. Sex and the Charlson comorbidity index did not differ between the three groups. Acute Physiology and Chronic Health Evaluation (APACHE) II, SOFA, National Early Warning (NEWS), and Modified Early Warning (MEWS) scores were significantly higher in sepsis and septic shock patients than in non-infectious organ failure patients. The 7-, 14-, 30-, and 90-day mortality rates were higher in patients with septic shock than in the other groups. Table 2 shows the principal clinical diagnoses of patients with non-infectious organ failure according to the affected organ systems: 52, central nervous system disorders; 41, cardiovascular disorders; 21, respiratory disorders; 19, hepatobiliary disorders; 14, renal disorders; and 7, coagulation disorders. The most common diagnoses were hypovolemic shock, metabolic encephalopathy, cerebral hemorrhage, heart failure, chronic obstructive pulmonary disease, asthma, seizure, and liver cirrhosis (Table 2).

Table 1
Baseline characteristics of the study population

Variables	Non-infectious organ failure (n = 142)	Sepsis (n = 141)	Septic shock (n = 137)	*p* value
Age, median (IQR)	66 (51–80)	76 (67–83)	77 (62–83)	< 0.001
Male, n (%)	85 (56)	85 (62)	74 (57)	0.519
Charlson comorbidity index	4 (3–5)	3 (3–5)	5 (4–6)	0.182
Site of infection, n (%)				
Respiratory		84 (60)	81 (59)	0.713
Genitourinary		35 (25)	33 (24)	0.367
Gastrointestinal		14 (10)	13 (10)	0.386
Others		13 (9)	15 (11)	0.281
APACHE II score, median (IQR)	23 (18–29)	26 (22–32)	29 (25–33)	< 0.001
SOFA score, median (IQR)	6 (3–8)	6 (5–8)	10 (8–12)	< 0.001
NEWS, median (IQR)	9 (7–11)	10 (8–12)	11 (9–14)	< 0.001
MEWS, median (IQR)	5 (4–7)	6 (5–7)	6 (5–8)	< 0.001
WBC (× 10^9/L), median (IQR)	11.30 (8.17–14.63)	11.94 (8.24–17.06)	11.22 (6.68–20.04)	0.343
CRP (mg/dL), median (IQR)	0.53 (0.13–2.42)	7.50 (3.33–16.66)	10.07 (3.99–20.70)	< 0.001
Procalcitonin (ng/mL), median (IQR)	0.10 (0.05–0.25)	0.98 (0.35–4.25)	4.22 (0.88–21.02)	< 0.001
Presepsin (pg/mL), median (IQR)	286 (170–417)	792 (450–1273)	1287 (589–2366)	< 0.001
Lactate (mmol/L), median (IQR)	2.5 (1.5–5.1)	2.2 (1.5–4.9)	4.4 (2.4–8.1)	< 0.001

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sepsis-related organ failure assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; WBC, white blood cell; CRP, C-reactive protein

Variables	Non-infectious organ failure (n = 142)	Sepsis (n = 141)	Septic shock (n = 137)	*p* value
7-day mortality	11 (7.2)	11 (8.0)	33 (25.2)	< 0.001
14-day mortality	16 (10.5)	19 (13.9)	40 (30.5)	< 0.001
30-day mortality	20 (13.2)	22 (16.1)	47 (35.9)	< 0.001
90-day mortality	21 (13.8)	33 (24.1)	52 (39.7)	< 0.001

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sepsis-related organ failure assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; WBC, white blood cell; CRP, C-reactive protein

Table 2
Principal diagnoses of non-infectious organ failure patients (n = 142) according to the affected organ systems

Organs	Main clinical diagnoses	n (%)
Central nervous system	Cerebral hemorrhage (ICH, IVH, SAH and SDH)	12 (8.5)
(n = 52)	Cerebral infarction	5 (3.5)
	Seizure	11 (7.7)
	Hypoglycemia	4 (2.8)
	Metabolic encephalopathy	13 (9.2)
	Heat stroke	2 (1.4)
	Others	5 (3.5)
Cardiovascular	Heart failure	12 (8.5)
(n = 41)	Pulmonary embolism	5 (3.5)
	Hypovolemic (hemorrhagic) shock	17 (12.0)
	Aortic dissection	4 (2.8)
	Others	3 (2.1)
Respiratory	COPD or asthma	12 (8.5)
(n = 21)	Malignancy in respiratory system	4 (2.8)
	Airway obstruction	3 (2.1)
	Others	2 (1.4)
Hepatobiliary	Liver cirrhosis aggravation	11 (7.7)
(n = 19)	Hepatobiliary malignancy	5 (3.5)
	Others	3 (2.1)
Renal	Acute kidney injury	9 (6.3)
(n = 14)	Underdialysis in pre-existing CKD	5 (3.5)
Coagulation	Hematologic malignancy	4 (2.8)
(n = 7)	Thrombocytopenia	3 (2.1)

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease

Presepsin, PCT, and CRP measurement. A comparison of presepsin, PCT, and CRP levels among all patients with organ failure is shown in Fig. 2 and Table 1. Presepsin, PCT, and CRP levels were

significantly higher in patients with sepsis or septic shock than in patients with non-infectious organ failure. Presepsin and PCT levels were significantly higher in patients with septic shock than in those with sepsis. In contrast, we observed no significant differences in CRP levels between the sepsis and septic shock groups (Fig. 2).

Diagnostic value of presepsin, PCT, and CRP. Receiver operating characteristics (ROC) curve analyses to discriminate between the three groups are shown in Fig. 3 and Table 3. The optimal cut-off value for presepsin to discriminate between sepsis and non-infectious organ failure was 582 pg/mL (sensitivity = 70.1%, specificity = 89.4, area under the curve [AUC] = 0.877, 95% confidence interval [CI], 0.841–0.906; $p < 0.001$). The cut-off value for presepsin to discriminate between sepsis and septic shock was 1285 pg/mL (sensitivity = 50.4%, specificity = 76.6%; AUC = 0.618, 95% CI = 0.558–0.675, $p < 0.001$). The optimal cut-off value for PCT to discriminate between sepsis and non-infectious organ failure was 0.51 ng/mL (sensitivity = 75.5%, specificity = 93.0%, AUC = 0.908, 95% CI = 0.877–0.934, $p < 0.001$). The cut-off value for PCT to discriminate between sepsis and septic shock was 2.81 ng/mL (sensitivity = 59.1%, specificity = 70.9%, AUC = 0.678%, 95% CI = 0.619–0.732, $p < 0.001$). The optimal cut-off value for CRP to discriminate between sepsis and non-infectious organ failure was 3.53 mg/L (sensitivity = 77.0%, specificity = 85.2%, AUC = 0.858, 95% CI = 0.821–0.890; $p < 0.001$). The cut-off value for CRP to discriminate between sepsis and septic shock was 6.62 mg/L (sensitivity = 65.7%; specificity = 46.8%; AUC = 0.559; 95% CI = 0.498–0.618, $p = 0.088$).

Table 3
Comparisons of the discriminating capacity of tested biomarkers presented as areas under the curve (95% CI)

Tested biomarker	AUC (95% CI)	*p* value	Cut-off value	Sensitivity, (%)	Specificity, (%)
Presepsin					
Sepsis vs. *Non-infectious organ failure*	0.877 (0.841–0.906)	< 0.001	582 (pg/mL)	70.1	89.4
Septic shock vs. *Sepsis*	0.618 (0.558–0.675)	< 0.001	1285 (pg/mL)	50.4	76.6
Procalcitonin					
Sepsis vs. *Non-infectious organ failure*	0.908 (0.877–0.934)	< 0.001	0.51 (ng/mL)	75.5	93.0
Septic shock vs. *Sepsis*	0.678 (0.619–0.732)	< 0.001	2.81 (ng/mL)	59.1	70.9
CRP					
Sepsis vs. *Non-infectious organ failure*	0.858 (0.821–0.890)	< 0.001	3.53 (mg/L)	77.0	85.2
Septic shock vs. *Sepsis*	0.559 (0.498–0.618)	0.088	6.62 (mg/L)	65.7	46.8

AUC, area under the curve; CRP, C-reactive protein

Prognostic value of presepsin. The 30-day mortality rate was 27% (74/278) in patients with sepsis and septic shock (Table 4). We compared clinical variables between 30-day survivors and non-survivors among patients with sepsis (non-infectious organ failure excluded). Survivors and non-survivors did not differ in age, sex, Charlson comorbidity index, sites of infection, or CRP and PCT levels. APACHE II, SOFA score, NEWS, and MEWS scores were significantly higher in non-survivors than in survivors. Presepsin levels were significantly higher in non-survivors than in survivors (1142 [650–2039] ng/mL vs. 815 [460–1678] ng/mL; $p < 0.001$). Lactate levels were significantly higher in non-survivors than in survivors (6.0 [2.9–9.9] mmol/L vs. 2.6 [1.6–5.2] mmol/L; $p < 0.001$).

Table 4
Comparison of clinical variables between 30-day survivors and non-survivors among patients with sepsis (non-infectious organ failure patients excluded)

Variables	All septic patients (n = 278)	Survivors (n = 204)	Non-survivors (n = 74)	*p* value
Age, median (IQR)	77 (64–84)	77 (64–83)	78 (65–85)	0.210
Male, n (%)	162 (58)	120 (59)	42 (57)	0.757
Charlson comorbidity index	4 (3–5)	3 (3–5)	5 (4–6)	0.157
Site of infection, n (%)				
Respiratory	165 (59)	119 (58)	46 (62)	0.658
Genitourinary	68 (24)	48 (24)	20 (27)	0.412
Gastrointestinal	27 (10)	20 (10)	7 (9)	0.348
Others	28 (10)	21 (10)	7 (9)	0.316
APACHE II score, median (IQR)	28 (24–33)	27 (22–31)	31 (26–37)	< 0.001
SOFA score, median (IQR)	9 (6–11)	8 (6–10)	11 (9–12)	< 0.001
NEWS, median (IQR)	11 (9–13)	10 (9–12)	12 (10–14)	0.002
MEWS, median (IQR)	6 (5–7)	6 (5–7)	6 (5–9)	0.043
WBC (× 10^9/L), median (IQR)	11.68 (7.65–18.07)	11.91 (8.38–19.66)	10.76 (5.06–15.75)	0.009
CRP (mg/L), median (IQR)	9.09 (3.87–17.34)	8.69 (3.57–17.07)	10.75 (4.80–19.04)	0.270
Procalcitonin (ng/mL), median (IQR)	1.74 (0.51–8.51)	1.61 (0.47–8.95)	2.06 (0.62–7.22)	0.666
Presepsin (pg/mL), median (IQR)	934 (512–1802)	815 (460–1678)	1142 (650–2039)	< 0.001
Lactate (mmol/L), median (IQR)	3.1 (1.9–6.6)	2.6 (1.6–5.2)	6.0 (2.9–9.9)	< 0.001

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sepsis-related organ failure assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; WBC, white blood cell; CRP, C-reactive protein

The optimal cut-off value for presepsin for predicting 30-day mortality was 821 pg/mL (sensitivity = 68.9%, specificity = 50.5%, AUC = 0.605, 95% CI = 0.545–0.663, p = 0.005) in patients with sepsis and

septic shock. The 30-day mortality rates were 18.4% (23/125) in patients with lower presepsin levels (< 821 pg/mL) and 33.3% (51/153) in patients with higher presepsin levels (≥ 821 pg/mL). Kaplan–Meier survival curve analysis showed that patients with higher presepsin levels had significantly higher mortality than patients with lower presepsin levels (log-rank test; p = 0.004) (Fig. 4).

Discussion

To the best of our knowledge, this is the largest prospective observational study on both the diagnostic and prognostic value of presepsin in non-infectious organ failure, sepsis, and septic shock, in accordance with the latest Sepsis-3 definitions. Presepsin had excellent accuracy in discriminating sepsis from non-infectious organ failure and had fair accuracy in discriminating septic shock from sepsis. The discriminating power of presepsin was comparable to that of PCT among patients with non-infectious organ failure, sepsis, and septic shock. The prognostic value of presepsin was superior to that of PCT and CRP in patients with sepsis and septic shock.

Our results showed that the optimal cut-off value to discriminate sepsis (including shock) from non-infectious organ failure was 582 pg/mL (AUC = 0.877, sensitivity = 70.1%, specificity = 89.4%). Several studies have reported different performance efficiencies of presepsin as an indicator of different types of infection. Optimal cut-off values (sensitivity, specificity, respectively) to discriminate sepsis from non-sepsis were 907 (70%, 83%)[18], 686 (47%, 91%)[19], 670 (70%, 81%)[20], 729 (81%, 63%)[21], 600 (86%, 72%)[22], 600 (79%, 62%)[23], 542 (77%, 76%)[24], 430 (88%, 82%)[25], and 466 (90%, 55%) pg/mL[26]. The difference in cut-off values reported by these studies may be caused by the heterogeneity of the studies in terms of clinical setting (ED vs. ICU), study design (prospective vs. retrospective), sepsis severity, comorbidities, and type of sample (plasma vs. whole blood vs. serum). However, these studies were performed according to the previous Sepsis-2 definitions.

A recent study using Sepsis-3 reported that presepsin and PCT were superior to CRP and lactate in discriminating sepsis, including shock from non-sepsis with SIRS and a SOFA score ≥ 2 [16]. The AUC values used to discriminate sepsis from non-sepsis were 0.88 for presepsin, 0.81 for PCT, and 0.65 for CRP 0.65, respectively. The AUC value of presepsin in the study was similar to that in our study (AUC = 0.877), and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of presepsin for diagnosing sepsis (including shock) using a cut-off value of 508 pg/mL were 87%, 86%, 93%, 76%, and 87%, respectively. The cut-off value found in the previous study (508 pg/mL) was lower than that in our study (582 pg/mL). Our study is similar to the previous study in that it was performed in the ED according to the latest Sepsis-3 definitions. However, we included a much larger population and used qSOFA as a screening tool instead of SIRS because it is no longer recommended as a diagnostic criterion for sepsis in the new definitions[1]. These differences might have caused the difference in the cut-off values between the two studies. Another study using Sepsis-3 in a Spanish population also reported that presepsin can effectively discriminate sepsis from non-infectious SIRS[16]. However, these two studies using Sepsis-3 did not evaluate the prognostic value of presepsin.

A previous study reported that presepsin was superior to PCT and CRP in discriminating sepsis from SIRS in acute abdominal conditions[27]. In contrast, another study showed that the diagnostic capacity of presepsin was not superior to that of PCT[19], suggesting that its introduction and routine use in clinical practice were not justified. Another study also reported that presepsin did not outperform traditional biomarkers in distinguishing sepsis from SIRS and predicting mortality[28]. In fact, results reported about the diagnostic value of presepsin are controversial, probably due to different study designs and settings. Therefore, specific decision levels are required to determine the clinical roles of presepsin in different settings of non-infectious and infectious diseases[29].

A multicenter prospective study reported that mean presepsin levels were significantly higher in non-survivors of sepsis than in survivors[23]. However, in that study, no significant correlation was observed between PCT levels and survival outcomes[23]. Similar to the previous study, our results showed that presepsin levels were significantly higher in non-survivors than in survivors. No significant differences in PCT levels were observed between the non-survivors and survivors. In our study, Kaplan–Meier survival curve analysis according to the optimal cut-off value of presepsin showed that 30-day mortality was significantly higher in patients with higher presepsin levels. In accordance with our study, a systematic review and meta-analysis revealed that presepsin levels on the first day had prognostic value in predicting in-hospital or 30-day mortality in adult patients with sepsis[30]. The combination of presepsin with PCT, Galectin-3, and soluble suppression of tumorigenicity-2 showed better performance in predicting mortality than the single use of presepsin in sepsis patients[10]. The study demonstrated that the combination of presepsin with other biomarkers could help clinicians predict mortality. Further studies with larger cohorts are required to determine the optimal cut-off value of presepsin for predicting mortality associated with sepsis.

The present study had some limitations. First, although the present study included a large sample size compared to that of previous studies, it was a single-center ED-based study. Thus, our results may not be applicable to other EDs or ICUs. Second, only plasma presepsin levels in the ED were measured, and follow-up changes in markers were not determined. Although a previous study reported that dynamic monitoring of presepsin could effectively predict prognosis[31,32], other trials demonstrated that single measurements of presepsin in the ED also had valuable prognostic value in patients with sepsis[12,23]. Third, although a previous study reported that presepsin levels were markedly elevated in patients with chronic kidney disease receiving hemodialysis[33], our study did not consider kidney function. Further studies are needed to investigate the influence of kidney dysfunction on presepsin levels using repeated marker measurements. Fourth, because the present study included patients with organ dysfunction enrolled in the ED, this might have resulted in selection bias. Nevertheless, we postulate that our study, based on an organ failure cohort, could reflect the clinical characteristics of patients in a real ED setting.

To summarize, the present study, according to the Sepsis-3 definitions, demonstrated the diagnostic and prognostic value of presepsin levels among patients with non-infectious organ failure, sepsis, and septic shock. Its ability to discriminate sepsis, including shock, from non-infectious organ failure was excellent,

and its prognostic ability could help clinicians to prognosticate patients with sepsis and septic shock. Further multicenter prospective studies with larger populations are needed to determine the optimal cut-off value of presepsin for the diagnosis and prognosis of sepsis.

Methods

Study Design and Setting. This single-center prospective observational study was performed at the ED of the Korea University Ansan Hospital, Korea. Our institution is a 910-bed tertiary care teaching hospital with approximately 50,000 annual patient visits to the ED. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Korea University Ansan Hospital (IRB no. 2020AS0031). Written informed consent was obtained from all patients or their legal representatives.

Study population. From July 2019 to August 2020, adults (≥ 18 years) who had a positive quick sepsis-related organ failure assessment (qSOFA) score upon ED presentation were screened for participation. This scoring system uses three criteria: low blood pressure (systolic blood pressure ≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min), and altered mental status (Glasgow coma score < 15). One point was assigned for each criterion, with a final score ranging from 0 to 3 points. A positive qSOFA score was defined as a qSOFA score ≥ 2. In the present study, another inclusion criterion was an increase in the SOFA score by ≥ 2 points in the ED, irrespective of the current infection. Since September 2017, our institution has been using the Intelligent Sepsis Management System (i-SMS), a qSOFA alert system, which helps ED clinicians promptly identify sepsis and manage sepsis according to the SSC 2016 guidelines[4,5]. The system automatically enrolled patients who had a positive qSOFA score upon ED arrival and assisted in the decision-making process for sepsis management. If the patients had baseline SOFA scores, we used the standard of an increase in SOFA score of at least 2. If the patients had no previous SOFA score, two infectious disease (ID) experts reviewed the medical records with laboratory data and determined the change in the SOFA score. Exclusion criteria were refusal to consent, an increase in SOFA score < 2, ED visit for trauma care, and unknown outcomes. Therefore, all enrolled patients had a qSOFA score ≥ 2 or an increase in the SOFA score by ≥ 2 points. Eligible patients were divided into the following three groups based on the presence of infection and sepsis severity: non-infectious organ failure, sepsis, and septic shock. All patients were carefully selected and reviewed by two ID experts and an emergency attending physician.

Definitions

According to Sepsis-3 definitions,

sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities pose a greater risk of mortality than sepsis alone[1,6]. Sepsis-3 recommends the use of the qSOFA score to identify patients with a poor prognosis outside the intensive care unit (ICU). The

diagnostic criteria for sepsis include an increase in the SOFA score by ≥ 2 points due to current infection. The criteria for septic shock include the requirement for a vasopressor to maintain a mean arterial pressure of 65 mmHg and serum lactate level > 2 mmol/L despite adequate fluid resuscitation. Finally, the criteria for “non-infectious organ failure” included a positive qSOFA score and an increase in SOFA score by ≥ 2 points without current infection. Two independent ID experts reviewed all patients to determine the presence of a current infection.

Assays. We sampled blood for presepsin and PCT from a peripheral vein within 6 hours of ED presentation. Plasma presepsin levels were measured using an automated chemiluminescent enzyme immunoassay (PATHFAST system, LSI Medience Corporation, Tokyo, Japan). This novel system, based on the chemiluminescent enzyme immunoassay principle, was developed to analyze blood samples, providing results within 17 min[34]. During incubation of the sample with alkaline phosphatase (ALP)-labeled anti-presepsin polyclonal antibodies and anti-presepsin monoclonal antibody-coated magnetic particles, presepsin binds to anti-presepsin antibodies, assembling an immunocomplex with the ALP-labeled antibodies and mouse monoclonal antibody-coated magnetic particles. The manufacturer-claimed assay range of presepsin was 20–20,000 pg/mL. Plasma presepsin concentrations were measured after the enrolled patients were discharged from the ED. Therefore, the assay results were unavailable to ED physicians and could not influence the management and disposition of the patients.

PCT levels were measured using the Elecsys BRAHMS procalcitonin automated electrochemiluminescence assay (BRAHMS, Henningsdorf, Germany) on the Roche Cobas e-System (Roche Diagnostics, Basel, Switzerland). The manufacturer-claimed assay range of PCT was 0.02–100 ng/mL.

Outcomes. The primary outcome in the present study was 30-day mortality, and the secondary outcome was 90-day mortality. We excluded patients who were lost to follow-up from the 30-day and 90-day analyses.

Statistical analysis. Statistical analyses were performed using MedCalc for Windows (version 19.1.6; MedCalc Software, Mariakerke, Belgium) and SPSS (version 23.0; IBM, Armonk, NY, USA). Statistical significance was set at $p < 0.05$. To compare clinical characteristics and outcomes (7-, 14-, 30-, and 90-day mortalities) between the three groups, continuous variables, presented as median (interquartile range [IQR]), were compared using the Kruskal–Wallis test. Data were tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables, presented as numbers and percentages, were compared using the chi-square test or Fisher’s exact test. Pairwise comparisons were performed separately for each pair of three groups. The Bonferroni method was used to adjust p-values in the post hoc analysis. To compare baseline characteristics between survivors and non-survivors among patients with sepsis and septic shock, continuous variables, presented as the median (IQR), were compared using Student’s t-test or the Mann–Whitney test according to the data distribution. Categorical variables, presented as numbers and percentages, were compared using the chi-square test or Fisher’s exact test. ROC curve analyses were performed for individual biomarkers, and their diagnostic value for

sepsis and septic shock was compared. The discriminating capacities of the tested biomarkers are presented as AUC (95% CI). The optimal cut-off value was identified for each ROC curve using the Youden index (maximum of the sum of sensitivity and specificity). ROC curve analysis was performed for presepsin to predict 30-day mortality. The optimal cut-off value for predicting 30-day mortality was set for presepsin using the Youden index. Kaplan–Meier survival curve analysis and log-rank tests were performed according to the cut-off values of presepsin levels.

Declarations

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Author contributions

J.S., S.L., and D.W.P. conceived and designed the study. J.S., H.S., J.Y.K., and J.P. processed and analyzed the data. J.C., J.S., S.A, and H.J. performed the statistical analyses. J.S., D.W.P., and S.L. wrote the manuscript. All authors have read and approved the final manuscript.

Data availability

Data are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

Additional information

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References

1. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA***315**, 801-810. https://doi.org/10.1001/jama.2016.0287 (2016).
2. Angus, D. C. & van der Poll, T. Severe sepsis and septic shock. *N. Engl. J. Med.***369**, 840-851. https://doi.org/10.1056/NEJMra1208623 (2013).

3. Gaieski, D. F., Edwards, J. M., Kallan, M. J. & Carr, B. G. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit. Care Med.***41**, 1167-1174. https://doi.org/10.1097/CCM.0b013e31827c09f8 (2013).
4. Rhodes, A. *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit. Care Med.***45**, 486-552. https://doi.org/10.1097/CCM.0000000000002255 (2017).
5. Song, J. *et al.* The Effect of the Intelligent Sepsis Management System on Outcomes among Patients with Sepsis and Septic Shock Diagnosed According to the Sepsis-3 Definition in the Emergency Department. *J. Clin. Med.***8**, 1800. https://doi.org/10.3390/jcm8111800 (2019).
6. Shankar-Hari, M. *et al.* Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA***315**, 775-787. https://doi.org/10.1001/jama.2016.0289 (2016).
7. Kibe, S., Adams, K. & Barlow, G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J. Antimicrob. Chemother.***66 Suppl 2**, ii33-ii40. https://doi.org/10.1093/jac/dkq523 (2011).
8. Larsen, F. F. & Petersen, J. A. Novel biomarkers for sepsis: A narrative review. *Eur. J. Intern. Med.***45**, 46-50. https://doi.org/10.1016/j.ejim.2017.09.030 (2017).
9. Wacker, C., Prkno, A., Brunkhorst, F. M. & Schlattmann, P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect. Dis.***13**, 426-435. https://doi.org/10.1016/s1473-3099(12)70323-7 (2013).
10. Kim, H., Hur, M., Moon, H. W., Yun, Y. M. & Di Somma, S. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. *Ann. Intensive Care***7**, 27. https://doi.org/10.1186/s13613-017-0252-y (2017).
11. Masson, S. *et al.* Circulating presepsin (soluble CD14 subtype) as a marker of host response in patients with severe sepsis or septic shock: data from the multicenter, randomized ALBIOS trial. *Intensive Care Med.***41**, 12-20. https://doi.org/10.1007/s00134-014-3514-2 (2015).
12. Liu, B., Chen, Y. X., Yin, Q., Zhao, Y. Z. & Li, C. S. Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. *Crit. Care***17**, R244. https://doi.org/10.1186/cc13070 (2013).
13. Masson, S. *et al.* Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. *Crit. Care***18**, R6. https://doi.org/10.1186/cc13183 (2014).
14. Kondo, Y. *et al.* Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis. *J. Intensive Care***7**, 22. https://doi.org/10.1186/s40560-019-0374-4 (2019).
15. Wu, C. C. *et al.* Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann. Intensive Care***7**, 91. https://doi.org/10.1186/s13613-017-0316-z (2017).

16. Contenti, J., Occelli, C., Lemoel, F., Ferrari, P. & Levraut, J. Presepsin versus other biomarkers to predict sepsis and septic shock in patients with infection defined by Sepsis-3 criteria: the PREDI study of diagnostic accuracy. *Emergencias***31**, 311-317 (2019).
17. Yamamoto, T. *et al.* Diagnostic accuracy of presepsin for sepsis by the new Sepsis-3 definitions. *Am. J. Emerg. Med.***37**, 1936-1941. https://doi.org/10.1016/j.ajem.2019.01.025 (2019).
18. Ali, F. T., Ali, M. A., Elnakeeb, M. M. & Bendary, H. N. Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis. *Clin. Chim. Acta***460**, 93-101. https://doi.org/10.1016/j.cca.2016.06.030 (2016).
19. de Guadiana Romualdo, L. G. *et al.* Diagnostic accuracy of presepsin (sCD14-ST) as a biomarker of infection and sepsis in the emergency department. *Clin. Chim. Acta***464**, 6-11. https://doi.org/10.1016/j.cca.2016.11.003 (2017).
20. Nakamura, Y. *et al.* Usefulness of presepsin in the diagnosis of sepsis in patients with or without acute kidney injury. *BMC Anesthesiol.***14**, 88. https://doi.org/10.1186/1471-2253-14-88 (2014).
21. de Guadiana Romualdo, L. G. *et al.* Diagnostic accuracy of presepsin (soluble CD14 subtype) for prediction of bacteremia in patients with systemic inflammatory response syndrome in the Emergency Department. *Clin. Biochem.***47**, 505-508. https://doi.org/10.1016/j.clinbiochem.2014.02.011 (2014).
22. Sargentini, V. *et al.* Presepsin as a potential marker for bacterial infection relapse in critical care patients. A preliminary study. *Clin. Chem. Lab. Med.***53**, 567-573. https://doi.org/10.1515/cclm-2014-0119 (2015).
23. Ulla, M. *et al.* Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. *Crit. Care***17**, R168. https://doi.org/10.1186/cc12847 (2013).
24. Cakır Madenci, Ö. *et al.* Evaluation of soluble CD14 subtype (presepsin) in burn sepsis. *Burns***40**, 664-669. https://doi.org/10.1016/j.burns.2013.08.024 (2014).
25. Kweon, O. J., Choi, J. H., Park, S. K. & Park, A. J. Usefulness of presepsin (sCD14 subtype) measurements as a new marker for the diagnosis and prediction of disease severity of sepsis in the Korean population. *J. Crit. Care***29**, 965-970. https://doi.org/10.1016/j.jcrc.2014.06.014 (2014).
26. Klouche, K. *et al.* Diagnostic and prognostic value of soluble CD14 subtype (Presepsin) for sepsis and community-acquired pneumonia in ICU patients. *Ann. Intensive Care***6**, 59. https://doi.org/10.1186/s13613-016-0160-6 (2016).
27. Vodnik, T., Kaljevic, G., Tadic, T. & Majkic-Singh, N. Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis. *Clin. Chem. Lab. Med.***51**, 2053-2062. https://doi.org/10.1515/cclm-2013-0061 (2013).
28. Brodska, H. *et al.* Diagnostic and prognostic value of presepsin vs. established biomarkers in critically ill patients with sepsis or systemic inflammatory response syndrome. *Clin. Chem. Lab. Med.***56**, 658-668. https://doi.org/10.1515/cclm-2017-0839 (2018).

29. Giavarina, D. & Carta, M. Determination of reference interval for presepsin, an early marker for sepsis. *Biochem. Med. (Zagreb)***25**, 64-68. https://doi.org/10.11613/bm.2015.007 (2015).
30. Yang, H. S. *et al.* Prognostic value of presepsin in adult patients with sepsis: Systematic review and meta-analysis. *PLoS One***13**, e0191486. https://doi.org/10.1371/journal.pone.0191486 (2018).
31. Behnes, M. *et al.* Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. *Crit. Care***18**, 507. https://doi.org/10.1186/s13054-014-0507-z (2014).
32. Yu, H. *et al.* Evaluating the value of dynamic procalcitonin and presepsin measurements for patients with severe sepsis. *Am. J. Emerg. Med.***35**, 835-841. https://doi.org/10.1016/j.ajem.2017.01.037 (2017).
33. Nagata, T. *et al.* Clinical impact of kidney function on presepsin levels. *PLoS One***10**, e0129159. https://doi.org/10.1371/journal.pone.0129159 (2015).
34. Memar, M. Y. & Baghi, H. B. Presepsin: A promising biomarker for the detection of bacterial infections. *Biomed. Pharmacother.***111**, 649-656. https://doi.org/10.1016/j.biopha.2018.12.124 (2019).

Tables

Table 1. Baseline characteristics of the study population

Variables	Non-infectious organ failure (n = 142)	Sepsis (n = 141)	Septic shock (n = 137)	*p* value
Age, median (IQR)	66 (51–80)	76 (67–83)	77 (62–83)	<0.001
Male, n (%)	85 (56)	85 (62)	74 (57)	0.519
Charlson comorbidity index	4 (3–5)	3 (3–5)	5 (4–6)	0.182
Site of infection, n (%)				
Respiratory		84 (60)	81 (59)	0.713
Genitourinary		35 (25)	33 (24)	0.367
Gastrointestinal		14 (10)	13 (10)	0.386
Others		13 (9)	15 (11)	0.281
APACHE II score, median (IQR)	23 (18–29)	26 (22–32)	29 (25–33)	<0.001
SOFA score, median (IQR)	6 (3–8)	6 (5–8)	10 (8–12)	<0.001
NEWS, median (IQR)	9 (7–11)	10 (8–12)	11 (9–14)	<0.001
MEWS, median (IQR)	5 (4–7)	6 (5–7)	6 (5–8)	<0.001
WBC ($\times 10^9$/L), median (IQR)	11.30 (8.17–14.63)	11.94 (8.24–17.06)	11.22 (6.68–20.04)	0.343
CRP (mg/dL), median (IQR)	0.53 (0.13–2.42)	7.50 (3.33–16.66)	10.07 (3.99–20.70)	<0.001
Procalcitonin (ng/mL), median (IQR)	0.10 (0.05–0.25)	0.98 (0.35–4.25)	4.22 (0.88–21.02)	<0.001
Presepsin (pg/mL), median (IQR)	286 (170–417)	792 (450–1273)	1287 (589–2366)	<0.001
Lactate (mmol/L), median (IQR)	2.5 (1.5–5.1)	2.2 (1.5–4.9)	4.4 (2.4–8.1)	<0.001
7-day mortality	11 (7.2)	11 (8.0)	33 (25.2)	<0.001
14-day mortality	16 (10.5)	19 (13.9)	40 (30.5)	<0.001
30-day mortality	20 (13.2)	22 (16.1)	47 (35.9)	<0.001
90-day mortality	21 (13.8)	33 (24.1)	52 (39.7)	<0.001

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sepsis-related organ failure assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; WBC, white blood cell; CRP, C-reactive protein

Table 2. Principal diagnoses of non-infectious organ failure patients (n = 142) according to the affected organ systems

Organs	Main clinical diagnoses	n (%)
Central nervous system (n = 52)	Cerebral hemorrhage (ICH, IVH, SAH and SDH)	12 (8.5)
	Cerebral infarction	5 (3.5)
	Seizure	11 (7.7)
	Hypoglycemia	4 (2.8)
	Metabolic encephalopathy	13 (9.2)
	Heat stroke	2 (1.4)
	Others	5 (3.5)
Cardiovascular (n = 41)	Heart failure	12 (8.5)
	Pulmonary embolism	5 (3.5)
	Hypovolemic (hemorrhagic) shock	17 (12.0)
	Aortic dissection	4 (2.8)
	Others	3 (2.1)
Respiratory (n = 21)	COPD or asthma	12 (8.5)
	Malignancy in respiratory system	4 (2.8)
	Airway obstruction	3 (2.1)
	Others	2 (1.4)
Hepatobiliary (n = 19)	Liver cirrhosis aggravation	11 (7.7)
	Hepatobiliary malignancy	5 (3.5)
	Others	3 (2.1)
Renal (n = 14)	Acute kidney injury	9 (6.3)
	Underdialysis in pre-existing CKD	5 (3.5)
Coagulation (n = 7)	Hematologic malignancy	4 (2.8)
	Thrombocytopenia	3 (2.1)

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease

Table 3. Comparisons of the discriminating capacity of tested biomarkers presented as areas under the curve (95% CI)

Tested biomarker	AUC (95% CI)	*p* value	Cut-off value	Sensitivity, (%)	Specificity, (%)
Presepsin					
Sepsis vs. Non-infectious organ failure	0.877 (0.841–0.906)	<0.001	582 (pg/mL)	70.1	89.4
Septic shock vs. Sepsis	0.618 (0.558–0.675)	<0.001	1285 (pg/mL)	50.4	76.6
Procalcitonin					
Sepsis vs. Non-infectious organ failure	0.908 (0.877–0.934)	<0.001	0.51 (ng/mL)	75.5	93.0
Septic shock vs. Sepsis	0.678 (0.619–0.732)	<0.001	2.81 (ng/mL)	59.1	70.9
CRP					
Sepsis vs. Non-infectious organ failure	0.858 (0.821–0.890)	<0.001	3.53 (mg/L)	77.0	85.2
Septic shock vs. Sepsis	0.559 (0.498–0.618)	0.088	6.62 (mg/L)	65.7	46.8

AUC, area under the curve; CRP, C-reactive protein

Table 4. Comparison of clinical variables between 30-day survivors and non-survivors among patients with sepsis (non-infectious organ failure patients excluded)

Variables	All septic patients (n = 278)	Survivors (n = 204)	Non-survivors (n = 74)	*p* value
Age, median (IQR)	77 (64–84)	77 (64–83)	78 (65–85)	0.210
Male, n (%)	162 (58)	120 (59)	42 (57)	0.757
Charlson comorbidity index	4 (3–5)	3 (3–5)	5 (4–6)	0.157
Site of infection, n (%)				
Respiratory	165 (59)	119 (58)	46 (62)	0.658
Genitourinary	68 (24)	48 (24)	20 (27)	0.412
Gastrointestinal	27 (10)	20 (10)	7 (9)	0.348
Others	28 (10)	21 (10)	7 (9)	0.316
APACHE II score, median (IQR)	28 (24–33)	27 (22–31)	31 (26–37)	<0.001
SOFA score, median (IQR)	9 (6–11)	8 (6–10)	11 (9–12)	<0.001
NEWS, median (IQR)	11 (9–13)	10 (9–12)	12 (10–14)	0.002
MEWS, median (IQR)	6 (5–7)	6 (5–7)	6 (5–9)	0.043
WBC (× 10^9/L), median (IQR)	11.68 (7.65–18.07)	11.91 (8.38–19.66)	10.76 (5.06–15.75)	0.009
CRP (mg/L), median (IQR)	9.09 (3.87–17.34)	8.69 (3.57–17.07)	10.75 (4.80–19.04)	0.270
Procalcitonin (ng/mL), median (IQR)	1.74 (0.51–8.51)	1.61 (0.47–8.95)	2.06 (0.62–7.22)	0.666
Presepsin (pg/mL), median (IQR)	934 (512–1802)	815 (460–1678)	1142 (650–2039)	<0.001
Lactate (mmol/L), median (IQR)	3.1 (1.9–6.6)	2.6 (1.6–5.2)	6.0 (2.9–9.9)	<0.001

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sepsis-related organ failure assessment; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; WBC, white blood cell; CRP, C-reactive protein

Figures

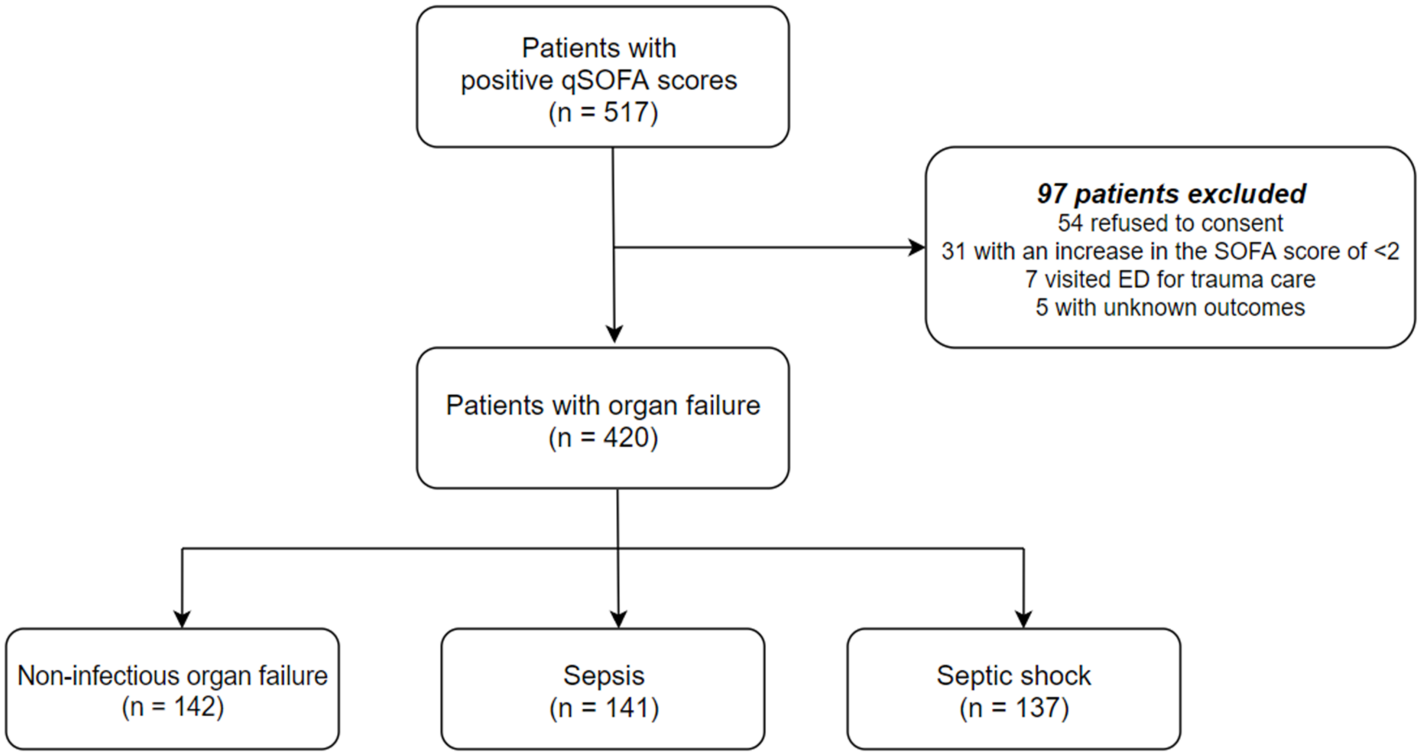

Figure 1

Flowchart of the study population.

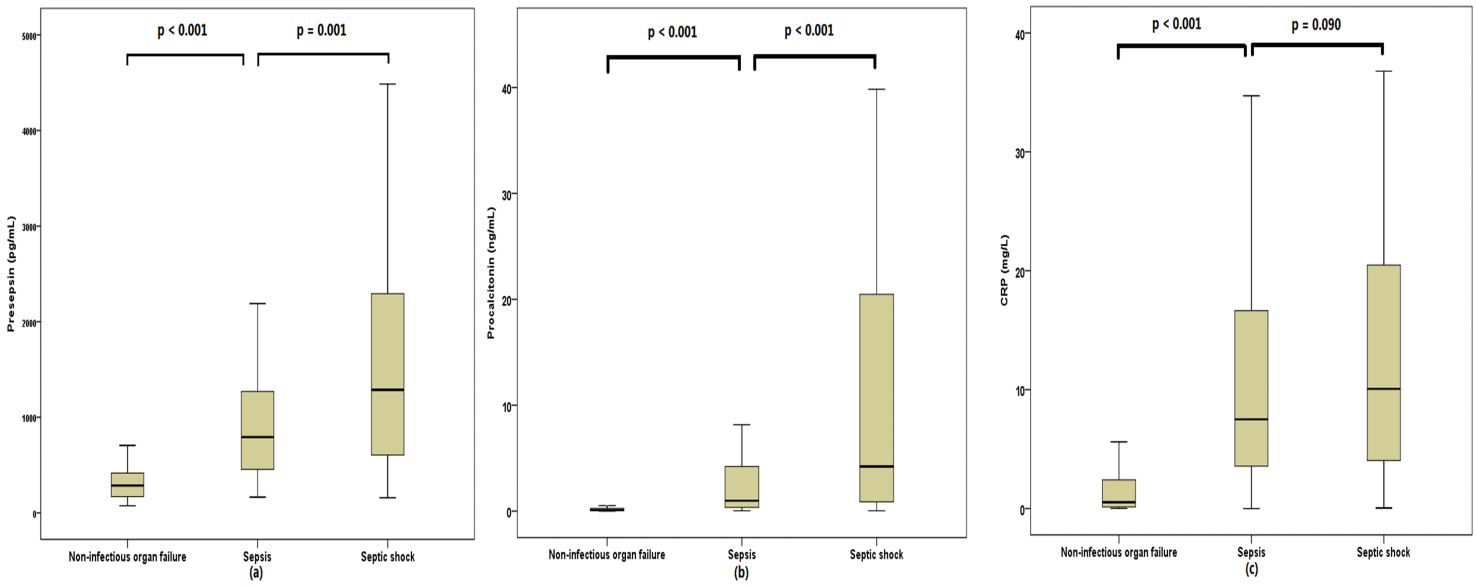

Figure 2

Comparison of presepsin (a), procalcitonin (b), and CRP (c) levels among all patients with organ failure in the emergency department.

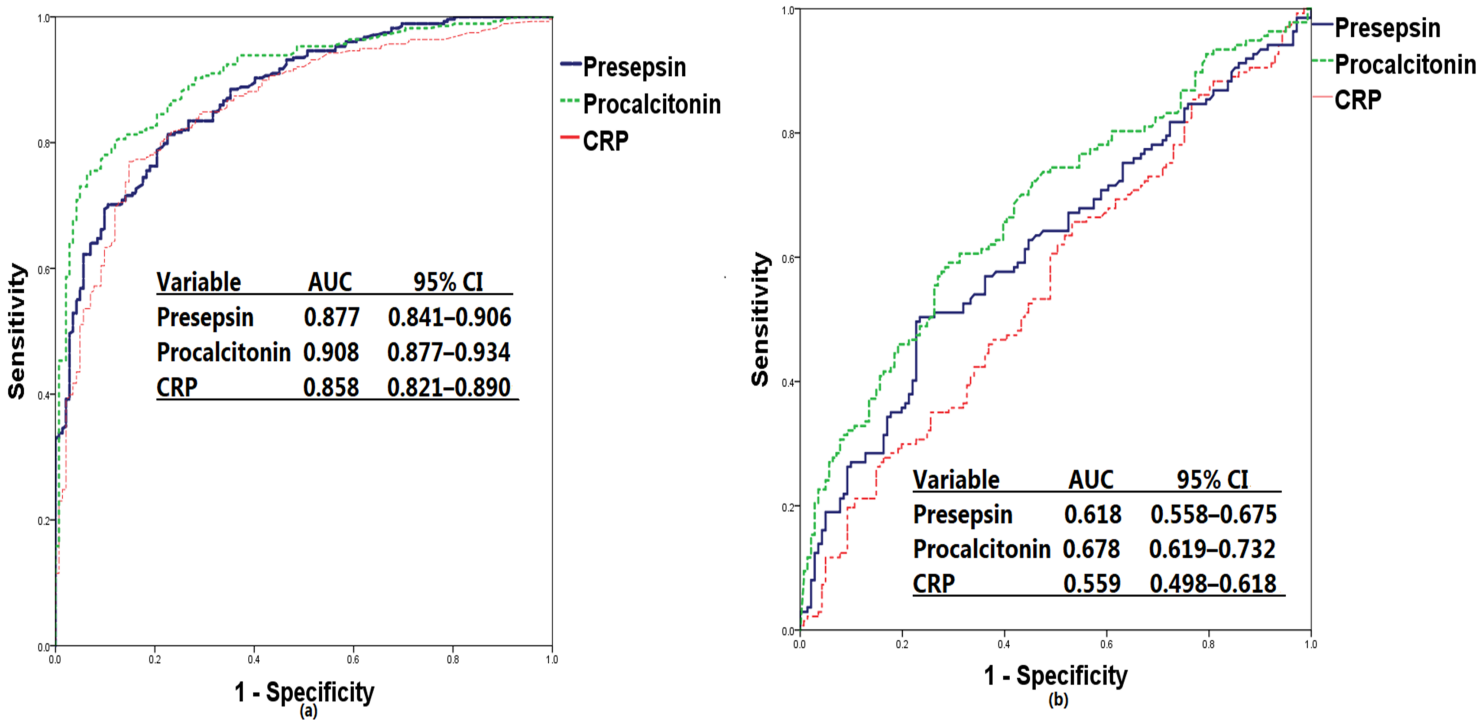

Figure 3

Receiver operating characteristic curves of presepsin, procalcitonin, and CRP for discriminating sepsis (including shock) from non-infectious organ failure (a) and discriminating septic shock from sepsis (b).

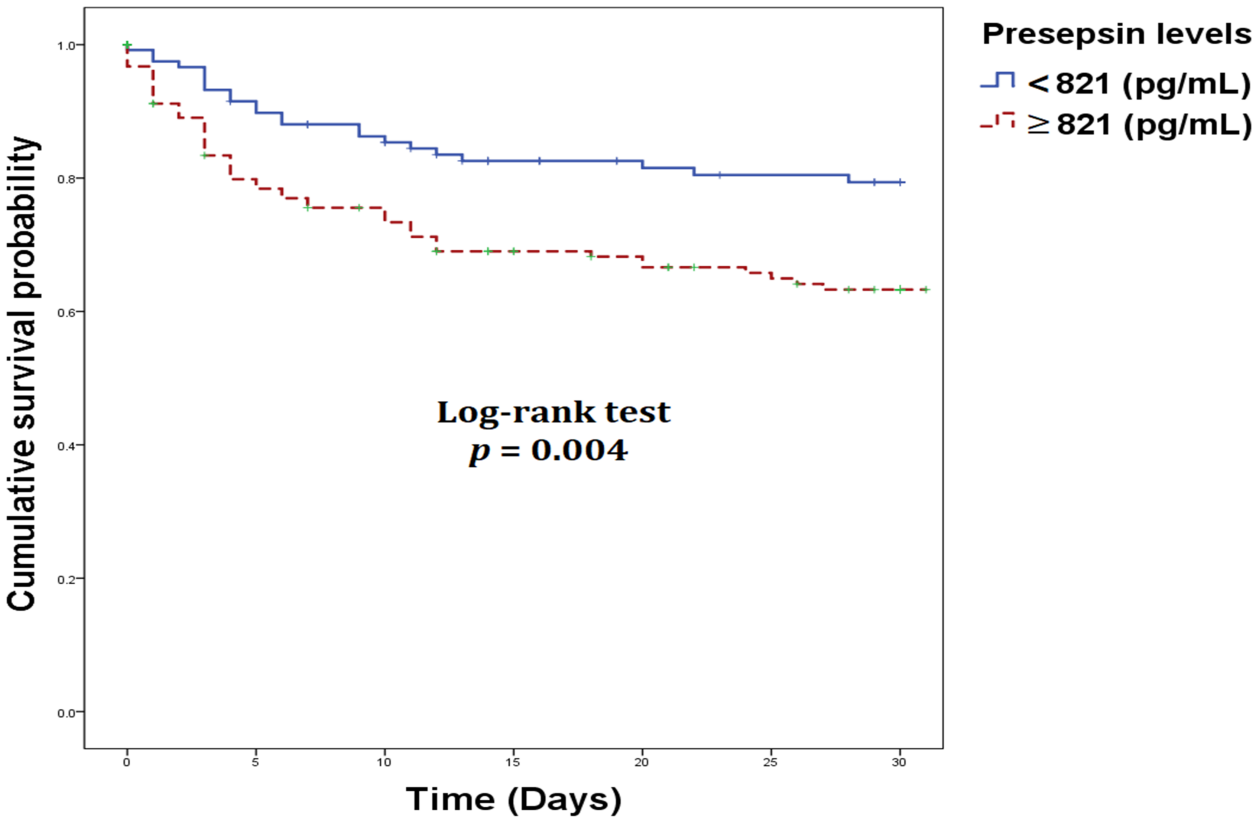

Figure 4

Kaplan–Meier survival curve analysis and log-rank test according to the optimal cut-off of presepsin for predicting 30-day mortality in patients with sepsis and septic shock.