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Diagnostic accuracy of presepsin in predicting bacteremia in elderly patients admitted to the emergency department

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Keywords:	presepsin, elderly patients, bacteremia, emergency department, biomarker

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Title Page**Diagnostic accuracy of presepsin in predicting bacteremia in elderly patients
admitted to the emergency department**

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Running title:

presepsin in predicting bacteremia in elderly patients

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Keywords: presepsin, elderly patients, bacteremia, emergency department, biomarker

Abstract

Objective

Early detection of bacteremia in the elderly is needed in the emergency department (ED). We aimed to compare the accuracy of detecting bacteremia between the new biomarker presepsin and the widely used procalcitonin (PCT) and C-reactive protein (CRP) in clinical situations.

Methods

This prospective study was conducted in the ED of a teaching hospital between September 2014 and March 2016. Forty-six elderly patients aged ≥ 70 years and who fulfilled the systemic inflammatory response syndrome criteria were included in this study. Blood sampling to evaluate CRP, PCT, presepsin plasma levels; two sets of blood sampling for bacterial cultures; and evaluations of the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were performed upon arrival at the ED. The results were compared between patients with bacteremia and those without bacteremia.

Results

The presepsin value was significantly higher in the bacteremia group than in the non-bacteremia group (866.6 ± 184.6 pg/mL vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). The PCT and CRP did not significantly differ between the groups. The area under the receiver-operating-characteristic curve (AUC) values were not significantly different among presepsin (0.69), PCT (0.61), and CRP (0.53). Multivariate analysis showed that presepsin was independently associated with bacteremia (odds ratio, 8.84; 95% confidence interval, 1.32–177.09; $p = 0.02$).

Conclusion

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5 Similar to CRP and PCT, presepsin was a useful biomarker to detect bacteremia in
6 elderly patients admitted to the ED.
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10 11 12 ***Strengths and limitations of this study*** 13

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15 • This work should be of interest to a broad readership, Early detection of bacteremia in the
16 elderly is needed in the emergency department (ED).
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19 • The work presented herein is original, has not been previously published in whole or in part
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22 • The present study include the relatively small sample size, the single-center design,
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24 and the relatively high exclusion ratio of the eligible patients.
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27 • Our findings may have been underpowered and represent type 2 statistical error.
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37 **Introduction**

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39 Bacteremia is a severe bacterial bloodstream infection that is associated with a
40 significant mortality^{1 2}. In particular, the susceptibility to bacteremia is increased in
41 elderly people who have decreased immunity due various underlying diseases, such as
42 diabetes and malignant disorders. In recent years, the number of elderly people who are
43 brought to the emergency department (ED) has increased in an aging society. Therefore,
44 early diagnosis of bacteremia upon arrival at the ED is important.
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54 Blood bacterial culture is the gold standard to diagnose bacteremia, but it
55 requires several days to obtain the results³. Various biomarkers, including C-reactive
56 protein (CRP) and procalcitonin (PCT), had been used to support the diagnosis of
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5 bacteremia. Presepsin, which is the soluble fraction of cluster-of-differentiation 14
6 (CD14), had been thought to be associated with infections⁴, based on the fact that a
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8 subtype of CD14 is present inside and on the cell membranes of macrophages,
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10 monocytes, and granulocytes and is responsible for intracellular transduction of
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12 endotoxin signals. Several studies demonstrated that presepsin was more useful than
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14 PCT for the diagnosis of sepsis^{5 6}. In a systematic review and meta-analysis, presepsin
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16 levels were significantly lower in sepsis survivors than in non-survivors⁷; however,
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18 most of these presepsin levels were taken at the intensive care unit, not at the ED.
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24 The aim of the present study was to evaluate the accuracy of presepsin, in
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26 comparison with PCT and CRP, in predicting bacteremia in elderly patients admitted to
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28 the ED for suspected infection with systemic inflammatory response syndrome (SIRS).
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30 **Materials and methods**

31 *Patients and study design*

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33 This study was prospectively conducted at the ED of Osaka Medical College Hospital
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35 between September 2014 and March 2016. Elderly patients aged ≥ 70 years and who
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37 fulfilled the SIRS criteria or were suspected to have bacteremia were eligible to enroll in
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39 this study. The exclusion criteria were terminal stage of malignant cancer, acquired
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41 immunodeficiency syndrome or end-stage liver disease, and absence of patient or
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43 relative consent to enroll in the study.
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49 Upon arrival to the ED, all eligible patients underwent two sets of collection of
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51 20 mL of blood samples for bacterial cultures and one collection of 10 mL of blood for
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53 measurements of CRP, PCT, and presepsin levels in plasma. SOFA⁸ and APACHE II⁹
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55 scores were also evaluated. The plasma levels of the 3 biomarkers and the morbidity
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57 scores were compared between 2 groups of patients: the bacteremia group (i.e., positive
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5 result on bacterial blood cultures) and the non-bacteremia group (i.e., negative result on
6 bacterial blood cultures). The study protocol was approved by the ethics committee of
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10 Osaka Medical College (1585). Written informed consent was obtained from each
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12
13 subject.

14 ***Measurement methods***

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17 The CRP, PCT, and presepsin levels were measured in the blood specimens collected at
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19 the ED before antimicrobial agent administration. Blood samples were collected in
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21 tubes that contained ethylenediaminetetraacetic acid, with slow mixing followed by
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23 immediate centrifugation at 3,000 rpm for 10 minutes. The separated plasma was
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25 collected and stored at -35°C until analysis. Plasma presepsin levels were determined
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27 by a chemiluminescent enzyme immunoassay (PATHFAST immunoassay analytical
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29 system; PROGEN Biotechnik GmbH, Heidelberg, Germany; Mitsubishi Chemical
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31 Medience Corporation, Japan), according to the manufacturer's recommendations. After
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33 sterilization of the sites (either percutaneous or from a vascular access device) with the
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35 use of a chlorhexidine–alcohol mixture¹⁰, 2 sets of 10-mL blood were obtained (1 each
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37 for the aerobic and anaerobic bottles) and submitted to our central laboratory for culture.
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41 ***Statistical analysis***

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44 Statistical analysis was performed using the JMP, version 13.0 (SAS Institute Inc.,
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46 Cary, NC, USA). Continuous variables were presented as mean \pm standard deviation
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48 (SD) and were compared using the Wilcoxon rank sum test. Chi-square test was used to
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50 compare differences in the categorical variables. A multivariate logistic regression
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52 analysis model was used to identify the influence of CRP, PCT, and presepsin on
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54 bacteremia. The receiver operating characteristic curve (ROC) was used to derive the
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56 optimal cutoff values, with sensitivity, specificity, predictive values, and likelihood
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5 ratios, of the biomarkers in predicting bacteremia; the corresponding area under the
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7 (AUC) values were calculated. Correlations between the biomarkers and the SOFA and
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9 APACHE II scores were analyzed using Spearman's rank correlation test. A p value of
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11 less than 0.05 was considered statistically significant.
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14 ***Patient and Public Involvement***

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17 The development of the research question and outcome measures was informed by the
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19 elderly patients who have decreased immunity due various underlying diseases admitted
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21 to the ED. During the study design period, elderly patients aged ≥ 70 years and who
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23 fulfilled the SIRS criteria or were suspected to have bacteremia were invited to
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25 participate in this study. Written informed consent was obtained from each subject.
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28 The results of our study will be disseminated to patient who wish to be notified.
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30 **Results**

31 ***Characteristics of the study population and microbiology results***

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33 Of 56 patients who were eligible for this study, 4 patients with terminal stage of
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35 malignant cancer, 4 patients with acquired immune deficiency syndrome, 1 patient with
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37 end-stage liver disease, and 1 patient who did not consent to enroll in this study were
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39 excluded. Therefore, 46 patients (28 men and 18 women) were included in this study.
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41 The mean age was 78 ± 6.7 years. Blood cultures were positive in 16 cases (35%) and
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43 negative in 30 cases (65%). Thee isolated bacteria were Gram-positive microorganisms
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45 in 11 cases (*Staphylococcus caprae* in 1, *Staphylococcus epidermidis* in 5,
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47 *Staphylococcus hominis* in 1, *Lactobacillus acidophilus* in 1, *Enterococcus species* in 1,
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49 *Streptococcus species* in 1, and *Streptococcus equisimilis* in 1) and Gram-negative
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51 microorganisms in 5 cases (*Serratia marcescens* in 1, *Morganella morganii* in 1,
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53 *Klebsiella pneumoniae* in 1, and *Escherichia coli* in 1).
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Comparison between the bacteremia and non-bacteremia groups

The univariate analysis showed no significant differences between the 2 groups in terms of sex ($p = 0.57$) and age ($p = 0.86$) (Table 1). The presepsin value was significantly higher in the bacteremia group than in the non-bacteremia group (866.6 ± 184.6 pg/mL vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). Both groups had similar PCT ($p = 0.18$), CRP ($p = 0.66$), SOFA ($p = 0.07$), and APACHE II ($p = 0.53$). The cutoff values derived from the ROC curves were 285 pg/mL for presepsin, 15.8 ng/mL for PCT, and 34.6 mg/mL for CRP (Table 2). The AUC value of presepsin (0.69) did not significantly differ with that of PCT (0.61, $p = 0.30$) and CRP (0.53, $p = 0.07$) (Figure 1).

In the multivariate analysis, only presepsin was the independent risk factor for bacteremia (hazard ratio, 8.84; 95% confidence interval, 0.95–81.8; $p = 0.02$) (Table 3). As shown in Figure 2, presepsin, PCT, and CRP significantly correlated with the SOFA ($p < 0.0001$, $p < 0.0001$, and $p < 0.0006$, respectively) and the APACHE II ($p < 0.0001$, $p = 0.0005$, and $p = 0.04$, respectively) scores. The Spearman's rank correlation values with the SOFA and APACHE II scores were higher for presepsin (0.56 and 0.59, respectively) than for PCT (0.53 and 0.49, respectively) and CRP (0.39 and 0.3, respectively).

Discussion

Early diagnosis of bacteremia at the ED is very important for the initiation of appropriate treatments and to improve outcomes, but it is not easy and often overlooked, especially in elderly patients, in whom symptoms are not always straightforward and can be misleading. In this prospective study on elderly patients admitted at the ED, we found that 1) presepsin levels were higher with bacteremia than with non-bacteremia; 2) presepsin was an independent predictor of bacteremia; and 3) there was no significant

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5 difference in the AUC values among presepsin, PCT, and CRP. Therefore, presepsin
6 was demonstrated as effective as CRP and PCT in diagnosing bacteremia in elderly
7 patients admitted to the ED.
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12 Liu et al⁵ and Carpio et al¹¹ reported that the cutoff values of presepsin for
13 mortality in septic ED patients were 556 and 825 pg/mL, respectively. Considering that
14 the outcome of those studies was mortality, a cutoff value of 285 pg/mL for bacteremia
15 in our study might be reasonable. Romualdo et al reported that the cutoff value for
16 bacteremic SIRS was 729 pg/mL for ED patients with a mean age of 67 years¹². In our
17 study, the sensitivity was 93.7% and the negative predictive value was 92.3%. In elderly
18 patients who are more prone to infections, the cutoff value for bacteremia might be
19 lower, compared with that in young people.
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31 There were no significant differences in the SOFA and APACHE II scores
32 between the groups. Notably, such physiologic estimations might have been offset by
33 the elderly pathophysiologic characteristics, including dementia, which could have
34 complicated consciousness assessment; potential hypertension, which could have
35 rendered the blood pressure as normal; and the intake of various oral medications for
36 other diseases. Nevertheless, the stronger correlations with the SOFA or APACHE II
37 scores of presepsin than of PCT and CRP suggested that compared with PCT and CRP,
38 presepsin more likely reflected the disease severity of elderly patients upon arrival at the
39 ED.
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52 In this study, blood culture contaminations were likely. The median adult
53 inpatient blood culture contamination rate was reported to be only 2.5%¹³ and 12.4%
54 rate of isolated coagulase-negative staphylococci (CNS) was reported to be clinically
55 significant¹⁴. Therefore, the presence of CNS in 7 of 16 (43%) positive blood cultures
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5 might have significantly affected the results of this study. However, our study
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8 population comprised elderly people who were susceptible to bacteremia due to
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10 decreased immunity; therefore, the probability of isolating the true pathogens on culture
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12 is higher than that in adults. The other limitations of the present study include the
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14 relatively small sample size, the single-center design, and the relatively high exclusion
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16 ratio of 18% (10 of 56) of the eligible patients. Therefore, our findings may have been
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18 underpowered and represent type 2 statistical error.
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21 **Conclusion**

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23 This cohort study suggested that similar to CRP and PCT, presepsin may be useful in
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25 detecting bacteremia in elderly patients admitted to the ED. Further study is needed to
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27 define the exact cutoff value for the prediction of bacteremia in these patients.
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33 **Figure 1. Receiver-operating characteristic curve**

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35 Diagnostic value of presepsin, PCT, and CRP for differentiating between positive and
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37 negative blood cultures
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42 **Figure 2. Correlations of the 3 biomarkers with the SOFA and APACHE II scores**

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44 a-1. Presepsin and SOFA score: $R = 0.56$ $p < 0.001$

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46 a-2. PCT and SOFA score: $R = 0.53$ $p < 0.001$

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48 a-3. CRP and SOFA score: $R = 0.39$ $p = 0.006$

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50 b-1. Presepsin and APACHE II score: $R = 0.59$ $p < 0.001$

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52 b-2. PCT and APACHE II score: $R = 0.49$ $p < 0.001$

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54 b-3. CRP and APACHE II score: $R = 0.30$ $p = 0.04$
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Table 1. Characteristics of the study population

	Non-bacteremia (n = 30)	Bacteremia (n = 46)	P-Value
Age, years	77.30±1.23	78.93±1.69	0.57
Sex, n. male/female	18/12	10/6	0.86
Presepsin (pg/mL)	639.93±137.10	866.56±184.58	0.03
PCT (ng/mL)	6.77±10.05	45.04±13.76	0.18
CRP (mg/L)	12.64±2.38	15.41±3.26	0.66
SOFA score	2.20±0.47	4.2±0.65	0.07
APACHE II score	13.63±1.0	14.56±1.37	0.53

PCT: procalcitonin

CRP: C-reactive protein

SOFA: Sequential Organ Failure Assessment

APACH II : Acute Physiology and Chronic Health Evaluation

Table 2. Prediction of bacteremia

	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Presepsin (pg/mL)	285	93.7	41.3	46.8	92.3
PCT (ng/mL)	15.8	43.7	86.7	63.6	74.2
CRP (mg/L)	34.6	25	93.3	66.6	70

PPV: positive predictive value, NPV: negative predictive value

Table 3. Multivariate analysis of the risk factors for bacteremia

	Hazard ratio	95%CI	P-Value
Presepsin (pg/mL)	8.84	0.95-81.79	0.02
PCT (ng/mL)	2.89	0.19-0.56	0.18
CRP (mg/L)	0.65	0.06-6.54	0.71

CI: confidence interval

Abbreviations

ED; emergency department, PCT; procalcitonin, CRP; C-reactive protein

SOFA; Sequential Organ Failure Assessment, APACH II; Acute Physiology and

Chronic Health Evaluation, AUC; area under the receiver-operating-characteristic curve

ROC; receiver operating characteristic curve, CD14; cluster-of-differentiation 14

SIRS; systemic inflammatory response syndrome, CNS; coagulase-negative

staphylococci

Authors' Contributions

Conception and design of the study: Y. Imai, A. Takasu. Acquisition of data: Y. Imai, R.

Iida, M. Nitta, A. Takasu. Analysis and interpretation of the data: Y. Imai, A. Takasu.

Material and financial support: Y. Imai, K. Taniguchi, R. Iida, M. Nitta, K. Uchiyama

and A. Takasu. Writing, review, and/or revision of the manuscript: Y. Imai, A. Takasu.

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Conflict of Interest:

No

Data availability statement

No additional data available

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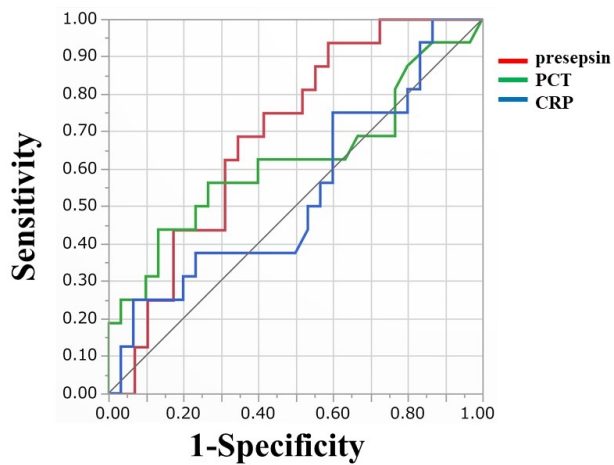
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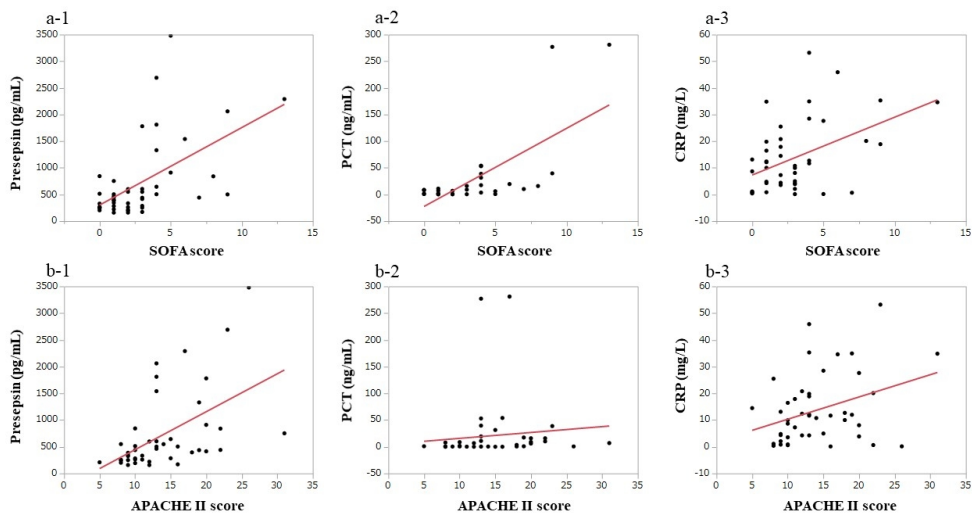
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Receiver-operating characteristic curve

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Correlations of the 3 biomarkers with the SOFA and APACHE II scores
338x190mm (96 x 96 DPI)

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Title Page

Diagnostic accuracy of presepsin in predicting bacteremia in elderly patients admitted to the emergency department : prospective study comparing the accuracy of detecting bacteremia between the presepsin, PCT and CRP.

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Running title:

presepsin in predicting bacteremia in elderly patients

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Abstract

Objective

Early detection of bacteremia in the elderly is needed in the emergency department (ED).

Design, Setting, and Participants

Prospective, singlecenter trial in patients with fulfilled the sepsis was conducted between September 2014 and March 2016. Forty-six elderly patients aged ≥ 70 years were included.

Interventions

Blood sampling to evaluate CRP, PCT, presepsin plasma levels; two sets of blood sampling for bacterial cultures; and evaluations of the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were performed upon arrival at the ED. The results were compared between patients with bacteremia and those without bacteremia.

Main Outcome Measure

The accuracy of detecting bacteremia

Results

The presepsin value was significantly higher in the bacteremia group than in the non-bacteremia group (866.6 ± 184.6 pg/mL vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). The PCT and CRP did not significantly differ between the groups. The area under the receiver-operating-characteristic curve (AUC) values were not significantly different among presepsin (0.69), PCT (0.61), and CRP (0.53). Multivariate analysis showed that presepsin was independently associated with bacteremia (odds ratio, 8.84; 95% confidence interval, 0.95–81.79; $p = 0.02$).

Conclusion

Presepsin could be a better biomarker to evaluate bacteremia in elderly patients with sepsis criteria admitted to the ED.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Strengths and limitations of this study

- Research limited to the elderly is original.
- The present study include the relatively small sample size, the single-center design, and the relatively high exclusion ratio of the eligible patients.
- Our findings may have been underpowered and represent type 2 statistical error.

Introduction

Bacteremia causes bacterial bloodstream infection that is associated with a significant mortality^{1 2}. In particular, the susceptibility to bacteremia is increased in elderly people who have decreased immunity due to various underlying diseases, such as diabetes and malignant disorders³. In recent years, the number of elderly people who are brought to the emergency department (ED) has increased in an aging society. Therefore, early diagnosis of bacteremia upon arrival at the ED is important.

Blood bacterial culture is the gold standard to diagnose bacteremia, but it requires several days to obtain the results⁴. Various biomarkers, including C-reactive protein (CRP) and procalcitonin (PCT), had been used to support the diagnosis of bacteremia⁵. Presepsin, which is the soluble fraction of cluster-of-differentiation 14 (CD14), had

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5 been thought to be associated with infections⁶, based on the fact that a subtype of CD14
6 is present inside and on the cell membranes of macrophages, monocytes, and
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8 granulocytes and is responsible for intracellular transduction of endotoxin signals.
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10 Several studies demonstrated that presepsin was more useful than PCT for the diagnosis
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12 of sepsis^{7 8}. In a systematic review and meta-analysis, presepsin levels were
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14 significantly lower in sepsis survivors than in non-survivors⁹; however, most of these
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16 presepsin levels were taken at the intensive care unit, not at the ED.
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21 The aim of the present study was to evaluate the accuracy of presepsin, in comparison
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23 with PCT and CRP, in predicting bacteremia in elderly patients admitted to the ED for
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25 suspected infection with sepsis.
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28 **Materials and methods**

29 *Patients and study design*

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31 This study was prospectively conducted at the ED of Osaka Medical College Hospital
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33 between September 2014 and March 2016. Elderly patients aged ≥ 70 years and who
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35 fulfilled the SIRS criteria or were suspected to have bacteremia were eligible to enroll in
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37 this study. The exclusion criteria were terminal stage of malignant cancer, acquired
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39 immunodeficiency syndrome or end-stage liver disease, and absence of patient or
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41 relative consent to enroll in the study.
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46 Upon arrival to the ED, all eligible patients underwent two sets of collection of 20 mL
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48 of blood samples for bacterial cultures and one collection of 10 mL of blood for
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50 measurements of CRP, PCT, and presepsin levels in plasma. SOFA¹⁰ and APACHE II
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52 scores were also evaluated. The plasma levels of the 3 biomarkers and the morbidity
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54 scores were compared between 2 groups of patients: the bacteremia group (i.e., positive
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56 result on bacterial blood cultures) and the non-bacteremia group (i.e., negative result on
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5 bacterial blood cultures).

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8 ***Measurement methods***
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10 The CRP, PCT, and presepsin levels were measured in the blood specimens collected
11 at the ED before antimicrobial agent administration. Blood samples of presepsin were
12 collected in tubes that contained ethylenediaminetetraacetic acid, with slow mixing
13 followed by immediate centrifugation at 3,000 rpm for 10 minutes. The separated
14 plasma of presepsin was collected and stored at -35°C until analysis. Plasma presepsin
15 levels were determined only by a chemiluminescent enzyme immunoassay
16 (PATHFAST immunoassay analytical system; Mitsubishi Chemical Medience
17 Corporation, Japan), according to the manufacturer's recommendations. After
18 sterilization of the sites (either percutaneous or from a vascular access device) with the
19 use of a chlorhexidine–alcohol mixture¹², 2 sets of 10-mL blood were obtained (1 each
20 for the aerobic and anaerobic bottles) and submitted to our central laboratory for culture.
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35 ***Statistical analysis***
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37 Statistical analysis was performed using the JMP, version 13.0 (SAS Institute Inc.,
38 Cary, NC, USA). Continuous variables were presented as mean \pm standard errors (SE)
39 and were compared using the Wilcoxon rank sum test. A chi-square test was used to
40 compare differences in the categorical variables. A multivariate logistic regression
41 analysis model which objective variable was presence of bacteremia, explanatory
42 variable was CRP, PCT, and presepsin was used to identify the influence of CRP, PCT,
43 and presepsin on bacteremia. The receiver operating characteristic curve (ROC) was
44 used to derive the optimal cutoff values, with sensitivity, specificity, predictive values,
45 and likelihood ratios, of the biomarkers in predicting bacteremia and an area under the
46 curve (AUC) differences were assessed with De Long test. A p-value of less than 0.05
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was considered statistically significant.

Patient and Public Involvement

The development of the research question and outcome measures was informed by the elderly patients who have decreased immunity due various underlying diseases admitted to the ED. During the study design period, elderly patients aged ≥ 70 years and who fulfilled the SIRS criteria or were suspected to have bacteremia were invited to participate in this study. Written informed consent was obtained from each subject.

The results of our study will be disseminated to patient who wish to be notified.

The study protocol was approved by the ethics committee of Osaka Medical College (1585).

Results

Characteristics of the study population and microbiology results

Of 56 patients who were eligible for this study, 4 patients with terminal stage of malignant cancer, 4 patients with acquired immune deficiency syndrome, 1 patient with end-stage liver disease, and 1 patient who did not consent to enroll in this study were excluded. Therefore, 46 patients (28 men and 18 women) were included in this study. The mean age was 78 ± 6.7 years. Blood cultures were positive in 16 cases (35%) and negative in 30 cases (65%). The isolated bacteria were Gram-positive microorganisms in 11 cases (*Staphylococcus caprae* in 1, *Staphylococcus epidermidis* in 5, *Staphylococcus hominis* in 1, *Lactobacillus acidophilus* in 1, *Enterococcus species* in 1, *Streptococcus species* in 1, and *Streptococcus equisimilis* in 1) and Gram-negative microorganisms in 5 cases (*Serratia marcescens* in 1, *Morganella morganii* in 1, *Klebsiella pneumoniae* in 1, and *Escherichia coli* in 1).

Comparison between the bacteremia and non-bacteremia groups

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6 The univariate analysis showed no significant differences between the 2 groups in terms
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8 of sex ($p = 0.57$) and age ($p = 0.86$) (Table 1). The presepsin value was significantly
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10 higher in the bacteremia group than in the non-bacteremia group (866.6 ± 184.6 pg/mL
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12 vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). Both groups had similar PCT ($p = 0.18$), CRP ($p =$
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14 0.66), SOFA ($p = 0.07$), and APACHE II ($p = 0.53$). The cutoff values derived from the
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16 ROC curves were 285 pg/mL for presepsin, 15.8 ng/mL for PCT, and 34.6 mg/L for
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18 CRP (Table 2). The AUC value of presepsin (0.69) did not significantly differ with that
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20 of PCT (0.61, $p = 0.30$) and CRP (0.53, $p = 0.07$) (Figure 1).
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24 In the multivariate analysis, only presepsin was the independent risk factor for
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26 bacteremia (hazard ratio, 8.84; 95% confidence interval, 0.95–81.79; $p = 0.02$) (Table
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28 3). Because the number of cases was small, so three biomarkers were examined in this
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30 study.
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33 Discussion

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35 Early diagnosis of bacteremia at the ED is very important for the initiation of
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37 appropriate treatments and to improve outcomes, but it is not easy and often overlooked,
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39 especially in elderly patients, in whom symptoms are not always straightforward and
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41 can be misleading. In this prospective study on elderly patients admitted at the ED, we
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43 found that 1) presepsin levels were higher with bacteremia than with non-bacteremia; 2)
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45 presepsin was an independent predictor of bacteremia; and 3) there was no significant
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47 difference in the AUC values among presepsin, PCT, and CRP. Therefore, presepsin
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49 was superior than CRP and PCT in diagnosing bacteremia in elderly patients admitted
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51 to the ED.
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55 Liu et al⁷ and Carpio et al¹³ reported that the cutoff values of presepsin for mortality in
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57 septic ED patients were 556 and 825 pg/mL, respectively. Considering that the outcome
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5 of those studies was mortality, a cutoff value of 285 pg/mL for bacteremia in our study
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7 might be reasonable. Romualdo et al reported that the cutoff value for bacteremic SIRS
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9 was 729 pg/mL for ED patients with a mean age of 67 years¹⁴. Leli et al reported that
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11 the cutoff value for bacteremia was 843.5 pg/mL for suspected sepsis ED not only in
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13 various departments¹⁵. In our study, the sensitivity was 93.7% and the negative
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15 predictive value was 92.3% at a cutoff value of 285 pg/mL for bacteremia. In elderly
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17 patients who are more prone to infections, the cutoff value for bacteremia might be
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19 lower, compared with that in young people.
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24 Updated definitions of sepsis in 2016. Sepsis is defined as a life-threatening organ
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26 dysfunction caused by a dysregulated response to infection. The diagnostic criteria for
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28 sepsis use SOFA instead of SIRS¹⁶.
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31 There were no significant differences in the SOFA and APACHE II scores between the
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33 groups. Notably, such physiologic estimations might have been offset by the elderly
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35 pathophysiologic characteristics, including dementia, which could have complicated
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37 consciousness assessment; potential hypertension, which could have rendered the blood
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39 pressure as normal; and the intake of various oral medications for other diseases.
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41 Nevertheless, the stronger correlations with the SOFA or APACHE II scores of
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43 presepsin than of PCT and CRP suggested that compared with PCT and CRP, presepsin
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45 more likely reflected the disease severity of elderly patients upon arrival at the ED.
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50 In this study, blood culture contaminations were likely. The median adult inpatient
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52 blood culture contamination rate was reported to be only 2.5%¹⁷ and 12.4% rate of
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54 isolated coagulase-negative staphylococci (CNS) was reported to be clinically
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56 significant¹⁸. Therefore, the presence of CNS in 7 of 16 (43%) positive blood cultures
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58 might have significantly affected the results of this study. However, our study
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5 population comprised elderly people who were susceptible to bacteremia due to
6 decreased immunity; therefore, the probability of isolating the true pathogens on culture
7 is higher than that in adults. The other limitations of the present study include the
8 relatively small sample size, the single-center design, and the relatively high exclusion
9 ratio of 18% (10 of 56) of the eligible patients. Therefore, our findings may have been
10 underpowered and represent type 2 statistical error.
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19 In our study, the PCT cutoff value of 15.8 ng/mL was higher as the ROC suggested
20 than the past study ⁵. The reason might be also explained by the small sample size and
21 lack of data on patient's medical history.
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26 Bacteremia can be identified in about 30% of septic patients and necessitates further
27 diagnostic evaluation ¹⁹. Therefore, the study which the primary outcome would be to
28 pick up patients at risk of adverse outcomes and not just bacteremia should be
29 necessary.
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38 **Conclusion**

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40 This cohort study suggested that Presepsin could be more useful in detecting
41 bacteremia in elderly patients admitted to the ED. Further study is needed to define the
42 exact cutoff value for the prediction of bacteremia in these patients.
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51 **Figure 1. Receiver-operating characteristic curve**

52 Diagnostic value of presepsin, PCT, and CRP for differentiating between positive and
53 negative blood cultures
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Table 1. Characteristics of the study population

	Non-bacteremia (n = 30)	Bacteremia (n = 46)	P-Value
Age, years	77.30±1.23	78.93±1.69	0.57
Sex, n. male/female	18/12	10/6	0.86
Presepsin (pg/mL)	639.93±137.10	866.56±184.58	0.03
PCT (ng/mL)	6.77±10.05	45.04±13.76	0.18
CRP (mg/L)	12.64±2.38	15.41±3.26	0.66
SOFA score	2.20±0.47	4.2±0.65	0.07
APACHE II score	13.63±1.0	14.56±1.37	0.53

PCT: procalcitonin

CRP: C-reactive protein

SOFA: Sequential Organ Failure Assessment

APACH II : Acute Physiology and Chronic Health Evaluation

Continuous variables were presented as mean ± standard errors (SE)

Table 2. Prediction of bacteremia

	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Presepsin (pg/mL)	285	93.7	41.3	46.8	92.3
PCT (ng/mL)	15.8	43.7	86.7	63.6	74.2
CRP (mg/L)	34.6	25	93.3	66.6	70

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PPV: positive predictive value, NPV: negative predictive value

Table 3. Multivariate analysis of the risk factors for bacteremia

	Hazard ratio	95%CI	P-Value
Presepsin (pg/mL)	8.84	0.95-81.79	0.02
PCT (ng/mL)	2.89	0.19-0.56	0.18
CRP (mg/L)	0.65	0.06-6.54	0.71

95%CI: 95% confidence interval

Data sharing statement

The data for this study were included in the manuscript. All data have been provided in the study and anyone is permitted to use the data provided that the article is properly cited.

Abbreviations

ED; emergency department, PCT; procalcitonin, CRP; C-reactive protein

SOFA; Sequential Organ Failure Assessment, APACH II; Acute Physiology and

Chronic Health Evaluation, AUC; area under the receiver-operating-characteristic curve

ROC; receiver operating characteristic curve, CD14; cluster-of-differentiation 14

SIRS; systemic inflammatory response syndrome, CNS; coagulase-negative staphylococci

Authors' Contributions

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6 Conception and design of the study: Y. Imai, A. Takasu. Acquisition of data: Y. Imai, R.
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8 Iida, M. Nitta, A. Takasu. Analysis and interpretation of the data: Y. Imai, A. Takasu.
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10 Material and financial support: Y. Imai, K. Taniguchi, R. Iida, M. Nitta, K. Uchiyama
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12 and A. Takasu. Writing, review, and/or revision of the manuscript: Y. Imai, A. Takasu.
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25 This research received no specific grant from any funding agency in the public,
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27 commercial, or not-for-profit sectors.
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30 **Conflict of Interest:**

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32 None declared
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35 **Data availability statement**

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37 No additional data available
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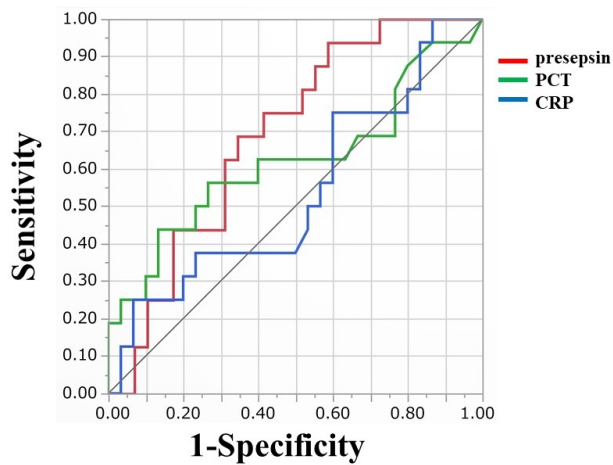
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Receiver-operating characteristic curve

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Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3
	4	Study objectives and hypotheses	3
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4
<i>Participants</i>	6	Eligibility criteria	4
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4,6
	9	Whether participants formed a consecutive, random or convenience series	4,6
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	4,5
	10b	Reference standard, in sufficient detail to allow replication	4,5
	11	Rationale for choosing the reference standard (if alternatives exist)	4,5
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5,6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5,6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	11
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	11
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	5,6
	15	How indeterminate index test or reference standard results were handled	5
	16	How missing data on the index test and reference standard were handled	5
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	5
	18	Intended sample size and how it was determined	4,6
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	6
	20	Baseline demographic and clinical characteristics of participants	6
	21a	Distribution of severity of disease in those with the target condition	6
	21b	Distribution of alternative diagnoses in those without the target condition	6
	22	Time interval and any clinical interventions between index test and reference standard	7
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	7,11
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	7,11
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	3,9
	27	Implications for practice, including the intended use and clinical role of the index test	8,9
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	12
	30	Sources of funding and other support; role of funders	12

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



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Diagnostic accuracy of presepsin in predicting bacteremia in elderly patients admitted to the emergency department : prospective study in Japan

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Title Page**Diagnostic accuracy of presepsin in predicting bacteremia in elderly patients admitted to the emergency department : prospective study in Japan**

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presepsin in predicting bacteremia in elderly patients

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Keywords: presepsin, elderly patients, bacteremia, emergency department, biomarker

Abstract**Objective**

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5 Early detection of bacteremia in the elderly is needed in the emergency department
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8 (ED).
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10 **Design, Setting, and Participants**

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12 Prospective study in Japan, single center trial in patients who satisfied the sepsis criteria
13
14 was conducted between September 2014 and March 2016. Forty-six elderly patients
15
16 aged ≥ 70 years were included.
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18 **Interventions**

19
20 Blood sampling to evaluate C-reactive protein (CRP), procalcitonin (PCT) and
21
22 presepsin plasma levels; two sets of blood sampling for bacterial cultures; and
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24 evaluations of the Sequential Organ Failure Assessment (SOFA) and Acute Physiology
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26 and Chronic Health Evaluation (APACHE II) scores were performed upon arrival at the
27
28 ED. The results were compared between patients with bacteremia and those without
29
30 bacteremia.
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35 **Main Outcome Measure**

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37 The accuracy of detecting bacteremia
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40 **Results**

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42 The presepsin value was significantly higher in the bacteremia group than in the non-
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44 bacteremia group (866.6 ± 184.6 pg/mL vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). The PCT
45
46 and CRP did not significantly differ between the groups. The area under the receiver-
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48 operating-characteristic curve (AUC) values were not significantly different among
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50 presepsin (0.69), PCT (0.61), and CRP (0.53). Multivariate analysis showed that
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52 presepsin was independently associated with bacteremia (odds ratio, 8.84; 95%
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54 confidence interval, 0.95–81.79; $p = 0.02$).
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58 **Conclusion**

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5 Presepsin could be a good biomarker to predict bacteremia in elderly patients with
6 sepsis criteria admitted to the ED.
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9 10 Funding

11
12 This research received no specific grant from any funding agency in the public,
13 commercial, or not-for-profit sectors.
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19 *Strengths and limitations of this study*

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21
- 22 • The number of elderly people who are brought to the emergency department (ED) has
23 increased in recent years. Moreover, decreased immunity due to various underlying
24 diseases, such as diabetes and malignant disorders, make early diagnosis of bacteremia in
25 the elderly important. This research was focused on the elderly, upon their arrival at the ED.
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 - 28 • The present study had a relatively small sample size, a single-center design, and a
29 relatively high exclusion ratio of eligible patients.
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 - 32 • Our findings may have been underpowered and represented type 2 statistical error.
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40 **Introduction**

41
42 Bacteremia causes bacterial bloodstream infection that is associated with a significant
43 mortality^{1 2}. In particular, the susceptibility to bacteremia is increased in elderly people
44 who have decreased immunity due to various underlying diseases, such as diabetes and
45 malignant disorders³. In recent years, the number of elderly people who are brought to
46 the emergency department (ED) has increased in an aging society. Therefore, early
47 prediction of bacteremia upon arrival at the ED is important.
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55 Blood bacterial culture is the gold standard to diagnose bacteremia, but it requires
56 several days to obtain the results⁴. Various biomarkers, including C-reactive protein
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(CRP) and procalcitonin (PCT), had been used to support the diagnosis of bacteremia⁵.

Presepsin, which is the soluble fraction of cluster-of-differentiation 14 (CD14), had been thought to be associated with infections⁶, based on the fact that a subtype of CD14 is present inside and on the cell membranes of macrophages, monocytes, and granulocytes and is responsible for intracellular transduction of endotoxin signals.

Several studies demonstrated that presepsin was more useful than PCT for the diagnosis of sepsis^{7,8}. In a systematic review and meta-analysis, presepsin levels were significantly lower in sepsis survivors than in non-survivors⁹; however, most of these presepsin levels were taken at the intensive care unit, not at the ED.

The aim of the present study was to evaluate the accuracy of presepsin, in comparison with PCT and CRP, in predicting bacteremia in elderly patients admitted to the ED for suspected infection with sepsis.

Materials and methods

Patients and study design

This study was prospectively conducted at the ED of Osaka Medical College Hospital between September 2014 and March 2016. Elderly patients aged ≥ 70 years and who fulfilled the SIRS criteria or were suspected to have bacteremia were eligible to enroll in this study. The exclusion criteria were terminal stage of malignant cancer, acquired immunodeficiency syndrome or end-stage liver disease, and absence of patient or relative consent to enroll in the study.

Upon arrival to the ED, all eligible patients underwent two sets of collection of 20 mL of blood samples for bacterial cultures and one collection of 10 mL of blood for measurements of CRP, PCT, and presepsin levels in plasma. SOFA¹⁰ and APACHE II

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¹¹ scores were also evaluated. The plasma levels of the 3 biomarkers and the morbidity scores were compared between 2 groups of patients: the bacteremia group (i.e., positive result on bacterial blood cultures) and the non-bacteremia group (i.e., negative result on bacterial blood cultures).

Measurement methods

Written informed consent was obtained from each subject. The results of our study will be disseminated to patient who wish to be notified. The study protocol was approved by the ethics committee of Osaka Medical College. Ethics Committee approval number was 1585.

The CRP, PCT, and presepsin levels were measured in the blood specimens collected at the ED before antimicrobial agent administration. Blood samples of presepsin were collected in tubes that contained ethylenediaminetetraacetic acid, with slow mixing followed by immediate centrifugation at 3,000 rpm for 10 minutes. The separated plasma of presepsin was collected and stored at -35°C until analysis. Plasma presepsin levels were determined only by a chemiluminescent enzyme immunoassay (PATHFAST immunoassay analytical system; Mitsubishi Chemical Medience Corporation, Japan), according to the manufacturer's recommendations. After sterilization of the sites (either percutaneous or from a vascular access device) with the use of a chlorhexidine–alcohol mixture¹², 2 sets of 10-mL blood were obtained (1 each for the aerobic and anaerobic bottles) and submitted to our central laboratory for culture.

Statistical analysis

Statistical analysis was performed using the JMP, version 13.0 (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented as mean \pm standard errors (SE)

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5 and were compared using the Wilcoxon rank sum test. A chi-square test was used to
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7 compare differences in the categorical variables. A multivariate logistic regression
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9 analysis model which response variable was presence of bacteremia, explanatory
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11 variables were CRP, PCT, and presepsin was used to identify the influence of CRP,
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13 PCT, and presepsin on bacteremia. The receiver operating characteristic curve (ROC)
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15 was used to derive the optimal cutoff values, with sensitivity, specificity, predictive
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17 values, and likelihood ratios, of the biomarkers in predicting bacteremia and an area
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19 under the curve (AUC) differences were assessed with De Long test. A p-value of less
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21 than 0.05 was considered statistically significant.
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26 ***Patient and Public Involvement***

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28 The development of the research question and outcome measures was informed by the
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30 elderly patients who have decreased immunity due various underlying diseases admitted
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32 to the ED. During the study design period, elderly patients aged ≥ 70 years and who
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34 fulfilled the SIRS criteria or were suspected to have bacteremia were invited to
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36 participate in this study.
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42 **Results**

43 ***Characteristics of the study population and microbiology results***

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45 Of 56 patients who were eligible for this study, 4 patients with terminal stage of
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47 malignant cancer, 4 patients with acquired immune deficiency syndrome, 1 patient with
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49 end-stage liver disease, and 1 patient who did not consent to enroll in this study were
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51 excluded. Therefore, 46 patients (28 men and 18 women) were included. The isolated
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53 bacteria were Gram-positive microorganisms in 11 cases (*Staphylococcus caprae* in 1,
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55 *Staphylococcus epidermidis* in 5, *Staphylococcus hominis* in 1, *Lactobacillus*
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6 *acidophilus* in 1, *Enterococcus species* in 1, *Streptococcus species* in 1, and
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8 *Streptococcus equisimilis* in 1) and Gram-negative microorganisms in 4 cases (*Serratia*
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10 *marcescens* in 1, *Morganella morganii* in 1, *Klebsiella pneumoniae* in 1, and
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12 *Escherichia coli* in 1).

13 14 **Comparison between the bacteremia and non-bacteremia groups**

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17 The univariate analysis showed no significant differences between the 2 groups in terms
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19 of sex ($p = 0.57$) and age ($p = 0.86$) (Table 1). The presepsin value was significantly
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21 higher in the bacteremia group than in the non-bacteremia group (866.6 ± 184.6 pg/mL
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23 vs. 639.9 ± 137.1 pg/mL, $p = 0.03$). Both groups were not significantly different PCT (p
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25 $= 0.18$), CRP ($p = 0.66$), SOFA ($p = 0.07$), and APACHE II ($p = 0.53$). The cutoff
26
27 values derived from the ROC curves were 285 pg/mL for presepsin, 15.8 ng/mL for
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29 PCT, and 34.6 mg/L for CRP (Table 2). The AUC value of presepsin (0.69) did not
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31 significantly differ with that of PCT (0.61, $p = 0.30$) and CRP (0.53, $p = 0.07$) (Figure
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1).

In the multivariate analysis, only presepsin was the only significant risk factor for
bacteremia (odds ratio, 8.84; 95% confidence interval, 0.95–81.79; $p = 0.02$). Because
the number of cases was small, so three biomarkers were examined in this study.

44 45 **Discussion**

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47 Early diagnosis of bacteremia at the ED is very important for the initiation of
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49 appropriate treatments and to improve outcomes, but it is not easy and often overlooked,
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51 especially in elderly patients, in whom symptoms are not always straightforward and
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53 can be misleading. In this prospective study on elderly patients admitted at the ED, we
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55 found that 1) presepsin levels were higher with bacteremia than with non-bacteremia; 2)
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57 presepsin was an independent predictor of bacteremia; and 3) there was no significant
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6 difference in the AUC values among presepsin, PCT, and CRP. Therefore, presepsin
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8 was superior to CRP and PCT in predicting bacteremia in elderly patients admitted to
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10 the ED.

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12 Liu et al⁷ and Carpio et al¹³ reported that the cutoff values of presepsin for mortality in
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14 septic ED patients were 556 and 825 pg/mL, respectively. Considering that the outcome
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16 of those studies was mortality, a cutoff value of 285 pg/mL for bacteremia in our study
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18 might be reasonable. Romualdo et al reported that the cutoff value for bacteremic SIRS
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20 was 729 pg/mL for ED patients with a mean age of 67 years¹⁴. Leli et al reported that
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22 the cutoff value for bacteremia was 843.5 pg/mL for suspected sepsis ED not only in
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24 various departments¹⁵. In our study, the sensitivity was 93.7% and the negative
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26 predictive value was 92.3% at a cutoff value of 285 pg/mL for bacteremia. In elderly
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28 patients who are more prone to infections, the cutoff value for bacteremia might be
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30 lower, compared with that in young people.
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36 There were no significant differences in the SOFA and APACHE II scores between the
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38 groups. Notably, such physiologic estimations might have been offset by the elderly
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40 pathophysiologic characteristics, including dementia, which could have complicated
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42 consciousness assessment; potential hypertension, which could have rendered the blood
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44 pressure as normal; and the intake of various oral medications for other diseases.
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46 Nevertheless, the stronger correlations with the SOFA or APACHE II scores of
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48 presepsin than of PCT and CRP suggested that compared with PCT and CRP, presepsin
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50 more likely reflected the disease severity of elderly patients upon arrival at the ED.
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55 In this study, blood culture contaminations were likely. The median adult inpatient
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57 blood culture contamination rate was reported to be only 2.5%¹⁶ and 12.4% rate of
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59 isolated coagulase-negative staphylococci (CNS) was reported to be clinically
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5 significant¹⁷. Therefore, the presence of CNS in 7 of 16 (43%) positive blood cultures
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7 might have significantly affected the results of this study. However, our study
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9 population comprised elderly people who were susceptible to bacteremia due to
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11 decreased immunity; therefore, the probability of isolating the true pathogens on culture
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13 is higher than that in adults. The other limitations of the present study include the
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15 relatively small sample size, the single-center design, and the relatively high exclusion
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17 ratio of 18% (10 of 56) of the eligible patients. Therefore, our findings may have been
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19 underpowered and represent type 2 statistical error.
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24 In our study, the PCT cutoff value of 15.8 ng/mL was higher as the ROC suggested by
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26 the ROC was higher than in a previous study⁵. The reason might be also explained by
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28 the small sample size and lack of data on patient's medical history.
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31 Bacteremia can be identified in about 30% of septic patients and necessitates further
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33 diagnostic evaluation¹⁸. Therefore, studies are needed in which the primary outcome
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35 would be to pick up patients at risk of adverse outcomes, not just the presence of
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37 bacteremia
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39 40 41 42 **Conclusion**

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45 This cohort study suggested that Presepsin could be more useful than PCT and CRP in
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47 predicting bacteremia in elderly patients admitted to the ED. Further studies are needed
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49 to define the exact cutoff value for the prediction of bacteremia in these patients.
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53 54 55 **Figure 1. Receiver-operating characteristic curve**

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58 Diagnostic value of presepsin, PCT, and CRP for differentiating between positive and
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negative blood cultures

Table 1. Characteristics of the study population

	Non-bacteremia (n = 30)	Bacteremia (n = 46)	P-Value (The univariate analysis)	Odds ratio	95%CI	P-Value (The multivariate analysis)
Age, years	77.30±1.23	78.93±1.69	0.57	N/A	N/A	N/A
Sex,n. male/female	18/12	10/6	0.86	N/A	N/A	N/A
Presepsin (pg/mL)	639.93±137.10	866.56±184.58	0.03	8.84	0.95-81.79	0.02
PCT (ng/mL)	6.77±10.05	45.04±13.76	0.18	2.89	0.19-0.56	0.18
CRP (mg/L)	12.64±2.38	15.41±3.26	0.66	0.65	0.06-6.54	0.71
SOFA score	2.20±0.47	4.2±0.65	0.07	N/A	N/A	N/A
APACHE II score	13.63±1.0	14.56±1.37	0.53	N/A	N/A	N/A

PCT: procalcitonin

CRP: C-reactive protein

SOFA: Sequential Organ Failure Assessment

APACH II : Acute Physiology and Chronic Health Evaluation

Continuous variables were presented as mean ± standard errors (SE)

95%CI: 95% confidence interval

N/A: not available

Table 2. Prediction of bacteremia

	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Presepsin (pg/mL)	285	93.7	41.3	46.8	92.3
PCT (ng/mL)	15.8	43.7	86.7	63.6	74.2
CRP (mg/L)	34.6	25	93.3	66.6	70

PPV: positive predictive value, NPV: negative predictive value

Data sharing statement

Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi: 10.5061/dryad.rbnzs7h70

Abbreviations

ED; emergency department, PCT; procalcitonin, CRP; C-reactive protein

SOFA; Sequential Organ Failure Assessment, APACH II; Acute Physiology and

Chronic Health Evaluation, AUC; area under the receiver-operating-characteristic curve

ROC; receiver operating characteristic curve, CD14; cluster-of-differentiation 14

SIRS; systemic inflammatory response syndrome, CNS; coagulase-negative

staphylococci

Authors' Contributions

Conception and design of the study: Y. Imai, A. Takasu. Acquisition of data: Y. Imai, R.

Iida, M. Nitta, A. Takasu. Analysis and interpretation of the data: Y. Imai, A. Takasu.

Material and financial support: Y. Imai, K. Taniguchi, R. Iida, M. Nitta, K. Uchiyama

and A. Takasu. Writing, review, and/or revision of the manuscript: Y. Imai, A. Takasu.

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Conflict of Interest:

None

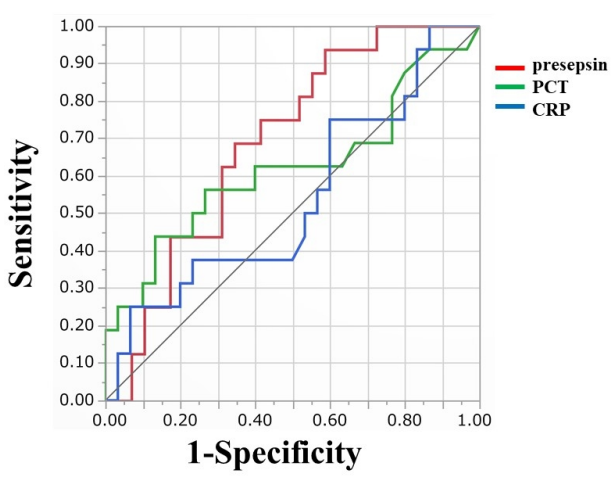
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Receiver-operating characteristic curve

338x190mm (96 x 96 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3
	4	Study objectives and hypotheses	3
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4
<i>Participants</i>	6	Eligibility criteria	4
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4,6
	9	Whether participants formed a consecutive, random or convenience series	4,6
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	4,5
	10b	Reference standard, in sufficient detail to allow replication	4,5
	11	Rationale for choosing the reference standard (if alternatives exist)	4,5
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5,6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5,6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	11
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	11
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	5,6
	15	How indeterminate index test or reference standard results were handled	5
	16	How missing data on the index test and reference standard were handled	5
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	5
	18	Intended sample size and how it was determined	4,6
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	6
	20	Baseline demographic and clinical characteristics of participants	6
	21a	Distribution of severity of disease in those with the target condition	6
	21b	Distribution of alternative diagnoses in those without the target condition	6
	22	Time interval and any clinical interventions between index test and reference standard	7
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	7,11
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	7,11
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	3,9
	27	Implications for practice, including the intended use and clinical role of the index test	8,9
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	12
	30	Sources of funding and other support; role of funders	12

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

