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ORIGINAL RESEARCH

Prognostic Value of Procalcitonin and Procalcitonin Clearance in Septic Shock Patients: A Study from a Tertiary Teaching Hospital in Southern China

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Objective: This study aimed to evaluate the potential prognostic value of procalcitonin (PCT) and procalcitonin clearance (PCTc) among patients with septic shock.

Methods: We conducted a prospective single-center observational study of septic shock patients admitted to the adult intensive care unit (ICU) of a tertiary teaching hospital in Southern China between January and December 2015. Serum PCT levels of surviving patients were measured at the onset of septic shock and subsequently on days 2 (24 h), 3 (48 h), 4 (72 h), and 5 (96 h), respectively. Similarly, PCTc on Days 2, 3, 4, and 5 were calculated to evaluate their prognostic performance.

Results: One hundred and twenty-eight adult patients with septic shock were included in the study. There was no significant difference between PCT concentrations measured at a single time point in survivors and non-survivors. However, PCTc on Day 2, 3, and 5 were significantly higher in survivors than in non-survivors. The best area under the receiver operating characteristic curve (AUC) values for prognosis were 0.74 (95% CI, 0.59–0.88), 0.74 (95% CI, 0.61–0.86), and 0.72 (95% CI, 0.54–0.90), respectively. In the logistic regression analysis, PCTc-day 2 > 12.7% and PCTc-day 3 > 49.6% were identified as independent predictors of survival for patients with septic shock. However, PCTc-day 5 was not independently associated with survival. The best cutoff for PCTc-day 2 and day 3 were 12.7% and 49.6%, respectively.

Conclusion: Compared with PCTc, PCT demonstrated lower prognostic performance for the survival of patients with septic shock. However, PCTc on Day 2 and 3 were significantly associated with survival in patients with septic shock and may serve as valuable prognostic indicators.

Keywords: procalcitonin, procalcitonin clearance, septic shock, prognosis, biomarker

Introduction

Sepsis, a dysregulated host response to infection with an estimated 19 million cases annually worldwide, is the leading cause of death among critically ill patients.[1–3] Septic shock is the most severe form of sepsis, accompanied by significant abnormalities in circulatory and cellular/metabolic parameters, leading to markedly increased mortality. According to studies, the prevalence of septic shock ranged from 3% to 23% among patients admitted to intensive care units (ICU), while mortality ranged from 26% to 51%.[4,5] The clinical presentation and physiological response of septic shock vary from patient to patient, and thus accurate assessment of patient prognosis is crucial. Studies have shown that early identification of high-risk features in septic shock can facilitate clinical decision-making and enhance treatment efficacy.[6,7] Procalcitonin (PCT), a precursor of calcitonin, is a 116-amino acid polypeptide. When a bacterial infection occurs, serum PCT levels rise rapidly.[8] Dynamic changes in PCT, also known as PCT clearance (PCTc), are closely related to the clinical status of patients, which can aid

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clinical assessment, potentially reduce antibiotic duration, and thereby improve survival in septic patients.[9,10] Studies have demonstrated a significant correlation between decreased PCT levels (reflected in PCTc) and survival rate, especially in the first few days of treatment.[11–13] Therefore, the aim of this study was to evaluate the predictive performance of PCTc at different time points during the management of patients with septic shock.

Materials and Methods

Study Cohort

A prospective observational study was conducted in a 33-bed medical ICU at a teaching hospital in Changsha, China, from January to December 2015. The study was approved by the Ethic Committee of the Xiangya Hospital, Central South University. All patients meeting Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012 for sepsis were enrolled,[14] and these patients also fulfilled the Sepsis 3.0 criteria.[1] The exclusion criteria included an age younger than 18 years, any recent surgery or trauma, tumor, hematological disorders, rheumatic diseases, or HIV–positive status. During the study period, 128 septic shock cases were identified and included in the final analysis. Furthermore, the diagnostic criteria for severe pneumonia were defined by the presence of any one of the following clinical manifestations: (1) tachypnea with respiratory rate exceeding 30 breaths per minute; (2) resting peripheral oxygen saturation levels below 93%; or (3) impaired oxygenation evidenced by PaO2/FiO2 ratios ≤300 mmHg (equivalent to 0.133 kPa per mmHg).

Data and Blood Samples Collection

Demographic characteristics (age, gender), vital signs, primary disease, and Acute Physiology and Chronic Health Evaluation (APACHE II) score were recorded as part of the baseline data. In addition, the Sequential Organ Failure Assessment (SOFA) score on admission and the site of infection were recorded. Complete Blood Count, coagulation function, blood gas analysis and blood biochemical tests were performed. Infection was diagnosed using standard clinical and microbiological laboratory parameters. All patients were followed up for 28 days. For the purpose of this study, the first 28 days after admission were defined as the primary outcome period, and length of stay, as well as patient outcomes, were also documented.

Blood specimens were collected at the time of septic shock diagnosis (baseline PCT) and the following extractions were obtained at 24 h, 48 h, 72h and on 96 h in patients who survived (PCT-initial, PCT-Day 2, PCT-Day 3, PCT-Day 4 and PCT-Day 5). Serum samples were isolated by centrifugation and stored at −80°C for future assays.

Measurement of Circulating PCT

Serum PCT concentrations were quantitatively analyzed using a one-step immunoassay sandwich method with enzyme-linked fluorescent assay (ELFA) technology (MINI VIDAS, bioMérieux, France), following the manufacturer's protocol. The assay demonstrated a detection range of 0.05–200 ng/mL.

PCT-c was calculated according to the following formula: PCT on occurrence of septic shock minus PCT of day 2, day 3, day 4, day 5, respectively, divided by the PCT on occurrence of septic shock, then multiplied by 100%.

Statistical Analysis

All data are expressed as mean ± SD for normally distributed variables or as median (interquartile range) for skewed distributions. Normally distributed data were compared using an independent *t*-test. Non-normally distributed data were analyzed using the Mann–Whitney U or Kruskal–Wallis tests. Categorical variables were compared using the Chi-Square test or Fisher's exact test. The prognostic accuracy of PCT and PCTc was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The optimal cut-off values were determined using Youden's Index. Logistic regression analysis was performed to evaluate the mortality-predicting ability of the different biological indicators. All data were analyzed using SPSS software (version 21.0; SPSS; Inc; Chicago; II; USA). A P-value < 0.05 was considered statistically significant.

Results

Study Population and Grouping

Of the 185 patients with septic shock who were admitted to ICU, 128 met our inclusion criteria (Figure 1). Reasons for excluding 57 patients were as follows: age < 18 years (n=5), surgery (n=8), trauma (n=10), tumor (n=15), hematological system diseases (n=5), and rheumatic diseases (n=14). Table 1 summarizes the characteristics of the surveyed population. The lung was the most frequent site of infection, and Gram-negative bacteria were the most common pathogens. Of these, 47 (36.7%) had severe pneumonia, and the in-hospital mortality rate was 49.2%. A detailed description of microorganisms isolated from various sites in patients with septic shock is shown in Table 2. Gram- negative bacteria, gram- positive and fungi were isolated in 72.3%, 9.2% and 18.5% of cultures, respectively. *Acinetobacter baumannii* and *Escherichia coli* were identified as the two most common Gram- negative bacteria, *Streptococcus spp. was the* most common Gram-positive bacteria, and *Candida albicans* was the most common fungus.

Furthermore, these pathogens include multidrug-resistant *Acinetobacter baumannii* (n=42), multidrug-resistant *Pseudomonasaeruginosa* (n=4), ESBL-producing bacteria (n=20), and carbapenem-resistant Escherichia coli (n=10), among others. The predominant antimicrobial agents employed in treatment regimens comprised carbapenem-class drugs, advanced-generation cephalosporins (third-generation), β-lactam antibiotics combined with β-lactamase inhibitors, as well as tigecycline. The adjustment of antimicrobial therapy was guided by clinical response indicators and pathogen susceptibility testing results.

Clinical Factors Associated with Survival

Baseline demography, clinical, and laboratory test results for survivors and non-survivors with septic shock are shown in Table 3. The findings indicate that survivors had lower age, APACHE II, and SOFA scores than non-survivors. In addition, survivors tended to have a longer hospital stay. Overall, younger age, lower APACHE II and SOFA scores, and a longer hospital stay were significantly associated with better survival in patients with septic shock.

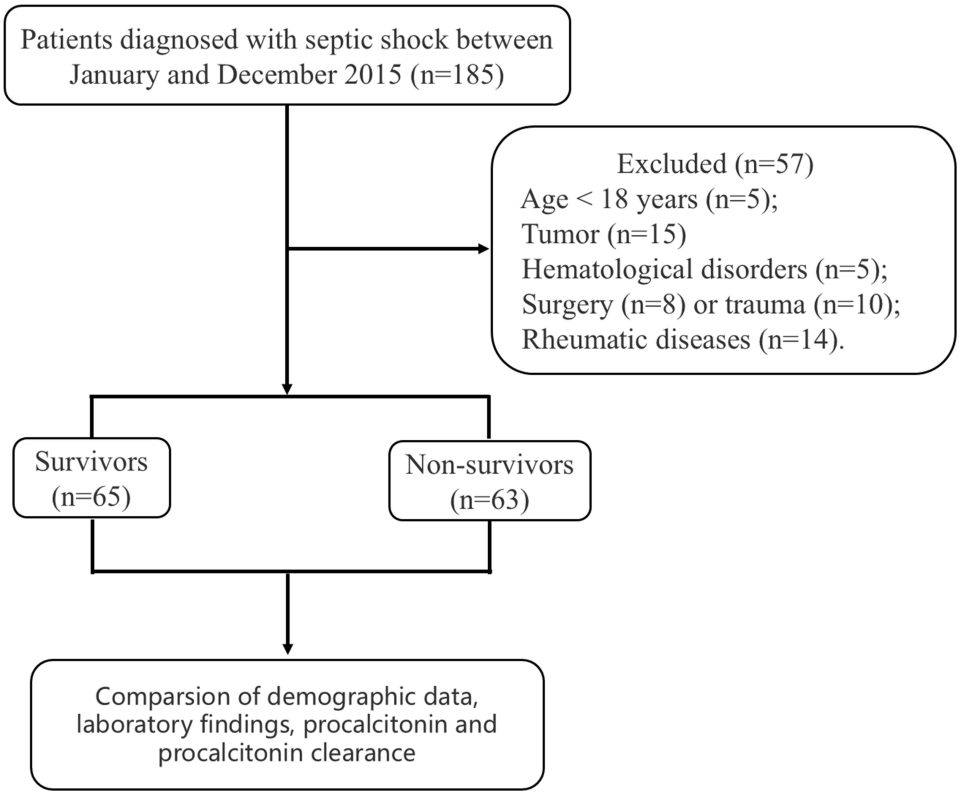

Figure 1 Workflow of the study.

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Table 1 Demographic and Clinical Characteristics of the Study Cohort

Age, y, mean (SD)	58.9 (17.2)
Man, n (%)	81 (63.3)
Female, n (%)	47 (36.7)
APACHE II, mean (SD)	15.3 (8.2)
SOFA score, mean (SD)	5.9 (3.6)
Length of ICU stay(days), Median (Interquartile)	6 (3.0–11.0)
Length of hospital stay(days), Median (Interquartile)	10 (5.3–19.0)
Site of sepsis, n (%)	
Lung	73 (57.0)
Abdomen*	24 (18.7)
Urinary tract	12 (9.4)
Skin/Soft tissue	5 (3.9)
Other infections[#]	8 (6.3)
Unknown	6 (4.7)

Notes:*The abdomen includes the hepatobiliary system, pancreas, and intestinal tract. [#]The other original sites of infection were intravascular catheter (n=1), bloodstream infection (n=2), heart valve (n=1), bone marrow (n=1), intracranial (n=2), and uterine cavity (n=1).

Table 2 Microorganisms Isolated From Different Infection Sites in Patients with Septic Shock

Category	Sputum	Abdomen	Urinary Tract	Skin/Soft Tissue	Blood
Gram-positive bacteria (n=11)					
Staphylococcus aureus	1	0	0	0	1
Enterococcus spp.	0	1	2	0	1
Streptococcus spp.	0	0	0	0	5
Gram-negative bacteria (n=86)					
Escherichia coli	0	6	2	1	4
Klebsiella pneumoniae	5	1	1	0	3
Acinetobacter baumannii	36	3	0	4	6
Pseudomonas aeruginosa	2	2	0	0	1
Burkholderia cepacia	2	0	0	0	0
*Other**	3	1	0	0	3
Fungus (n=22)					
Candida albicans	12	1	6	0	3

Notes: *Other includes Ochrobactrum anthropi, Acinetobacter lwoffii, and Moraxella catarrhalis.

PCT and PCTc for Prediction of Prognosis

The results of PCT and PCTc between the survivors and the non-survivors are presented in Table 4. The findings showed no significant difference in PCT on Day 1, 2, 3, 4, and 5 or PCTc-day 4 between the two groups. However, for patients who survived, PCTc-day 2 (PCTc-24 h), 3 (PCTc-48 h), and 5 (PCTc-96 h) were all significantly higher than those of the non-survivors. There were no significant differences in PCTc-day 4 (P=0.214).

The area under the ROC curve was 0.74 (95% CI, 0.59–0.88) for PCTc-day 2 (Figure 2A), 0.74 (95% CI, 0.61–0.86) for PCTc-day 3 (Figure 2B), and 0.72 (95% CI, 0.54–0.90) for PCTc-day 5 (Figure 2C).

A cutoff of 12.7% for PCTc-day 2 was associated with a sensitivity of 79.2%, specificity of 69.2%, positive predictive value of 78.3%, and negative predictive value of 70.4% for identifying survivors. Hospital mortality was significantly higher in patients with PCTc-day 2 < 12.7% (group A2) compared with those > 12.7% (group B2) (70.4% versus 21.7%, ChiSquare, P=0.001).

A cutoff of 49.6% was identified for PCTc-day 3. A value above 49.6% was associated with a sensitivity of 81.8%, specificity of 61.8%, positive predictive value of 84.0%, and negative predictive value of 58.1% for predicting case

Table 3 Comparison of Baseline Characteristics Between Survivors and Non-Survivors in the Study Population

Variables	Survivors (n=65)	Non-Survivors (n=63)	*P* value
Female, n (%)	27 (41.5)	20 (31.7)	0.275
Male, n (%)	38 (58.5)	43 (68.3)	
	Mean±SD	Mean±SD	
Age(years)	55.4±18.9	63.2±14.6	0.010
APACHE II score	12.8±6.7	17.9±8.8	0.000
SOFA score	5.1±3.4	6.4±3.8	0.008
Temperature (°C)	37.4±0.8	37.2±1.0	0.266
Blood WBC*(*10^9/L)	14.4±7.6	13.6±6.3	0.502
Blood PH	7.40±0.09	7.38±0.12	0.199
	Median (Interquartile)	Median (Interquartile)	
Platelet (*10^9/L)	149.0 (84.5 to 233.5)	116.0 (62.0 to 189.0)	0.118
Tbil[#](umol/l)	13.6 (8.1 to 26.8)	12.5 (6.6 to 26.2)	0.446
Creatinine (umol/l)	100.6 (67.2 to 175.9)	139.0 (79.5 to 273.6)	0.081
CRP[&]	86.3 (33.4 to 137.5)	89.3 (51.6 to 147.0)	0.369
INR[$]	1.16 (1.0 to 1.3)	1.21 (1.1 to 1.5)	0.051
Length of ICU stay (days)	7.0 (4.0 to 11.0)	5.0 (3.0 to 9.0)	0.136
Length of hospital stay (days)	16.0 (10 to 22.5)	6.0 (3.0 to 11.0)	0.000

Abbreviations: *WBC, White blood cells; [#]TBil, Total bilirubin; [&]CRP, C-reactive protein; [$]INR, International normalized ratio.

Table 4 Comparison of PCT and PCTc Levels Between Survivors and Non-Survivors in Patients with Septic Shock

	Survivors	Non-Survivors	*P* value
Serum PCT (ng/mL)	Median (Interquartile)	Median (Interquartile)	
Day 1	6.1 (2.2 to 34.2)	5.0 (1.2 to 33.8)	0.640
Day 2	7.8 (2.4 to 27.6)	8.1 (3.3 to 35.1)	0.435
Day 3	4.9 (1.2 to 16.5)	5.4 (1.5 to 54.5)	0.435
Day 4	3.7 (0.53 to 10.0)	3.2 (2.1 to 19.4)	0.477
Day 5	1.9 (0.4 to 10.9)	2.5 (1.0 to 7.6)	0.668
PCTc (%)			
Day 2	28.3 (4.7 to 38.3)	−14.0 (−65.1 to −9.5)	0.004
Day 3	60.7 (2.6 to 73.8)	11.1 (−39.2 to 46.6)	0.003
Day 4	71.5 (51.0 to 84.1)	63.5 (−128.8 to 81.2)	0.214
Day 5	77.0 (40.1 to 87.2)	36.6 (−140.9 to 73.2)	0.039

fatality on day 28. Hospital mortality was significantly lower in patients with PCTc-day 3 > 49.6% (group B3), than in those < 49.6% (group A3) (16.0% versus 58.1%, ChiSquare, *P*=0.001).

In the ROC curve analysis of PCTc-day 5, a level of 52.2% showed a sensitivity of 75.0%, specificity of 75.0%, positive predictive value of 83.3% and negative predictive value of 64.3% for prediction survival. Hospital mortality was significantly higher in patients with PCTc-day 5 < 52.2% (group A5) compared with those > 52.2% (group B5) (62.3% versus 16.7%, ChiSquare, *P*=0.006).

PCTc in groups B2 and B3 were found to be independent predictors of survival through logistic regression analysis (OR:11.36〔95% CI: 2.47–52.28〕, *P*<0.01; OR:7.09〔95% CI: 1.25–40.40〕, *P*=0.03, respectively), after adjusting for age, gender, APACHE II score, SOFA score, and length of hospital stay. However, PCTc-day 5 was not identified as an independent survival marker.

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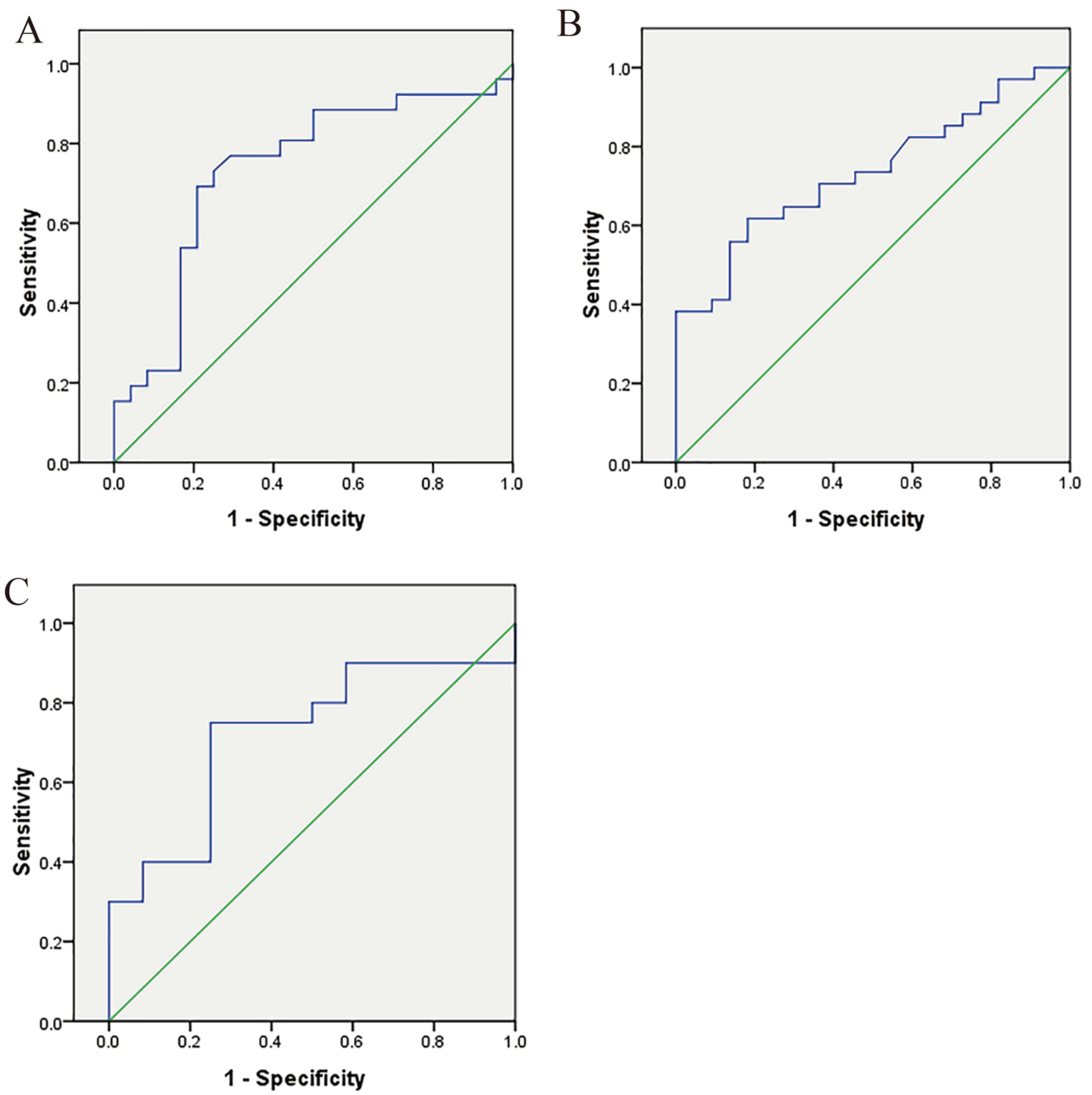

Figure 2 ROC curves of PCTc-day 2 (**A**), PCTc-day 3 (**B**), and PCTc-day 5 (**C**) for predicting survival in sepsis. The AUC were 0.74 (95% CI, 0.59–0.88; P=0.004) for PCTc-day 2, 0.74 (95% CI, 0.61–0.86; P=0.003) for PCTc-day 3, and 0.72 (95% CI, 0.54–0.90; P=0.039) for PCTc-day 5.

Discussion

There are still high mortality rates associated with septic shock, even in high-income countries with optimal resuscitation protocols, mortality from severe sepsis and septic shock can remains as high as 20% to 40%.[15,16] However, in our study, mortality among patients with septic shock reached 49.2%, which may be attributed to the relatively high proportion of elderly patients. Age was significantly higher among non-survivors compared with survivors, potentially because respiratory and immune function gradually decline in elderly patients.[17,18] Martin et al[19] also noted that age is a critical risk factor for both incidence and mortality of sepsis, with patients over 65 years having three times the risk of death compared with younger individuals. Furthermore, several additional factors may contribute to the observed outcomes. First, as the study was conducted in regional medical centers, the enrolled patients typically presented with

more severe conditions and a higher burden of comorbidities. Second, the prevalent antibiotic resistance in these clinical settings significantly contributed to the poor prognosis observed in this patient population.

In the management of septic shock, identifying biomarkers and clinical indicators associated with prognosis is crucial for improving patient outcomes.[20] The value of dynamic PCT changes in sepsis treatment has been extensively explored in multiple studies. Most findings suggest that changes in PCT have a strong ability to discriminate patients at high risk of death.[21,22] For example, a retrospective study demonstrated that patients with higher PCT levels on admission had a significantly increased risk of death within 30 days, and that changes in PCT values were strongly associated with patient clinical outcome.[21] Another prospective study emphasized the importance of PCT monitoring in septic patients, showing that dynamic PCT changes differ statistically between survivors and non-survivors.[22] These data support the use of PCT as a powerful tool for the prognosis assessment in septic patients. PCT levels rise rapidly, peaking within 12 to 24 hours,[23] thus making early dynamic PCT changes critical for the diagnosis and management of infection.[24] In this study, we employed dynamic PCT monitoring to evaluate its prognostic impact in patients with septic shock. The PCTc-day 2, day 3 and day 5 among non-survivors was significantly lower than that of survivors. To facilitate timely adjustment of treatment regimen, the ideal prognostic index of septic shock must be identified during the early treatment stage. We found that patients with PCTc-24 h > 12.7% were more likely to survive than those with clearance < 12.7%, and the optimal cut-off was 49.6% for PCTc-48 h. Therefore, a higher PCT clearance rate is associated with improved patient prognosis. This correlation may be explained by more effective infection control in septic shock patients during treatment, which reduces sustained pathogenic stimulation of PCT production, thereby increasing PCT clearance.

In the present study, the PCTc-day 5 did not demonstrate independent prognostic value. This finding may be explained by several factors associated with prolonged ICU stays: (1) increased microbial diversity leading to a higher incidence of polymicrobial infections;[25] and (2) progressive clinical complexity introducing additional confounding prognostic factors,[26] (3) the smaller sample size at later time points (attrition bias).

This study has several limitations. The foremost limitation is that it was conducted at a single center with a relatively small sample size, which may limit the generalizability of our findings. In addition, non-survivors were generally older than survivors, possibly due to the large proportion of severe pneumonia cases in the elderly. A large multicenter study stratified by age and primary disease is necessary to validate the relationship between PCTc and prognosis in patients with septic shock.

Conclusions

Dynamic changes in PCT are associated with patient prognosis. PCTc-day 2 and PCTc-day 3 may serve as reliable indicators of survival in patients with septic shock. In addition, PCTc may help indicate treatment success or failure and guide clinical assessment of disease progression. Future studies with larger sample sizes are warranted to validate these findings.

Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation; AUC, area under the receiver operating characteristic curve; ICU, intensive care unit; PCT, procalcitonin; PCTc, procalcitonin clearance; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment.

Data Sharing Statement

The original data in this study can be obtained from the corresponding authors.

Ethics Statement

The study protocol received approval from the Ethics Committee of Xiangya Hospital of Central South University (Approval No. 201412106). Prior to any medical interventions or diagnostic procedures, informed consent was acquired from all participating patients. This study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

We declare that we have no conflict of interest to disclose.

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