

# BMJ Open Diagnostic accuracy of presepsin in predicting bacteraemia in elderly patients admitted to the emergency department: prospective study in Japan

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## ABSTRACT

**Objective** Early prediction of bacteraemia in the elderly is needed in the emergency department (ED).

**Design, setting and participants** A prospective study in Japan; single-centre trial in patients who satisfied the sepsis criteria was conducted between September 2014 and March 2016. Forty-six elderly patients aged  $\geq 70$  years were included. The study protocol was approved by the ethics committee of Osaka Medical College. Ethics Committee approval number was 1585.

**Interventions** Blood sampling to evaluate C-reactive protein (CRP), procalcitonin (PCT) and presepsin plasma levels; two sets of blood sampling for bacterial cultures; and evaluations of the Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation scores were performed on arrival at the ED. The results were compared between patients with bacteraemia and those without bacteraemia.

**Main outcome measure** The accuracy of detecting bacteraemia.

**Results** The presepsin value was significantly higher in the bacteraemia group than in the non-bacteraemia group ( $866.6 \pm 184.6$  vs  $639.9 \pm 137.1$  pg/mL,  $p=0.03$ ). The PCT and CRP did not significantly differ between the groups. The area under the receiver operating characteristic curve 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 bacteraemia (OR 8.84; 95% CI 0.95 to 81.79;  $p=0.02$ ).

**Conclusion** Presepsin could be a good biomarker to predict bacteraemia in elderly patients with sepsis criteria admitted to the ED.

## INTRODUCTION

Bacteraemia causes bacterial bloodstream infection that is associated with a significant mortality.<sup>1 2</sup> In particular, the susceptibility to bacteraemia is increased in elderly people who have decreased immunity due to various underlying diseases, such as diabetes and malignant disorders.<sup>3</sup> In recent years, the number of elderly people who are brought to the emergency department (ED) has

## Strengths and limitations of this study

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

increased in an ageing society. Therefore, early prediction of bacteraemia on arrival at the ED is important.

Blood bacterial culture is the gold standard to diagnose bacteraemia, but it requires several days to obtain the results.<sup>4</sup> Various biomarkers, including C-reactive protein (CRP) and procalcitonin (PCT), had been used to support the diagnosis of bacteraemia.<sup>5</sup> Presepsin, which is the soluble fraction of cluster of differentiation 14 (CD14), had been thought to be associated with infections,<sup>6</sup> 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.<sup>7 8</sup> In a systematic review and meta-analysis, presepsin levels were significantly lower in sepsis survivors than in non-survivors<sup>9</sup>; 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 bacteraemia

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 the Osaka Medical College Hospital between September 2014 and March 2016. Elderly patients aged  $\geq 70$  years and who fulfilled the systemic inflammatory response syndrome (SIRS) criteria or were suspected to have bacteraemia were eligible to enrol in this study. The exclusion criteria were terminal stage of malignant cancer, AIDS or end-stage liver disease, and absence of patient or relative consent to enrol in the study.

On arrival at 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 sample for measurements of CRP, PCT and presepsin levels in plasma. Sequential Organ Failure Assessment (SOFA)<sup>10</sup> and Acute Physiology and Chronic Health Evaluation (APACHE II)<sup>11</sup> scores were also evaluated. The plasma levels of the three biomarkers and the morbidity scores were compared between two groups of patients: the bacteraemia group (ie, positive result on bacterial blood cultures) and the non-bacteraemia group (ie, 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 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 3000 rpm for 10 min. The separated plasma of presepsin was collected and stored at  $-35^{\circ}\text{C}$  until analysis. Plasma presepsin levels were determined only by a chemiluminescent enzyme immunoassay (PATHFAST immunoassay analytical system; Mitsubishi Chemical Medience Corporation, Tokyo, Japan), according to the manufacturer's recommendations. After sterilisation of the sites (either percutaneous or from a vascular access device) with the use of a chlorhexidine-alcohol mixture,<sup>12</sup> two sets of 10 mL blood were obtained (one each for the aerobic and anaerobic bottles) and submitted to our central laboratory for culture.

### Statistical analysis

Statistical analysis was performed using the JMP V.13.0 (SAS Institute, Cary, North Carolina, USA). Continuous variables were presented as mean $\pm$ SE and were compared using the Wilcoxon rank-sum test. A  $\chi^2$  test was used to compare differences in the categorical variables. A multivariate logistic regression analysis model, which response variable was presence of bacteraemia, and explanatory

variables were CRP, PCT and presepsin, was used to identify the influence of CRP, PCT and presepsin on bacteraemia. The receiver operating characteristic (ROC) curve was used to derive the optimal cut-off values, with sensitivity, specificity, predictive values and likelihood ratios, of the biomarkers in predicting bacteraemia and area under the curve (AUC) differences were assessed with DeLong test. A p value of less than 0.05 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 to various underlying diseases admitted to the ED. During the study design period, elderly patients aged  $\geq 70$  years and who fulfilled the SIRS criteria or were suspected to have bacteraemia were invited to participate in this study.

## 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 AIDS, 1 patient with end-stage liver disease and 1 patient who did not consent to enrol in this study were excluded. Therefore, 46 patients (28 men and 18 women) were included. The isolated bacteria were Gram-positive microorganisms in 11 cases (*Staphylococcus caprae* in 1, *S. epidermidis* in 5, *S. 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 4 cases (*Serratia marcescens* in 1, *Morganella morganii* in 1, *Klebsiella pneumoniae* in 1 and *Escherichia coli* in 1).

### Comparison between the bacteraemia and non-bacteraemia groups

The univariate analysis showed no significant differences between the two groups in terms of sex ( $p=0.57$ ) and age ( $p=0.86$ ) (table 1). The presepsin value was significantly higher in the bacteraemia group than in the non-bacteraemia group ( $866.6\pm 184.6$  vs  $639.9\pm 137.1$  pg/mL,  $p=0.03$ ). Both groups were not significantly different PCT ( $p=0.18$ ), CRP ( $p=0.66$ ), SOFA ( $p=0.07$ ) and APACHE II ( $p=0.53$ ). The cut-off values derived from the ROC curves were 285 pg/mL for presepsin, 15.8 ng/mL for PCT and 34.6 mg/L 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 only significant risk factor for bacteraemia (OR 8.84; 95% CI 0.95 to 81.79;  $p=0.02$ ). Because the number of cases was small, so three biomarkers were examined in this study.

**Table 1** Characteristics of the study population

	Non-bacteraemia (n=30)	Bacteraemia (n=46)	P value (the univariate analysis)	OR	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 to 81.79	0.02
PCT (ng/mL)	6.77±10.05	45.04±13.76	0.18	2.89	0.19 to 0.56	0.18
CRP (mg/L)	12.64±2.38	15.41±3.26	0.66	0.65	0.06 to 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

Continuous variables were presented as mean±SE.

APACHE II, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; N/A, not available; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment.

## DISCUSSION

Early diagnosis of bacteraemia 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 to the ED, we found that (1) presepsin levels were higher with bacteraemia than with non-bacteraemia; (2) presepsin was an independent predictor of bacteraemia and (3) there was no significant difference in the AUC values among presepsin, PCT and CRP. Therefore, presepsin was superior to CRP and PCT in predicting bacteraemia in elderly patients admitted to the ED.

Liu *et al*<sup>7</sup> and Carpio *et al*<sup>13</sup> reported that the cut-off values of presepsin for mortality in septic ED patients were 556 and 825 pg/mL, respectively. Considering that the outcome of those studies was mortality, a cut-off value of 285 pg/mL for bacteraemia in our study might be reasonable. Romualdo *et al* reported that the cut-off value for bacteraemic SIRS was 729 pg/mL for ED patients with a mean age of 67 years.<sup>14</sup> Leli *et al* reported that the cut-off value for bacteraemia was 843.5 pg/mL for suspected sepsis in internal medicine wards, in oncohaematology, in intensive care units and in surgery wards.<sup>15</sup> In our study, the sensitivity was 93.7% and the negative predictive value was 92.3% at a cut-off value of 285 pg/mL for bacteraemia. In elderly patients who are more prone to infections, the cut-off

value for bacteraemia might be lower compared with that in young people.

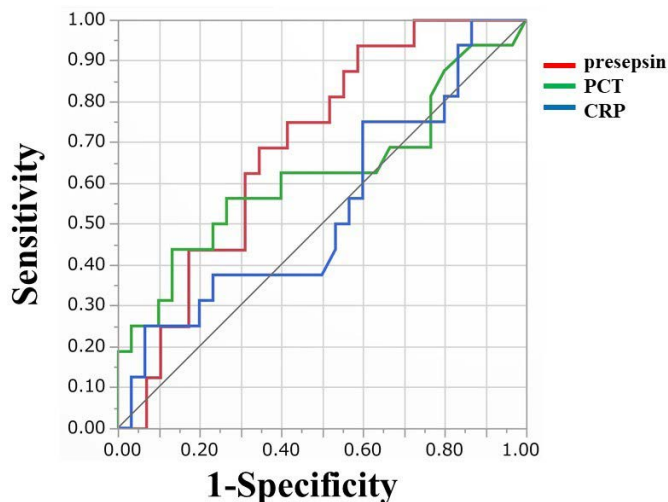
There were no significant differences in the SOFA and APACHE II scores between the groups. Notably, such physiologic estimations might have been offset by the elderly pathophysiologic characteristics, including dementia, which could have complicated consciousness assessment; potential hypertension, which could have rendered the blood pressure as normal; and the intake of various oral medications for other diseases. Nevertheless, the stronger correlations with the SOFA or APACHE II scores of presepsin than of PCT and CRP suggested that compared with PCT and CRP, presepsin more likely reflected the disease severity of elderly patients on arrival at the ED.

In this study, blood culture contaminations were likely. The median adult inpatient blood culture contamination rate was reported to be only 2.5%,<sup>16</sup> and 12.4% rate of isolated coagulase-negative staphylococci (CNS) was reported to be clinically significant.<sup>17</sup> Therefore, the presence of CNS in 7 of 16 (43%) positive blood cultures might have significantly affected the results of this study. However, our study population comprised elderly people who were susceptible to bacteraemia due to decreased immunity; therefore, the probability of isolating the true pathogens on culture is higher than that in adults. The other limitations of the present study include the relatively small sample size, the single-centre design and the relatively high exclusion ratio of 18% (10 of 56) of the eligible patients. Therefore, our

**Table 2** Prediction of bacteraemia

	Cut-off	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

CRP, C-reactive protein; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.



**Figure 1** Receiver operating characteristic curve diagnostic value of presepsin, PCT and CRP for differentiating between positive and negative blood cultures. CRP, C-reactive protein; PCT, procalcitonin.

findings may have been underpowered and represented type 2 statistical error.

In our study, the PCT cut-off value of 15.8 ng/mL suggested by the ROC was higher than in a systematic review and meta-analysis.<sup>5</sup> The reason might be also explained by the small sample size and lack of data on patient's medical history.

Bacteraemia can be identified in about 30% of septic patients and necessitates further diagnostic evaluation.<sup>18</sup> Therefore, studies are needed in which the primary outcome would be to pick up patients at risk of adverse outcomes, not just the presence of bacteraemia.

## CONCLUSION

This cohort study suggested that presepsin could be more useful than PCT and CRP in predicting bacteraemia in elderly patients admitted to the ED. Further studies are needed to define the exact cut-off value for the prediction of bacteraemia in these patients.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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**Data availability statement** All data relevant to the study are included in the article.

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