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ORIGINAL RESEARCH

Presepsin levels for discriminating sepsis and predicting mortality among organ failure patients stratified by hypercreatinemia

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Abstract

To evaluate the accuracy of presepsin levels in diagnosing sepsis and predicting mortality among organ failure patients with and without hypercreatinemia in the emergency department (ED). This retrospective study was conducted on patients with positive quick sequential organ failure assessment (qSOFA) score and increase in SOFA score of $\geq$2 points. Hypercreatinemia, indicated by a creatinine level of $\geq$1.2 mg/dL, was defined as points $\geq$1 on the renal component of the SOFA score. The patients were divided into group 1 (sepsis with hypercreatinemia), group 2 (sepsis without hypercreatinemia), group 3 (non-sepsis with hypercreatinemia), and group 4 (non-sepsis without hypercreatinemia), and their presepsin levels were compared. Receiver operating characteristic curve (ROC) analyses were performed to determine the accuracy of presepsin in diagnosing sepsis and predicting 30-day mortality. The optimal cutoff values were obtained to determine the presence of sepsis and predict the 30-day mortality. In all, 420 patients were eligible for this study. The presepsin levels in all pairwise comparisons between the groups were different (Group 1; 1311.5 (732.0–2179.5), Group 2; 566.5 (353.0–928.0), Group 3; 400.0 (291.0–579.0), Group 4; 231.0 (154.0–346.0)). Among patients with hypercreatinemia, the presepsin area under the ROC (AUROC) for diagnosing sepsis was 0.884 (optimal cutoff: 706 pg/mL). Among patients without hypercreatinemia, the presepsin AUROC for diagnosing sepsis was 0.854 (optimal cutoff: 352 pg/mL). The optimal cutoff values for predicting the patients' 30-day mortality with and without hypercreatinemia were 1077 pg/mL and 393 pg/mL, respectively. Different cutoff values of presepsin based on creatinine levels could effectively diagnose sepsis in ED patients with organ failure. Further, presepsin was found to be associated with 30-day mortality in ED patients with organ failure, regardless of hypercreatinemia.

Keywords

Kidney; Short-term mortality; Procalcitonin; Organ dysfunction scores

1. Introduction

The soluble cluster of differentiation 14 subtype (sCD14-ST; presepsin), identified in 2005, is a biomarker involved in pathogen recognition by the innate immunity [1]. CD14 is a free fragment of glycoprotein expressed on the surface of monocytes and macrophages. Soluble CD14 is secreted from cells or produced when membrane-bound CD14 detaches from cells such as phagocytes [2]. sCD14-ST is a 13 kDa protein composed of N-terminal fragments and mediates immune responses to lipopolysaccharides [1, 3].

Presepsin was reported to be a valuable biomarker for sepsis, with both diagnostic and prognostic significance [3–8]. Meta-analyses have shown that the diagnostic value of presepsin was comparable to that of procalcitonin (PCT) in discriminating sepsis [9, 10]. Yang *et al.* [11] showed that presepsin had prognostic value in adult patients with sepsis in various clinical settings. Some emergency department (ED)-based studies have also demonstrated the promising diagnostic and prognostic values of presepsin in patients with sepsis [12–14]. Since the release of the International Consensus Definitions for Sepsis-3 [15], studies have validated the diagnostic value of presepsin based on these definitions [16, 17]. Presepsin levels have been shown to significantly correlate with the severity of sepsis [18, 19] and kidney functions [20–24]. It has also been positively correlated with serum creatinine levels but negatively correlated with glomerular filtration rate (GFR) [21–23]. According to the findings of an observational study, presepsin levels were found to be correlated with cystatin C levels in patients with chronic kidney disease (CKD) [23] and

were also reported to predict sepsis-related acute kidney injury (AKI) in patients with sepsis [24].

To our knowledge, no study has investigated the diagnostic and prognostic values of presepsin levels in ED patients stratified by creatine levels and sepsis status using the Sepsis-3 definitions. Thus, this study aimed to investigate the clinical significance of presepsin in diagnosing sepsis and predicting the mortality risk of organ failure patients with and without hypercreatinemia in an ED setting.

2. Materials and methods

2.1 Study design and population

This is a single-center retrospective cohort study conducted using the data of patients collected from July 2019 to August 2020 who had positive quick sequential organ failure assessment (qSOFA) scores. The patients were treated at the ED of the Korea University Ansan Hospital, which is a 910-bed tertiary teaching hospital with approximately 50,000 ED visits annually. The study adhered to the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients who met the qSOFA criteria at ED presentation were initially screened by the qSOFA alert system of our institution. Adult ($\geq$18 years old) patients whose SOFA score increased by $\geq$2 points from the baseline were included in this study. For patients without a baseline (previous) SOFA score, an independent infectious disease expert reviewed their medical records and laboratory results to estimate their baseline SOFA score and determine the association between their presenting infection and the SOFA score. Patients whose presepsin and PCT levels were measured in the ED were selected. Their clinical data on age, sex, underlying diseases, initial vital signs, and laboratory results were collected, and their early warning scores and severity indices, such as the National Early Warning Score (NEWS), Modified Early Warning Score (MEWS), Acute Physiology and Chronic Health Evaluation (APACHE) II, and SOFA score, were calculated. Cases with unknown clinical outcomes (30-day mortality), a SOFA score of $<$2, experienced cardiac arrest upon ED arrival, visited the ED for trauma care, or without presepsin or PCT levels data were excluded.

The enrolled patients were classified into four groups according to the presence of sepsis and hypercreatinemia: group 1 (sepsis with hypercreatinemia), group 2 (sepsis without hypercreatinemia), group 3 (non-sepsis with hypercreatinemia), and group 4 (non-sepsis without hypercreatinemia), and their clinical variables, laboratory results, biomarkers, and clinical outcomes were compared. The accuracy of presepsin for diagnosing sepsis was compared with that of PCT and C-reactive protein (CRP) in patients stratified by hypercreatinemia. Receiver operating characteristic (ROC) curve analyses were used to evaluate the diagnostic and prognostic performance of the individual biomarkers and determine the optimal cutoff values for diagnosing sepsis and predicting the patients' 30-day mortality, respectively. The accuracy of presepsin in predicting 30-day mortality was also compared with that of PCT and CRP. The Kaplan-Meier survival curve analysis and the log-rank test were performed based on the obtained optimal cutoff value to diagnose sepsis and predict the 30-day mortality in patients with and without hypercreatinemia.

2.2 Definitions

The qSOFA score is a screening tool for identifying sepsis patients with poor prognoses and is calculated using the following criteria: a Glasgow coma scale (GCS) score of $<$15, a respiratory rate of $\geq$22 and a systolic blood pressure of $\leq$100 mmHg [15]. Each component is assigned with a score of 1 point, and a total score of $\geq$2 is considered a positive qSOFA score. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. The SOFA score is composed of scores from six organ systems: respiratory, coagulation, hepatic, cardiovascular, neurological, and renal systems [15]. The score for each system ranges from 0 to 4 points, depending on the severity of organ dysfunction. The criteria for diagnosing sepsis include an increase in the SOFA score by $\geq$2 points due to current infection [15]. An infectious disease expert independently determined the presence of infection in all patients by reviewing their medical records and laboratory results. In this present study, hypercreatinemia, indicated by a creatinine level of $\geq$1.2 mg/dL, was defined as SOFA scores $\geq$1 point. Early warning scores have been established to improve the early detection and rapid response to patient deterioration. NEWS and NEWS2 have been used to differentiate between an increased risk of unplanned intensive care unit (ICU) admission, cardiac arrest, and mortality [25, 26]. MEWS was used to assess an increased mortality risk based on physiological factors and is used in various clinical settings, including triage [27].

2.3 Measurement

Plasma presepsin levels were measured in the ED using an automated chemiluminescent enzyme immunoassay (PATHFAST system; LSI Medience Corporation, Tokyo, Japan) and ranged between 20–20,000 pg/mL, according to the manufacturer's manual. Since the measurement was performed after the disposition of patients, the ED physicians were unaware of the patients' presepsin levels. Therefore, the presepsin levels did not affect the physicians' diagnosis, management, or disposition. The PCT levels were measured using an automated electrochemiluminescence assay (BRAHMS; Hennigsdorf, Germany) based on the Roche Cobas e-system (Roche Diagnostics, Basel, Switzerland), with a range of 0.02–100 ng/mL, according to the manufacturer's manual.

2.4 Statistical analysis

Based on the findings of previous studies, the 30-day mortality of patients with sepsis is estimated to be 30% [2, 3]. A study using the Sepsis-3 definitions showed that the area under the ROC (AUROC) to discriminate sepsis from non-sepsis was 0.88 for presepsin [17]. Hence, we hypothesized that a similar AUROC would be observed in this present study. Assuming a 90% power with two-sided alpha levels of 0.05, this present study required 393 patients (252 patients with sepsis and 141 with organ failure without infection). To compare

the clinical variables and outcomes among the four groups, continuous variables, expressed as median and interquartile range, were compared using the Kruskal-Wallis test. The data were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables, expressed 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 the four groups. The Bonferroni correction was used to adjust the p values of post-hoc analyses. The diagnostic accuracy of presepsin in patients with and without hypercreatinemia was assessed using AUROC analysis. The optimal cutoff values for the diagnosis of sepsis in patients with and without hypercreatinemia were calculated using the Youden's index, and the optimal cutoff value for predicting the 30-day mortality was also calculated. Kaplan-Meier survival curve analysis and log-rank tests were performed according to the presepsin diagnostic and prognostic cutoff. The R (version 4.0, R Foundation for Statistical Computing, Vienna, Austria), SPSS (version 25.0, IBM, Armonk, NY, USA) and MedCalc for Windows (version 19.8, MedCalc Software, Mariakerke, Belgium) software were used for statistical analyses. A statistician from our institution oversaw all the analyses during the study period. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Baseline characteristics of the study population

A flowchart of the study protocol is shown in Fig. 1. Of the 609 patients with a qSOFA score $\geq$2 points screened, 189 were excluded because 92 patients were without measurement data on presepsin or PCT levels, 33 had unknown outcomes (30-day mortality), 29 received trauma care at the ED, 23 had a SOFA score $<$2 points and 12 experienced cardiac arrest upon arrival at the ED. Thus, 420 patients were eligible for the analysis. Among them, 176 patients were assigned to group 1, 102 to group 2, 53 to group 3, and 89 assigned to group 4. The baseline characteristics of the study population are presented in Table 1. The patients' age, sex, comorbidities, initial GCS and vital signs, infection-related biomarkers, arterial blood gas analysis, laboratory results, clinical severity scores, and clinical outcomes among the four groups were compared. Our results showed that patients from group 1 had the highest 7-day, 14-day and 30-day mortality rates among all groups, while those from group 4 had the lowest 7-day, 14-day and 30-day mortality rates (Table 1).

The presepsin levels between each group were also compared and presented using box plots (Fig. 2). Bonferroni correction showed that the significant p-value in each pairwise comparison was 0.05/6 (=0.0083). Our results showed that the presepsin levels of group 1 were significantly higher than group 2 ($p < 0.001$). We also observed that the presepsin levels of group 2 were higher than group 3 ($p = 0.002$), and those of group 3 were higher than group 4 ($p < 0.001$). Table 2 shows the presepsin levels according to the different levels of creatinine and stratified by the renal component of the SOFA score.

3.2 Diagnostic value of presepsin

Fig. 3 shows the ROC curves of presepsin, PCT and CRP levels for diagnosing sepsis in patients with and without hypercreatinemia. Table 3 shows the AUROC (95% confidence interval (CI)), optimal cutoff value, sensitivity and specificity of each biomarker for diagnosing sepsis among the patients stratified by hypercreatinemia. The AUROC and optimal cutoff values of presepsin for diagnosing sepsis in patients with hypercreatinemia were 0.884 (0.836–0.923) and 706 pg/mL, respectively, while those in patients without hypercreatinemia were 0.854 (0.795–0.901) and 352 pg/mL, respectively. Among all patients, the AUROC and optimal cutoff values were 0.877 (0.841–0.906) and 572 pg/mL, respectively.

3.3 Prognostic value of presepsin

The prognostic value of each biomarker is presented as AUROC, optimal cutoff value, sensitivity and specificity (Table 4). The overall AUROC (95% CI; p value) and optimal cutoff values of presepsin for predicting 30-day mortality were 0.645 (0.588–0.699; $p < 0.001$) and 881 pg/mL, respectively. Among patients with hypercreatinemia, the AUROC and optimal cutoff values for predicting 30-day mortality were 0.607 (0.531–0.680; $p = 0.018$) and 1077 pg/mL, respectively, while those in patients without hypercreatinemia were 0.691 (0.604–0.768; $p < 0.001$) and 393 pg/mL, respectively. Our results showed that PCT level could effectively predict 30-day mortality among patients without hypercreatinemia (AUROC = 0.630; $p = 0.015$), but could not be used to predict 30-day mortality (AUROC = 0.576; $p = 0.093$) among hypercreatinemia patients. CRP level could not predict 30-day mortality regardless of hypercreatinemia.

Kaplan-Meier survival curve analyses were performed using the presepsin 30-day mortality prognostic and sepsis diagnostic optimal cutoff values in patients with and without hypercreatinemia (Fig. 4), and significant differences were observed between all survival curves (log-rank test: $p = 0.001$, $p < 0.001$, $p = 0.008$, and $p = 0.001$, respectively) (Fig. 4a–d).

4. Discussion

Although presepsin levels are known to be affected by CKD stage [20–23], there have been no studies on the diagnostic and prognostic value of presepsin in critically ill ED patients stratified by hypercreatinemia. In this present study, we found that presepsin levels could be effectively used to diagnose sepsis among ED patients with organ failure. However, the cutoff values of presepsin were affected by creatine levels, and different presepsin cutoffs were obtained for discriminating sepsis. In addition, we also found that different cutoff values of presepsin could be used to predict the 30-day mortality in ED patients with organ failure with and without hypercreatinemia.

An observational study reported that presepsin had diagnostic capability for sepsis regardless of the AKI status [28]. The optimal cutoff value for diagnosing sepsis in patients without AKI was 670 pg/mL (AUROC = 0.784), and was 864 pg/mL (AUROC = 0.698) in patients with AKI. However, the study excluded patients with end-stage kidney disease because they had extremely high presepsin levels, regardless of the sepsis

TABLE 1. Baseline characteristics of the study population.

Clinical variables	Sepsis with hypercreatinemia (n = 176)	Sepsis without hypercreatinemia (n = 102)	Non-sepsis with hypercreatinemia (n = 53)	Non-sepsis without hypercreatinemia (n = 89)	*p* value
Age	77.0 (62.0–84.0)	77.0 (67.0–83.0)	74.0 (58.0–84.0)	63.0 (49.0–77.0)	<0.001
Male Gender	101 (57.4%)	61 (59.8%)	37 (69.8%)	45 (50.6%)	0.156
Comorbidities					
DM	76 (43.2%)	29 (28.4%)	15 (28.3%)	22 (24.7%)	0.007
Hypertension	98 (55.7%)	46 (45.1%)	26 (49.1%)	34 (38.2%)	0.048
Malignancy	27 (15.3%)	15 (14.7%)	11 (20.8%)	12 (13.5%)	0.694
Lung diseases	11 (6.2%)	11 (10.8%)	4 (7.5%)	5 (5.6%)	0.482
Liver diseases	14 (8.0%)	5 (4.9%)	3 (5.7%)	6 (6.7%)	0.785
CKD	25 (14.2%)	2 (2.0%)	6 (11.3%)	1 (1.1%)	<0.001
ESKD on dialysis	14 (8.0%)	0 (0.0%)	2 (3.8%)	1 (1.1%)	<0.001
Cardiovascular diseases	20 (11.4%)	8 (7.8%)	4 (7.5%)	6 (6.7%)	0.563
Cerebrovascular diseases	38 (21.6%)	22 (21.6%)	6 (11.3%)	14 (15.7%)	0.279
Initial GCS and vital sign					
GCS	12 (9–14)	10 (9–13)	11 (9–14)	11 (9–14)	0.214
SBP (mmHg)	95 (83–122)	99 (89–129)	119 (96–149)	111 (94–154)	<0.001
DBP (mmHg)	57 (49–70)	64 (55–74)	68 (56–92)	68 (58–91)	<0.001
HR	106 (86–121)	104 (90–126)	102 (84–128)	99 (79–120)	0.327
RR	24 (18–28)	24 (20–28)	24 (22–26)	22 (22–24)	0.593
BT (°C)	36.9 (36.0–38.1)	37.2 (36.3–38.1)	36.6 (36.1–37.3)	36.8 (36.3–37.2)	0.010
SpO_2	95 (91–98)	95 (90–99)	97 (92–98)	97 (95–99)	0.007
Infection-related biomarkers					
Presepsin (pg/mL)	1311.5 (732.0–2179.5)	566.5 (353.0–928.0)	400.0 (291.0–579.0)	231.0 (154.0–346.0)	<0.001
CRP (mg/dL)	9.4 (3.9–18.2)	7.9 (3.8–15.1)	0.7 (0.2–2.5)	0.5 (0.1–2.3)	<0.001
Procalcitonin (ng/dL)	2.2 (0.7–11.0)	1.3 (0.3–5.6)	0.1 (0.1–0.3)	0.1 (0.0–0.2)	<0.001
Arterial blood gas analysis					
pH	7.342 (7.264–7.436)	7.388 (7.331–7.464)	7.235 (7.196–7.7.408)	7.379 (7.339–7.456)	0.001
PaO_2 (mmHg)	78.4 (59.9–113.3)	72.0 (57.0–113.1)	86.5 (75.0–131.0)	89.0 (72.3–133.2)	<0.001
$PaCO_2$ (mmHg)	30.7 (24.0–39.4)	35.0 (30.0–47.3)	38.4 (30.8–49.1)	37.8 (30.6–45.4)	<0.001
HCO_3 (mmol/L)	18.8 (13.2–23.4)	21.8 (18.3–27.4)	19.6 (15.3–22.0)	23.4 (20.6–26.2)	<0.001
PO_2/FiO_2	160.8 (88.5–292.4)	128.0 (77.1–236.2)	245.0 (96.2–390.6)	254.7 (170.8–339.9)	<0.001
Laboratory results					
Lactate (mmol/L)	3.8 (2.0–7.2)	2.4 (1.7–5.7)	3.1 (1.8–6.5)	2.2 (1.5–4.0)	0.002
Hematocrit	32.1 ± 9.1	33.0 ± 7.1	37.5 ± 10.5	37.9 ± 7.1	<0.001
WBC (1000/mL)	11.8 (8.3–19.8)	11.1 (6.8–16.2)	11.8 (7.3–15.8)	11.0 (8.6–14.0)	0.175
Platelet (1000/mL)	183 (103–276)	209 (152–295)	200 (142–250)	231.0 (181–293)	<0.001
Bilirubin (mg/dL)	0.8 (0.4–1.5)	0.6 (0.4–0.9)	0.6 (0.3–1.1)	0.5 (0.3–0.7)	0.001
Creatinine (mg/dL)	2.1 (1.5–3.3)	0.8 (0.6–1.0)	1.5 (1.3–2.2)	0.8 (0.6–0.9)	<0.001

TABLE 1. Continued.

Clinical variables	Sepsis with hypercreatinemia (n = 176)	Sepsis without hypercreatinemia (n = 102)	Non-sepsis with hypercreatinemia (n = 53)	Non-sepsis without hypercreatinemia (n = 89)	*p* value
Clinical severity scores					
NEWS	10.8 ± 3.0	10.7 ± 2.9	9.5 ± 3.3	8.8 ± 2.8	<0.001
NEWS II	10.7 ± 3.0	10.8 ± 3.0	9.5 ± 3.4	8.6 ± 2.8	<0.001
MEWS	6 (5–7)	6 (5–8)	5 (4–7)	5 (4–7)	0.012
SOFA	9 (7–12)	7 (5–9)	7 (5–9)	4 (3–6)	<0.001
APACHE II	29.6 ± 7.5	26.1 ± 6.6	25.9 ± 7.5	21.9 ± 7.5	<0.001
Clinical outcomes					
7-day mortality	34 (19.3%)	14/102 (13.7%)	4/53 (7.5%)	3/89 (3.4%)	0.009
14-day mortality	43 (24.4%)	21/102 (20.6%)	6/53 (11.3%)	5/89 (5.6%)	0.012
30-day mortality	50 (28.4%)	24/102 (23.5%)	8/53 (15.1%)	7/89 (7.9%)	0.020

DM, diabetes mellitus; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GCS, Glasgow coma scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; BT, body temperature; SpO_2, peripheral oxygen saturation; CRP, C-reactive protein; PaO_2, pressure of arterial oxygen; $PaCO_2$, pressure of arterial carbon dioxide; HCO_3, bicarbonate; FiO_2, fraction of inspired oxygen; WBC, white blood cell; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; SOFA, sequential organ failure assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

TABLE 2. Presepsin levels according to the different levels of creatinine stratified by renal component of SOFA score.

Creatinine levels (mg/dL)	Presepsin levels (pg/mL)		
	Total (n = 420)	Non-sepsis (n = 142)	Sepsis (n = 278)
<1.2	547 ± 642	273 ± 190	787 ± 687
1.2–1.9	937 ± 1012	354 ± 148	1217 ± 1125
2.0–3.4	1919 ± 1714	620 ± 289	2153 ± 1887
3.5–4.9	2699 ± 2018	625 ± 604	3044 ± 2125
>5.0	4305 ± 3644	852 ± 266	4933 ± 4794

SOFA, sequential organ failure assessment.

TABLE 3. Comparisons of diagnostic value (discriminating sepsis) of tested biomarkers, expressed as the area under the receiver operating characteristic curve.

Biomarkers	Patients	AUROC (95% CI)	Cutoff value	Sensitivity	Specificity
Presepsin					
	Hypercreatinemia (n = 229)	0.884 (0.836–0.923)	706 pg/mL	76.6 (69.8–82.7)	88.7 (77.0–95.7)
	Without hypercreatinemia (n = 191)	0.854 (0.795–0.901)	352 pg/mL	75.5 (66.0–83.5)	78.7 (68.7–86.6)
	Total (n = 420)	0.877 (0.841–0.906)	582 pg/mL	70.1 (64.4–75.5)	89.44 (83.2–94.0)
Procalcitonin					
	Hypercreatinemia (n = 229)	0.925 (0.883–0.955)	0.597 ng/mL	77.3 (70.4–83.2)	96.2 (87.0–99.5)
	Without hypercreatinemia (n = 191)	0.873 (0.817–0.917)	0.512 ng/mL	67.7 (57.7–76.6)	93.3 (85.9–97.5)
	Total (n = 420)	0.908 (0.877–0.934)	0.512 ng/mL	75.5 (70.0–80.5)	93.0 (87.4–96.6)
CRP					
	Hypercreatinemia (n = 229)	0.879 (0.830–0.918)	3.53 mg/dL	77.3 (70.4–83.2)	86.8 (74.7–94.5)
	Without hypercreatinemia (n = 191)	0.834 (0.773–0.883)	2.84 mg/dL	80.4 (71.4–87.6)	80.9 (71.2–88.5)
	Total (n = 420)	0.858 (0.821–0.890)	3.53 mg/dL	77.0 (71.6–81.8)	85.2 (78.3–90.6)

AUROC, area under the receiver operator characteristic curve; CI, confidence interval; CRP, C-reactive protein.

TABLE 4. Comparisons of prognostic value (predicting 30-day mortality) of tested biomarkers, expressed as the area under the receiver operating characteristic curve.

Biomark	Patients	AUROC (95% CI)	*p* value	Cutoff value	Sensitivity	Specificity
Presepsin						
	Hypercreatinemia (n = 229)	0.607 (0.531–0.680)	0.018	1077 pg/mL	67.2 (53.7–79.0)	56.0 (46.5–65.2)
	Without hypercreatinemia (n = 191)	0.691 (0.604–0.768)	<0.001	393 pg/mL	77.4 (58.9–90.4)	61.0 (50.7–70.6)
	Total (n = 420)	0.645 (0.588–0.699)	<0.001	881 pg/mL	56.2 (45.3–66.7)	67.1 (60.4–73.4)
Procalcitonin						
	Hypercreatinemia (n = 229)	0.576 (0.499–0.651)	0.093	0.615 ng/mL	72.4 (61.0–84.7)	40.5 (31.5–50.0)
	Without hypercreatinemia (n = 191)	0.630 (0.541–0.712)	0.015	0.112 ng/mL	93.6 (78.6–99.2)	35.9 (25.7–45.2)
	Total (n = 420)	0.608 (0.550–0.663)	0.002	0.483 ng/mL	71.8 (61.4–80.9)	48.2 (41.3–55.0)
CRP						
	Hypercreatinemia (n = 229)	0.570 (0.493–0.645)	0.134	7.18 mg/dL	62.1 (48.4–74.5)	52.6 (43.1–61.9)
	Without hypercreatinemia (n = 191)	0.601 (0.512–0.686)	0.091	5.61 mg/dL	61.3 (42.2–78.2)	64.0 (53.8–73.4)
	Total (n = 420)	0.593 (0.536–0.649)	0.099	7.42 mg/dL	57.3 (46.4–67.7)	61.6 (54.7–68.1)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CRP, C-reactive protein.

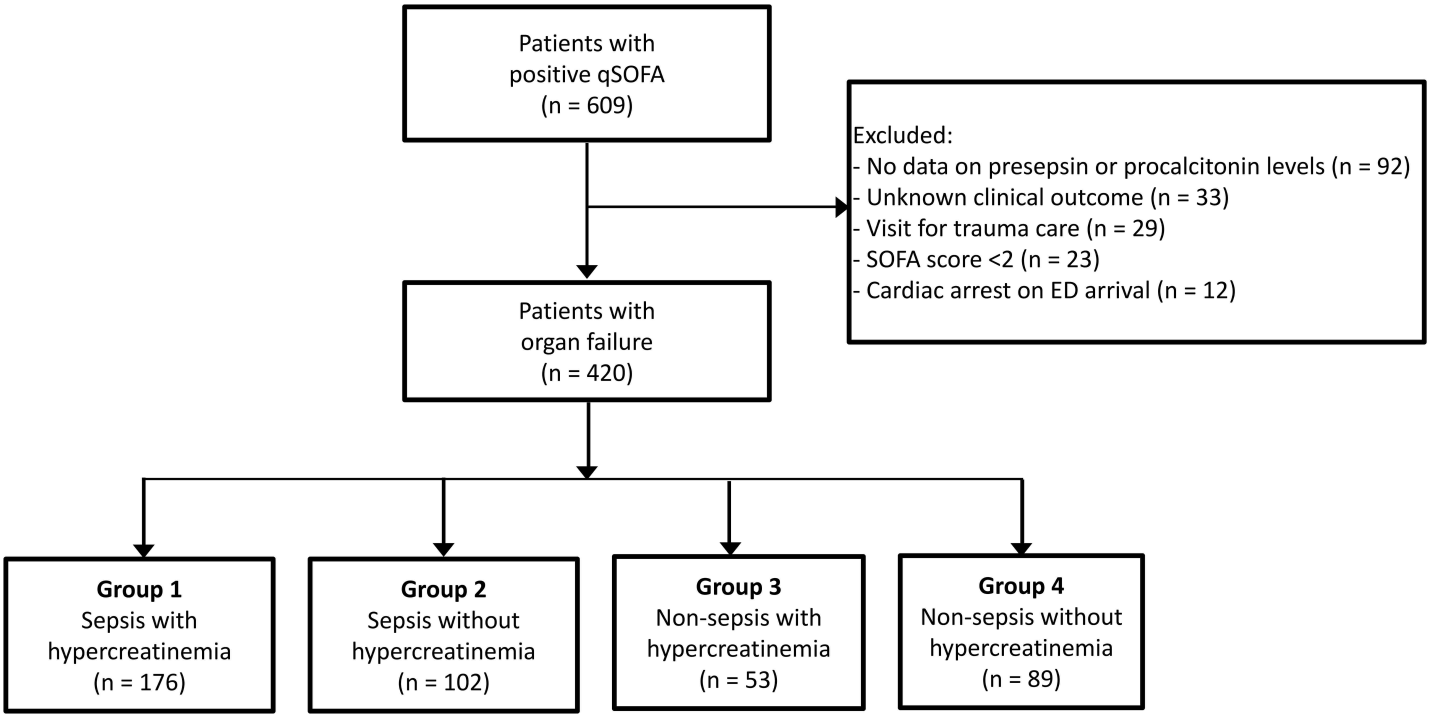

FIGURE 1. Flowchart of the study population. SOFA, sequential organ failure assessment; ED, emergency department.

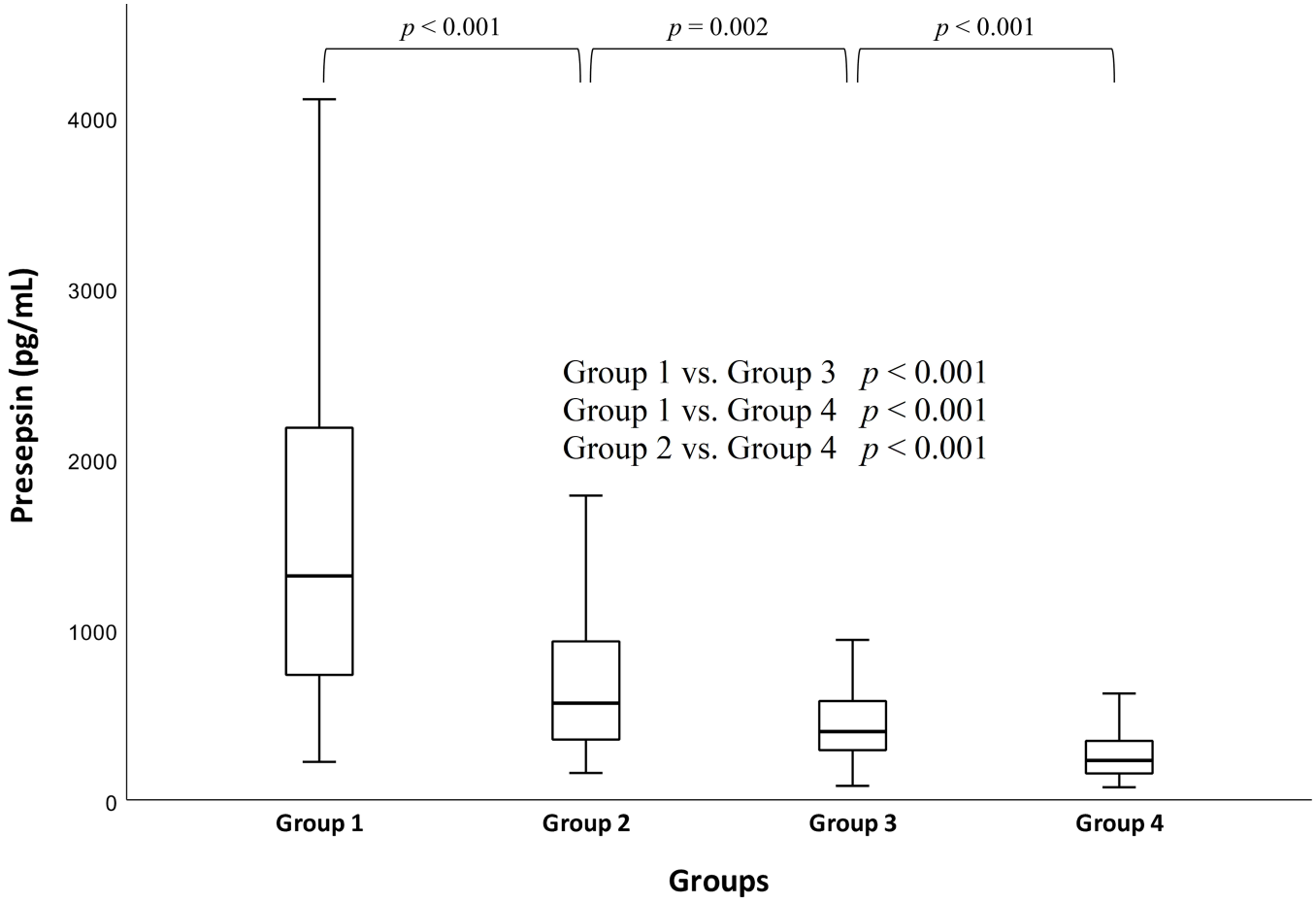

FIGURE 2. Comparison of presepsin levels between the groups using box plot. Group 1: Sepsis with hypercreatinemia; Group 2: Sepsis without hypercreatinemia; Group 3: Non-sepsis with hypercreatinemia; Group 4: Non-sepsis without hypercreatinemia.

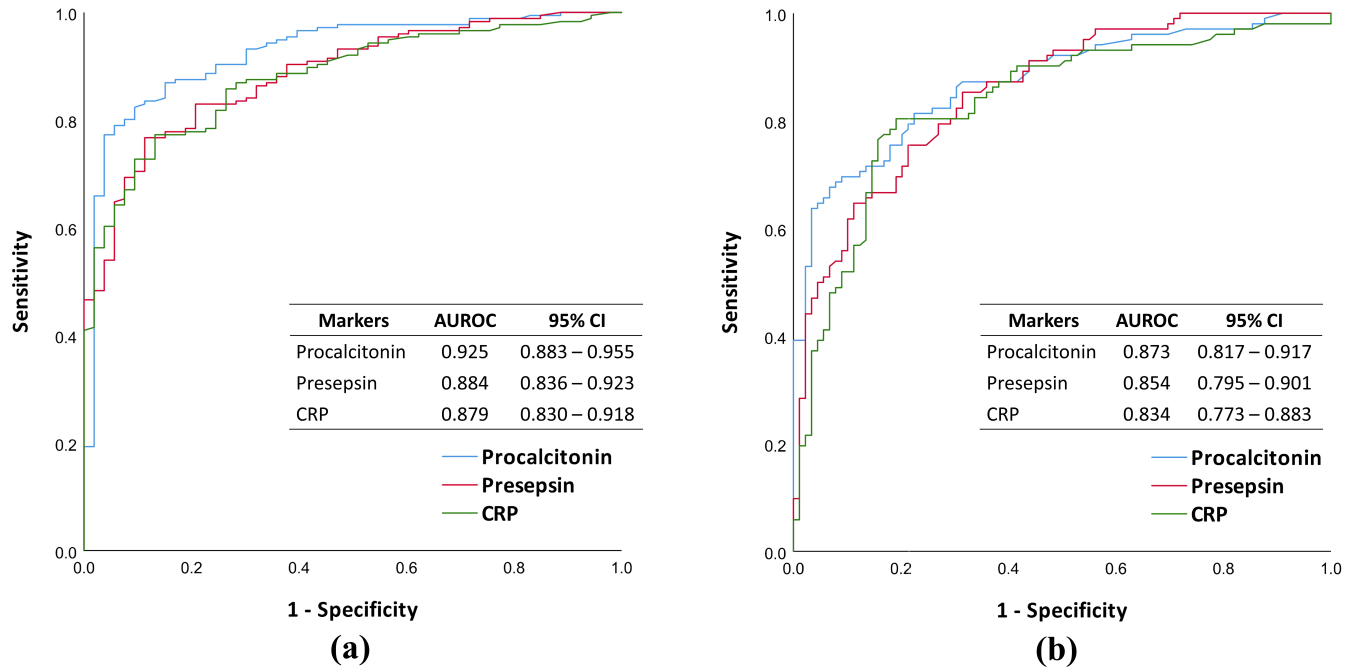

FIGURE 3. Receiver operating characteristic curves of presepsin, procalcitonin and CRP for diagnosing sepsis among patients with hypercreatinemia (a) and without hypercreatinemia (b). AUROC: area under the receiver operating characteristic curve; CI: confidence interval; CRP: C-reactive protein.

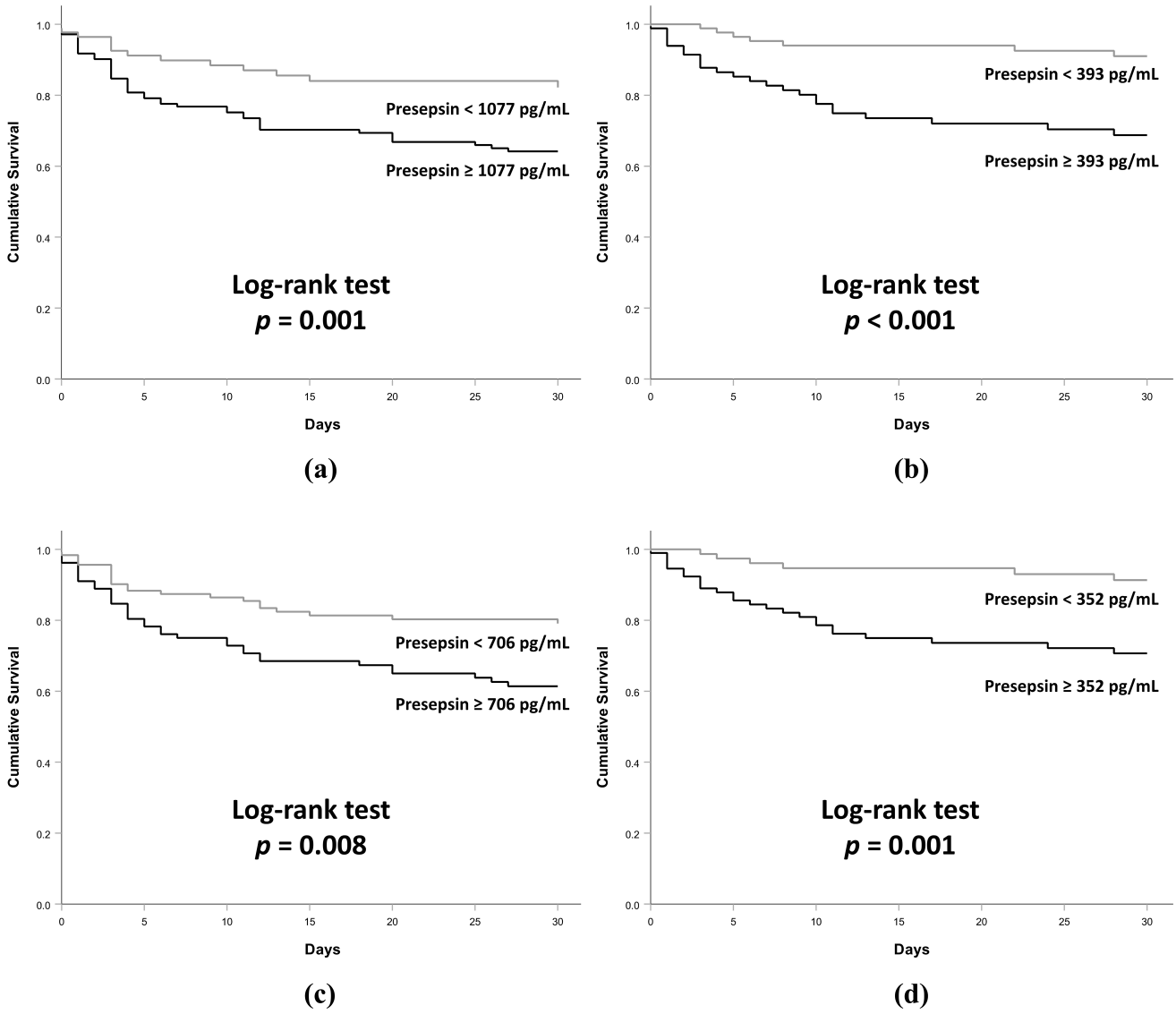

FIGURE 4. Kaplan-Meier survival analysis and log-rank test according to the optimal cutoff values for predicting the 30-day mortality and diagnosing sepsis in ED patients with organ failure. (a) Survival curves of patients with hypercreatinemia according to the prognostic cutoff value. (b) Survival curves of patients without hypercreatinemia according to the prognostic cutoff value. (c) Survival curves of patients with hypercreatinemia according to the diagnostic cutoff value. (d) Survival curves of patients without hypercreatinemia according to the diagnostic cutoff value.

status. A subsequent study by the same author showed that the diagnostic value of presepsin for sepsis was comparable to that of PCT [29]. Another study showed presepsin as a useful adjunct to distinguish between the absence and presence of infections in patients with AKI [23]. The optimal cutoff value to determine sepsis was higher in patients with AKI than those without AKI.

This present study showed that the prognostic value of presepsin was superior to PCT and CRP in critically ill ED patients. Presepsin successfully predicted 30-day mortality irrespective of hypercreatinemia, while PCT could not predict the 30-day mortality in patients with hypercreatinemia, and CRP failed to predict the 30-day mortality irrespective of hypercreatinemia.

According to a recent meta-analysis, the presepsin levels of non-survivors were significantly higher than survivors of sepsis [11]. Most studies included in the meta-analysis directly compared the median presepsin levels between survivors and non-survivors, whereas our study assessed the prognostic value of presepsin using AUROC, the optimal cutoff value to predict mortality, as well as its sensitivity and specificity. In addition, the number of ED-based studies included in previous meta-analyses was limited. It was reported that the plasma levels of presepsin increase early during sepsis and have a half-life of 4–5 h [30]. Therefore, the presepsin levels measured in the ED can help clinicians identify the early occurrence of sepsis. Further, most of the included studies defined sepsis using the Sepsis-2 criteria, while one of the strengths of our study is that it was performed in an ED setting using the Sepsis-3 definition.

The systemic inflammatory response syndrome (SIRS) criteria have a relatively higher sensitivity but lower specificity for screening severe sepsis (Sepsis-2), which corresponds to

sepsis (Sepsis-3), indicating that it might be valuable to compare previous studies using the SIRS criteria with those using the Sepsis-3 definitions to further determine the diagnostic value of presepsin. Contrary to the SIRS criteria, the Sepsis-3 definitions mainly focus on the presence of organ failure caused by pathologic infections [15]. The 2021 Surviving Sepsis Campaign guidelines do not recommend using qSOFA compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis and septic shock due to its poor sensitivity [31].

An observational study showed that an optimal presepsin cutoff value of 957.5 ng/L could be used to predict the 28-day mortality of patients with sepsis [32], and screening performed with the SIRS criteria could identify an earlier increase in presepsin levels. Another study showed that presepsin could predict 30-day mortality in sepsis patients admitted to the ICU using an optimal cutoff value of 2455 pg/mL, while PCT level was not a predictor of 30-day mortality [2]. A previous study in ICU settings further demonstrated that an optimal presepsin cutoff value of 2623 pg/mL could more effectively predict in-hospital mortality than PCT [33]. It can be seen that the cutoff values reported by these previous studies were higher than in our present study. We hypothesized that this difference might not only be due to using different screening tools (SIRS *vs.* qSOFA) but also due to the different clinical settings (ICU *vs.* ED).

Our study had some limitations. First, this was a single-center ED-based retrospective study. Second, the study was performed using the data from a registry containing patients who met qSOFA criteria at ED presentation. Therefore, critically ill patients who did not meet the qSOFA criteria were not included in this study. Third, kidney dysfunction was not classified as either AKI or CKD, and the retrieved data did not contain other biomarkers such as neutrophil gelatinase-associated lipocalin or cystatin C, which can reflect kidney dysfunction. Fourth, patients with hypercreatinemia were considered as a single group and were not classified into several groups based on disease severity. Therefore, future studies containing data on patients classified by kidney dysfunction severity are required. Fifth, although serum creatinine levels have different reference ranges in men (0.6–1.2 mg/dL) and women (0.5–1.0 mg/dL), our study used the renal component of the SOFA score to define hypercreatinemia. Thus, a larger sample size might be required to analyze the probable gender bias in our study. Lastly, we excluded patients whose presepsin levels were not measured, which might have caused a certain level of selection bias.

5. Conclusions

In conclusion, this study showed that presepsin had better prognostic value than PCT and CRP, and could be a vital tool to help clinicians diagnose sepsis in ED patients with organ failure and predict their 30-day mortality. However, our results also showed that the optimal cutoff value of presepsin was higher in patients with hypercreatinemia than those without hypercreatinemia, indicating that clinicians might need to consider different diagnostic cutoff values for presepsin based on creatinine levels. Prospective multicenter studies are required to validate our findings and further evaluate the association between kidney dysfunction and presepsin levels in patients with organ failure.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

JS, HK, SL, DWP, SA, JK, JP, HC, SM and SC—Conceptualization; JS—Data curation; JS, SL and HK—Formal analysis; JS, SL and DWP—Investigation; JS, HK, SL and DWP—Methodology; JS, HK and SL—Resources; JS, SL and SA—Software; HC, SM and SC—Supervision; JS, HK and SL—Writing-original draft; JS, HK and SL—Writing-review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2020AS0031). The requirement for informed consent was waived due to the retrospective nature of the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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