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Comparison of the accuracy of procalcitonin, neutrophil CD64, and C-reactive protein for the diagnosis and prognosis of septic patients after antibiotic therapy

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ABSTRACT

Background: The performance of the inflammatory biomarkers in the management of septic patients who received antimicrobial therapies is largely neglected. This study aimed to compare the accuracy of procalcitonin (PCT), neutrophil CD64 (CD64), and C-reactive protein (CRP) for the diagnosis and prognosis of septic patients after antimicrobial therapy.

Methods: This study prospectively recruited consecutive patients without infection and those diagnosed with infection but had received initial antimicrobial therapies. Sepsis was diagnosed according to sepsis-3 criteria. Serum PCT, CD64 and CRP levels were measured upon entry to the ICU. We also collected each patient's baseline characteristics. The diagnostic and prognostic performance of these parameters was evaluated from the area under the receiver operator characteristic curve (AUC).

Results: A total of 635 consecutive ICU patients were screened for eligible and 289 (45.5 %) patients were diagnosed with sepsis upon entry to the ICU. The area under the curve (AUC) for PCT, CD64 and CRP in the identification of sepsis is 0.726, 0.692 and 0.719, respectively. Neither PCT ($p = 0.587$) nor CD64 ($p = 0.373$) is superior to CRP in the diagnosis of septic patients who received antimicrobial therapies. The AUC for PCT, CD64 and CRP in the prediction of ICU mortality in these sepsis patients is 0.702, 0.637 and 0.593, respectively. The prognostic performance of PCT ($p = 0.006$) rather than CD64 ($p = 0.509$) is better than CRP.

Conclusions: Both PCT and CD64 are not superior to CRP in the identification of septic patients who received antimicrobial therapies. However, PCT instead of CD64 has a better prognostic accuracy than CRP for the prediction of ICU mortality of these septic patients.

Abbreviations: APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AUC, area under the curve; CD64, neutrophil CD64; CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin; ROC curve, receiver operating characteristic curve.

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1. Introduction

Sepsis remains the leading cause of death within intensive care unit (ICU) despite progress has been made in the management of this critical illness [1–3]. The early recognition and prompt treatment is critical to improve the outcome of these patients [4,5]. Although clinical guidelines for the management of sepsis have been established and updated [6], the early identification of sepsis is still challenging in clinical practice due to that multiple clinical and laboratory parameters are required for its diagnosis according to these guidelines.

In the past decade, many studies found that the usefulness of biomarkers to identify sepsis was promising [7–9]. C-reactive protein (CRP) is a classical inflammatory marker and has been wildly used in clinic for the identification of infection and sepsis [10,11]. However, a lack of specificity hampered its use as an ideal biomarker in clinical practice [12]. In the past decade, numerous studies were conducted to search new biomarkers for the diagnosis of sepsis [7,13]. PCT, a 116 amino acid residue mainly produced by parafollicular cells, increases rapidly in response to infection [14]. As an inflammatory marker it has been widely studied for its diagnostic value in various clinical situations, particularly in the context of bacterial infections. More recently, neutrophil CD64 was recognized as a promising marker for the detection of sepsis [15,16]. Initial studies demonstrated that PCT and CD64 are superior to CRP in the diagnosis of sepsis in different populations of patients [17]. Moreover, PCT-guided treatments were shown to be effective for reducing infection-associated adverse events [18,19], while CD64-guided treatments led to increased efficacy of antibiotic treatment [20]. Therefore, PCT and CD64 have become routine tests in the ICU worldwide. However, some other studies reported conflicting results about their performance for sepsis identification [21–23]. For instance, Parlato et al., evaluated the diagnostic accuracy of more than fifty circulating biomarkers in the diagnosis of sepsis and found that no biomarker performed better than CRP [24]. In addition, there were wide ranges of cutoff value, sensitivity and specificity for PCT (cutoff 0.1–15.75 ng/ml, se 0.41–0.97, sp 0.53–1.00) and CD64 (cutoff 1.58–2.2, se 0.63–1.00, sp 0.65–1.00) in sepsis detection across different studies [15,18].

These inconsistent findings are considered to be due to the substantial heterogeneity within the patients included in previous studies [15,16,18,19,25]. Apart from the difference in sample sizes and severity of sepsis between studies, whether having previous antimicrobial therapies may have important impact on the diagnostic accuracy of these biomarkers in the identification of sepsis. This is due to the fact that the appropriate antimicrobial therapies could significantly reduce the level of inflammatory markers, while as inappropriate treatments would result in deterioration of infection and the increase of the levels of these markers [26,27]. Therefore, mixed septic patients (with or without previous antimicrobial therapies) included in previous studies might lead to unproper interpretation of the performance of these biomarkers in the diagnosis and prognosis of sepsis [15,25]. Given that the most ICU patients were transferred from other medical places and had likely received initial treatments (e.g., empirical antibiotic therapy) before admission [28], the identification of sepsis among these patients by the established biomarkers is critical in real clinical setting. However, this issue is largely neglected by the field as very limited studies have been conducted to evaluate the performance of these well-used inflammatory markers for the identification and prediction of septic patients after empiric antimicrobial therapy.

Therefore, we undertook a prospective, observational study to compare of the accuracy of PCT, CD64, and CRP for the diagnosis and prognosis of septic patients who have received initial antimicrobial therapies.

2. Methods

2.1. Participants

This prospective, observational study recruited consecutive adult patients (age≥18 years old) admitted to the ICU of Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine during a total of 13 months. A priori was set to include patients if they meet either one or these: 1) were not accompanied with infection upon entry to the ICU; 2) had a diagnosis of infection and had been on antimicrobial therapies for at least 12 h prior to ICU admission. Patients were excluded if they: 1) were on immunosuppressive therapies, including chemotherapy and glucocorticoid therapy; 2) have ongoing malignancy or organ transplantation. Patients died or discharged from the ICU within 4 h after admission were also excluded due to the unavailability of collecting sufficient clinical and laboratory parameters for these patients. This study was approved by the Shanghai Jiaotong University Xinhua Hospital Ethics Committee and in accordance with the Declaration of Helsinki. The need for written informed consent was waived by the ethical review board because all laboratory parameters (including PCT, CD64 and CRP) observed in this observational study were commonly measured for all patients in our ICU department and no additional blood sampling was needed.

2.2. Definition of sepsis

Patients were diagnosed with sepsis according to sepsis-3 criteria [6]. All patients upon entry to the ICU were independently evaluated whether accompanying with infection, including previous known and newly identified, based on their clinical symptoms, laboratory parameters, specimen culture and radiological findings. The final decisions were made by consensus of one attending physician and one consultant.

2.3. Laboratory measurements and clinical follow up

Blood samples were obtained from all eligible patients when they were admitted to the ICU to measure the levels of PCT, CD64, CRP

and other laboratory indices. PCT was measured using an electrochemiluminescence assay from Roche Diagnostics GmbH Company (Mannheim, Germany), and ranged from 0.02 to 100 ng/ml. Readings >100 ng/ml were taken as 100 ng/ml. Reported total coefficient of variation is 8.8 % at concentration 0.06 ng/ml, and 2.1 % at 41.2 ng/ml. Serum cystatin C was measured by using Hitachi 7600–120 analyzer (Hitachi, Tokyo, Japan). Neutrophil CD64 was measured by flow cytometry using a Beckman Coulter FC500 (Beckman Coulter Ltd, USA). CRP levels were measured using Quick Read CRP test kit (Orion Corporation, Orion Diagnostica, Espoo, Finland). Serum creatinine, glucose, lactate, electrolytes and albumin levels were also measured by the Hitachi 7600–120 analyzer.

We also prospectively collected each patient's demographic and clinical characteristics, including the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score (which can range from 0 to 71, with higher scores indicating more severe illness). The patients were then followed up during the ICU and hospital stay.

2.4. Statistical analysis

Continuous variables were presented as mean value ± SD, and categorical variables are expressed as percentages. Baseline characteristics between septic and non-septic patients were compared with unpaired Student's t-test or Mann-Whitney test for continuous variables and chi-square or Fisher's exact tests for categorical variables. The receiver operating characteristic (ROC) curve was used to evaluate the performance of variables to identify sepsis and mortality. The curve represented a plot of sensitivity (se) vs 1-specificity (sp). The area under the curve (AUC) was derived from the ROC curve. The differences between AUC (C-index) were tested by Hanley-McNeil methods [29]. A statistically derived value, based on the Youden index, maximizing the sum of the sensitivity and specificity was used to define the optimal cut-off value [30]. A two-sided P-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with SPSS 25.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics

A total of 635 ICU patients were screened for eligibility during the study period. The baseline clinical and laboratory characteristics of the patients are listed in Table 1. The mean age was 66.83 and 59.4 % were male. Mean APACHE- II score was 15.95. A total of 87 patients died during their ICU stay. Upon entry to the ICU, there were 312 patients without infection and 323 patients with a diagnosis of infection who had been on antimicrobial therapies for at least 12 h before admitting to the ICU. Among the patient with infection, 289 patients were met sepsis criteria (89.5 %). The level of PCT, CD64 and CRP were significantly higher in septic patients than in non-septic patients (all $p < 0.001$) (Table 1 and Fig. 1). Compared with non-septic patients, septic patients were older ($p = 0.027$) and had worse organ function indicted by different parameters and higher APACHE- II score ($p < 0.001$). There was no significant difference in ICU mortality between septic and non-septic patients.

Table 1
Baseline clinical and laboratory characteristics of study subjects.

	All (n = 635)	Non-sepsis (n = 346)	Sepsis (n = 289)	*P* value
Age (years)	66.83 ± 17.19	65.45 ± 16.95	68.48 ± 17.36	0.027
Male (%)	377(59.4 %)	197 (56.9 %)	180 (62.3 %)	0.172
WBC	10.54 ± 5.81	9.68 ± 4.81	11.55 ± 6.68	<0.001
Neutrophil (10^9)	8.57 ± 5.21	7.68 ± 4.64	9.64 ± 5.64	<0.001
Monocyte (10^9)	0.61 ± 0.33	0.62 ± 0.34	0.60 ± 0.33	0.407
Lymphocyte (10^9)	1.18 ± 0.84	1.29 ± 0.67	1.05 ± 0.98	<0.001
Platelet (10^9)	164.79 ± 70.70	163.38 ± 60.83	166.46 ± 80.93	0.597
Total bilirubin (mg/dL)	17.52 ± 13.32	17.75 ± 12.20	17.24 ± 14.55	0.645
Direct bilirubin (mg/dL)	5.19 ± 7.35	4.79 ± 6.61	5.67 ± 8.13	0.150
BUN (mmol/L)	9.50 ± 7.88	8.12 ± 5.87	11.13 ± 9.49	<0.001
Scr (μmol/L)	120.63 ± 126.99	99.87 ± 75.44	145.59 ± 166.10	<0.001
ALT (U/L)	84.78 ± 373.86	55.08 ± 153.65	119.98 ± 525.09	0.046
AST (U/L)	169.20 ± 965.10	114.30 ± 772.65	234.77 ± 1151.72	0.134
Albumin (g/L)	34.68 ± 5.51	36.66 ± 4.98	32.32 ± 5.17	<0.001
Glucose (mmol/L)	7.53 ± 3.26	7.54 ± 3.41	7.51 ± 3.09	0.916
Myoglobin (ng/ml)	307.46 ± 685.51	231.87 ± 511.44	399.82 ± 843.10	0.004
CK-MB (ng/ml)	16.11 ± 44.15	19.58 ± 54.63	11.99 ± 26.41	0.026
Troponin T (ng/ml)	3.98 ± 14.54	5.46 ± 18.09	2.25 ± 8.39	0.004
D-Dimer (mg/L)	1.45 ± 2.66	1.27 ± 2.39	1.66 ± 2.94	0.073
PCT (ng/ml)	5.65 ± 21.77	1.44 ± 5.98	10.53 ± 30.65	<0.001
CD64	1.83 ± 1.37	1.41 ± 0.57	2.27 ± 1.76	<0.001
CRP (mg/L)	55.74 ± 55.63	36.34 ± 43.49	78.85 ± 59.61	<0.001
APACHE-II score	15.95 ± 8.78	14.27 ± 7.46	17.94 ± 9.77	<0.001
Mortality	13.7 % (87)	11.8 % (41)	15.9 % (46)	0.138

WBC: white blood cell; ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; Scr: serum creatinine; CK-MB: creatine kinase-MB; PCT, procalcitonin; CD64, neutrophil CD64; CRP, C-reactive protein (CRP); APACHE II score, Acute Physiology and Chronic Health Evaluation II score.

3.2. Value for PCT, CD64 and CRP in diagnosis of sepsis

ROC curves were constructed to examine the performance of PCT, CD64 and CRP for the diagnosis of sepsis (Fig. 2). The AUC, optimal cutoff value, sensitivity and specificity of each indicator were showed in Table 2. The AUC for PCT, CD64 and CRP were 0.726, 0.692 and 0.719, respectively (all $p < 0.001$). There were no significant differences in AUC between any two of indicators (all $p > 0.05$). The optimal cut-off values of PCT, CD64 and CRP for diagnosing sepsis were 0.08 ng/ml, 1.70 and 69 mg/L, respectively. Moreover, combination of either two or three of these indicators didn't significantly improve their performances in the diagnosis of sepsis (all $p > 0.05$).

3.3. Association between indicators and ICU mortality in septic patients

To evaluate association between PCT, CD64 and CRP and ICU mortality in septic patients, we divided septic patients into survivor and non-survivor group. The baseline clinical and laboratory characteristics of the patients are listed in Table 3. Non-survivors were older ($p = 0.024$) and had higher serum creatinine ($p = 0.008$), lower albumin ($p = 0.001$) and higher Apache- II score ($p < 0.001$). Among the three indicators, only the level of PCT was significantly higher in non-survivors than in survivors ($p = 0.011$) (Table 3 and Fig. 3).

3.4. Value for PCT, CD64 and CRP in prediction of ICU mortality

ROC curves were constructed to examine the performance of PCT, CD64 and CRP for the prediction of ICU mortality (Fig. 4). The AUC, optimal cutoff value, sensitivity and specificity of each indicator are shown in Table 4. The AUC for PCT, CD64 and CRP were 0.702 ($p < 0.001$), 0.637 ($p = 0.001$) and 0.593 ($p = 0.027$), respectively. PCT ($p = 0.006$) rather than CD64 ($p = 0.509$) has better performance than CRP in the prediction of ICU mortality of these septic patients. The optimal cut-off values of PCT, CD64 and CRP for predicting ICU mortality were 0.73 ng/ml, 1.49 and 32 mg/L, respectively. Combination of any two or three indicators didn't improve the performance in the prediction of ICU mortality of these septic patients (all $p > 0.05$).

4. Discussions

In this large-scale study of 635 unselected medical ICU patients, we found that neither PCT nor CD64 is superior to CRP in the diagnosis of septic patients who received antimicrobial therapy. PCT rather than CD64 has a better performance than CRP in the prediction of ICU mortality in these septic patients. To the best of our knowledge, the present study is among the very few studies that investigated the performances of PCT, CD64, and CRP for the diagnosis and prognosis of septic patients who received antimicrobial therapy. The present study provides some useful information for the use of these biomarkers in clinic. First, the current study recruited one of the largest scales of ICU patients and therefore provided more statistic power than previous studies. Second, we tested the levels of PCT, CD64, and CRP in the same population, which allows a direct comparation of the accuracy of these well-known inflammatory biomarkers for the diagnosis and prognosis of sepsis. Third, this study included unselected ICU patients who received initial antimicrobial therapy. These patients represent a large proportion of critical ill patients in real settings in ICU where patients were usually transferred from emergency department or other hospital floors in both developed and developing countries [31]. Therefore, our data address an essential issue in this neglected population, which provide useful messages for the proper use of these biomarkers to identify sepsis among these patients.

Although PCT may have better discernibility than CRP in the diagnosis of new-onset septic patients, the appropriate antimicrobial treatment could reduce its level rapidly (within 24 h) [32]. This could make it difficult to distinguish septic patients from non-septic patients by measuring of PCT after exposure to antimicrobial. In comparison, CD64 and CRP have a slower response to antibiotic

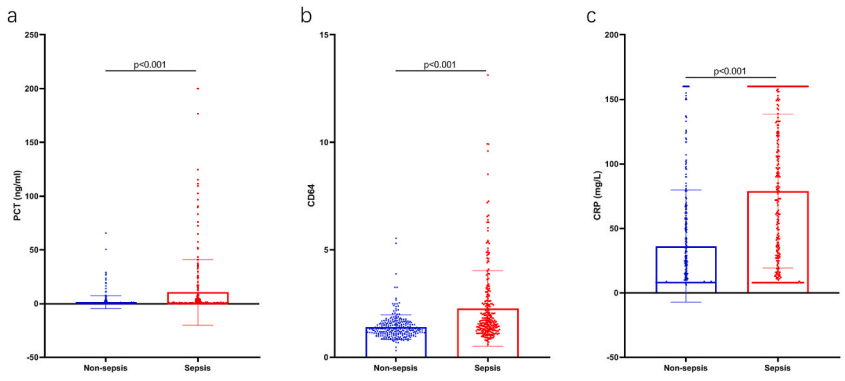

Fig. 1. Levels of PCT (a), CD64 (b) and CRP (c) in septic and non-septic patients[a]
[a]PCT, procalcitonin; CD64, neutrophil CD64; CRP, C reactive protein (CRP).

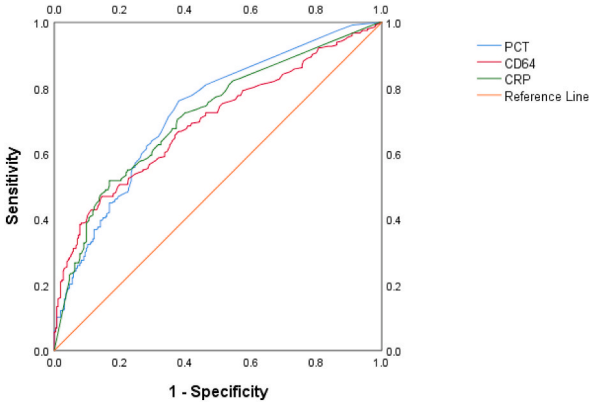

Fig. 2. Receiver operating characteristic curves for PCT, CD64 and CRP in the diagnosis of sepstic patients who received antimicrobial therapies[a]
[a]PCT, procalcitonin; CD64, neutrophil CD64; CRP, C reactive protein (CRP).

Table 2
Measures of diagnostic accuracy for PCT, CD64 and CRP for detection of septic patients who received antimicrobial therapies, using the optimum cutoff values.

	AUC (95 % CI)	*P* value	Cut-off	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	LR+ (95% CI)	LR–(95% CI)
PCT	0.726 (0.689–0.762)	<0.001	0.08 ng/ml	75.8 (70.3–80.7)	62.9 (57.4–68.2)	63.8 (60.1–67.4)	75.1 (70.7–79.1)	2.05 (1.7–2.4)	0.38 (0.3–0.5)
CD64	0.692 (0.651–0.732)	<0.001	1.70	47.2 (41.0–53.6)	84.5 (79.5–88.6)	74.5 (68.2–80.0)	62.5 (59.4–65.4)	3.04 (2.2–4.1)	0.62 (0.5–0.7)
CRP	0.719 (0.682–0.754)	<0.001	>69 mg/L	51.1 (45.1–57.0)	83.6 (79.2–87.4)	72.4 (66.7–77.4)	67.1 (64.2–69.8)	3.12 (2.4–4.1)	0.59 (0.5–0.7)

PCT, procalcitonin; CD64, neutrophil CD64; CRP, C-reactive protein (CRP).
PCT vs CRP, z = 0.543, p = 0.587.
CD64 vs CRP, z = 0.892, p = 0.373.
PCT vs CD64, z = 1.149, p = 0.251.

Table 3
Baseline clinical and laboratory characteristics of septic patients.

	Survivor (n = 243)	Non-survivor (n = 46)	*P* value
Age (years)	67.64 ± 17.91	72.89 ± 13.38	0.024
Male (%)	152 (62.6 %)	28 (60.9 %)	0.829
PCT (ng/ml)	8.51 ± 27.77	21.25 ± 41.55	0.011
CD64	2.23 ± 1.80	2.53 ± 1.44	0.356
CRP (mg/L)	76.16 ± 60.00	93.43 ± 55.87	0.077
APACHE-II score	15.31 ± 7.00	31.80 ± 10.63	<0.001

PCT, procalcitonin; CD64, neutrophil CD64; CRP, C-reactive protein (CRP); APACHE II score, Acute Physiology and Chronic Health Evaluation II score.

therapies. CRP takes 12–24 h to rise and remains elevated for up to 3–7 days [33], while CD64 takes 4 days to reduce after appropriate antibiotic therapy [34]. Thus, the superiority of PCT for identifying septic patients may be compromised after antimicrobial treatments. This explains why the current study found that there was no significant difference between PCT, CD64 and CRP in the diagnosis of septic patients who received antimicrobial therapy. Moreover, the cutoff of PCT in current study is lower than previous reported of mixed septic patients [18], most likely due to the prior antimicrobial therapies. Nonetheless, PCT was still shown to be a better predictor than CRP in the prediction of ICU mortality in these septic patients. Indeed, studies reported that PCT instead of CRP is correlated with the severity of sepsis [35]. PCT is shown to be more specific than CRP in response to infection [18,19]. Moreover, sustained elevated PCT level indicates unfavorable clinical outcome in septic patients [36], while as a decrease of PCT level associates with a declining of the mortality rate [37]. The septic patients with elevated PCT level may reflect those who were unresponsive to antimicrobial treatment and therefore had a worse clinical outcome than those who had a better response to these therapies.

Several limitations of our study should be mentioned. First, we didn't collect the detailed information (e.g. duration and dose) about antimicrobial therapies of those patients before admission to the ICU. Second, appropriate or inappropriate antimicrobial therapies were not recorded during the study period, despite we treated patients based on international guidelines, with initial empirical antimicrobial therapies followed by definitive therapies once organism was identified. Third, we didn't compare the

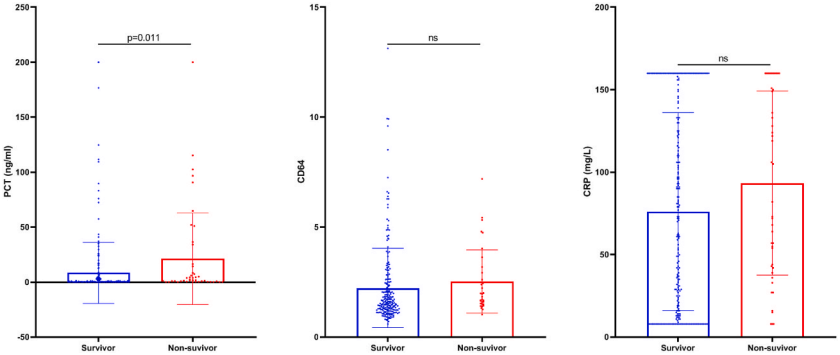

Fig. 3. Levels of PCT (a), CD64 (b) and CRP (c) in survivor and non-survivor[a]
[a]PCT, procalcitonin; CD64, neutrophil CD64; CRP, C reactive protein (CRP).

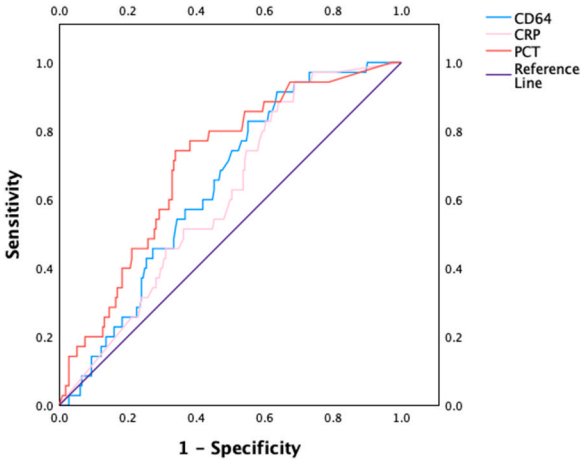

Fig. 4. Receiver operating characteristic curves for PCT, CD64 and CRP in the prediction of ICU mortality of sepstic patients who received antimicrobial therapies[a]
[a]PCT, procalcitonin; CD64, neutrophil CD64; CRP, C reactive protein (CRP).

Table 4
Measures of prognostic accuracy for PCT, CD64 and CRP for ICU mortality among septic patients who received antimicrobial therapies, using the optimum cutoff values.

	AUC (95 % CI)	*P* value	Cut-off	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	LR+ (95 % CI)	LR– (95 % CI)
PCT	0.702 (0.616–0.787)	<0.001	0.73 ng/ml	72.7 (57.2–85.0)	67.0 (60.5–73.0)	29.4 (24.3–35.0)	92.9 (88.8–95.5)	2.20 (1.7–2.8)	0.41 (0.2–0.7)
CD64	0.637 (0.575–0.697)	0.001	1.49	82.9 (66.4–93.4)	44.8 (38.0–51.6)	19.3 (16.5–22.5)	94.2 (88.6–97.2)	1.50 (1.2–1.8)	0.38 (0.2–0.8)
CRP	0.593 (0.534–0.651)	0.027	32 mg/L	84.1 (69.9–93.4)	37.4 (31.2–43.9)	19.9 (17.4–22.6)	92.7 (86.3–96.2)	1.34 (1.1–1.6)	0.43 (0.2–0.9)

PCT, procalcitonin; CD64, neutrophil CD64; CRP, C-reactive protein (CRP).
PCT vs CRP, z = 2.772, p = 0.006.
CD64 vs CRP, z = 0.660, p = 0.509.
PCT vs CD64, z = 1.350, p = 0.177.

diagnostic and prognostic value of these indicators between patients with and without previous antimicrobial therapies, because very few patients with signs of infection in our health care facility didn't receive any antimicrobial therapies. Fourth, this study was conducted in a single ICU though a large number of patients were recruited. Multicenter studies need to be conducted to further confirm the current findings. Fifth, PCT is currently measured with various methods and there is no standard approach to transfer the values between these methods. Therefore, the optimal cut-off values of PCT in predicting outcomes of septic patients in different centers requires further investigation.

5. Conclusions

In this large-scale study of 635 unselected medical ICU patients, we found that both PCT and CD64 are not superior to CRP in the diagnosis of septic patients who received antimicrobial therapies. PCT instead of CD64 has better performance than CRP in the prediction of ICU mortality in these septic patients. Our study sheds light on the appropriate use of these classic inflammation markers to diagnose sepsis and predict ICU mortality.

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CRediT authorship contribution statement

Qingteng Zhu: Writing – original draft, Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization, Resources. **Hui Wang:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization. **Liang Chen:** Software, Validation, Data curation, Project administration. **Yang Yu:** Software, Validation, Data curation, Project administration. **Miao Chen:** Writing – review & editing, Methodology, Supervision, Validation, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no competing interests.

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None.

Data availability

Data will be made available on request.

References

[1] C. Rhee, T.M. Jones, Y. Hamad, A. Pande, J. Varon, C. O'Brien, et al., Prevalence, underlying causes, and preventability of sepsis-associated mortality in US Acute care hospitals, JAMA Netw. Open 2 (2) (2019) e187571.
[2] D.C. Angus, T. van der Poll, Severe sepsis and septic shock, N. Engl. J. Med. 369 (9) (2013) 840–851.
[3] T. Oami, T. Imaeda, T.A. Nakada, T. Abe, N. Takahashi, Y. Yamao, et al., Temporal trends of medical cost and cost-effectiveness in sepsis patients: a Japanese nationwide medical claims database, J. Intensive Care 10 (1) (2022) 33.
[4] C. Rhee, K. Chiotos, S.E. Cosgrove, E.L. Heil, S.S. Kadri, A.C. Kalil, et al., Infectious diseases society of America position paper: recommended revisions to the national severe sepsis and septic shock early management bundle (SEP-1) sepsis quality measure, Clin. Infect. Dis. 72 (4) (2021) 541–552.
[5] I. Coloretti, M. Tosi, E. Biagioni, S. Busani, M. Girardis, Management of sepsis in the first 24 hours: bundles of care and individualized approach, Semin. Respir. Crit. Care Med. 45 (4) (2024) 503–509.
[6] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801–810.
[7] T. Barichello, J.S. Generoso, M. Singer, F. Dal-Pizzol, Biomarkers for sepsis: more than just fever and leukocytosis-a narrative review, Crit. Care 26 (1) (2022) 14.
[8] A. Blangy-Letheule, A. Persello, B. Rozec, M. Waard, B. Lauzier, New approaches to identify sepsis biomarkers: the importance of model and sample source for mass spectrometry, Oxid. Med. Cell. Longev. 2020 (2020) 6681073.
[9] L.R. Van Nynatten, M. Slessarev, C.M. Martin, A. Leligdowicz, M.R. Miller, M.A. Patel, et al., Novel plasma protein biomarkers from critically ill sepsis patients, Clin. Proteonomics 19 (1) (2022) 50.
[10] T. Tian, B. Wei, J. Wang, Study of C-reactive protein, procalcitonin, and immunocyte ratios in 194 patients with sepsis, BMC Emerg. Med. 21 (1) (2021) 81.
[11] P. Póvoa, C-reactive protein: a valuable marker of sepsis, Intensive Care Med. 28 (3) (2002) 235–243.
[12] P. Póvoa, L. Coelho, F. Dal-Pizzol, R. Ferrer, A. Huttner, A. Conway Morris, et al., How to use biomarkers of infection or sepsis at the bedside: guide to clinicians, Intensive Care Med. 49 (2) (2023) 142–153.
[13] F.F. Larsen, J.A. Petersen, Novel biomarkers for sepsis: a narrative review, Eur. J. Intern. Med. 45 (2017) 46–50.
[14] H.G. Schneider, Q.T. Lam, Procalcitonin for the clinical laboratory: a review, Pathology 39 (4) (2007) 383–390.
[15] C.F. Yeh, C.C. Wu, S.H. Liu, K.F. Chen, Comparison of the accuracy of neutrophil CD64, procalcitonin, and C-reactive protein for sepsis identification: a systematic review and meta-analysis, Ann. Intensive Care 9 (1) (2019) 5.
[16] X. Wang, Z.Y. Li, L. Zeng, A.Q. Zhang, W. Pan, W. Gu, et al., Neutrophil CD64 expression as a diagnostic marker for sepsis in adult patients: a meta-analysis, Crit. Care 19 (1) (2015) 245.
[17] B.M. Biron, A. Ayala, J.L. Lomas-Neira, Biomarkers for sepsis: what is and what might Be? Biomark. Insights 10 (Suppl 4) (2015) 7–17.
[18] C. Wacker, A. Prkno, F.M. Brunkhorst, P. Schlattmann, Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis, Lancet Infect. Dis. 13 (5) (2013) 426–435.
[19] E. Kyriazopoulou, L. Liaskou-Antoniou, G. Adamis, A. Panagaki, N. Melachroinopoulos, E. Drakou, et al., Procalcitonin to reduce long-term infection-associated adverse events in sepsis. A randomized trial, Am. J. Respir. Crit. Care Med. 203 (2) (2021) 202–210.
[20] W. Qian, G.Z. Huang, Neutrophil CD64 as a marker of bacterial infection in Acute exacerbations of chronic obstructive pulmonary disease, Immunol. Invest. 45 (6) (2016) 490–503.
[21] P. Sridharan, R.S. Chamberlain, The efficacy of procalcitonin as a biomarker in the management of sepsis: slaying dragons or tilting at windmills? Surg Infect (Larchmt). 14 (6) (2013) 489–511.

[22] J.J. Hoffmann, Neutrophil CD64 as a sepsis biomarker, Biochem Med (Zagreb) 21 (3) (2011) 282–290.
[23] A. Lamrous, E. Repetto, T. Depp, C. Jimenez, A.C. Chua, R. Kanapathipillai, T.O. Jensen, C-reactive protein and procalcitonin use in adults in low- and middle-income countries: a narrative review, JAC Antimicrob Resist 5 (3) (2023) dlad057.
[24] M. Parlato, F. Philippart, A. Rouquette, V. Moucadel, V. Puchois, S. Blein, et al., Captain Study Group, Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study, Intensive Care Med. 44 (7) (2018) 1061–1070.
[25] Y.H. Huang, C.J. Chen, S.C. Shao, C.H. Li, C.H. Hsiao, K.Y. Niu, et al., Comparison of the diagnostic accuracies of monocyte distribution width, procalcitonin, and C-reactive protein for sepsis: a systematic review and meta-analysis, Crit. Care Med. 51 (5) (2023) e106–e114.
[26] D.T. Huang, D.M. Yealy, M.R. Filbin, A.M. Brown, C.H. Chang, Y. Doi, et al., Procalcitonin-guided use of antibiotics for lower respiratory tract infection, N. Engl. J. Med. 379 (3) (2018) 236–249.
[27] F. Tang, H. Yuan, X. Li, L. Qiao, Effect of delayed antibiotic use on mortality outcomes in patients with sepsis or septic shock: a systematic review and meta-analysis, Int. Immunopharm. 129 (2024) 111616.
[28] S.S. Kadri, Y.L. Lai, S. Warner, J.R. Strich, A. Babiker, E.E. Ricotta, et al., Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals, Lancet Infect. Dis. 21 (2) (2021) 241–251.
[29] J.A. Hanley, B.J. McNeil, A method of comparing the areas under receiver operating characteristic curves derived from the same cases, Radiology 148 (3) (1983) 839–843.
[30] W.J. Youden, Index for rating diagnostic tests, Cancer 3 (1) (1950) 32–35.
[31] B. Du, Y. An, Y. Kang, X. Yu, M. Zhao, X. Ma, et al., Characteristics of critically ill patients in ICUs in mainland China, Crit. Care Med. 41 (1) (2013) 84–92.
[32] W. Nargis, M. Ibrahim, B.U. Ahamed, Procalcitonin versus C-reactive protein: usefulness as biomarker of sepsis in ICU patient, Int. J. Crit Illn Inj Sci. 4 (3) (2014) 195–199.
[33] K.M. Ho, J. Lipman, An update on C-reactive protein for intensivists, Anaesth. Intensive Care 37 (2) (2009) 234–241.
[34] A. Dimoula, O. Pradier, Z. Kassengera, D. Dalcomune, H. Turkan, J.L. Vincent, Serial determinations of neutrophil CD64 expression for the diagnosis and monitoring of sepsis in critically ill patients, Clin. Infect. Dis. 58 (6) (2014) 820–829.
[35] M. Meisner, K. Tschaikowsky, T. Palmaers, J. Schmidt, Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS, Crit. Care 3 (1) (1999) 45–50.
[36] P. Schuetz, P. Maurer, V. Punjabi, A. Desai, D.N. Amin, E. Gluck, Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients, Crit. Care 17 (3) (2013) R115.
[37] S. Karlsson, M. Heikkinen, V. Pettilä, S. Alila, S. Väisänen, K. Pulkki, et al., Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study, Crit. Care 14 (6) (2010) R205.