Original Contribution

Procalcitonin as a diagnostic marker for sepsis/septic shock in the emergency department; a study based on Sepsis-3 definition

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ABSTRACT

Introduction: The recent definition of sepsis was modified based on a scoring system focused on organ failure (Sepsis-3). It would be a time-consuming process to detect the sepsis patient using Sepsis-3. Procalcitonin (PCT) is a well-known biomarker for diagnosing sepsis/septic shock and monitoring the efficacy of treatment. We conducted a study to verify the predictability of PCT for diagnosing sepsis based on Sepsis-3 definition.
Materials & methods: This is a retrospective cohort study. The patients whose PCT was measured on the emergency department (ED) arrival and had final diagnosis related infection were enrolled. The patients were categorized by infection, sepsis, or septic shock followed by Sepsis-3 definition. "Pre-septic shock" was defined when a patient was initially diagnosed with sepsis, following which his/her mean arterial blood pressure decreased to under 65 mmHg refractory to fluid resuscitation and there was need for vasopressor use during ED admission. Receiver operating characteristics (ROC) curve and area under the curve (AUC) analysis were performed to verify sensitivity and specificity of PCT.
Results: 866 patients were enrolled in the final analysis. There are 287 cases of infection, 470 cases of sepsis, and 109 cases of septic shock. An optimal cutoff value for diagnosing sepsis was 0.41 ng/dL (sensitivity: 74.8% and specificity: 63.8%; AUC: 0745), septic shock was 4.7 ng/dL (sensitivity: 66.1% and specificity: 79.0%; AUC: 0.784), and "pre-septic shock" was 2.48 ng/dL (sensitivity: 72.8%, specificity: 72.8%, AUC: 0.781), respectively.
Conclusion: PCT is a reliable biomarker to predict sepsis or septic shock according to the Sepsis-3 definitions.

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1. Introduction

Despite the development of various diagnostic and therapeutic modalities, the mortality of sepsis and septic shock remains high [1,2]. It is important to diagnose these patients as soon as possible because early resuscitation and intensive care can improve survival [3,4]. Therefore, the early detection of sepsis/septic shock is one of the essential processes in the emergency department (ED) [4,5]. Various diagnostic tools have been introduced to promote the diagnosis of sepsis/septic shock, but there has been no gold standard guideline until now [6-8]. Furthermore, the validation of previous diagnostic tools should be performed because the definition of sepsis/septic shock was recently revised in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [9]. However, the diagnosis of sepsis/septic shock using the Sepsis-3 definitions is a time-consuming challenge in overcrowded EDs because it is based on total sequential organ failure assessment (SOFA) scores calculated after the evaluation of multiple organs [10].

Procalcitonin (PCT), the precursor of the hormone calcitonin, has been used as a biomarker for diagnosing bacterial infections of sepsis [11]. It is one of the most reliable biomarkers to detect infection-related disease and its usability was proven in a study based on the Sepsis-2 definitions [12-15]. We conducted a study to investigate the usefulness of PCT level on ED arrival for the diagnosis of sepsis/septic shock.

2. Methods

This retrospective observational study evaluated patients with infection admitted to the ED of a tertiary university hospital between March 2011 and June 2016. The study protocol was approved by the

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2.1. Data source

We reviewed the medical records of 1351 patients older than 18 years who directly visited our ED with infection-related disease and who underwent laboratory tests including serum PCT and lactate within one hour of ED arrival. In case of patients with a mean arterial blood pressure (MAP) <65 mmHg or lactate concentration >2 mmol/L at ED admission, MAP or lactate concentration after fluid resuscitation was also collected to diagnose septic shock. Patients who transferred to other hospitals during their hospital stay ($n = 159$); those with incomplete data ($n = 20$), hematologic malignancies ($n = 32$), and neutropenic fever ($n = 45$); those undergoing chemotherapy ($n = 77$); who received drugs inducing the suppression of bone marrow such as steroids ($n = 91$); those without an infection-related diagnosis at discharge summary ($n = 61$) were excluded.

2.2. Study variables

The following clinical and laboratory parameters were obtained from the medical records: age, gender, mean arterial blood pressures during ED stay, infusion volumes of crystalloid or 5% albumin during ED stay, vasopressor use, in-hospital mortality, SOFA score, lactate level, PCT level, delta neutrophil index (DNI), and c-reactive protein (CRP) level. SOFA scores and all laboratory parameters were collected within one hour of ED admission.

2.3. Categories of infection

The infections were divided into 10 categories according to the National Nosocomial Infections Surveillance System definitions from the Centers for Disease Control as follows: bone and joint infection; central nervous system infection; cardiovascular system infection; eye, ear, nose, throat, or mouth infection; gastrointestinal system infection; lower respiratory system infection; reproductive tract infection; skin and soft tissue infection, urinary system infection; and undistinguishable infection [16]. Infections hard to categorize for a specific organ, such as Hantann disease and Tsutsugamushi disease, were defined as undistinguishable infections. Infections of multiple organs (i.e. pneumonia + acute pyelonephritis) were counted as the cumulative frequencies.

2.4. Definitions of sepsis, septic shock, and pre-septic shock

Sepsis was defined as SOFA score of 2 or more consequent to the infection, according to the Sepsis-3 definitions [9]. Septic shock was defined as a MAP <65 mmHg or lactate concentration >2 mmol/L despite fluid resuscitation with 30 mL/kg or more of crystalloid or 5% albumin in patients diagnosed with sepsis. Patients with SOFA scores of 0 or 1 were categorized as having an infection.

For verifying PCT level in patients with sepsis progressing to septic shock, we defined "pre-septic shock" as a patient initially diagnosed with sepsis whose MAP subsequently decreased to below 65 mmHg, who was refractory to fluid resuscitation of 30 mL/kg or more of crystalloid or 5% of albumin, and who required vasopressor use during ED admission.

2.5. Predictability of the quick SOFA (qSOFA)

To verify the usability of the qSOFA suggested in the Sepsis-3 definitions, we calculated the sensitivity and specificity of qSOFA for the diagnosis of sepsis and septic shock [9].

2.6. Statistical analysis

Continuous variables were presented as median and interquartile range and compared using independent sample t, Mann-Whitney U, or Kruskal-Wallis tests as appropriate. Nominal variables were presented as percentages of the frequency of occurrence and compared using chi-square or Fisher's exact tests as appropriate. Receiver operating characteristic (ROC) analysis and comparison of the area under the curve (AUC) were performed to evaluate the predictability of PCT to diagnose sepsis or septic shock. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA) and RStudio version 1.1.383 (RStudio Inc., MA, USA).

3. Results

3.1. General characteristics

A total of 866 patients were enrolled in the final analysis. There were 383 (44%) women and the mean age was 69 (± 15) years. The mean SOFA score was 3 (± 3) and was highest in the septic shock group ($p < 0.001$). Lactate, PCT, and DNI levels were also highest in the septic shock group ($p < 0.001$, respectively), but there was no difference in CRP between groups ($p = 0.293$). The in-hospital mortality was highest in the septic shock group ($p < 0.001$) (Table 1) (Supplement).

Table 1
General characteristics.

	Total ($n = 866$)	Infection ($n = 287$)	Sepsis ($n = 470$)	Septic shock ($n = 109$)	p-Value
Female, n (%)	383 (44)	134 (47)	213 (45)	36 (33)	<0.001
Age (years)	73 (61–80)	70 (57–79)	73 (62–80)	74 (63–80)	0.024
		aa	bb	ab	
SOFA score	3 (1–5)	1 (0–1)	3 (2–5)	8 (6–10)	<0.001
		a	b	c	
Lactate (mmol/L)	1.69 (1.14–2.74)	1.32 (0.97–1.96)	1.62 (1.17–2.59)	3.86 (2.89–6.70)	<0.001
		a	b	c	
PCT (ng/mL)	0.8 (0.22–5.12)	0.24 (0.11–0.82)	1.27 (0.34–5.34)	12.27 (1.90–33.78)	<0.001
		a	b	c	
CRP	8.62 (3.34–14.50)	9.09 (3.37–14.70)	8.80 (3.54–14.42)	7.16 (2.57–13.95)	0.293
		a	a	a	
DNI	1.70 (0.00–4.00)	0.80 (0.00–1.90)	2.20 (0.50–4.12)	6.40 (1.60–15.70)	<0.001
		a	b	c	
In-hospital mortality, n (%)	107 (12)	11 (4)	53 (11)	43 (39)	<0.001

*Variables are presented as median (interquartile range) or frequencies (%).
#SOFA: sequential organ failure assessment, PCT: procalcitonin, CRP: c-reactive protein, DNI: delta neutrophil index.
§The different letters indicate significantly different groups based on the Kruskal-Wallis test with multiple comparisons using the Bonferroni correction method.

Table 2
Cumulative frequencies of the categories of infection.

Infection category	N (%)
Lower respiratory	445 (51)
Urinary tract	211 (24)
Gastrointestinal system	192 (22)
Skin and soft tissue	34 (4)
Cardiovascular	181 (21)
Eye, ear, nose, throat, or mouth	12 (1.3)
Central nervous	5 (0.5)
Reproductive tract	2 (0.2)
Bone and joint	7 (7)
Non-distinguished	36 (3.7)

The cumulative frequencies of the infection categories are shown in Table 2. The highest frequency occurred for lower respiratory infection ($n = 445$, 51%), followed by urinary tract ($n = 211$, 24%) and gastrointestinal system infections ($n = 192$, 22%).

3.2. Predictability of the qSOFA to diagnose sepsis or septic shock

The sensitivity and specificity of the qSOFA for the diagnosis of sepsis was 17.6% and 99.3%, respectively, and 38.5% and 91.8%, respectively, for septic shock.

3.3. Predictability of procalcitonin and DNI for the diagnosis of sepsis or septic shock

In ROC analysis of PCT, the optimal cutoff concentrations were 0.41 ng/mL (sensitivity: 74.8%, specificity: 63.8%, AUC: 0.745) for sepsis and 4.7 ng/mL (sensitivity: 66.1%, specificity: 79.0%, AUC: 0.784) for septic shock. The optimal DNI cutoffs were 2.0 (sensitivity: 55.8%, specificity: 77.0%, AUC: 0.691) for sepsis and 3.8 (sensitivity: 63.3%,

specificity: 78.5%, AUC: 0.742) for septic shock. The corresponding ROC curves are shown in Figs. 1 and 2.
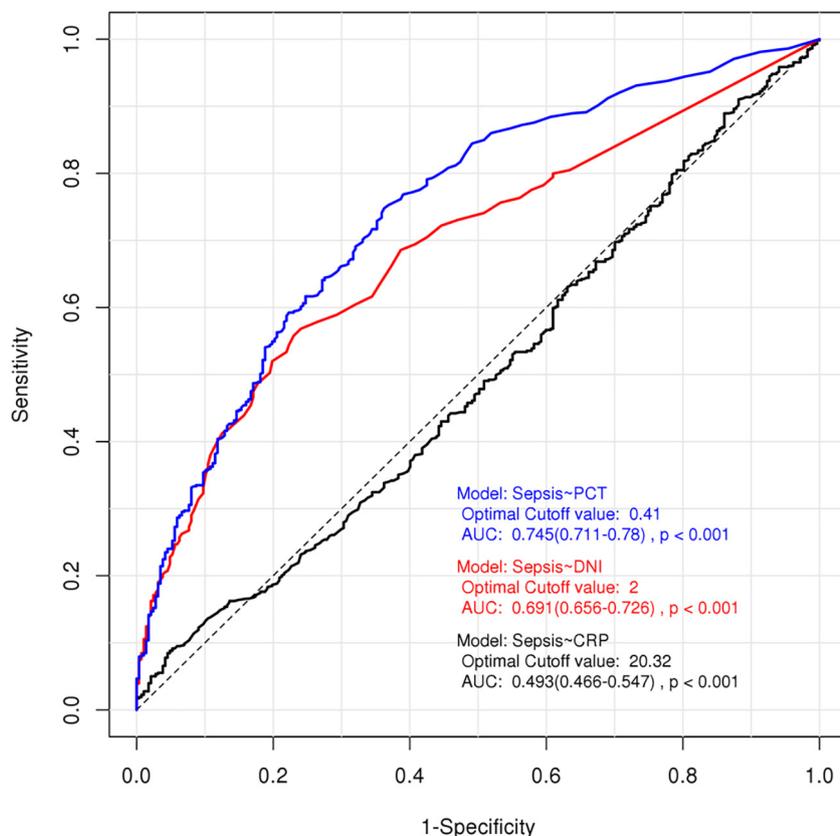
3.4. Predictability of PCT and DNI for the diagnosis of pre-septic shock

In ROC analysis of PCT level to predict pre-septic shock, the optimal cutoff was 2.48 ng/mL (AUC: 0.781) with sensitivity and specificity of 72.8%, respectively. The optimal DNI cutoff was 3.8 (AUC: 0.722) with sensitivity 58.3% and specificity of 80.1%, respectively (Fig. 3).

4. Discussion

In our study, PCT was a reliable biomarker for the diagnosis of sepsis or septic shock according to the definitions in Sepsis-3. It is important to diagnose and treat patients with sepsis or septic shock as soon as possible because they are in a vulnerable state that could rapidly progress to multiple organ dysfunctions [3-5,17]. The new sepsis/septic shock definitions in Sepsis-3 are based on the SOFA scoring system that provides guidance for physicians to identify multiple organ dysfunctions; however, Sepsis-3 requires the evaluation of all factors of the SOFA score to define sepsis or septic shock, which is a time-consuming process. This evaluation process is impossible in EDs overcrowded with critically ill patients requiring urgent care [18-21]. The qSOFA was proposed as an early screening tool to minimize evaluation time, but it showed low sensitivity and specificity in previous and our own studies [22,23]. PCT is easily measured in point-of-care assays of blood and requires little time to measure [24]. Therefore, the measurement of PCT level might be a time-saving modality to diagnose sepsis/septic shock patients with high sensitivity and specificity rather than evaluating all SOFA factors.

PCT as a biomarker for the diagnosis of sepsis or septic shock performed better DNI and CRP in the present study. Various biomarkers or indexes have been proposed to promote the accuracy of diagnosis

Model: Sepsis~PCT
Optimal Cutoff value: 0.41
AUC: 0.745(0.711-0.78) , p < 0.001

Model: Sepsis~DNI
Optimal Cutoff value: 2
AUC: 0.691(0.656-0.726) , p < 0.001

Model: Sepsis~CRP
Optimal Cutoff value: 20.32
AUC: 0.493(0.466-0.547) , p < 0.001

Fig. 1. Receiver operating characteristics curve of procalcitonin level, delta neutrophil index and C - reactive protein (CRP) level for the diagnosis of sepsis.
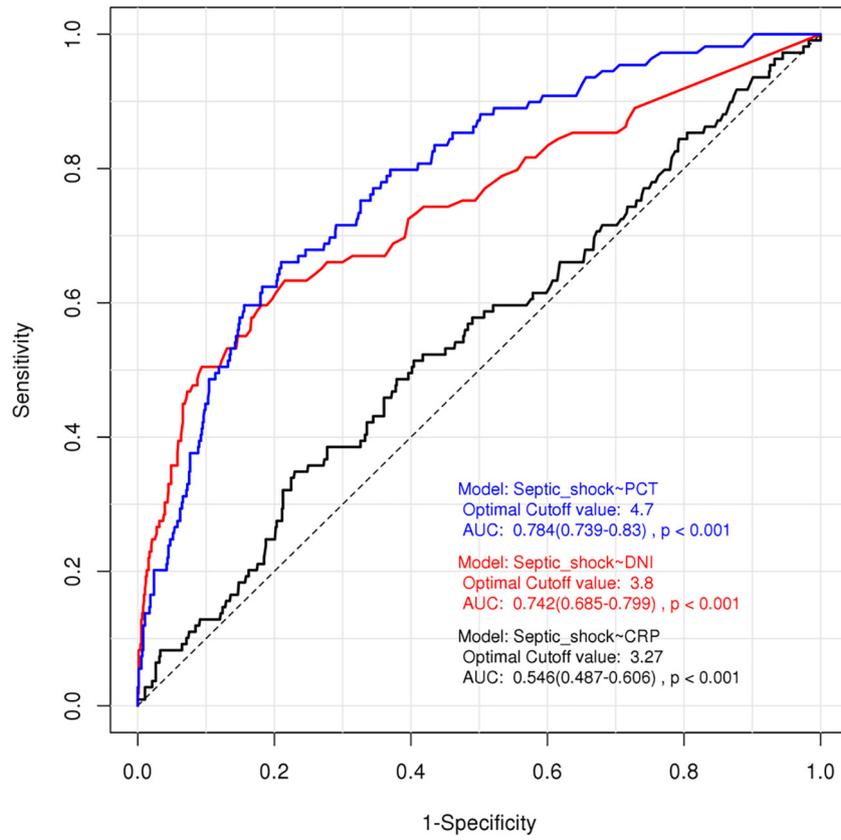
Fig. 2. Receiver operating characteristics curve of procalcitonin level, delta neutrophil index and C - reactive protein (CRP) level for the diagnosis of septic shock.
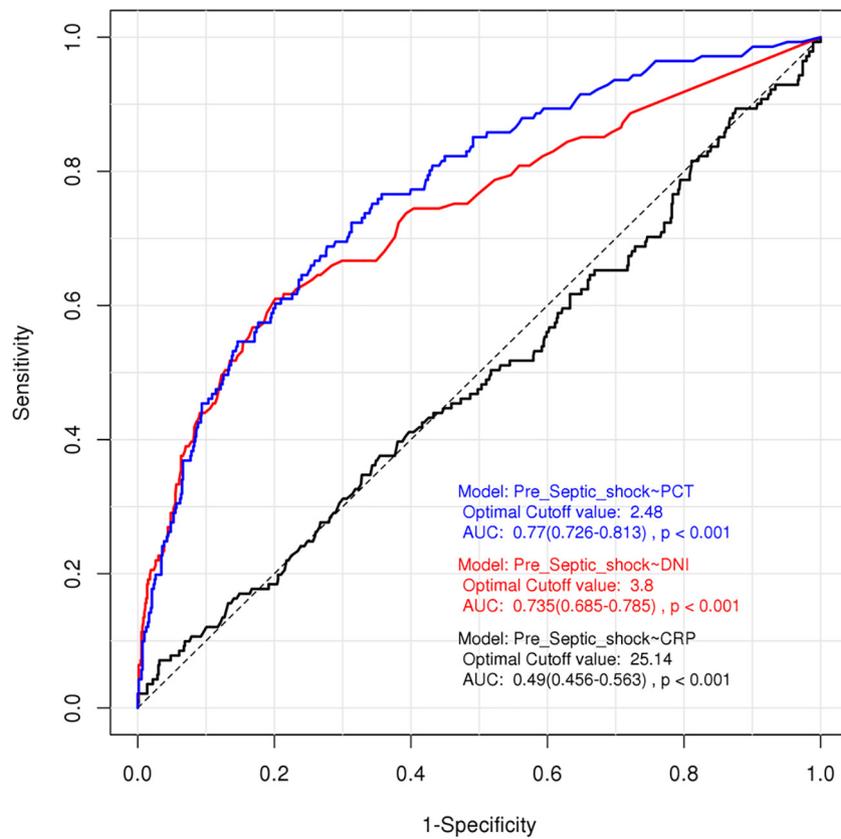

Fig. 3. Receiver operating characteristics curve of procalcitonin level, delta neutrophil index and C - reactive protein (CRP) level for the diagnosis of pre-septic shock.

of sepsis or septic shock and reduce the time for diagnosis. The DNI was recently introduced and has shown reliable predictability for the diagnosis of various infection statuses in previous studies, similar to the results of our study [25,26]. However, PCT would be more useful than DNI for the diagnosis of sepsis/septic shock because DNI had a lower reliability based on AUC analysis in the present study and PCT is also useful to determine the duration of antibiotic treatment in repeated measurements [27]. CRP is reportedly a useful biomarker, but it showed poor usability in the present study and other studies [28-31]. CRP is a nonspecific inflammatory biomarker also released in non-infection-related conditions such as obesity, dyslipidemia, insulin resistance, or statin therapy [32-36]. These conditions might also affect the accuracy of diagnosis for sepsis/septic shock in our study [37].

PCT was also useful for the prediction of pre-septic shock in the present study, with relatively high sensitivity and specificity. Medical personnel in EDs overcrowded with various patients may miss or delay the secondary triage of patients with a low priority for care, which may be related to the deterioration of a patient's condition [38]. Therefore, the use of PCT may minimize the risk of emergency medical personnel missing septic patients who deteriorate after initial triage.

This study has several limitations. First, the sampling timing of the laboratory tests and clinical history suggesting the source of infection might have been biased because the data were obtained retrospectively. Second, even though this study was based on a relatively large population, there may be a selection bias in patient enrollment because the data were collected from a single medical center. Third, the sampling timing was not consistent. Fourth, we routinely evaluated procalcitonin in most of patients with suspicious infection-related disease in our emergency department, several patients might be missed from sampling so that it could affect the cut-off value of procalcitonin in this study.

5. Conclusions

PCT is a reliable biomarker to diagnose sepsis or septic shock according to the Sepsis-3.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.05.047.

Conflict of interest

All authors have nothing to declare on conflict of interest.

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