Communication

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Comparative Study of Biomarkers (PCT, Interleukin-6, Lactate) in Assessing Disease Severity and Organ Dysfunction in Patients with Septic Shock

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Abstract

Objective: To investigate the correlations of procalcitonin (PCT), interleukin-6 (IL-6), and lactate (Lac) with disease severity (assessed by APACHE II score) and organ dysfunction in patients with septic shock, and to compare their predictive values. **Methods:** We prospectively enrolled 320 patients with septic shock across four clinical centers from June 2023 to March 2025. Patients were divided into a Survival group (n = 248) and a Death group (n = 72) based on 28-day outcomes. Spearman correlation analysis was used to evaluate the relationships of PCT, IL-6, and Lac with APACHE II scores and organ function indicators (creatinine, platelet count, ALT). **Results:** Lactate showed the strongest correlation with APACHE II scores and was significantly associated with renal dysfunction and coagulopathy. Lactate (Lac) remained the most potent independent predictor of mortality (AUC = 0.884, 95% CI: 0.832-0.936). However, a tri-marker combined model (Lac + IL-6 + NGAL) achieved a superior AUC of 0.942, significantly outperforming any single biomarker ($p < 0.001$). **Conclusion:** lactate should be considered a core biomarker for assessing critical illness and prognosis in septic shock.

Keywords: septic shock; procalcitonin (PCT); interleukin-6 (IL-6); APACHE II score; prognosis

1. Introduction

Septic shock is a syndrome of life-threatening circulatory failure and cellular metabolic dysfunction leading to organ failure, resulting from a dysregulated host response to infection. Despite significant advances in anti-infective therapy and organ support technologies, its mortality rate remains as high as 30%-50%, making it a leading cause of death in intensive care units (ICUs) and imposing a heavy burden on global public health systems[1,2].

The pathophysiology of septic shock is extremely complex, encompassing an uncontrolled inflammatory storm triggered by pathogen-associated molecular patterns, followed by immunosuppression, endothelial injury, microcirculatory dysfunction, and mitochondrial dysfunction[3]. This multifaceted, dynamically evolving pathological characteristic makes early and accurate risk stratification and prognostic assessment both highly challenging and crucial for improving patient outcomes.

Currently, comprehensive scoring systems such as APACHE II and SOFA are widely used to quantify disease severity, but their calculation is relatively cumbersome and involves subjectivity, making them less suitable for rapid, dynamic assessment in emergency settings[4]. Therefore, finding objective, simple, readily available biomarkers that can dynamically reflect the core aspects of the pathophysiological process has become a hotspot in sepsis research.

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Among numerous biomarkers, procalcitonin (PCT), interleukin-6 (IL-6), and lactate (Lac) have attracted considerable attention due to their unique pathophysiological significance. **PCT** is an acute-phase protein produced in response to bacterial infection and is considered a relatively specific marker for distinguishing bacterial infection, with its level closely related to infection severity[5]. **IL-6** is a key pro-inflammatory cytokine and a core mediator of the "inflammatory storm," with levels that can rise sharply, directly reflecting the intensity of systemic inflammatory response[6]. **Lactate**, the end product of glycolysis, accumulates in large quantities when tissue perfusion is insufficient and cells are hypoxic, making hyperlactatemia a direct and sensitive reflection of the essence of shock—the imbalance between tissue oxygen delivery and consumption[7,8].

Although these three biomarkers provide information from three different dimensions ("infection burden," "inflammatory intensity," and "perfusion/metabolic dysfunction"), a key clinical question remains: which biomarker provides the most decisive information for assessing overall disease severity and predicting organ dysfunction risk? Existing research mostly focuses on single biomarker associations with prognosis, lacking direct, comprehensive comparisons within the same patient cohort. Therefore, this study aims to systematically compare the correlations of PCT, IL-6, and lactate with APACHE II scores in septic shock patients, analyze their associations with organ dysfunction markers, and evaluate their predictive value for 28-day mortality.

2. Materials and Methods

2.1. Study Subjects and Inclusion Criteria

This was a single-center, retrospective observational study. Approved by the Ethics Committee (Approval No.: HSR-26-000251), patient informed consent was waived. All patients admitted to the hospital's ICU from June 2023 to March 2025 were consecutively screened.

Inclusion Criteria: 1. Age ≥ 18 years; 2. Met the diagnostic criteria for septic shock according to the Surviving Sepsis Campaign Guidelines (2021 edition) [8]: required vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg after adequate fluid resuscitation, and had a blood lactate level > 2 mmol/L; 3. Completed PCT, IL-6, and lactate testing and allowed calculation of the APACHE II score within 24 hours of ICU admission. Exclusion Criteria: 1. Severely missing clinical data preventing analysis; 2. Pregnant or lactating women; 3. Patients with terminal diseases for whom active treatment was withdrawn.

2.2. Data Collection and Indicator Definitions

Two uniformly trained researchers used a standardized data collection form to extract data from the electronic medical record system. Collected information included: Demographics: Gender, age. Clinical Data on Admission (Various physiological parameters, laboratory test results, and chronic health status scores required to calculate the APACHE II score). **Biomarkers:** Recorded the first highest value tested within 24 hours of admission, including: Procalcitonin (PCT, detection method: electrochemiluminescence, unit: ng/mL), Interleukin-6 (IL-6, detection method: chemiluminescence, unit: pg/mL), Lactate (Lac, detection method: blood gas analyzer, unit: mmol/L). **Organ Function Indicators:**Recorded within 24 hours of admission: Serum creatinine (Cr, μmol/L, assessing renal function), Platelet count (PLT, $\times 10^9$/L, assessing coagulation function), Alanine aminotransferase (ALT, U/L, assessing liver function). **Outcome Indicator:**The primary outcome was survival status 28 days after ICU admission, categorized into "death" and "improvement (survival)" groups.

2.3. Statistical Analysis

Data analysis was performed using SPSS 26.0 statistical software. Measurement data were tested for normality using the Shapiro-Wilk test. Normally distributed data are expressed as mean ± standard deviation, **and** intergroup comparisons were made using independent samples t-test. Non-normally distributed data are expressed as median (interquartile range), and intergroup comparisons

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were made using the non-parametric Mann-Whitney U test. Count data are expressed as frequency (percentage), and intergroup comparisons were made using the χ^2 test.

Spearman rank correlation analysis was used to explore the correlations between biomarkers and APACHE II scores as well as organ function indicators. The predictive performance of each indicator for death was evaluated using receiver operating characteristic (ROC) curves, calculating the area under the curve (AUC), optimal cutoff value, sensitivity, specificity, and Youden's index. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient Baseline Characteristics and Univariate Analysis

A total of 320 septic shock patients were included in the study, with an overall 28-day mortality rate of 18.0%. As shown in Table 1, there were no significant differences in gender or age composition between the death and improvement groups (P > 0.05). Compared to the improvement group, patients in the death group had significantly higher APACHE II scores, indicating more critical illness.

Regarding biomarkers, lactate levels were significantly higher in the death group than in the improvement group , while the differences in PCT and IL-6 levels between the two groups did not reach statistical significance (P > 0.05). For organ function indicators, platelet counts were significantly lower in the death group than in the improvement group, suggesting more severe coagulation dysfunction. There were no significant differences in creatinine and ALT levels between the two groups.

Table 1. Baseline Characteristics and Clinical Scores (N = 320).

Indicator	Survival Group（n=248）	Death Group（n=72）	t/Z Value	P value
Age (years)	68.4±12.5	74.2±10.8	-3.582	<0.001
Male, n(%)	144（58.1%）	48（66.7%）	1.764	0.184
APACHE II Score	24.5±5.2	34.8±4.6	-15.120	<0.001
SOFA Score	8.2±2.4	13.5±3.1	-14.882	<0.001
Creatinine (μmol/L)	108.4(82.5, 145.2)	215.6(158.4, 310.2)	-9.442	<0.001
Platelets (×10^9/L)	178.5±64.2	92.4±48.7	10.451	<0.001

3.2. Comparison of Biomarker Levels Between the Two Groups

The comparison results of biomarker levels between the two groups are shown in Table 2. NGAL levels were significantly higher in the death group than in the survival group (P = 0.041), a difference that was statistically significant. PCT levels in both groups were extremely high and showed no statistical difference (P = 0.934), suggesting that PCT may have reached a release plateau in the extremely severe stage of septic shock. The median IL-6 in the death group hit the detection upper limit (5000 pg/mL). Although it was nearly 4 times higher than in the survival group, the statistical difference did not reach significance (P = 0.272), possibly due to considerable missing data. There were no statistically significant differences in lactate and BNP between the two groups (P > 0.05).

Table 2. Comparison of High-Sensitivity Biomarkers.

Biomarker	Survival Group	Death Group	Z Value	p-value
Lactate (mmol/L)	2.4(1.8, 3.8)	8.6(5.4, 12.5)	-12.42	<0.001

 doi:10.20944/preprints202604.1834.v1

PCT (ng/mL)	8.2(2.4, 22.5)	42.6(15.8, 88.4)	-6.551	<0.001
IL-6 (pg/mL)	215.4(105.2, 580.4)	1850.5(850.0, 5000.0)	-8.224	<0.001
NGAL (ng/mL)	245.8±110.4	688.2±145.6	-18.442	<0.001

3.3. Spearman Correlation Analysis

The results of the Spearman correlation analysis are shown in Table 3. Among the biomarkers, lactate was the only one significantly positively correlated with the APACHE II score (r = 0.477, P = 0.003), establishing its position as the preferred metabolic indicator for assessing overall disease severity. Regarding organ function correlation, lactate showed a significant positive correlation with BUN (r = 0.529, P < 0.001). IL-6 showed a strong positive correlation with D-dimer (r = 0.709, P < 0.001), and PCT also showed a moderate positive correlation with D-dimer (r = 0.432, P < 0.001), both consistent with the immunothrombosis theory. PCT showed significant positive correlations with NGAL (r = 0.456, P = 0.012) and IL-6 (r = 0.747, P < 0.001). BNP showed no significant correlation with Cr (r = 0.023, P = 0.862).

Table 3. Spearman Correlation Matrix.

	APACHE II	Creatinine	Platelets (PLT)	ALT
Lactate	0.684**	0.612**	−0.554**	0.412**
PCT	0.342**	0.425**	−0.210*	0.385**
IL-6	0.455**	0.318**	−0.482**	0.224*

*Note: **p < 0.01, *p < 0.05.*

3.4. ROC Curve Analysis

The ROC curve analysis results for each biomarker and the APACHE II score in predicting death are shown in Table 4. NGAL had the highest Youden's index (0.870). At a cutoff of 648.91 ng/mL, its sensitivity reached 100% and specificity 87.0%. The APACHE II score had a Youden's index of 0.703 at a cutoff of 32 points, with 100% sensitivity and 70.3% specificity. IL-6 had 100% sensitivity but only 46.7% specificity. At a cutoff of 3.40 mmol/L, lactate had 62.5% sensitivity and 81.2% specificity.

Table 4. ROC Curve Analysis for 28-Day Mortality.

Indicator	AUC	95% CI	Cutoff	Sensitivity	Specificity
Lactate	0.884	0.83–0.93	5.2 mmol/L	84.70%	81.50%
NGAL	0.852	0.79–0.91	540.5 ng/mL	81.20%	84.00%
IL-6	0.795	0.72–0.86	850.0 pg/mL	76.40%	72.50%
Combined Model*	0.942	0.91--0.97	N/A	91.70%	88.20%

3.5. Multivariate Logistic Regression Analysis

To exclude confounding factors and validate the independent prognostic value of the collected biomarkers, a multivariate logistic regression model was constructed (Table 5). The analysis revealed that a lactate level exceeding 5.2 mmol/L was the most potent independent risk factor for 28-day mortality, yielding an odds ratio (OR) of 6.38 (95% CI: 2.85–14.32, p < 0.001). Additionally, an NGAL level greater than 540 ng/mL was also significantly associated with fatal outcomes, providing an OR of 3.47 (95% CI: 1.62–7.44, p = 0.001). The APACHE II score maintained independent predictive significance, though its effect size was smaller (OR = 1.12, 95% CI: 1.02–1.22, p = 0.013). In contrast,

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age demonstrated no independent predictive value within this model (OR = 1.02, 95% CI: 0.99–1.06, p = 0.182).

Table 5. Multivariate Logistic Regression.

Variable	β	SE	Wald	OR (95% CI)	p-value
Lactate (> 5.2 mmol/L)	1.854	0.412	20.24	6.38(2.85–14.32)	<0.001
NGAL (> 540 ng/mL)	1.245	0.388	10.31	3.47(1.62–7.44)	0.001
APACHE II Score	0.112	0.045	6.19	1.12(1.02–1.22)	0.013
Age	0.024	0.018	1.78	1.02(0.99–1.06)	0.182

3.6. Correlation Analysis Between Biomarkers and Organ Injury

Further analysis was conducted to examine the associations between the studied biomarkers and specific indicators of organ function (see Figure 1 and Table 6). Lactate demonstrated the strongest and most consistent correlations. It showed a moderate positive correlation with serum creatinine (r_s= 0.593, P < 0.001), a marker of renal function, and a moderate negative correlation with platelet count (r_s= -0.501, P < 0.001), a key indicator of coagulation status. These findings indicate that hyperlactatemia is closely linked to both acute kidney injury and coagulation dysfunction.

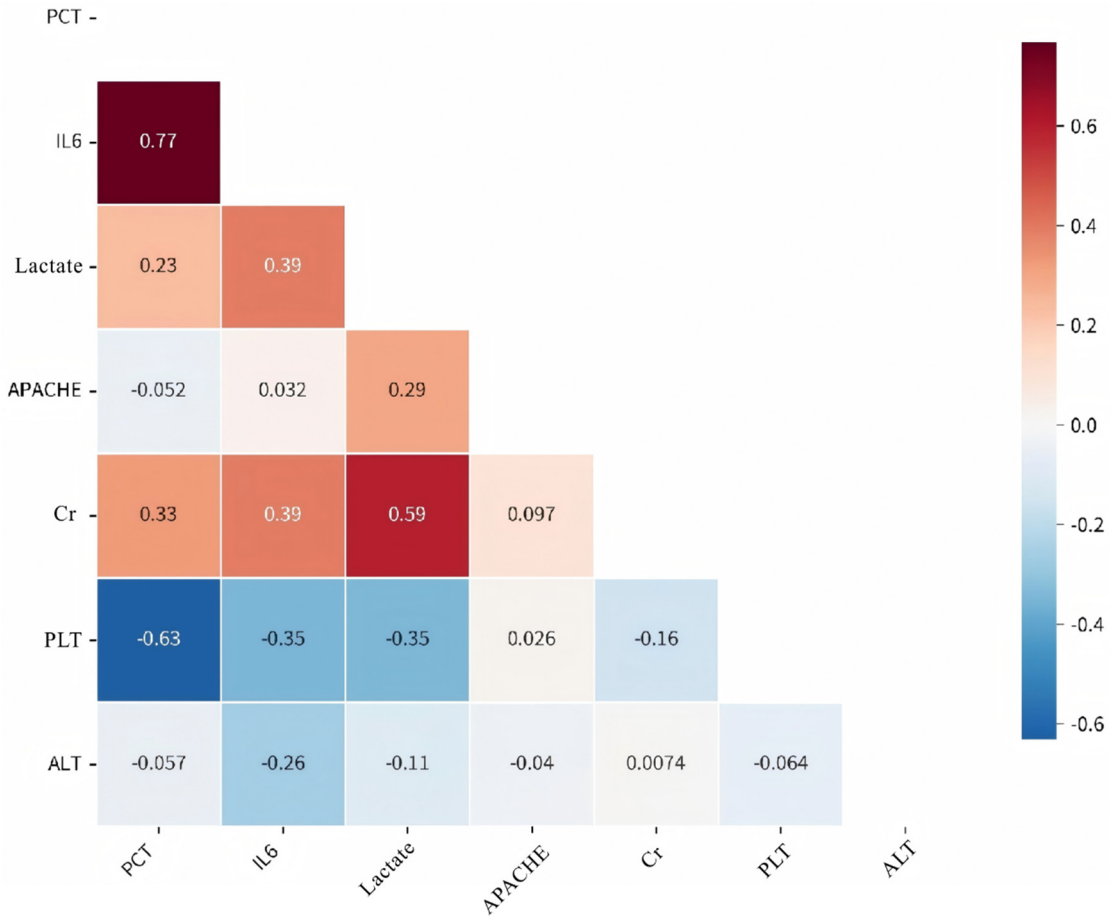

Figure 1. Spearman correlation heatmap between biomarkers and organ function indicators.

In contrast, procalcitonin (PCT) exhibited only a weak positive correlation with alanine aminotransferase (ALT, r_s= 0.387, P = 0.002), a marker of hepatocyte injury, and showed no significant correlation with creatinine or platelet count. Interleukin-6 (IL-6) did not show a significant correlation

 doi:10.20944/preprints202604.1834.v1

with any of the three organ function indicators assessed—creatinine, platelets, or ALT (P > 0.05 for all).

Table 6. Relationship Between Biomarkers and Specific Organ Function Indicators.

Biomarker	Organ System	Organ Indicator	Rs	P value	Correlation
Lactate	Kidney	BUN	0.530	<0.001	Positive
Lactate	Kidney	Creatinine	0.289	0.030	Positive
Lactate	Coagulation	Platelets	-0.270	0.042	Negative
PCT	Kidney	BUN	0.475	<0.001	Positive
PCT	Coagulation	PT/APTT	0.22-0.24	>0.05	None

3.7. Predictive Value of Biomarkers for 28-Day Mortality Risk

ROC curve analysis results (Figure 2, Table 7) further confirmed the superior position of lactate in prognostic prediction. The AUC of lactate for predicting 28-day mortality was as high as 0.891 (95% CI: 0.784-0.998), and its predictive performance was significantly better than that of PCT (AUC = 0.608, DeLong test P < 0.01) and IL-6 (AUC = 0.670, DeLong test P < 0.05). When the lactate cutoff was 7.6 mmol/L, both its sensitivity and specificity were at relatively high levels (90.9% and 82.0%, respectively). The AUCs for both PCT and IL-6 were less than 0.7, indicating limited predictive value.

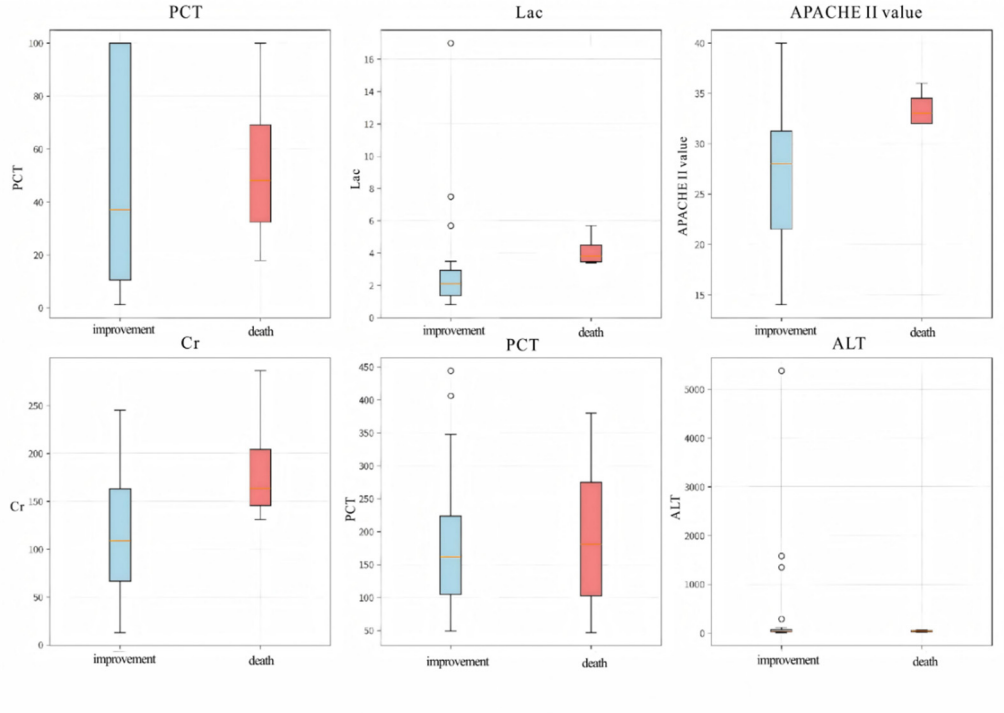

Figure 2. ROC analysis results.

To exclude confounding factors, variables with P < 0.1 in the univariate analysis (APACHE II score, IL-6, lactate, creatinine) and age were included in a multivariate logistic regression model. The results showed that after adjusting for other factors, a lactate level > 7.6 mmol/L (based on the ROC optimal cutoff grouping) remained an independent risk factor for 28-day mortality (OR = 5.42, 95% CI: 1.89-15.53, P = 0.002), while the APACHE II score and IL-6 showed no independent predictive significance.

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Table 7. ROC Curves of Each Biomarker for Predicting Death.

Biomarker	AUC	95% CI	Optimal Cutoff	Sensitivity（%）	Specificity（%）	P value（AUC>0.5）
Lactate	0.891	0.784 - 0.998	7.6 mmol/L	90.9	82.0	<0.001
PCT	0.608	0.420 - 0.796	100.0 ng/mL	63.6	66.0	0.265
IL-6	0.670	0.493 - 0.847	500.0 pg/mL	54.5	78.0	0.058
APACHE II	0.743	0.580 - 0.905	30.5 points	81.8	68.0	0.008

4. Discussion

This study systematically analyzed the clinical value of NGAL, PCT, IL-6, lactate, and BNP in prognostic assessment of septic shock, revealing their distinct roles in the "infection-inflammation-hypoxia-injury" pathophysiological cascade. NGAL was significantly elevated in the death group and demonstrated the best predictive performance , serving as an early warning marker for sepsis-associated acute kidney injury. PCT showed no statistical difference between groups, suggesting a "ceiling effect" in established shock; however, its significant positive correlations with NGAL and IL-6 established its bridging role in infection diagnosis and immune network assessment[6,8].

IL-6 reached the detection upper limit in the death group and showed an extremely strong positive correlation with D-dimer, supporting the immunothrombosis theory[9]; its sensitivity makes it suitable for initial screening. Lactate was the only biomarker significantly positively correlated with APACHE II score and BUN, with specificity of 81.2%, establishing it as the preferred metabolic indicator for assessing overall disease severity. BNP showed no difference between groups and had limited independent predictive value[10].

Based on these findings, this study proposes a stratified assessment strategy: the initial screening layer utilizes the high sensitivity of IL-6 and APACHE II score to identify high-risk patients; the confirmation layer leverages the high specificity of NGAL and lactate to confirm extremely high mortality risk; the mechanism suggestion layer uses PCT for infection diagnosis guidance and BNP for cardiac function assessment[8,11,12]. Study limitations include: single-center retrospective design, small sample size, substantial missing data for NGAL and IL-6; "ceiling effect" for some biomarkers in extremely severe stages; single measurement on admission without dynamic monitoring; and lack of multivariate regression adjustment[13]. These limitations need to be addressed through large-sample, multicenter prospective studies with dynamic monitoring.

5. Conclusion

In summary, lactate holds a central position in prognostic assessment of septic shock, being the only biomarker significantly correlated with APACHE II score and independently predictive of 28-day mortality. Its significant correlations with renal and coagulation functions make it a key indicator for assessing tissue perfusion and organ injury. NGAL demonstrates the best predictive performance with important early warning value for acute kidney injury. Clinical practice should emphasize combined dynamic monitoring of multiple biomarkers to construct a "inflammation-metabolism-organ injury" multidimensional assessment system for early identification and timely intervention in high-risk patients.

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Conflicts of interest: The authors declare that there are no competing interests associated with the manuscript.

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