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Original Contribution

Diagnostic accuracy of presepsin for sepsis by the new Sepsis-3 definitions

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ABSTRACT

1. Introduction

Early diagnosis of sepsis in the Emergency Department and intensive care unit (ICU) is important when treating septic patients. Novel biomarkers of sepsis have been developed and are being widely adopted in clinical settings. Among them, procalcitonin (PCT) has been widely used as biomarker in septic patients but has limited specificity. It increases transiently in patients with non-septic conditions and systemic inflammatory response syndromes (SIRS) (e.g., trauma, surgery, and heatstroke) [1].

Cluster of differentiation 14 (CD14) is a free fragment of glycoprotein expressed on monocytes and macrophages. It serves as a receptor of the lipopolysaccharide (LPS)-lipopolysaccharide binding protein complexes. Its soluble form, soluble CD14 (sCD14), is produced from cell secretion or when membrane-bound, CD14 (mCD14) detaches from cells such as phagocytes. The N-terminal fragments of 13 kDa consist of s CD14 subtype (sCD14-ST) called presepsin are related to mediating the immune response to LPS [2]. Presepsin is currently under investigation in clinical practice as a new biomarker of sepsis [3,4]. Four meta-analyses suggested that presepsin showed moderate diagnostic capacity for the detection of sepsis and may be a helpful and valuable biomarker in the early diagnosis of sepsis [5-8].

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) recently presented new definitions for sepsis and septic shock [9]. The international consensus has defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, but there has been little discussion about exactly how to determine whether infection is suspected. There are no clear guidelines to help the clinician identify the presence of early infection. Biomarkers for early diagnosis of infection are expected because a long time is required to evaluate clinical infection and obtain microbiological culture data in clinical practice before a diagnosis of infection can be made. It might be easy to diagnose septic shock in the early phase because these patients are truly critically ill and require catecholamine treatment. The early diagnosis of sepsis in patients without shock or obvious infection with systemic inflammation remains the most challenging problem. Most of the recent studies have discussed biomarkers for sepsis including shock, but no reports are currently available on diagnostic markers of sepsis without shock under the new definitions. Thus, the aim of this study was to investigate the diagnostic accuracy of presepsin compared to

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other biomarkers of sepsis, especially sepsis without shock, by the new Sepsis-3 definitions.

2. Material and methods

2.1. Patient inclusion and exclusion criteria

This prospective study was performed in the ICU of a tertiary university hospital. Inclusion criteria were patients fulfilling both SIRS criteria and an acute change in total Sequential Organ Failure Assessment (SOFA) score of 2 or more who were admitted to our ICU from February 2014 to August 2015. Exclusion criteria were age <18 years, post cardiac arrest syndrome, and a SOFA score of <2.

We retrospectively divided the patients into three groups based on the new definitions for sepsis: non-sepsis group, sepsis group, and septic shock group. Septic shock was defined as a change in SOFA score >2, hypotension with vasopressors, and a lactate level >2 mmol/L. Blood samples for biomarker measurements of presepsin, PCT, C-reactive protein (CRP), and white blood cells (WBC) were collected immediately after clinical onset of disease resulting in an acute change in the total SOFA score of 2 or more. A diagnosis of disseminated intravascular coagulation (DIC) was made on the basis of the Japanese Association for Acute Medicine DIC diagnostic criteria [10].

This study was approved by the institutional review boards of our university and each participating institution. Written informed consent was obtained from the patients or the patients' families at the clinical onset of symptoms fulfilling the criteria for SIRS.

2.2. Diagnosis of infection

Evaluation of infection in our study was based on clinical course, imaging tests, and laboratory findings according to the criteria of the International Sepsis Forum Consensus Conference on Definitions of Infection [11]. The six most common infectious conditions were identified as pneumonia, bloodstream infections, intravascular catheter-related sepsis, intra-abdominal infections, and urinary tract and skin, and soft-tissue infections. After the end of hospital treatment, three study physicians independently reviewed all clinical data of the study patients and determined the presence of infection based on the above criteria. The study physicians were blinded to the results of tested biomarker measurements, such as presepsin, PCT, CRP, and WBC.

2.3. Statistical analysis

To estimate the sample size, we assumed the incidence of sepsis in the patients with high presepsin levels to be 70% and the incidence of sepsis in the patients with low presepsin levels to be 30% based on the results of the previous study [12]. Assuming 90% power with a 2-sided α levels of 0.05, this study required a total of 72 patients to detect the significance in 40% difference between the groups. Continuous variables were given as median and interquartile range and were compared using the Mann-Whitney *U* test. Between-group differences in categorical variables were compared using Fisher's exact test or a $\chi 2$ test as appropriate. The Kruskal-Wallis test with Bonferroni correction for multi-group comparisons was used to explore the results in each group (non-sepsis, sepsis, and septic shock) at the first clinical onset of a SOFA score of 2 or more. A receiver operating characteristic (ROC) analysis was performed for each of the biomarkers, and their diagnostic performance for septic shock/sepsis without shock vs. non-sepsis or sepsis without shock vs. non-sepsis were compared and the areas under the ROC curves (AUCs) were determined. The optimal cutoff values for each of the biomarkers in this study population were calculated for each ROC curve through the Youden index (corresponding to the maximum of the sum "sensibility + specificity"). On the basis of cutoff values, prognostic parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) and accuracy were also calculated.

For the multivariable analysis, odds ratios (OR) for septic shock/sepsis without shock compared to non-sepsis and sepsis without shock compared to non-sepsis in relation to the levels of each diagnostic marker and their 95% confidence intervals (CI) for the explanatory variables were computed using a logistic regression model. Variables for $p < 0.20$ in univariate analysis or those including age, CRP and WBC considered as medically significant or having potential associations with sepsis from previous studies [9,13,14] were employed in the multivariable analysis. Finally, we performed a multivariable logistic regression analysis adjusted for sex, age, SOFA score, presepsin, PCT, CRP, and WBC to evaluate the relations between these biomarkers. We did not use the APACHE II score as an adjustment variables because not all patients in this study were included within 24 h after admission. The cutoff values for each of the biomarkers from previous studies [13,14] were used in the multivariable analysis. We used the following cut-off values for the diagnosis of sepsis: 600 pg/mL for presepsin, 0.96 ng/mL for PCT, 8.4 mg/dL for CRP from recent systemic and meta-analysis [13], and <4000 or >12,000/mm^3 for WBC from the definition of SIRS [14]. The multivariable analysis using the optimal cutoff values for each of the biomarkers in this study population from ROC analysis was not employed because such models were not appropriately fitted due to strong correlation between presepisin and sepsis. The values for continuous variables, age and SOFA score in the multivariable analysis were categorized according to each mean value. A two-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using JMP Version 11.2 and SAS 9.3 (SAS Institute Inc., Cary, NC).

3. Results

Of 1014 patients admitted to the ICU during the 18-month study period, 109 consecutive patients fulfilled the SIRS criteria. After excluding 18 patients who did not meet the inclusion criteria, we enrolled 91 patients with an acute change in total SOFA score of 2 or more. We divided these patients into three groups based on the new definitions for sepsis: non-sepsis group (n = 29), sepsis group (n = 29), and septic shock group (n = 33) (Fig. 1). Nine patients in the non-sepsis group and 11 patients in the sepsis group were included during their ICU stay (median: 8 [8-13] days, median: 8 [8-10] days, respectively). All other patients were included at admission to the ICU.

Patient characteristics are presented in Table 1. The SOFA score at the first clinical onset of an acute change in the total score of 2 or more and the percentages of patients with shock, disseminated intravascular coagulation, renal replacement therapy, and in-hospital mortality were higher in the septic shock group than in the non-sepsis group or sepsis group. However, there was no significant difference between the non-sepsis 乏 group and the sepsis group in SOFA score (p = 0.20).

The definitive diagnosis and infectious foci of patients included in the study as obtained by analysis of the patients' digital medical records are shown in Table 2. CRP and WBC values were not significantly different between each group, but the median concentrations of PCT and presepsin were significantly higher in both the sepsis and septic shock groups compared to the non-sepsis group (non-sepsis vs. sepsis vs. septic shock group: PCT, 0.6 vs. 1.4 vs. 11.0 ng/mL, $p < 0.001$; presepsin, 349 vs. 817 vs. 1217 pg/mL, $p < 0.001$) (Fig. 2).

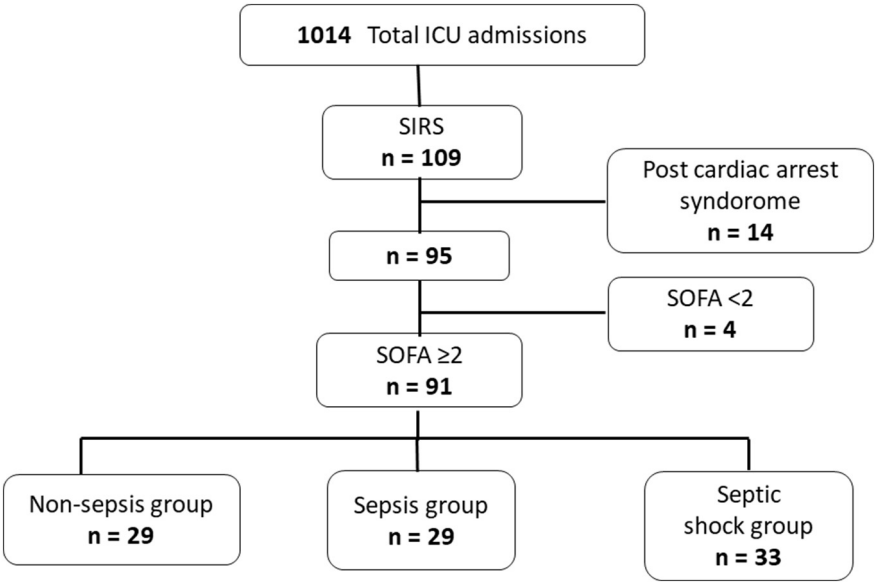

Fig. 1. Patient enrollment and classification. ICU, intensive care unit; SIRS, systemic inflammatory response syndromes; SOFA, Sequential Organ Failure Assessment.

Table 1
Patient characteristics.

Characteristic	Non-sepsis	Sepsis	Septic shock	
	n = 29	n = 29	n = 33	p value
Male, n (%)	15 (52)	19 (66)	24 (73)	0.13
Age (years)	66 (43–74)	63 (40–79)	69 (58–77)	0.39
SOFA score	5 (4–7)	6 (4–9)	12 (9–14)	<0.001
Shock, n (%)	4 (14)	0 (0)	33 (100)	<0.001
DIC, n (%)	3 (27)	14 (48)	22 (67)	<0.001
Renal replacement therapy, n (%)	0 (0)	4 (14)	12 (36)	0.005
In-hospital mortality, n (%)	1 (3)	3 (10)	13 (39)	<0.001

Abbreviations: SOFA, sequential organ failure assessment; DIC, disseminated intravascular coagulation.
Data are presented as median (25th to 75th percentile).

Table 2
Definitive diagnosis and infectious sites of the patients.

	Non-sepsis		Sepsis	Septic shock
	n = 29		n = 29	n = 33
Definitive diagnosis, n (%)		Primary site of infection, n (%)		
Major trauma	12 (41.4)	Pulmonary	11 (38.0)	12 (36.4)
GI bleeding	3 (10.4)	Urinary tract	4 (13.8)	8 (24.2)
Stroke	3 (10.4)	Intra-abdominal	6 (20.7)	3 (9.1)
Severe acute pancreatitis	2 (6.9)	Skin and soft tissue	4 (13.8)	6 (18.2)
Burns	2 (6.9)	Catheter related	2 (6.9)	0 (0)
Pulmonary embolism	1 (3.4)	Bloodstream	1 (3.4)	1 (3.0)
Acute coronary syndrome	1 (3.4)	No clear source	1 (3.4)	3 (9.1)
COPD	1 (3.4)	Causative organisms, n (%)		
Others	4 (13.8)	Infecting organism identified	18 (62.1)	29 (87.9)
		Blood culture positive	10 (34.5)	19 (58)
		Gram-positive bacteria	14 (48.3)	14 (42.4)
		Gram-negative bacteria	6 (20.7)	12 (36.4)
		Others (fungi, etc.)	1 (3.4)	2 (6.1)

Abbreviations: COPD, chronic obstructive lung disease; GI, gastrointestinal.
Data are presented as number (%).

The area under the curve (AUC) values of presepsin to distinguish sepsis including shock (septic shock/sepsis group) from non-sepsis (non-sepsis group) were 0.88 (95% CI, 0.77–0.94) for presepsin, 0.81 (95% CI, 0.71–0.88) for procalcitonin, 0.65 (95% CI, 0.53–0.75) for CRP, and 0.57 (95% CI, 0.45–0.68) for WBC (Fig. 3a). In the other hand, the area under the curve (AUC) values of presepsin to distinguish sepsis without shock (sepsis group) from non-sepsis (non-sepsis group) were 0.90 (95% CI, 0.76–0.96) for presepsin, 0.71 (95% CI, 0.57–0.83) for procalcitonin, 0.67 (95% CI, 0.52–0.79) for CRP, and 0.57 (95% CI, 0.42–0.72) for WBC (Fig. 3b). According to these AUC values, the sensitivity, specificity, PPV, NPV, and accuracy of presepsin to diagnose septic shock/sepsis using a cutoff value of 508 pg/mL were 87%, 86%, 93%, 76%, and 87%, respectively; those of PCT were 68%, 86%, 91%, 56%, and 74%

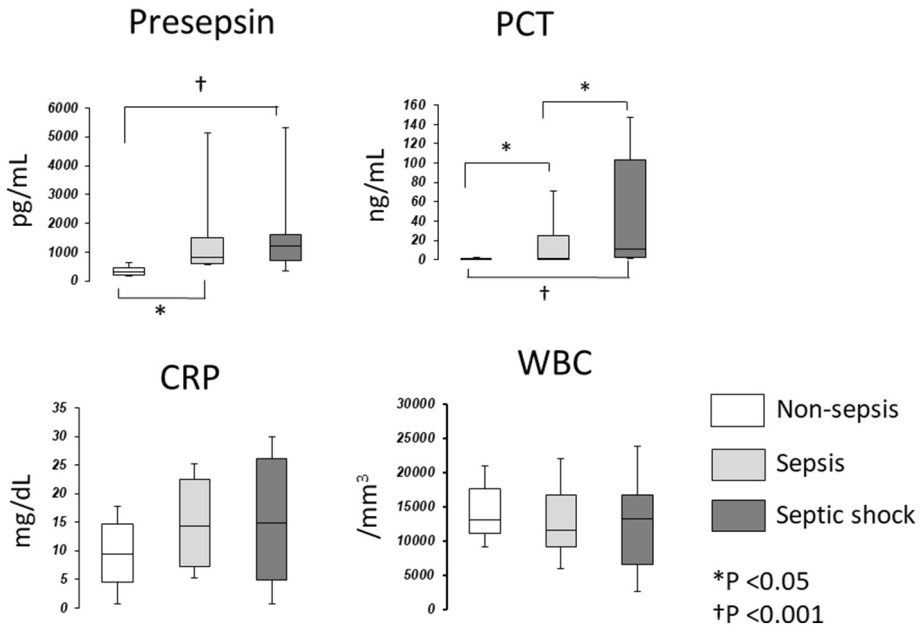

Fig. 2. Median values of diagnostic markers of sepsis in each group. White columns represent data for the non-sepsis group, light gray columns for the sepsis group, and dark gray columns for the septic shock group. Lines denote median values, boxes represent 25th to 75th percentiles, and whiskers indicate the range. CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cells.

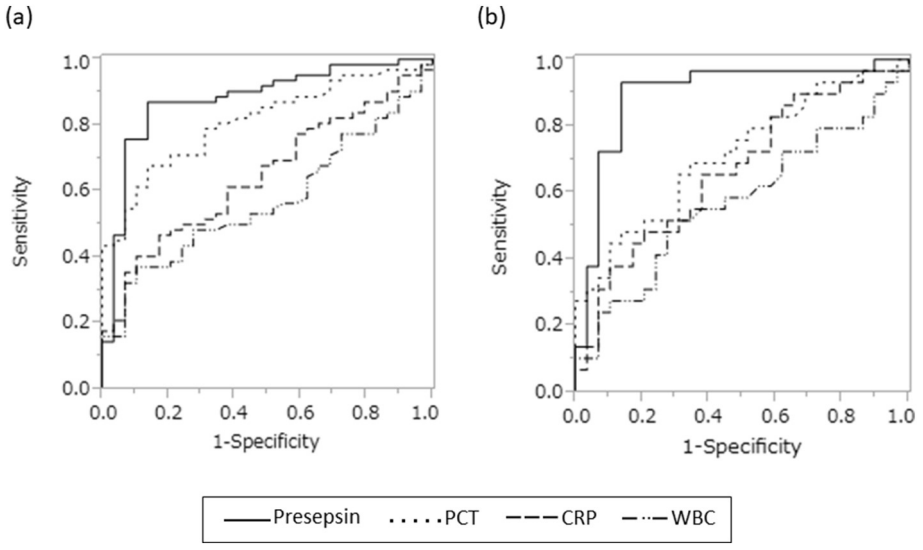

Fig. 3. Receiver operating characteristic curve for diagnostic markers of sepsis. The area under the curve for septic shock/sepsis without shock was 0.88 for presepsin, 0.81 for procalcitonin, 0.65 for CRP, and 0.57 for WBC (a). The area under the curve for sepsis without shock was 0.90 for presepsin, 0.71 for procalcitonin, 0.67 for CRP, and 0.57 for WBC (b). CRP, C-reactive protein; WBC, white blood cells.

using a cutoff value of 1.5 ng/mL; and those of CRP were 40%, 90%, 89%, 41%, and 56% using a cut-off value of 17.6 mg/dL. In the other hand, those of presepsin to diagnose sepsis without shock using a cutoff value of 557 pg/mL were 93%, 86%, 87%, 93%, and 90%, respectively; those of PCT were 69%, 66%, 67%, 68%, and 67% using a cutoff value of 0.79 ng/mL; and those of CRP were 66%, 62%, 63%, 64%, and 64% using a cutoff value of 11.9 mg/dL.

A multivariable logistic regression analysis adjusted for sex, age, SOFA score, presepsin, PCT, CRP, and WBC revealed that the OR of a high presepsin level (≥600 pg/mL) for sepsis including shock significantly increased compared to that of a low presepsin level (<600 pg/mL) (OR, 22.24; 95% CI, 5.59–121.88; $p < 0.001$) and the OR of a high PCT level (≥0.96 pg/mL) increased compared to that of a low PCT level (<0.96 pg/mL) (OR, 8.33; 95% CI, 2.27–36.69; $p = 0.001$). CRP, and WBC levels were not significantly associated with a diagnosis of sepsis including shock (Table 3). The multivariable analysis also revealed that the OR of a high presepsin level for sepsis without shock significantly increased compared to that of a low presepsin level (OR, 24.30; 95% CI, 5.21–176.24; $p < 0.001$) and the OR of a high PCT level increased compared to that of a low PCT level (OR, 4.97; 95% CI, 1.11–26.27; $p = 0.04$). CRP, and WBC levels were not significantly associated with a diagnosis of sepsis without shock (Table 4).

4. Discussion

This study investigated the diagnostic value of presepsin compared to other biomarkers (PCT, CRP, and WBC) of sepsis, especially

Table 3
Odds ratios of each diagnostic marker level for sepsis including shock (septic shock and sepsis group) compared to non-sepsis (non-sepsis group).

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Sex				
Male	2.42 (0.98–6.09)	0.006	4.56 (1.15–22.05)	0.03
Age (years)				
≥65	1.20 (0.49–2.93)	0.69	0.85 (0.22–3.17)	0.81
SOFA score				
≥5	6.30 (2.28–18.6)	<0.001	1.90 (0.47–7.56)	0.36
Presepsin (pg/mL)				
≥600	19.58 (6.42–74.98)	<0.001	22.24 (5.59–121.88)	<0.001
PCT (ng/mL)				
≥0.96	7.62 (2.93–21.34)	<0.001	8.33 (2.27–36.69)	0.001
CRP (mg/dL)				
≥8.4	1.60 (0.63–4.00)	0.32	0.59 (0.14–2.23)	0.44
WBC (/mm^3)				
<4000, >12,000	0.89 (0.35–2.22)	0.81	0.79 (0.19–3.08)	0.73

Abbreviations: SOFA, sequential organ failure assessment; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; OR, odds ratio; WBC, white blood cells.

Table 4
Odds ratios of each diagnostic marker level for sepsis without shock (sepsis group) compared to non-sepsis (non-sepsis group).

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Sex				
Male	2.04 (0.72–6.00)	0.18	2.11 (0.45–11.17)	0.35
Age (years)				
≥65	0.76 (0.27–2.13)	0.6	0.37 (0.06–1.81)	0.23
SOFA score				
≥5	2.45 (0.84–7.57)	0.1	0.94 (0.20–4.06)	0.94
Presepsin (pg/mL)				
≥600	16.41 (4.71–70.56)	<0.001	24.30 (5.21–176.24)	<0.001
PCT (ng/mL)				
≥0.96	3.64 (1.26–11.21)	0.017	4.97 (1.11–26.27)	0.04
CRP (mg/dL)				
≥8.4	1.85 (0.62–5.73)	0.27	1.00 (0.20–4.99)	0.99
WBC (/mm^3)				
<4000, >12,000	0.56 (0.19–1.61)	0.28	0.45 (0.08–2.04)	0.30

Abbreviations: SOFA, sequential organ failure assessment; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; OR, odds ratio; WBC, white blood cells.

sepsis without shock, considering the new Sepsis-3 definitions. Although no significant difference was observed in SOFA scores in the non-sepsis group and the sepsis group, the results showed that the AUC to distinguish septic shock/sepsis or non-sepsis and sepsis without shock or non-sepsis were the highest for presepsin. The logistic regression analysis using another cutoff values from previous reports also revealed that a high presepsin level was significantly associated with a diagnosis of sepsis including shock or sepsis without shock.

A recent systematic review and meta-analysis reported that PCT, CRP, and presepsin presented a moderate degree of diagnostic value with AUCs of 0.85, 0.77, and 0.88, respectively [13]. However, new definitions for sepsis and septic shock were published under Sepsis-3 in 2016, but since then, only a few reports have been published on diagnostic markers of sepsis under the new definitions. All previous studies classified patients as having SIRS, severe sepsis, and septic shock, or as having SIRS and sepsis including severe sepsis/septic shock. Only a few studies evaluated the diagnostic value of biomarkers including presepsin by comparing patients with SIRS with sepsis versus patients without severe sepsis/septic shock [12,15]. In addition, all previous studies used univariate analysis to evaluate diagnostic markers of sepsis, and no study has used multivariable analysis to evaluate the relations between these biomarkers.

The OR of presepsin for sepsis including shock or sepsis without shock compared to non-sepsis was significantly high among the biomarkers for sepsis. In addition, this study revealed the higher OR of presepsin for sepsis without shock than that of PCT. A few previous studies have suggested that the presepsin concentration was significantly higher in patients with sepsis in comparison to non-septic SIRS patients [12,15], but these were reports of retrospective observational studies and the evaluation of biomarkers including presepsin was conducted by univariate analysis. There was also some possibility of bias in relation to each of the biomarkers at the time of diagnosis of sepsis.

Several limitations of this study should be acknowledged. First, we used SIRS as the diagnosis for the first screening, so it is possible that patients who did not meet the SIRS criterion of a change in SOFA score of 2 or more were excluded from this study. The need for two or more SIRS criteria to define severe sepsis excluded one of eight otherwise similar patients with infection and organ failure [16]. Second, this study analyzed a limited number of patients from a single center. Third, this study focused on the diagnostic value of biomarkers for sepsis, but we could not evaluate relations between the biomarkers and prognosis. Future multicenter studies are needed to further evaluate diagnostic markers including presepsin for sepsis under the new Sepsis-3 definitions.

5. Conclusions

Presepsin appears to be useful in aiding in the diagnosis of sepsis including shock or especially sepsis without shock versus non-sepsis in patients with a change in SOFA score of 2 or more. Additional prospective research may be needed to evaluate the

diagnostic accuracy of presepsin for sepsis considering the new Sepsis-3 definitions.

List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
AUC	area under the curve
CI	confidence interval
CRP	C-reactive protein
ICU	intensive care unit
OR	odds ratio
ROC	receiver operating characteristic
PCT	procalcitonin
Sepsis-3	Third International Consensus Definitions for Sepsis and Septic Shock
SIRS	systemic inflammatory response syndromes
SOFA	Sequential Organ Failure Assessment
WBC	white blood cells

Ethics approval and consent to participate

The study was carried out according to the principles of the declaration of Helsinki and was approved by the Ethics Committee of Osaka City University Hospital. Written informed consent was obtained from all participating patients or their families.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TY, HY, TN and YM conceived of the study. TY, NS, SK, KU and ME collected the data. TY, WF and KK performed the statistical analyses. TY drafted the manuscript. All authors contributed to the interpretation of the data, revised the manuscript, and read and approved the final manuscript.

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Not applicable.

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