Clinica Chimica Acta 490 (2019) 200–206

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Comparison of accuracy of presepsin and procalcitonin concentrations in diagnosing sepsis in patients with and without acute kidney injury

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ARTICLE INFO

Keywords:
Kidney Disease Improving Global Outcomes
Acute kidney injury
Accuracy
Sepsis
Diagnosis

ABSTRACT

Background: Levels of the biomarkers presepsin and procalcitonin are affected by renal function. We evaluated the accuracies of presepsin and procalcitonin levels for diagnosing sepsis in patients with and without acute kidney injury (AKI).

Methods: We evaluated patients with presepsin and procalcitonin data, and classified them into AKI and non-AKI groups based on the Kidney Disease Improving Global Outcomes criteria. Each group was then subdivided according to sepsis status for each stage of AKI. Receiver operating characteristic curve analyses were used to investigate the accuracies of biomarker levels for diagnosing sepsis.

Results: In the non-AKI group, the area under the curves (AUCs) for procalcitonin and presepsin levels were 0.897 and 0.880, respectively ($p = .525$) and optimal cut-off values were 0.10 ng/ml (sensitivity: 85.1%, specificity: 79.1%) and 240 pg/ml (sensitivity: 80.9%, specificity: 83.2%), respectively. In the stage 3 subgroup, the AUC for procalcitonin (0.946) was significantly higher than that for presepsin (0.768, $p < .001$). The optimal cut-off values for diagnosing sepsis were 4.07 ng/ml (sensitivity: 87.2%, specificity: 93.5%) for procalcitonin and 500 pg/ml (sensitivity: 89.7%, specificity: 59.7%) for presepsin.

Conclusions: In patients with severe AKI, the accuracy of the diagnosis of sepsis with procalcitonin was significantly higher than with presepsin.

1. Introduction

Many studies have reported that early treatment of sepsis using appropriate antibiotics improves patient's prognosis, and increases the survival rates after severe sepsis or septic shock [1–4]. The definition of sepsis was proposed in 1991 [5]. Since then, > 170 biomarkers have been identified for evaluating sepsis [6]. Among them, procalcitonin (PCT) is used in many parts of the world to assist in the diagnosis of acute infection. Moreover, PCT is weakly recommended to support the discontinuation of empiric antibiotics in the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock: 2016 [4]. Furthermore, the Food and Drug Administration approved PCT assay in guiding the starting or stopping of antibiotic treatment in suspected lower respiratory tract infection [7]. However, the concentrations of PCT can be elevated in various non-sepsis situations such as the early stage of severe trauma, invasive surgical procedures, and critical burn injuries. Therefore, physicians must be aware of the possibility of false-positive results [8]. In addition, renal function is a major determinant of PCT concentrations [9]. The most common cause of acute kidney injury (AKI) among critically ill patients is sepsis [10]. Thus, there is an urgent need for more effective biomarkers to diagnose sepsis in patients with AKI.

Recently, several meta-analyses have reported that presepsin (P-SEP) may be a helpful and valuable biomarker for the early diagnosis of sepsis [11–13]. Interestingly, we have also recently reported that P-SEP concentrations are elevated during sepsis; they are also elevated in non-sepsis patients with severe AKI [14]. Again, we have reported that in patients with severe AKI, the diagnostic accuracy of PCT concentration is significantly lower than that in non-AKI patients [15]. However, only a few other studies have also assessed the usefulness of P-SEP and PCT as markers of sepsis in AKI [16].

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https://doi.org/10.1016/j.cca.2018.09.013
Received 26 June 2018; Received in revised form 25 August 2018; Accepted 6 September 2018
Available online 08 September 2018
0009-8981/

2. Materials and methods

This study was a single-center retrospective study. The study protocol was approved by the Institutional Review Board of Fukuoka University Hospital. The need for informed consent was waived given the retrospective and anonymous nature of the study.

2.1. Study population

We included patients aged ≥18 y, without cardiopulmonary arrest on arrival, who were admitted to our intensive care unit between July 2013 and June 2015. We excluded patients with cardiopulmonary arrest on arrival, those in whom urine output was not evaluated, those for whom P-SEP or PCT concentrations were not measured, as well as those with end-stage kidney disease (ESKD) [17] and Sequential Organ Failure Assessment (SOFA) scores [18] < 2. In this study, we divided patients into non-AKI or AKI groups based on the Kidney Disease Improving Global Outcomes (KDIGO) AKI definition [19]. Furthermore, we classified the patients in each group as having or not having sepsis based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [20]. In other words, the definition of sepsis included organ failure caused by an infection which resulted in a SOFA score ≥ 2. Furthermore, patients were basically managed and diagnosed with sepsis as per the Japanese guidelines for the management of sepsis [21]. Based on these groups, we compared the patients' ages, sex, white blood cell counts, hematocrit concentrations, platelet counts, albumin concentrations, C-reactive protein (CRP) concentrations, creatinine (Cr) concentrations, lactate concentrations, PCT concentrations, P-SEP concentrations, Acute Physiology and Chronic Health Evaluation (APACHE) II [22], and SOFA scores [18] at admission.

2.2. P-SEP measurement

P-SEP concentrations were measured using a compact automated immunoanalyzer (Pathfast®; LSI Medience Corp.) based on a chemiluminescent enzyme immunoassay [23,24].

2.3. PCT measurement

PCT concentrations were measured using the Elecsys Brahms PCT assay (Roche Diagnostics).

2.4. Classification of AKI severity

AKI severity was determined based on the KDIGO AKI definition [19], and involved measuring blood Cr concentrations and evaluating the patient's urine output during the first 24 h of admission. The patients' baseline Cr concentrations were extracted from their admission records, or were defined as the lowest Cr concentrations during their stay in the intensive care unit if there was no admission record. Each patient's AKI status was evaluated using both their Cr concentrations and urine output, and the more severe AKI classification was selected if we observed any discrepancy between the 2 measures.

2.5. Accuracy of detecting sepsis according to AKI severity

We evaluated the accuracy of detecting sepsis by using receiver operating characteristic curves (ROCs). Furthermore, we calculated the area under the curves (AUCs) to compare the accuracy of P-SEP and PCT concentrations for diagnosing sepsis according to AKI severity.

2.6. Relationships between severity of illness or AKI and concentrations of P-SEP or PCT

We also evaluated the relationships between concentrations of P-SEP or PCT and the severity of illness (organ dysfunction) or AKI, as P-SEP and PCT concentrations are positively correlated with the severity of sepsis [15,25–29] and AKI [14,15].

2.7. Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQRs), and the two groups were compared using the Wilcoxon signed rank test. Moreover, various groups were compared using the Steel-Dwass test. The Youden index was used to identify the cut-off values for P-SEP and PCT concentrations that might have diagnostic value. To investigate the effect of AKI severity on P-SEP concentrations, we performed analyses of variance (ANOVA) that included AKI severity, sepsis (yes/no), and SOFA score as covariates. These analyses were performed using JMP software (ver 12; SAS Institute) and MedCalc software (ver 14; MedCalc Software bvba). Furthermore, a post-hoc power calculation was performed for the difference in AUCs between P-SEP and PCT based on data from stage 1 and 3 using SAS ver 9.4. Differences with $p < .05$ were considered statistically significant.

3. Results

3.1. The number of patients and patients' characteristics

We included 366 patients in the AKI group and 440 in the non-AKI group. Based on the KDIGO criteria, the patients in the AKI group were categorized as 226 patients in stage 1, 39 patients in stage 2, and 101 patients in stage 3 (Fig. 1). The patients' clinical diagnoses are listed in Table 1. Among the patients with sepsis, the commonest clinical diagnosis was pneumonia, followed by bacteremia and peritonitis. The results of the bacteriological examinations are shown in Table 2. The characteristics of the patients with and without sepsis at admission are shown in Table 3. Patients with sepsis exhibited significantly higher age, CRP, Cr, PCT, P-SEP concentrations, SOFA, and APACHE II scores. Patients without sepsis exhibited significantly higher hematocrit concentrations, platelet counts, and albumin concentrations, in contrast to significantly lower hematocrit concentrations and platelet counts in those with sepsis.

3.2. Comparing P-SEP and PCT concentrations in each AKI classification

The P-SEP and PCT concentrations were significantly higher in the sepsis group compared with the non-sepsis group (Table 4). The P-SEP and PCT concentrations were significantly higher in the stage 3 subgroup compared to those in the non-AKI group, regardless of their sepsis status (Table 5).

3.3. Accuracy for diagnosing sepsis

In the non-AKI group, the AUC for P-SEP was 0.880 (95% confidence interval [CI]: 0.814–0.925). In the AKI group, the AUC values were 0.806 (95% CI: 0.724–0.866) in the stage 1 subgroup, 0.704 (95% CI: 0.491–0.854) in the stage 2 subgroup, and 0.768 (95% CI: 0.666–0.847) in the stage 3 subgroup (Table 6).

In the non-AKI group, the AUC for PCT was 0.897 (95% CI: 0.842–0.934). In the AKI group, the AUC values were 0.910 (95% CI: 0.841–0.950) in the stage 1 subgroup, 0.867 (95% CI: 0.680–0.953) in the stage 2 subgroup, and 0.946 (95% CI: 0.881–0.976) in the stage 3 subgroup (Table 6). Thus, PCT concentrations were accurate in diagnosing sepsis, regardless of the presence or severity of AKI. The ROCs are shown in Fig. 2.

For P-SEP, the AUC values for the stages 1 and 3 subgroups were significantly lower than those for the PCT AKI group ($p = .002$ in stage 1 and $p < .001$ in stage 3). In stage 1, the difference in AUCs and its standard error were estimated to be 0.103 and 0.033, respectively. From these estimates, the power was calculated to be 88.0%. Moreover, in stage 3, the difference in AUCs and its standard error were estimated

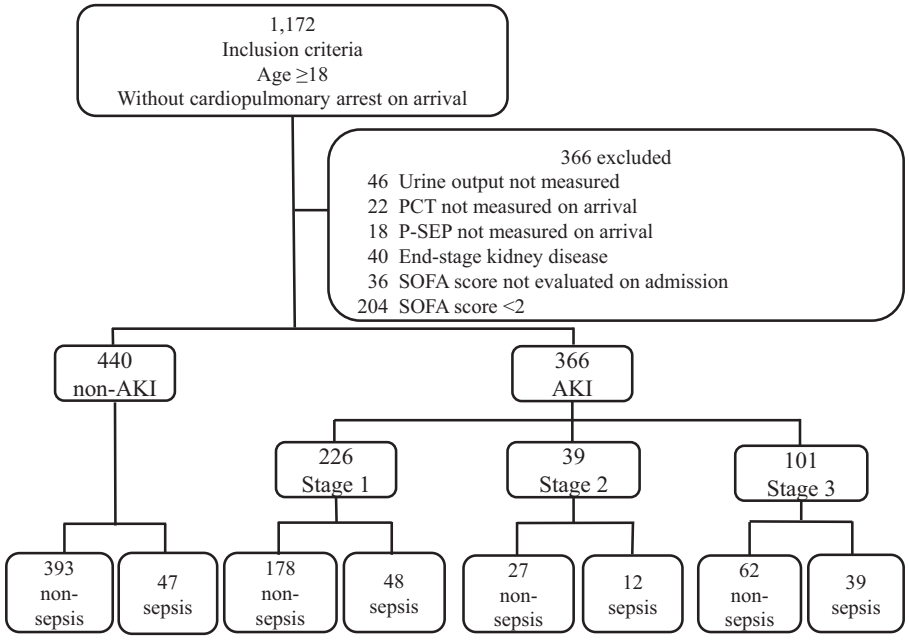

Fig. 1. Patient enrollment, exclusion, and classification.
PCT, procalcitonin; P-SEP, presepsin; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury.

Table 1
The number of clinical diagnoses.

Sepsis or non-sepsis	Diagnosis	n	Total
Sepsis	Pneumonia	46	146
	Bacteremia	37	
	Peritonitis	23	
	Skin, bone, and soft tissue infection	14	
	Biliary tract infection	5	
	Urinary tract infection	5	
	Bacterial translocation	3	
	Enteritis	3	
	Meningitis	3	
	Other	7	
Non-sepsis	Stroke	188	660
	Trauma	181	
	Aortic disease	43	
	Heart failure	38	
	Gastrointestinal bleeding	26	
	Poisoning	26	
	Epilepsy	24	
	Acute coronary syndrome	21	
	Burn	9	
	Heat stroke	7	
	Pancreatitis	7	
	Allergic disease	6	
	Other	84	

Table 2
Results of the bacteriological examinations of patients with sepsis.

Infectious agent[a]	n
Gram-negative rods	44
Gram-positive cocci	39
Not detected	39
Gram-positive coccus and Gram-negative bacillus	19
Fungus	2
Gram-positive coccus, Gram-negative bacillus, and fungus	2
Mycobacterium avium complex	1
Total	146

[a] The microbiological test results were obtained using samples that were taken from the presumed site of infection or via blood culture.

Table 3
Characteristics of the patients with or without sepsis at admission.

	non-sepsis (n = 660)	sepsis (n = 146)	P-value
Age, years	65 (50–77)	73 (63–79)	< 0.001
Sex, % female	38.9 (257)	36.3 (53)	NS
WBC count, $\times 10^3/mm^3$	10.4 (7.6–13.9)	11.6 (6.6–18.2)	NS
Hematocrit, %	38.0 (32.2–42.5)	33.6 (27.7–37.0)	< 0.001
Platelet counts, $\times 10^4/mm^3$	20.2 (15.2–25.7)	15.7 (9.6–23.2)	< 0.001
Albumin, g/dl	3.9 (3.3–4.4)	2.6 (2.2–3.1)	< 0.001
C-reactive protein, mg/dl	0.2 (0.1–1.0)	11.6 (4.2–19.3)	< 0.001
Creatinine, mg/dl	0.9 (0.7–1.1)	1.2 (0.7–2.3)	< 0.001
Lactate, mg/dl	21 (13–37)	21 (13–42)	NS
P-SEP, pg/ml	141 (92–288)	603 (355–1219)	< 0.001
PCT, ng/ml	0.05 (0.03–0.12)	4.28 (0.51–28.84)	< 0.001
SOFA score	4 (3–6)	7 (5–10)	< 0.001
APACHE II score	17 (13 − 22)	20 (16–27)	< 0.001

Data are expressed as median (interquartile range) or % (number).
WBC, white blood cell; P-SEP, presepsin; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4
Comparison of levels of P-SEP and PCT between patients with or without sepsis according to AKI severity.

	AKI severity	non-sepsis	sepsis	p value
P-SEP (pg/ml)	non-AKI	115 (84–190)	473 (258–743)	< 0.001
	Stage 1	206 (111–367)	587 (345–987)	< 0.001
	Stage 2	176 (108–805)	744 (277–2501)	0.046
	Stage 3	365 (214–1096)	1181 (654–2603)	< 0.001
PCT (ng/ml)	non-AKI	0.04 (0.02–0.09)	0.47 (0.14–2.00)	< 0.001
	Stage 1	0.05 (0.03–0.14)	6.95 (0.95–20.68)	< 0.001
	Stage 2	0.06 (0.03–0.32)	3.36 (0.25–42.00)	0.001
	Stage 3	0.27 (0.06–1.01)	31.17 (9.43–100.00)	< 0.001

Data are expressed as median (interquartile range).
P-SEP, presepsin; PCT, procalcitonin; AKI, acute kidney injury.

Table 5
Comparison of presepsin and procalcitonin levels according to AKI severity.

A. Non-sepsis				
n	393	178	27	62
AKI severity	non-AKI	Stage 1	Stage 2	Stage 3
P-SEP (pg/ml)	115 (84–190)	206 (111–367)†	176 (108–805)†††	365 (214–1096)†#
PCT (ng/ml)	0.04 (0.02–0.09)	0.05 (0.03–0.14)††	0.06 (0.03–0.32)	0.27 (0.06–1.01)†##*

B. Sepsis				
n	47	48	12	39
AKI severity	non-AKI	Stage 1	Stage 2	Stage 3
P-SEP (pg/ml)	473 (258–743)	587 (345–987)	744 (277–2501)	1188 (654–2603)†#
PCT (ng/ml)	0.47 (0.14–2.00)	6.95 (0.95–20.68)†	3.36 (0.25–42.00)	31.17 (9.43–100.00)†#

Data are expressed as median (interquartile range), and the groups were compared using Steel-Dwass test.
P-SEP, presepsin; PCT; procalcitonin, AKI; acute kidney injury.
† $p < .001$, vs. non-AKI.
†† $p < .01$, vs. non-AKI.
††† $p < .05$, vs. non-AKI.
# $p < .001$, vs. stage 1.
$p < .01$, vs. stage 1.
* $p < .01$, vs. stage 2.

to be 0.177 and 0.047, respectively. From these estimates, the power was calculated to be 96.8%. Thus, our study had sufficient power to detect the AUC difference in stages 1 and 3. Thus, P-SEP concentrations had low accuracy for diagnosing sepsis in the AKI subgroup, especially in stage 3 (AUC: 0.768). Furthermore, the AUC value for the stage 3 subgroup was significantly lower than that in the non-AKI group ($p = .038$) for P-SEP. Therefore, P-SEP concentrations had low accuracy for diagnosing sepsis in the stage 3 subgroup. In the comparison of AUC values, that of the stage 2 subgroup was low and was excluded from the statistical analysis due to the small number of patients (Table 6).

In the non-AKI patients, optimal cut-off values were 240 pg/ml (sensitivity: 80.9%, specificity: 83.2%) for P-SEP, and 0.10 ng/ml (sensitivity: 85.1%, specificity: 79.1%) for PCT. In the stage 3 subgroup, the optimal cut-off values were 500 pg/ml (sensitivity: 89.7%, specificity: 59.7%) in the concentrations of P-SEP, and 4.07 ng/ml (sensitivity: 87.2%, specificity: 93.5%) in the concentrations of PCT. Thus, P-SEP and PCT optimal cut-off values were relatively high in the stage 3 subgroup (Table 6).

3.4. Relationship between the severity of illness or AKI and concentrations of P-SEP and PCT

The results of the ANOVA are shown in Table 7. The severity of AKI was significantly associated with increasing concentrations of P-SEP and PCT. Moreover, the adjusted means of P-SEP and PCT concentrations increased with AKI severity.

4. Discussion

This retrospective study indicated that the PCT was significantly more accurate in diagnosing sepsis than P-SEP in patients with severe AKI. We have previously reported that P-SEP may not be a reliable indicator of sepsis in patients with more advanced forms of AKI [14]. Our previous study [14] evaluated the accuracy of diagnosis of sepsis only among the non-AKI vs. AKI groups because of the small sample size. However, the present study included a larger sample size compared to our previous report. Therefore, we could compare the accuracy of diagnosis of sepsis in each AKI classification. Even in patients without sepsis, the concentrations of P-SEP increased with AKI severity. Especially in the stage 3 KDIGO criteria subgroup, the AUC value was significantly lower than that in the non-AKI group with P-SEP (Table 6). Moreover, the optimal cut-off value (Table 6) and value of adjusted mean in the ANOVA (Table 7A) were higher in the stage 3 subgroup than that in the non-AKI group. Saito et al. [30] have reported that patients with ESKD exhibited pre-living kidney transplantation (LKT) P-SEP concentrations that were markedly above the upper limit of normal

Table 6
Accuracy of diagnosing sepsis according to acute kidney injury severity.

AKI severity		AUC	95% CI	Optimal cut-off value	Se (%)	Sp (%)	PPV (%)	NPV (%)
Non-AKI	P-SEP	0.880	0.814–0.925	240 pg/ml	80.9	83.2	36.5	97.3
	PCT	0.897	0.842–0.934	0.10 ng/ml	85.1	79.1	32.8	97.8
Stage 1	P-SEP	0.806*	0.724-0.866	323 pg/ml	83.3	69.1	42.1	93.9
	PCT	0.910	0.841–0.950	0.74 ng/ml	83.3	91.6	72.7	95.3
Stage 2†	P-SEP	0.704	0.491-0.854	253 pg/ml	83.3	55.6	45.5	88.2
	PCT	0.867	0.680–0.953	0.59 ng/ml	75.0	88.9	75.0	88.9
Stage 3	P-SEP	0.768**$	0.666-0.847	500 pg/ml	89.7	59.7	58.3	90.2
	PCT	0.946	0.881–0.976	4.07 ng/ml	87.2	93.5	89.5	92.1

AKI, acute kidney injury; P-SEP, presepsin; PCT, procalcitonin; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.
* $p = .002$, vs. PCT Stage 1.
** $p < .001$, vs. PCT Stage 3.
† Excluded from the statistical analysis due to the small number of patients.
$ $p = .038$ vs. non-AKI P-SEP.

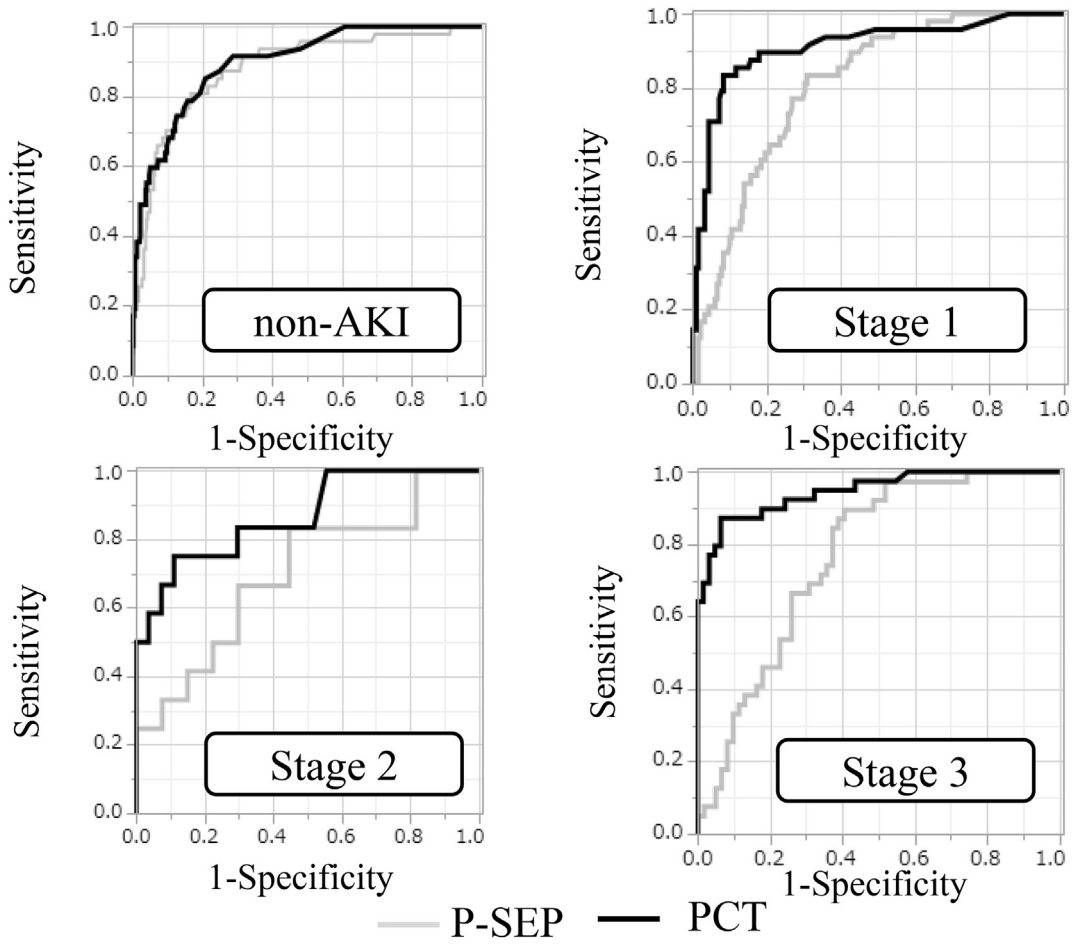

Fig. 2. Receiver operating characteristic curves in the non-AKI and AKI groups. AKI, acute kidney injury; P-SEP, presepsin; PCT, procalcitonin.

Table 7
Analysis of variance regarding the effect of acute kidney injury severity.

A. P-SEP		
	Adjusted mean (pg/ml)	P-value
Sepsis (yes or no)		< 0.001
KDIGO criteria		< 0.001
non-AKI	470	
Stage 1	649	
Stage 2	873	
Stage 3	1123	
SOFA score		< 0.001

B. PCT		
	Adjusted mean (ng/ml)	P-value
Sepsis (yes or no)		< 0.001
KDIGO criteria		0.005
non-AKI	8.4	
Stage 1	10.43	
Stage 2	9.79	
Stage 3	19.17	
SOFA score		< 0.001

P-SEP, presepsin; PCT, procalcitonin; KDIGO, The Kidney Disease Improving Global Outcomes; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment.
The criterion valuables were P-SEP or PCT, and the explanatory valuables were sepsis (yes or no), KDIGO criteria, SOFA score.

(1252 ± 451 pg/ml), and that their P-SEP concentrations consistently decreased after the LKT. These results suggest that the metabolism of P-SEP might involve a renal component. Therefore, the accuracy of P-SEP concentrations for diagnosing sepsis might be significantly lower for patients in the stage 3 subgroup, compared to the non-AKI group. From these results, we need to consider different cut-off points for the diagnosis of sepsis and carefully evaluate the diagnosis of sepsis using P-SEP concentrations in patients with severe AKI. In contrast, the optimal cut-off value of P-SEP for discriminating between bacterial and non-bacterial infectious diseases was determined to be 600 pg/ml [31]. However, our study indicated that the optimal cut-off value of P-SEP for diagnosing sepsis in non-AKI patients is 240 pg/ml (Table 6). This result suggests that we need to consider lower concentrations of P-SEP for the diagnosis of sepsis in non-AKI patients.

Recently, Takahashi et al. [16] reported that the accuracy of P-SEP for the diagnosis of sepsis was significantly higher than that of PCT concentrations in AKI patients. These results differ from those of the present study. Takahashi et al. defined AKI by using plasma neutrophil gelatinase-associated lipocalin, plasma cystatin C and/or estimated glomerular filtration rate. In contrast, we defined AKI according to the KDIGO criteria. KDIGO is the latest international criteria for defining AKI and is more predictive of in-hospital mortality compared to the RIFLE (the Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease) criteria [32]. Therefore, we considered the KDIGO criteria as the most appropriate definition of AKI. Moreover, our study of the clinical diagnosis at admission was different from the study by Takahashi et al. Furthermore, they analyzed P-SEP and PCT concentrations not only on admission but also on days 1, 3, 5, and 7. However, the concentrations of P-SEP and PCT may have varied with the initial therapy. These differences in study design may be responsible for the differences in the outcomes between our study and that of Takahashi et al.

In our previous study, we reported that the diagnostic accuracy of PCT concentration was significantly lower in AKI patients in the "Failure" subgroup (AUC: 0.857, 95% CI: 0.730–0.930) according to the RIFLE criteria than that in non-AKI patients (AUC: 0.958, 95% CI: 0.923–0.978, $p < .05$) [15]. However, the present study showed that even in severe forms of AKI, the accuracy of the diagnosis of sepsis was acceptable with PCT. In contrast, the present study demonstrated that the optimal cut-off value was relatively high in the stage 3 subgroup than in the non-AKI, and stages 1 and 2 subgroups of AKI (Table 6). Moreover, ANOVA showed that the adjusted mean value of PCT in the stage 3 subgroup of AKI was higher than that in the non-AKI, and stages 2 and 3 subgroups of AKI (Table 7B). These results suggest that we need to consider different cut-off values for the diagnosis of sepsis using PCT in patients with severe AKI.

Some studies have reported that P-SEP [25–27] and PCT [15,28,29] concentrations increase with increasing severity of sepsis. The present study's ANOVA findings indicate that P-SEP and PCT concentrations increased with increasing AKI severity, regardless of sepsis status, and that elevated concentrations of P-SEP and PCT were independently predicted by the severity of illness and/or organ dysfunction (SOFA score), as well as AKI severity. These results suggested that not only the severity of sepsis but also AKI severity are indicators for increasing P-SEP and PCT concentrations. Thus, even for non-sepsis patients, we need to carefully evaluate the relationship of P-SEP, PCT concentrations and renal function.

This study has several limitations that warrant consideration. First, we used a retrospective single-center design with a small sample size, especially in the stage 2 subgroup of AKI. Second, we did not consider the effect of the patients' cellular immunity status (e.g., receiving chemotherapy or steroids) and/or antibiotic use before ICU admission on their P-SEP and PCT concentrations since this was a retrospective study. Third, we could not examine the etiologies of AKI. Fourth, P-SEP and PCT were not standardized in in vitro diagnostic industries. Therefore, cut-off values may need to be adjusted according to each measuring reagent and/or equipment.

5. Conclusions

This study indicates that the diagnostic accuracy of PCT was significantly higher than that of P-SEP in AKI patients, especially in severe forms of AKI such as stage 3 according to the KDIGO criteria. There is the need to consider different thresholds when using P-SEP and PCT concentrations to diagnose sepsis in patients with severe AKI.

Acknowledgments

We thank Ms. Kanae Misumi (Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University) for her help in the data coding. We would also like to thank Editage (www.editage.jp) for English language editing.

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