

Presepsin level in predicting patients' in-hospital mortality from sepsis under sepsis-3 criteria

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Background: Early recognition of septic patients with poor prognosis is important for clinicians to prescribe personalized therapies which include timely fluid resuscitation therapy and appropriate antimicrobial therapy. We aimed to evaluate the effect of the presepsin level on predicting the prognosis of patients with sepsis under the sepsis-3 criteria.

Methods: Patients who were diagnosed as sepsis under the sepsis-3 criteria were recruited and assigned to the survivor group and the non-survivor group according to their in-hospital mortality. The two groups' baseline characteristics were analyzed with Pearson's chi-square (χ^2) test or Kruskal–Wallis test. Binary logistic regression analysis was performed to determine the independent predictors of in-hospital mortality from sepsis. Receiver operating characteristic analysis was conducted to evaluate the efficacy of presepsin in predicting patients' in-hospital mortality from sepsis. The correlation between presepsin and the Sequential Organ Failure Assessment (SOFA) score was measured with Spearman's rank correlation coefficient. *P*-values of less than 0.05 were considered to indicate statistical significance.

Results: Overall, 138 patients were included in this study. The presepsin level of the non-survivor group was significantly higher than that of the other group (*P*=0.000). Binary logistic regression showed that the presepsin level was an independent risk factor of patients' in-hospital mortality from sepsis (OR =1.221 *P*=0.026). The presepsin level was positively associated with the SOFA score (ρ =0.396, *P*=0.000). ROC curve analysis revealed the presepsin level was highly accurate in predicting patients' in-hospital mortality from sepsis (AUC =0.703, *P*=0.000). The AUC value of a combination of presepsin and the SOFA score was significantly larger than that of the SOFA score alone (AUC: 0.817 vs 0.793, *P*=0.041).

Conclusions: Presepsin is a prognostic biomarker with high accuracy in predicting the prognosis of sepsis under the sepsis-3 criteria.

Keywords: presepsin, sepsis, biomarker, mortality, outcomes

Introduction

Sepsis is one of the leading causes of death worldwide.¹ Early recognition of patients with poor prognosis is important for clinicians to prescribe personalized therapies, including timely fluid, resuscitation therapy,^{2–4} and appropriate antimicrobial therapy.⁵ However, not all patients with sepsis present with infection-related symptoms, and patients' clinical signs, along with several comorbidities, can be misleading. Thus, it is crucial to find out ways to predict the prognosis of sepsis.^{6–8} Biomarkers, as inflammatory variables, have been introduced to guide treatment and predict the prognosis of sepsis.

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Among various molecules, presepsin seems to be a promising biomarker since it has been reported to be associated with the early stage of the septic process.⁹ Presepsin was first discovered in 2004.¹⁰ When monocytes are activated by infectious agents, presepsin, as a soluble CD14 subtype, will be released into the plasma.¹¹ The level of presepsin continues to increase in the early stage of sepsis.⁹ It has been reported in several studies that presepsin is a hopeful diagnostic marker of sepsis.^{12,13} Increasing numbers of studies have highlighted the superior value of presepsin to procalcitonin (PCT), interleukin-6, and C reactive protein in the diagnosis of sepsis.¹⁴ However, the prognostic performance of the presepsin level in patients' with sepsis is uncertain. This study aimed to evaluate the efficacy of the presepsin level in predicting the prognosis of patients with sepsis under the sepsis-3 criteria.

Materials and methods

Patients and study design

This prospective observational study was conducted among the ICU patients who were diagnosed as sepsis in Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences from June 2017 to November 2018. The inclusion criteria were: sepsis under the sepsis-3 criteria;¹⁵ more than 18 years old; measurement of the presepsin level. Exclusion criteria were: age ≤ 18 years; pregnancy; cancers; hematologic disorders; a history of transplantation; and immunosuppressive drug use. All participants included in the study were assigned to two groups according to their in-hospital mortality: the survivor group and the non-survivor group.

Data collection

Age, sex, laboratory data (white blood cell and platelet count, and levels of total bilirubin, creatinine, PCT, and lactate), and blood samples were collected upon admission. The blood samples were used to measure the levels of presepsin with an automatic analyzer (LSI Medience Corporation, Tokyo, Japan), and the detection range was 20–20,000 pg/mL. During hospitalization, clinical data (mechanical ventilation, SOFA score, APACHE II score, sources of infection, and pathogens) related to the patient's prognosis were collected. Patients were observed from the admission day to the day of discharge or death. Subsequently, a retrospective analysis was carried out.

Statistical analysis

The categorical variables were expressed as counts (percentages) and analyzed with Pearson's chi-square (χ^2) test, while the continuous variables were represented as medians (interquartile ranges) and analyzed with Kruskal–Wallis test. Binary logistic regression analysis was employed to determine the independent predictors of patients' in-hospital mortality. Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the prediction accuracy. A correlation analysis was performed with Spearman's rank correlation coefficient. All statistical analyses were done using SPSS 20.0. *P*-values of less than 0.05 were considered to indicate statistical significance.

Results

Patients' baseline characteristics

Overall 138 patients met the inclusion criteria, including 74 survivors and 64 non-survivors. Their baseline characteristics are listed in Table 1. The differences in age and sex between the two groups were not statistically significant (age: $P=0.553$; sex: $P=0.251$).

Comparison of the SOFA score, APACHE II score, and levels of presepsin, PCT and lactate between the two groups

The levels of presepsin and lactate in the non-survivor group were significantly higher than those of the survivor group (presepsin: $P=0.000$; lactate: $P=0.000$) (Figure 1A and B). There was no significant difference in the PCT level between the two groups ($P=0.403$) (Figure 1C). The SOFA scores and APACHE II scores of the non-survivor group were significantly higher than those of the survivor group (SOFA score: $P=0.000$; APACHE II score: $P=0.002$) (Figure 1D and E).

Independent predictors of patients' in-hospital mortality determined by binary logistic regression analysis

Binary logistic regression showed that the presepsin level (Odds ratio (OR) =1.221, 95% confidence interval (CI): 1.024–1.455, $P=0.026$), lactate level (OR =1.296, 95% CI: 1.071–1.569, $P=0.008$) and SOFA score (OR =1.404, 95% CI: 1.209–1.632, $P=0.000$) were risk factors for patients' in-hospital mortality from sepsis. However, there was no association between patients' in-hospital mortality and

Table 1 Patients' baseline characteristics

	All patients, n=138	Survivors, n=74	Non-survivors, n=64	P-value
Age (years)	62 (51–73)	61 (50–71)	62 (52–74)	0.553
Male (%)	89 (64)	45 (61)	44 (69)	0.251
Laboratory values				
White blood cells ($10^9/L$)	12.0 (7.7–18.3)	11.2 (7.3–18.0)	13.1 (8.0–19.1)	0.588
Platelets ($10^9/L$)	141 (74–232)	152 (81–228)	130 (67–247)	0.544
Total bilirubin (mg/dL)	1.3 (0.8–2.9)	1.3 (0.8–3.0)	1.3 (0.8–2.7)	0.842
Creatinine (mg/dL)	1.4 (0.9–2.7)	1.3 (0.9–2.0)	1.9 (1.0–3.5)	0.010
Procalcitonin (ng/mL)	6.26 (1.82–31.02)	6.01 (1.54–34.78)	6.73 (2.55–27.42)	0.403
Presepsin (pg/mL)	1,348 (661–3273)	1,125 (484–2268)	1,692 (1028–4286)	0.000
Lactate (mmol/L)	1.6 (1.1–2.7)	1.4 (0.9–2.2)	2.3 (1.4–4.2)	0.000
Mechanical ventilation				
Number of patients	100 (72)	44 (59)	56 (88)	0.000
Severity of sepsis				
SOFA score	8 (5–11)	6 (4–8)	10 (8–12)	0.000
APACHE II score	21 (16–26)	20 (14–23)	24 (17–31)	0.002
Sources of infection				
Respiratory tract	67 (49)	23 (31)	44 (69)	0.001
Urinary tract	12 (9)	9 (12)	3 (5)	0.070
Intra-abdomen	44 (32)	32 (43)	12 (19)	0.000
Others	15 (11)	10 (14)	5 (8)	0.336
Pathogens				
Gram-negative rods	41 (30)	18 (24)	23 (36)	0.137
Gram-positive cocci	7 (5)	4 (5)	3 (5)	0.848
Fungi	10 (7)	5 (7)	5 (8)	0.811
Gram-negative bacilli and Gram-positive cocci	8 (6)	3 (4)	5 (8)	0.346
Gram-negative bacilli and fungi	12 (9)	7 (9)	5 (8)	0.732
Gram-positive cocci and fungi	2 (1)	1 (1)	1 (2)	0.918
Gram-positive cocci, Gram-negative bacilli, and fungi	1 (1)	0 (0)	1 (2)	0.280
Negative cultures	57 (41)	36 (49)	21 (33)	0.060

Note: The categorical variables are expressed as counts (percentages) and analyzed with Pearson's chi-square (χ^2) test, while the continuous variables are expressed as medians (interquartile ranges) and analyzed with Kruskal–Wallis test.

Abbreviations: SOFA score, Sequential Organ Failure Assessment score; APACHE II score, Acute Physiology and Chronic Health Evaluation II score.

their PCT levels (OR =0.995, 95% CI: 0.957–1.089, $P=0.527$) and APACHE II scores (OR =1.021, 95% CI: 0.985–1.006, $P=0.403$) (Table 2).

Prognostic value of the presepsin level, lactate level, and SOFA score

The performance of the presepsin level, lactate level, and SOFA score in predicting patients' in-hospital mortality from sepsis was evaluated with ROC curves (Figure 2). The levels of presepsin and lactate had good performance in predicting the prognosis of sepsis (presepsin: AUC =0.703, $P=0.000$; lactate: AUC =0.711, $P=0.000$). The

SOFA score had the best performance with the highest AUC value (AUC =0.793, $P=0.000$). Furthermore, the AUC value of a combination of the SOFA score and the presepsin level was significantly higher than that of the SOFA score alone in predicting patients' in-hospital mortality (AUC: 0.817 vs 0.793, $P=0.041$). The best prognostic cutoff point for presepsin was 2,623 pg/mL, at which level the sensitivity and specificity were 62.71% (95% CI: 49.15% to 74.96%) and 72.6% (95% CI: 60.91% to 82.39%), respectively. The patients' levels of presepsin and lactate upon admission were positively associated with their SOFA scores (presepsin: $\rho=0.396$, $P=0.000$, lactate: $\rho=0.411$, $P=0.000$), however, there was no positive

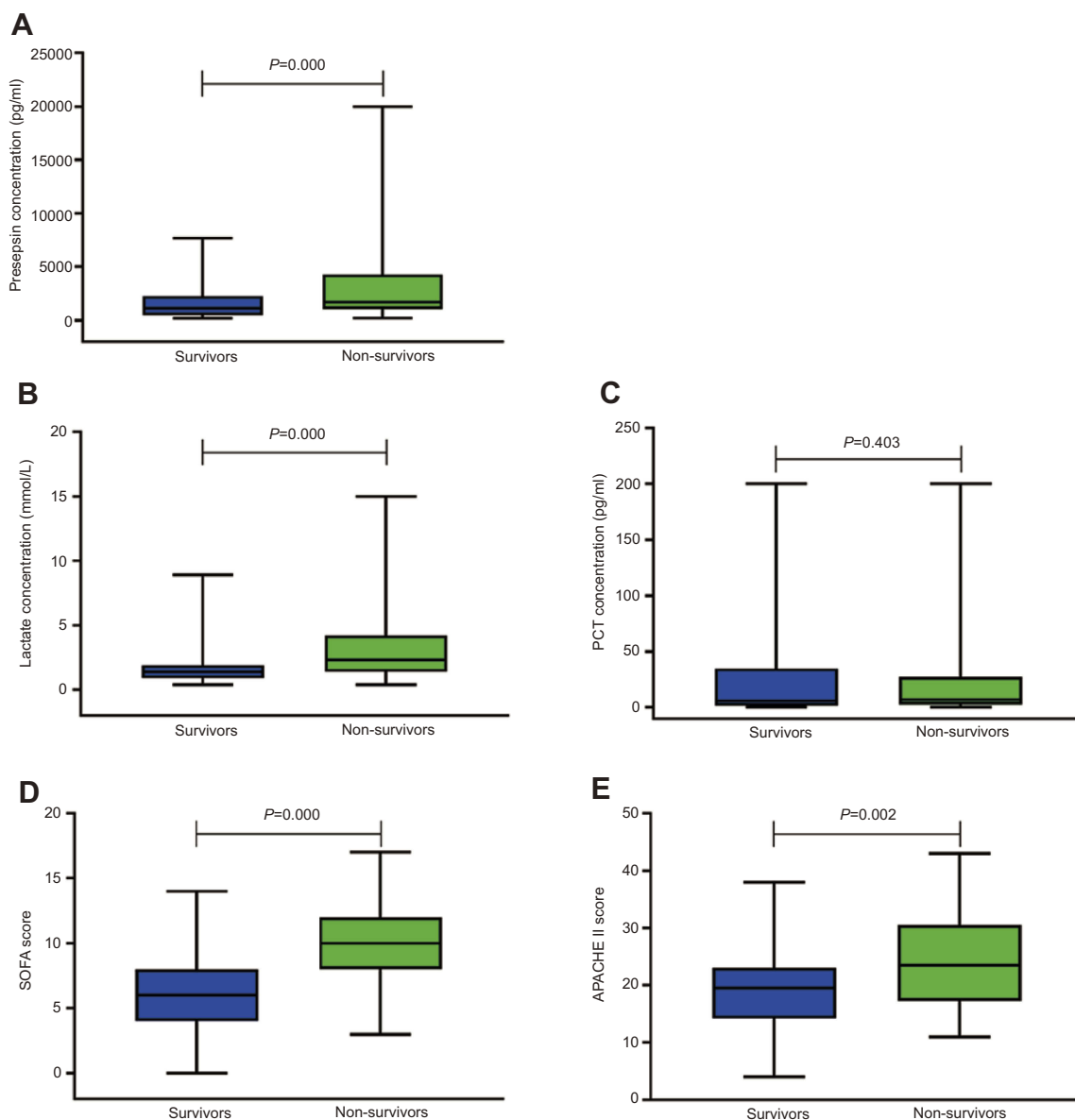


Figure 1 The SOFA score, APACHE II score, and the levels of presepsin, PCT and lactate upon admission in the survivor and non-survivor groups. **(A and B)** The levels of presepsin and lactate in the non-survivor group are significantly higher than those of the survivor group (presepsin: $P=0.000$; lactate: $P=0.000$). **(C)** There is no significant difference in the PCT level between the two groups ($P=0.403$). **(D and E)** The SOFA score and APACHE II score of the non-survivor group are significantly higher than those of the survivor group (SOFA score: $P=0.000$; APACHE II score: $P=0.002$).

Abbreviations: SOFA score, Sequential Organ Failure Assessment score; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; PCT, procalcitonin.

correlation between their PCT levels and SOFA scores ($\rho=0.136$, $P=0.114$) (Figure 3).

Discussion

This observational study was conducted on adult patients with sepsis who were diagnosed under the sepsis-3 criteria.¹⁵ The patients were assigned to two groups while doing retrospective analysis according to their in-hospital mortality: the survivor group and the non-survivor group. We aimed to evaluate the performance of presepsin

as a biomarker in predicting patients' in-hospital mortality from sepsis. The performance of the presepsin level in predicting patients' in-hospital mortality was compared with that of the lactate level and SOFA score. Correlation between the presepsin level and SOFA score was also analyzed.

It has been reported that the presepsin level is capable of predicting the mortality from sepsis under the sepsis-1 criteria and sepsis-2 criteria.^{16–19} ICU patients' mortality from sepsis was reported to be associated with the

Table 2 Univariate binary logistic regression analysis results

Parameters	Odds ratio	95% CI	P-value
Procalcitonin (ng/mL)	0.995	0.957–1.089	0.527
Presepsin (pg/mL)	1.221	1.024–1.455	0.026
Lactate (mmol/L)	1.296	1.071–1.569	0.008
APACHE II score	1.021	0.985–1.006	0.403
SOFA score	1.404	1.209–1.632	0.000

Abbreviations: CI, confidence interval; SOFA score, Sequential Organ Failure Assessment score; APACHE II score, Acute Physiology and Chronic Health Evaluation II score.

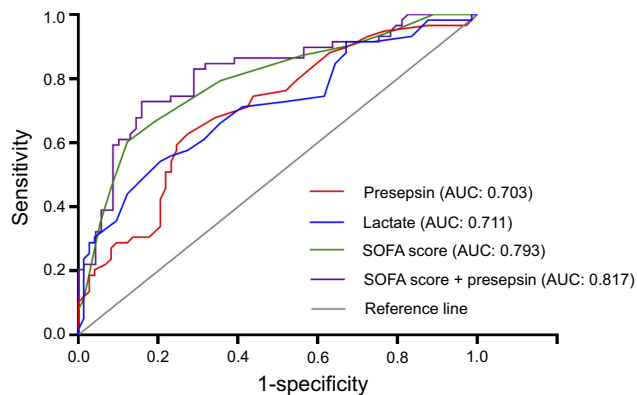


Figure 2 Receiver operating characteristic curves of the presepsin level, lactate level, and the SOFA score in predicting patients' in-hospital mortality. Areas under the receiver operating characteristic (ROC) curves: the lactate level (blue line): 0.711 (95% confidence interval (CI): 0.622 to 0.800, $P=0.000$); the presepsin level (red line): 0.703 (95% CI: 0.614 to 0.793, $P=0.000$); the SOFA score (green line): 0.793 (95% CI: 0.716 to 0.870, $P=0.000$); the SOFA score + the presepsin level (purple line): 0.817 (95% CI: 0.742 to 0.892, $P=0.000$). The AUC value of a combination of the SOFA score and the presepsin level is significantly larger than that of the SOFA score alone in predicting patients' in-hospital mortality from sepsis (AUC: 0.817 vs 0.793, $P=0.041$).

Abbreviation: CI, confidence interval; SOFA score, Sequential Organ Failure Assessment score; APACHE II score, Acute Physiology and Chronic Health Evaluation II score.

presepsin level and the non-survivors' presepsin levels were significantly higher than the survivors' presepsin levels.¹⁶ In the present study, the presepsin level of the non-survivor group is higher than that of the survivor group. Besides, analysis of the ROC curves demonstrates that the presepsin level has a good performance in predicting the in-hospital mortality from sepsis under the sepsis-3 criteria. The best prognostic cutoff point for presepsin in this study is 2,623 pg/mL, which is similar to the level of 2,455 pg/mL reported previously.¹⁷ It was reported that the presepsin level upon admission, not the level of PCT, was significantly correlated with patients' in-hospital mortality from sepsis.¹⁸ Besides, the presepsin level showed better prognostic performance than the PCT level in predicting patients' 30-day mortality.¹⁹ Similar findings are obtained in this study. There is no significant

difference in the PCT level between the two groups, and binary logistic regression shows that the PCT level is not correlated with patients' in-hospital mortality. Furthermore, the correlation analysis reveals that there is no significant association between the PCT level and the SOFA score. These results suggest that the level of PCT is not correlated with the severity of sepsis in the early hours.

Binary logistic regression shows that the presepsin level, lactate level, and the SOFA score are independent risk factors for patients' in-hospital mortality from sepsis. Analysis of the ROC curves shows that the presepsin and lactate levels have similar performance in predicting the prognosis of sepsis (AUC: 0.703 vs 0.711). The SOFA score has a better prognostic performance than the presepsin level (AUC: 0.793 vs 0.703). However, the presepsin level upon admission is positively associated with the SOFA score, and the prognostic performance of a combination of the SOFA score and the presepsin level is significantly better than that of the SOFA score alone. These results suggest that presepsin is a biomarker which helps recognize patients with poor prognosis in the early period and plays a significant role in guiding the treatment of sepsis.

This study has several limitations. Firstly, the sample size is relatively small. However, to the best of our knowledge, other studies have similar or smaller samples in size.^{19–21} Secondly, this study is a single-center study, which might lead to inherent selection bias. Thirdly, patients' presepsin levels were only measured upon admission, rather than monitored daily.

The results in this study demonstrate that presepsin is a powerful prognostic biomarker of the short-term prognosis of sepsis under the sepsis-3 criteria. These preliminary findings suggest that the presepsin level may be of clinical importance in identifying high-risk patients earlier.

Conclusions

The presepsin level is valuable in predicting patients' in-hospital mortality from sepsis under the sepsis-3 criteria. Combining use with the SOFA score increases its prognostic accuracy significantly.

Ethics approval

The study protocol was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China (No. GDREC 2016318H). All patients

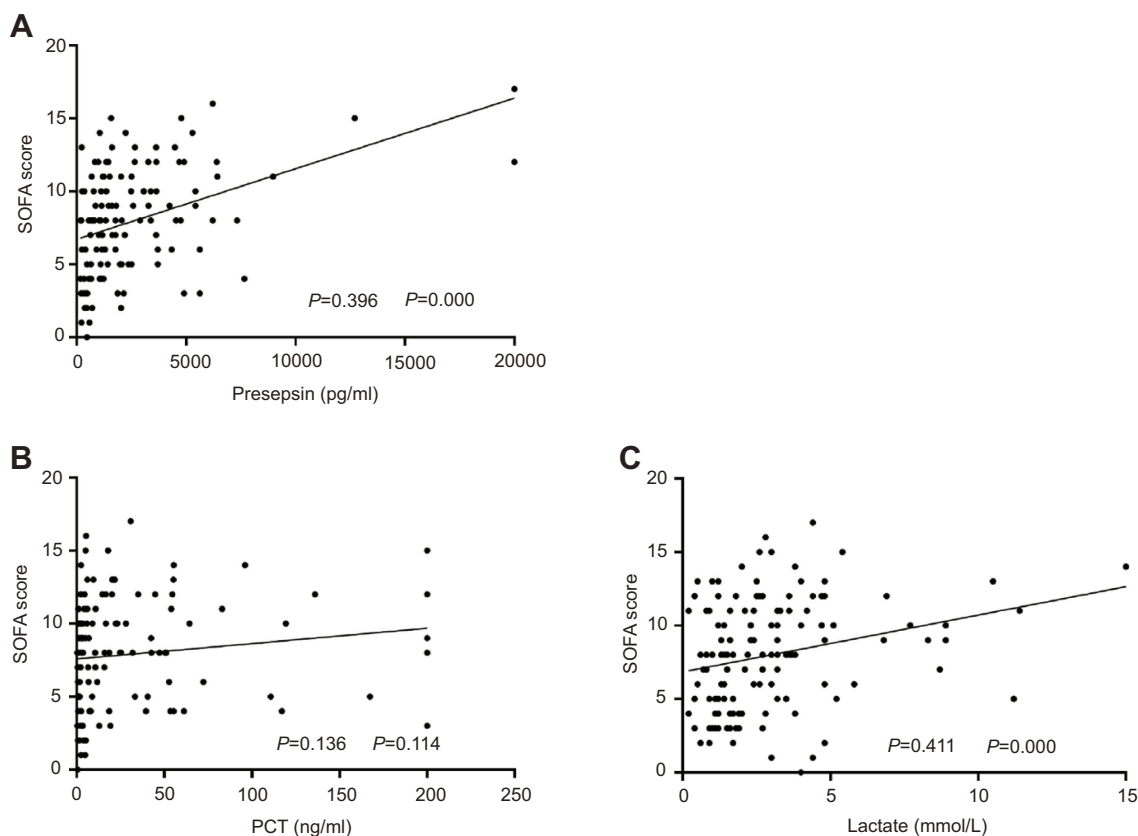


Figure 3 Association between the levels of preprocalcitonin, lactate, and PCT and the SOFA score. The levels of preprocalcitonin and lactate are positively correlated with the SOFA score (preprocalcitonin: $\rho=0.396$, $P=0.000$; lactate: $\rho=0.411$, $P=0.000$), while no correlation between the PCT level and the SOFA score is observed ($\rho=0.136$; $P=0.114$).

Abbreviations: SOFA score, Sequential Organ Failure Assessment score; PCT, procalcitonin.

provided written informed consent, and that this study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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