Am J Cancer Res 2024;14(12):5839-5850
www.ajcr.us /ISSN:2156-6976/ajcr0160612

Original Article

Predictive value of peripheral blood indicators plus procalcitonin clearance rate for mortality in cancer patients with sepsis

Ting Zhu*, Biao Tian*, Lei Wang

*Department of Critical Care Medicine, South China Hospital of Shenzhen University, Shenzhen 518100, Guangdong, PR China. *Equal contributors.*

Received September 18, 2024; Accepted December 10, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: This study investigated the predictive value of combining peripheral blood indicators with procalcitonin clearance rate (PCTc) to assess mortality risk in cancer patients with sepsis, aiming to develop a more sensitive and specific clinical tool. A retrospective analysis was conducted on 393 cancer patients with sepsis admitted to South China Hospital of Shenzhen University from January 2019 to January 2024. Collected data included clinical demographics, laboratory indicators such as white blood cell count, neutrophil count (NEUT), platelet count (PLT), lymphocyte count (LYC), C-reactive protein, procalcitonin (PCT), alanine aminotransferase, and the ratio of arterial oxygen partial pressure to inspired oxygen fraction, as well as functional scores like Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment. Multivariate logistic regression and receiver operating characteristic curves assessed the predictive ability of these factors for 28-day survival. Results showed significantly higher NEUT ($P<0.001$) and lower PLT and LYC ($P<0.001$) in the death group, while APACHE II score (area under the curve (AUC) = 0.776) and PCT 24h (AUC = 0.723) demonstrated strong predictive value for mortality risk. The joint projection model's AUC reached 0.966, significantly outperforming individual indicators, indicating that combining multiple indicators offers a more accurate prediction of survival versus mortality risk. Additionally, 24h LCR and 24h PCTc were notably lower in the death group compared to the survival group, reinforcing the advantage of combined indicators for prognosis. Overall, using both peripheral blood indicators and PCTc significantly improves the accuracy of mortality risk assessment in cancer patients with sepsis, enhancing prognostic evaluation and supporting optimized clinical decision-making.

Keywords: Cancer, sepsis, peripheral blood indicators, procalcitonin clearance rate, prognosis, mortality risk prediction

Introduction

Sepsis incidence is on the rise globally, posing one of the greatest mortality risks for critically ill patients. In the United States, one in five patients hospitalized with sepsis also has a cancer diagnosis [1]. For cancer patients, sepsis worsens quality of life and escalates healthcare costs, especially during intensive care. Within the first year after cancer diagnosis, sepsis incidence reaches 3.7%, with nearly one-third of cases progressing to septic shock and a mortality rate as high as 35.5% [2]. This condition not only prolongs hospital stays but also amplifies demands on critical care resources, posing substantial challenges for patients and the healthcare system. This vulnerability is compounded by intensive cancer therapies, including chemotherapy, major surgeries, bone marrow transplants, and radiotherapy [3]. These treatments, while prolonging survival, can weaken the immune defenses and increase the likelihood of infections. Furthermore, cancer type and location influence sepsis risk and outcomes; for instance, lung cancer patients are more susceptible to respiratory infections, elevating sepsis incidence [4, 5].

Cancer patients with sepsis face unique challenges due to compounded immune suppression from both malignancy and treatment regimens. The combination of sepsis with active cancer further intensifies immune system impairment, leading to increased risk of multi-

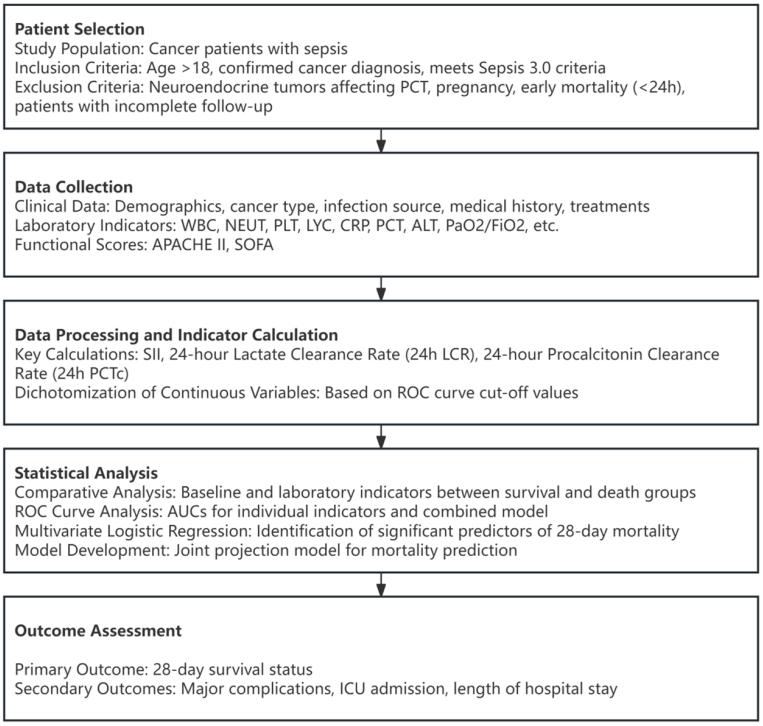

Figure 1. Study flow chart.

organ failure [6]. When sepsis occurs, it can result in rapid and severe disease progression. Large-scale retrospective studies confirm that sepsis mortality is significantly higher in patients with active cancer than in those with inactive disease, likely due to ongoing tumor cell proliferation and metastasis, which weakens overall recovery capacity [7-9]. Additionally, mortality rates vary by cancer type, with patients with hematologic malignancies at higher risk than those with solid tumors [10, 11]. Among solid tumor patients, those with lung tumors are particularly prone to respiratory infections, partly due to airway obstruction, chemotherapy-related immunosuppression, and radiation-induced lung changes [12]. This complex, high-risk population requires precise and sensitive prognosis tools tailored to their unique profiles.

Peripheral blood indicators are gaining recognition as valuable tools for assessing prognosis in sepsis, due to their accessibility, cost-effectiveness, and ability to reflect systemic inflammation and immune response [13]. The procalcitonin (PCT) clearance rate (PCTc), in particular, provides a dynamic measure of inflammation resolution, closely associated with sepsis outcomes [14]. Studies have shown that PCTc outperforms single PCT measurements in assessing prognosis, as it provides a better view of the inflammatory status and progression in sepsis patients [15, 16]. The combination of peripheral blood indicators and PCTc allows a more comprehensive assessment of mortality risk in cancer patients with sepsis, overcoming limitations posed by single indicators that may not fully reflect the complex interactions in this population. Therefore, this study aims to explore the role of peripheral blood indicators alongside PCTc for enhanced prognostic assessment, with the expectation that this combined approach will yield a sensitive and specific predictive tool for mortality risk in cancer patients with sepsis, ultimately aiding in more timely and informed clinical decision-making.

Methods and materials

Research design

This is a retrospective single-center investigation aimed at probing into the predictive value of the combination of peripheral blood indicators and PCTc for the risk of mortality in cancer patients with sepsis. The subjects (n = 393) were malignant tumor patients with sepsis admitted to South China Hospital of Shenzhen University between January 2019 and January 2024. This study was approved by the Ethics Committee of South China Hospital of Shenzhen University. The study design is presented in a flow chart (**Figure 1**).

Patient selection criteria

Inclusion criteria: age greater than 18 years old; confirmed diagnosis of malignancy; meeting the Sepsis 3.0 diagnostic criteria [17].

Exclusion criteria: patients with neuroendocrine tumors such as medullary thyroid carcinoma and small cell lung cancer that signifi-

cantly affect PCT levels; pregnant and lactating women; patients who died within 24 hours after admission; patients who gave up treatment and hospice care; patients for whom the 28-day survival status cannot be determined.

Data sources

The data used in this study are sourced from the electronic medical record system of our hospital. The collected data can be classified into clinical data, laboratory indicators, and functional scores. Clinical data included patients' basic demographic information (e.g., age and sex), malignant tumor types (e.g., lung, gastric, and colorectal cancers), sepsis-related clinical manifestations (temperature, pulse, respiratory rate, mean arterial pressure, etc.), past medical history (hypertension, diabetes, heart disease, etc.), and treatment schemes (e.g., anti-infection treatment, surgery, chemoradiotherapy, targeted therapy). Laboratory indicators included (1) peripheral blood routine examination results, such as white blood cell count (WBC), neutrophil count (NEUT), platelet count (PLT), and lymphocyte count (LYC); (2) inflammatory markers like C-reactive protein (CRP) and PCT; (3) the liver function index alanine aminotransferase (ALT); (4) the renal function indicator creatinine (Cre); and (5) the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2). Functional scores comprised two sepsis-related scale scores, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA). The time range for data collection is from January 2019 to January 2024. All data have undergone rigorous data cleansing and anonymization to ensure the reliability of the study and the protection of patient privacy. Note: systemic inflammatory index (SII) = (NEUT * PLT)/LYC, 24-hour lactic acid (LAC) clearance rate (24h LCR) = (Lac 0h - Lac 24h)/Lac 0h, 24-hour PCTc (24h PCTc) = (PCT 0h - PCT 24h)/PCT 0h.

Functional score definition

APACHE II: The APACHE II score is a widely utilized illness scoring system for critically ill patients to evaluate the severity and prognosis of patients in the intensive care unit (ICU). The scoring is based on age, physiological indicators (body temperature, mean arterial pressure, heart rate, etc.), and prior health status. APACHE II scores range from 0 to 71, with higher scores indicating more severe disease and a greater risk of mortality [18].

SOFA: The SOFA score evaluates the organ function of septic patients and assists in determining the degree of organ failure. The scoring is based on the functions of six organ systems, including respiration, cardiovascular, liver, coagulation, kidney, and central nervous system. The score range of SOFA is from 0 to 24 points. A higher score indicates more severe organ failure and a worse patient prognosis [19].

Outcome measures

The primary outcome is the patient's 28-day survival status (death vs. survival), which was utilized to assess the predictive capability of peripheral blood indicators and PCTc for the risk of mortality in cancer patients with sepsis.

Secondary outcomes include the occurrence of major complications during hospitalization (e.g., acute kidney injury, respiratory failure, multiple organ failure), length of hospital stay, and ICU admission (yes vs. no). These secondary outcomes were employed to further explore the role of peripheral blood indicators and PCTc in predicting the mortality and therapeutic efficacy.

Statistical analysis

All data were analyzed using SPSS 26.0 statistical software. Measurement data were represented by mean ± standard deviation (Mean ± SD), and independent sample t-tests or Mann-Whitney U tests were employed for intergroup comparisons. Count data were presented as case numbers and percentages, and chi-square tests or Fisher's exact tests were utilized for intergroup comparisons. The independent factors influencing the risk of mortality were determined through multivariate logistic regression analysis, with statistical significance level set at $P<0.05$. Additionally, the receiver operating characteristic (ROC) curve was employed to evaluate the predictive ability of peripheral blood indicators and PCTc for the patients' 28-day survival status, and the area under the curve (AUC) was calculated to assess

Table 1. Baseline data

Variable	Total	Death group (n = 112)	Survival group (n = 281)	χ^2/Z	P
Age	66.00 (61.00, 73.00)	67.50 (62.00, 74.50)	66.00 (60.00, 73.00)	2.512	0.012
Gender					
Male	261	78	183	0.733	0.392
Female	132	34	98		
Temperature (°C)	38.00 (37.00, 38.00)	38.00 (38.00, 38.00)	38.00 (37.00, 38.00)	0.989	0.279
Pulse (minute/time)	89.07±10.30	90.00 (83.00, 94.00)	89.16±10.21	-0.15	0.881
Respiration (minute/time)	21.00 (18.00, 25.00)	21.00 (18.00, 24.00)	22.00 (18.00, 25.00)	-1.531	0.125
Mean arterial pressure (mm/Hg)	87.00 (76.00, 97.00)	89.00 (77.75, 100.00)	86.00 (76.00, 96.00)	1.74	0.082
Hypertension					
With	166	45	121	0.273	0.602
Without	227	67	160		
Heart disease					
With	90	28	62	0.391	0.532
Without	303	84	219		
Diabetes					
With	73	22	51	0.118	0.731
Without	320	90	230		
Tumor source					
Lung	114	30	84	5.247	0.155
Upper digestive tract	125	32	93		
Lower digestive tract	55	13	42		
Others	99	37	62		
Infection source					
Respiratory	240	71	169	1.254	0.534
Blood	54	17	37		
Others	99	24	75		

the predictive efficacy of the model. Statistical differences are indicated when P<0.05.

Results

Comparison of baseline characteristics

Upon analyzing the baseline data of 393 cancer patients with sepsis, including 112 patients in the death group and 281 in the survival group, we observed significant differences in age between the groups (P = 0.012). The median age was 67.50 years (interquartile range [IQR]: 62.00, 74.50) in the death group and 66.00 years (IQR: 60.00, 73.00) in the survival group. Other baseline characteristics, such as gender, body temperature, pulse, respiration, mean arterial pressure, history of hypertension, heart disease, diabetes, tumor origin, and source of infection, showed no statistically significant differences between the two groups (P>0.05), indicating a generally similar distribution of these variables across groups (**Table 1**).

Comparison of laboratory indicators and functional scores

Upon analyzing the laboratory indicators and functional scores of cancer patients with sepsis (**Table 2**), several indicators were found to exhibit significant differences between the death and survival groups: NEUT was significantly higher in the death group compared to the survival group (P<0.001), with decreased PLT (P<0.001), reduced LYC (P<0.001), and elevated SII (P = 0.006). In addition, the death group exhibited lower PaO_2/FiO_2 (P = 0.017), as well as higher levels of ALT and scores of SOFA and APACHE II, than the survival group (P< 0.001). The differences in other indexes, including WBC, CRP, and Cre, were not statistically significant between the two groups (P>0.05).

Comparison of LAC clearance rate

We analyzed the LAC clearance rate in cancer patients with sepsis and found no significant

Table 2. Laboratory indicators and function scores

Variable	Total	Death group (n = 112)	Survival group (n = 281)	t/Z	P
WBC (×10^9/L)	11.30±3.72	11.23±3.04	11.33±3.96	-0.252	0.801
NEUT (×10^9/L)	12.90 [10.00, 15.60]	14.50 [12.55, 16.88]	12.00 [9.20, 14.40]	5.821	<0.001
PLT (×10^9/L)	183.00 [141.00, 233.00]	155.61±40.32	203.11±69.39	-8.444	<0.001
LYC (×10^9/L)	1.14 [0.92, 1.41]	1.01±0.25	1.22 [0.98, 1.51]	-5.784	<0.001
SII	1932.80 [1318.60, 2795.70]	2270.35 [1561.27, 3106.18]	1862.00 [1188.00, 2716.30]	2.739	0.006
CRP (mg/L)	169.77±51.64	162.72±52.57	172.58±51.08	-1.692	0.092
PaO_2/FiO_2 (mmol/L)	238.15±40.15	230.55±39.07	241.18±40.23	-2.414	0.017
ALT (U/L)	30.81±4.98	33.19±4.34	29.60 [26.80, 32.60]	6.318	<0.001
Cre (μmol/L)	67.15±19.82	68.67±20.04	66.55±19.74	0.954	0.341
SOFA score	7.00 [5.00, 10.00]	9.00 [7.00, 12.00]	7.00 [5.00, 9.00]	6.317	<0.001
APACHE II score	20.00 [16.00, 24.00]	25.28±6.80	19.00 [15.00, 22.00]	8.539	<0.001

Note: WBC, white blood cell count; NEUT, neutrophil count; PLT, platelet count; LYC, lymphocyte count; SII, systemic inflammatory index; CRP, C-reactive protein; PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen; ALT, alanine aminotransferase; Cre, creatinine; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

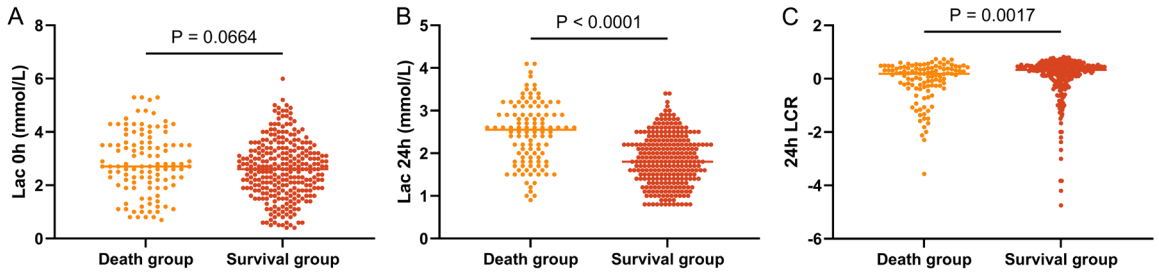

Figure 2. Comparison of LAC clearance rate between the death group and the survival group. A. The distribution of Lac 0h. B. The distribution of Lac 24h. C. The distribution of 24h LCR. Note: LAC, lactic acid; Lac 0h, lactic acid at 0 hour; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate.

inter-group difference in Lac 0h (P = 0.066). However, significant differences were present between the two groups in Lac 24h and 24h LCR. Specifically, Lac 24h (P<0.001) was notably higher in the death group compared to the survival group, while 24h LCR (P = 0.002) was significantly higher in the survival group, indicating that patients in the survival group had stronger lactate clearance capacity (Table S1; **Figure 2**).

Comparison of PCTc

The analysis of PCTc in cancer patients with sepsis revealed no statistical between-group difference in PCT 0h (P = 0.265). However, PCT 24h and 24h PCTc differed significantly between the two groups. Specifically, PCT 24h (P<0.001) was notably higher in the death group compared to the survival group, while 24h PCTc (P<0.001) was significantly higher in the survival group, suggesting that patients in the survival group had stronger lactate clearance capacity (Table S2; **Figure 3**).

ROC curves of various indexes for predicting patient death

ROC curve analysis was conducted on the measurement data of cancer patients with sepsis. The APACHE II score demonstrated strong predictive ability, as evidenced by an AUC of 0.776, which was the highest among all the indicators. Lac 24h exhibited an AUC of 0.742, also showing excellent predictive performance. Additionally, the AUCs of 24h PCTc, PLT, PCT 24h, ALT, SOFA score, and NEUT all exceeded 0.68, suggesting a certain degree of predictive value. Other indicators such as age, LYC, SII, PaO_2/FiO_2, and 24h LCR had relatively lower AUCs and weaker predictive capabilities (Table S3 and **Figure 4**).

Multivariate logistic regression analysis and comparison of ROC curves for joint projections

First, the data were dichotomously assigned based on the cut-off values of the ROC curve (Table S4). Following univariate analysis, we

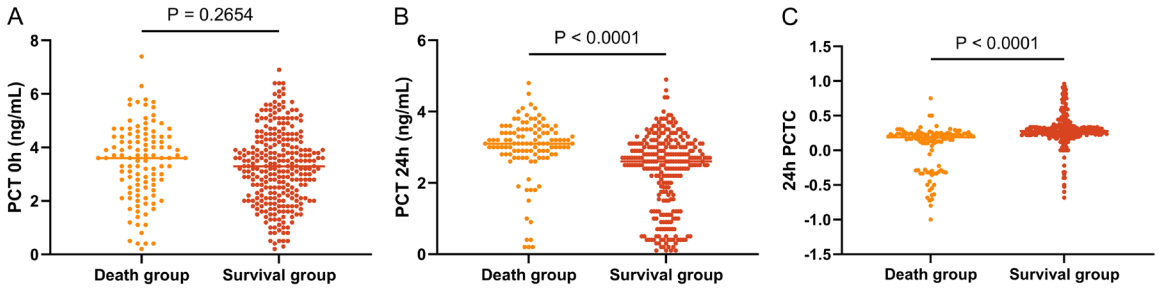

Figure 3. Comparison of PCT clearance rate between the death group and the survival group. A. The distribution of PCT 0h. B. The distribution of PCT 24h. C. The distribution of 24h PCTc. Note: PCT, procalcitonin; PCT 0h, procalcitonin at 0 hour; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

identified several factors with significant differences between survival and death groups, which informed their inclusion in the multivariate logistic regression analysis. Specifically, APACHE II score, NEUT, Lac 24h, PCT 24h, and ALT showed notable associations with mortality risk in cancer patients with sepsis. These factors were selected due to their statistical significance in univariate analysis (P<0.05) and their established relevance in sepsis prognosis. In the multivariate logistic regression, each of these indicators continued to demonstrate significant impacts on mortality risk, with regression coefficients and odds ratios of 3.418, 3.151, 5.75, 17.91, and 3.778, respectively, highlighting their importance in influencing patient survival (**Table 3**). The joint projection model's ROC curve exhibited a highly robust predictive accuracy, achieving an AUC of 0.966, which significantly outperformed the individual indicators (**Figure 5**). This outcome emphasizes the value of combining these key indicators for a comprehensive assessment of mortality risk.

Comparison of ROC curves of joint projections and individual indicators

AUC values range from 0 to 1, with a greater value suggesting better predictive performance of the model. An AUC<0.5 suggests a poor predictive ability of the model, even inferior to random prediction, indicating that the model has nearly no practical value. An AUC between 0.5 and 0.7 indicates that the model has low predictive ability; although slightly better than random prediction, its accuracy is not high and its clinical application value is limited. An AUC between 0.7 and 0.9 suggests that the model has moderate to good predictive ability and can better distinguish positive and negative results, with certain clinical application value. An AUC>0.9 indicates that the model has extremely high predictive ability and can accurately distinguish positive and negative results, with significant guiding significance in clinical practice. We constructed a joint prediction model based on the logistics regression β coefficient, log = 1.142 Age + 1.148 NEUT 1.769 PLT 1.386 LYC 1.55 FiO_2/PaO_2 + 1.329 ALT + 1.229 APACHE II score + 1.749 Lac 24h + 2.885 PCT 24h. We calculated the score for each patient and drew the ROC curve by the formula. When comparing the ROC curve of the joint projection model with that of individual indicators, we found that the AUC of the joint projection model was significantly higher than that of the individual indicators (P<0.001), such as age, NEUT, PLT, PaO_2/FiO_2, ALT, APACHE II score, Lac 24h, and PCT 24h (**Table 4**).

Discussion

Sepsis presents remarkably high morbidity and mortality rates among cancer patients, particularly in those undergoing intensive treatments. Although these treatment modalities can extend patient survival, they also substantially weaken the immune system and heighten the risk of infection [20]. Research indicates a statistically higher 30-day mortality rate in sepsis patients complicated with cancer versus patients without, underscoring the necessity of conducting a more precise assessment of mortality risk for this high-risk group [21]. Consequently, this study aims to provide a more sensitive and specific predictive tool for this particular population by analyzing the predictive value of peripheral blood indicators plus PCTc.

Age exerts a crucial role in the prognosis of cancer patients with sepsis. With age, the immune

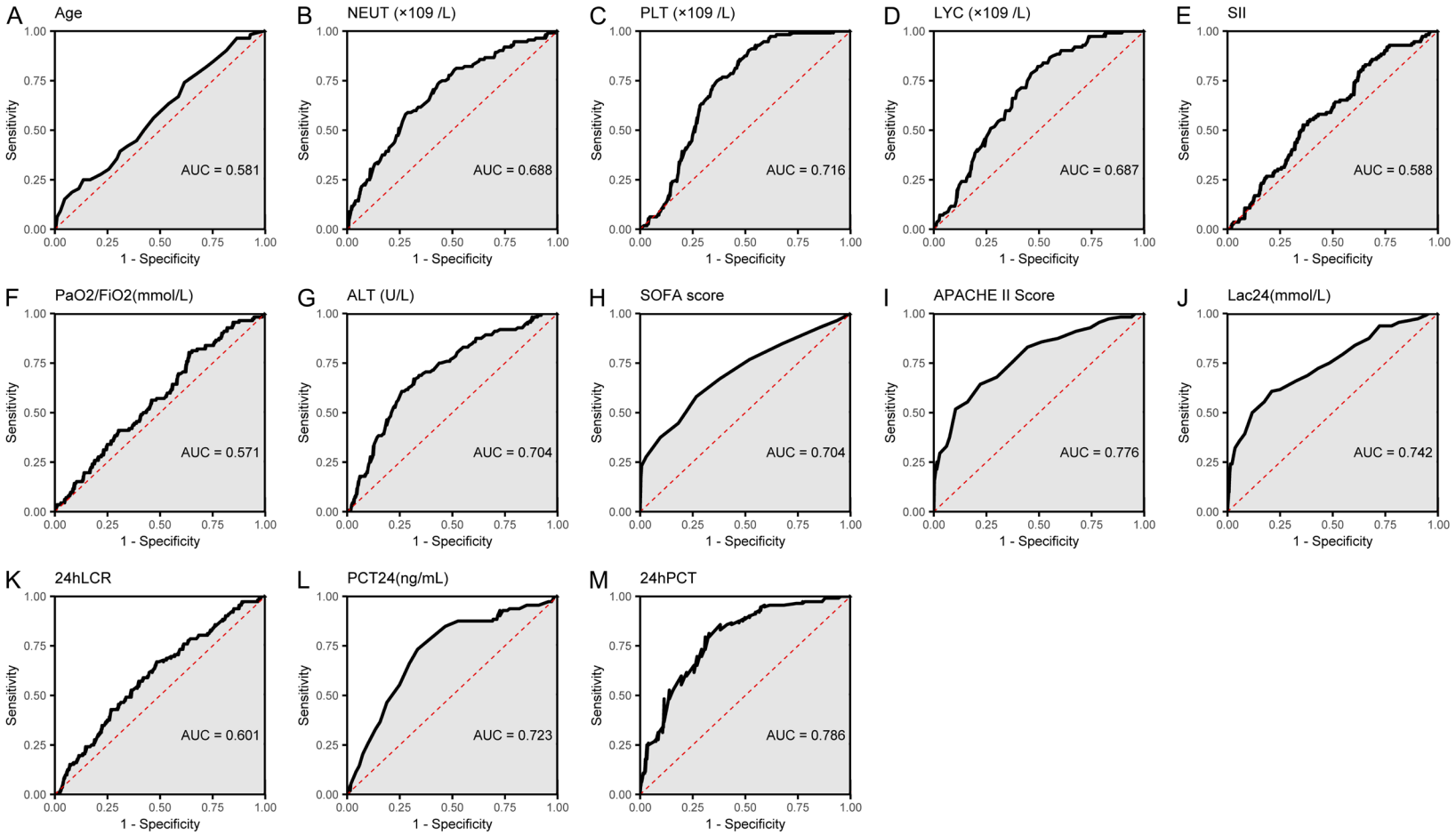

Figure 4. ROC curves of measurement data with significant differences between the survival group and the death group. A. ROC curve of age (AUC = 0.581, Cut-off = 62.500). B. ROC curve of NEUT (AUC = 0.688, Cut-off = 12.650). C. ROC curve of PLT (AUC = 0.716, Cut-off = 209.500). D. ROC curve of LYC (AUC = 0.687, Cut-off = 1.215). E. ROC curve of SII (AUC = 0.588, Cut-off = 1438.200). F. ROC curve of PaO_2/FiO_2 (AUC = 0.571, Cut-off = 259.100). G. ROC curve of ALT (AUC = 0.704, Cut-off = 31.550). H. ROC curve of SOFA score (AUC = 0.704, Cut-off = 8.500). I. ROC curve of APACHE II score (AUC = 0.776, Cut-off = 22.500). J. ROC curve of Lac 24h (AUC = 0.742, Cut-off = 2.350). K. ROC curve of 24h LCR (AUC = 0.601, Cut-off = 0.317). L. ROC curve of PCT 24h (AUC = 0.723, Cut-off = 2.850). M. ROC curve of 24h PCTc (AUC = 0.786, Cut-off = 0.247). Note: AUC, area under the curve; NEUT, neutrophils; PLT, platelets; LYC, lymphocytes; SII, systemic inflammatory index; PaO_2/FiO_2, partial pressure of oxygen/fraction of inspired oxygen; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

Table 3. Multivariate logistic regression analysis

Variable	β	Standard error	Wald	P	OR	95% CI
Age	1.142	0.512	4.98	0.026	3.133	1.149-8.543
NEUT	1.148	0.543	4.465	0.035	3.151	1.087-9.135
PLT	-1.769	0.514	11.845	0.001	0.17	0.062-0.467
LYC	-1.386	0.501	7.667	0.006	0.25	0.094-0.667
SII	0.723	0.624	1.341	0.247	2.061	0.606-7.005
PaO_2/FiO_2	-1.55	0.539	8.275	0.004	0.212	0.074-0.610
ALT	1.329	0.42	10.007	0.002	3.778	1.658-8.610
SOFA score	0.448	0.469	0.909	0.340	1.565	0.624-3.925
APACHE II score	1.229	0.482	6.512	0.011	3.418	1.330-8.783
Lac 24h	1.749	0.485	12.987	<0.001	5.75	2.221-14.888
24h LCR	-0.262	0.49	0.286	0.593	0.769	0.294-2.011
PCT 24h	2.885	0.565	26.114	<0.001	17.91	5.922-54.162
24h PCTc	-3.6	0.59	37.263	<0.001	0.027	0.009-0.087

Note: OR, odds ratio; CI, confidence interval; NEUT, neutrophil count; PLT, platelet count; LYC, lymphocyte count; SII, systemic inflammatory index; PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

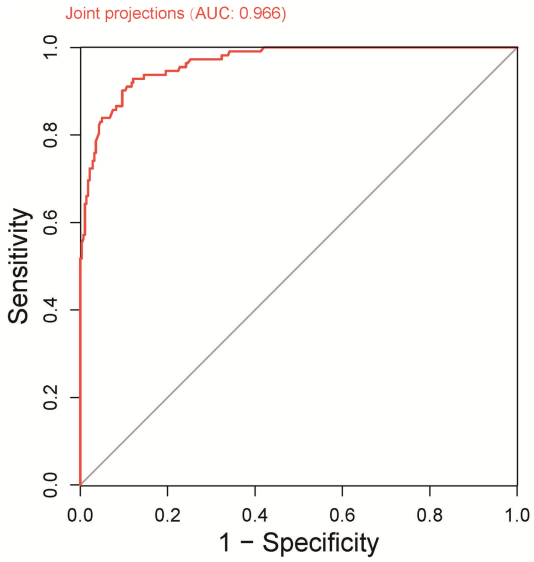

Figure 5. ROC curve of joint projections for distinguishing patient death and survival. Note: ROC, receiver operating characteristic; AUC, area under the curve.

function and organ reserve capacity gradually diminish, rendering elderly patients more vulnerable when confronted with severe infections [22]. In this study, the death group was significantly older than the survival group, indicating that increasing age is correlated with a higher risk of mortality. The research conducted by Wardi et al. [22] reveals that sepsis mortality was significantly higher in older patients than in younger patients, especially in those over 85 years old. Although some patients may have a better chance of survival during treatment, the overall prognosis remains poor. Elderly patients are typically more susceptible to multi-organ failure and the exacerbation of chronic diseases, which collectively increase their mortality rate in sepsis. Consequently, age, as an independent risk factor, holds significant importance in evaluating the prognosis of patients with malignancy and sepsis.

The inflammatory response and immune status play a crucial role in the prognosis of sepsis patients, particularly for those with malignancies complicated by sepsis [23]. These indicators not only reflect infection severity but also provide insights into the body's immune response capacity. A marked elevation in NEUT often indicates a robust inflammatory reaction, typically signifying the immune system's active fight against infections. However, an excessive NEUT response can cause tissue damage and multi-organ dysfunction, ultimately increasing mortality risk [24]. Additionally, lactate levels, SOFA score, and the occurrence of septic shock are primary risk factors for acute kidney injury (AKI) in sepsis patients, all of which are associated with poor clinical outcomes [25]. The significant reductions in PLT and LYC highlight a

Table 4. Comparison of ROC curves of joint projections and individual indicators

Marker1	Marker2	Z_value	*P*_value	AUC_difference	CI_lower_upper
Age	Joint projections	-11.677	<0.001	-0.384	-0.449 - -0.320
NEUT (×10^9/L)	Joint projections	-9.279	<0.001	-0.278	-0.336 - -0.219
PLT (×10^9/L)	Joint projections	-9.73	<0.001	-0.25	-0.300 - -0.200
PaO_2/FiO_2 (mmol/L)	Joint projections	-12.028	<0.001	-0.394	-0.459 - -0.330
ALT (U/L)	Joint projections	-9.334	<0.001	-0.262	-0.316 - -0.207
APACHE II score	Joint projections	-7.101	<0.001	-0.19	-0.242 - -0.137
Lac 24h (mmol/L)	Joint projections	-7.873	<0.001	-0.223	-0.279 - -0.168
PCT 24h (ng/mL)	Joint projections	-8.745	<0.001	-0.243	-0.297 - -0.188
24h PCTc	Joint projections	-7.784	<0.001	-0.18	-0.225 - -0.134

Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NEUT, neutrophil count; PLT, platelet count; PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; Lac 24h, lactic acid at 24 hours; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

compromised immune defense. Specifically, a decrease in PLT not only raises the risk of bleeding but also suggests possible bone marrow suppression or consumptive coagulopathy [26]. Meanwhile, reduced LYC levels, particularly of T cells, weaken the body's ability to resist infection, making patients more vulnerable to severe bacterial or viral infections [27]. These findings underscore the prognostic value of monitoring inflammatory markers, as they offer critical insights into immune competence and potential complications, ultimately helping clinicians assess mortality risk.

Assessing organ function and metabolic status is critical for understanding illness severity in sepsis patients. A notable decline in PaO_2/FiO_2 indicates potential severe pulmonary impairment, such as acute respiratory distress syndrome, which exacerbates the overall prognosis. Studies have shown that cancer patients are particularly susceptible to severe AKI, correlating with a higher mortality rate during hospitalization [28]. Elevated ALT levels indicate impaired liver function, which, as the body's main organ for metabolism and detoxification, is essential for maintaining homeostasis. Liver dysfunction can result in toxin accumulation, further increasing the risk of multi-organ failure [26]. Similarly, high lactate levels at 24 hours (Lac 24h) are associated with tissue hypoxia and metabolic dysregulation, often reflecting an increase in anaerobic cellular metabolism - a critical marker for assessing sepsis severity [8]. These findings emphasize the importance of assessing organ function and metabolic parameters, as they provide comprehensive insights into disease severity, guiding timely interventions for better patient outcomes.

The APACHE II score provides a comprehensive evaluation of the patient's overall condition by integrating physiological parameters, such as body temperature, blood pressure, heart rate, and prior health status, along with PCT-related indicators. Notably, patients in the death group exhibited significantly higher APACHE II scores than those in the survival group, indicating a greater severity of illness and a higher mortality risk [26]. Furthermore, mortality has been observed to increase significantly in older patients with sepsis, especially as the severity of AKI worsens [29]. High PCT levels at 24 hours (PCT 24h) suggest an active infection, while reduced PCT clearance at 24 hours (24h PCTc) points to an inadequate inflammatory control response [30]. These factors are closely associated with increased mortality risk. A combined analysis of these variables enables clinicians to better predict mortality in cancer patients with sepsis, allowing for the development of individualized treatment plans and potentially improving patient outcomes. The predictive value of APACHE II, combined with PCT metrics, highlights the utility of these scores for stratifying sepsis patients by risk, allowing clinicians to tailor interventions based on severity, so as to improve prognosis.

Based on our findings, we performed multivariate logistic regression analysis to identify key prognostic indicators and constructed a comprehensive prediction model using the beta coefficients of these indicators. The Delong

test confirmed that the model's AUC was 0.966, indicating a high level of discriminatory power. This predictive model, which combines crucial physiological and biochemical parameters, offers a more accurate assessment of mortality risk in sepsis patients with malignancy than any single indicator alone. Traditional sepsis models often rely on single metrics, which may not fully capture the unique immunosuppressive status and altered inflammatory response seen in cancer patients with sepsis. By incorporating indicators specific to this high-risk group, such as PCT 24h and 24h PCTc, our model addresses these unique challenges, providing a more tailored assessment of mortality risk in cancer-associated sepsis.

Our results align with other studies utilizing machine learning methods for 28-day mortality prediction, demonstrating the predictive superiority of integrated models. For example, Yang et al.'s XGBoost model achieved an AUC of 0.873 in predicting mortality risk for sepsis-related AKI patients [31]. Similarly, Zhou et al. reported AUC values ranging from 0.828 to 0.923 for the XGBoost model across various validation sets, underscoring the robustness and clinical relevance of predictive models [32]. In summary, our model demonstrates strong predictive capability, addressing the unique clinical context of sepsis in cancer patients and reinforcing the value of integrated analysis for accurate mortality risk assessment in this distinct population.

Despite the widespread use of APACHE II and Lac 24h as key indicators in sepsis prognosis, our study integrates PCT 24h and 24h PCTc with standard indicators (such as age, NEUT, and PLT) to offer a more nuanced predictive perspective. This combined approach holds several clinical advantages: APACHE II and Lac 24h primarily reflect the severity of sepsis and tissue hypoxia, while the dynamic changes in PCT, including 24h PCTc, provide a direct measure of infection control and the rate of inflammatory response resolution. Together, PCT 24h and 24h PCTc can more accurately capture the trajectory of disease progression or improvement, providing timely insights that can guide clinical interventions. Furthermore, the multi-indicator integration significantly enhances the predictive accuracy of the model. Using individual markers like PCT or Lac alone may lead to predictive uncertainty due to the complexity of sepsis; however, in our combined model, these indicators complement each other to create a more reliable risk assessment. Specifically, our findings show that the combined model's AUC reaches 0.966, markedly outperforming any single indicator. This integration enables the early detection of potential risks, ultimately helping clinicians develop targeted interventions earlier in the treatment course, thereby improving survival outcomes and optimizing care.

This study presents several limitations that merit attention. First, being a single-center study, the sample size is restricted, potentially impacting the wide applicability of the results. Second, the research employs a retrospective design, and the data are dependent on past medical records, entailing the risk of incomplete or inaccurate information. Finally, this study only assesses short-term prognosis and lacks long-term follow-up data, precluding a comprehensive understanding of the long-term survival and quality of life of patients. In future studies, a larger sample scope and long-term follow-up data are required to validate these findings.

Conclusion

The combination of peripheral blood indicators and PCTc demonstrates remarkable advantages in predicting the risk of mortality in cancer patients with sepsis. The joint projection model significantly enhances the accuracy of evaluating patient prognosis, aids in optimizing clinical decisions, enhances treatment efficacy, and consequently improves patient survival rates.

Disclosure of conflict of interest

None.

Address correspondence to: Lei Wang, Department of Critical Care Medicine, South China Hospital of Shenzhen University, No. 1 Fuxin Road, Pinghu Street, Longgang District, Shenzhen 518100, Guangdong, PR China. Tel: +86-0755-89698999; E-mail: Wanglei_md@163.com

References

[1] Nadelson S, Reed D, Massey M, Lowder T and Yarberry F. Faculty perceptions of curiosity in the education of nursing and health science students. J Mod Nurs Pract Res 2022; 2: 1.

[2] Sadaka F, EthmaneAbouElMaali C, Cytron MA, Fowler K, Javaux VM and O'Brien J. Predicting mortality of patients with sepsis: a comparison of APACHE II and APACHE III scoring systems. J Clin Med Res 2017; 9: 907-910.
[3] Awad WB, Nazer L, Elfarr S, Abdullah M and Hawari F. A 12-year study evaluating the outcomes and predictors of mortality in critically ill cancer patients admitted with septic shock. BMC Cancer 2021; 21: 709.
[4] Liu X, Shen Y, Li Z, Fei A, Wang H, Ge Q and Pan S. Prognostic significance of APACHE II score and plasma suPAR in Chinese patients with sepsis: a prospective observational study. BMC Anesthesiol 2016; 16: 46.
[5] Zhou J, Zhang Y, Yang T, Zhang K, Li A, Li M, Peng X and Chen M. Causal relationships between lung cancer and sepsis: a genetic correlation and multivariate mendelian randomization analysis. Front Genet 2024; 15: 1381303.
[6] Wang W and Liu CF. Sepsis heterogeneity. World J Pediatr 2023; 19: 919-927.
[7] Williams JC, Ford ML and Coopersmith CM. Cancer and sepsis. Clin Sci (Lond) 2023; 137: 881-893.
[8] Shen Y, Yu J, Zhou F, Yan J, Yang J, Guo Y and Lin L. The predictive performance of the lactate clearance rate combined with the APACHE II score in the prediction of sepsis-associated acute kidney injury in 7 days. Transl Androl Urol 2022; 11: 543-553.
[9] Wang YG, Zhou JC and Wu KS. High 28-day mortality in critically ill patients with sepsis and concomitant active cancer. J Int Med Res 2018; 46: 5030-5039.
[10] Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K and McGuffie C; Scottish Trauma Audit Group Sepsis Steering Group. Utility of a single early warning score in patients with sepsis in the emergency department. Emerg Med J 2014; 31: 482-487.
[11] Shvetsov YB, Ogino MH, Glibetic N, Asato CB, Wilkens LR, Le Marchand L and Matter ML. Association of sepsis mortality with specific cancer sites and treatment type: the multiethnic cohort study. J Pers Med 2021; 11: 146.
[12] Huang CY, Daniels R, Lembo A, Hartog C, O'Brien J, Heymann T, Reinhart K and Nguyen HB; Sepsis Survivors Engagement Project (SSEP). Life after sepsis: an international survey of survivors to understand the post-sepsis syndrome. Int J Qual Health Care 2019; 31: 191-198.
[13] Ehizogie E, Maghari I, Lo S and Albrecht J. Hidradenitis suppurativa, systemic inflammatory response syndrome and sepsis: a database study. Br J Dermatol 2024; 191: 451-453.
[14] Xie Y, Zhuang D, Chen H, Zou S, Chen W and Chen Y. 28-day sepsis mortality prediction model from combined serial interleukin-6, lactate, and procalcitonin measurements: a retrospective cohort study. Eur J Clin Microbiol Infect Dis 2023; 42: 77-85.
[15] Zheng G, Zhang J, Yuan Y, Xu D, Dong S and Wang H. Application value of procalcitonin clearance rate on clinical outcome in patients with severe pneumonia. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019; 31: 566-570.
[16] Miao Q, Chen SN, Zhang HJ, Huang S, Zhang JL, Cai B and Niu Q. A pilot assessment on the role of procalcitonin dynamic monitoring in the early diagnosis of infection post cardiac surgery. Front Cardiovasc Med 2022; 9: 834714.
[17] Costa RT, Nassar AP Jr and Caruso P. The comparisons and limitations of sepsis 2.0 and sepsis 3.0. J Crit Care 2018; 47: 351.
[18] Tekin B, Kiliç J, Taşkin G, Solmaz İ, Tezel O and Başgöz BB. The comparison of scoring systems: SOFA, APACHE-II, LODS, MODS, and SAPS-II in critically ill elderly sepsis patients. J Infect Dev Ctries 2024; 18: 122-130.
[19] Iba T, Maier CL, Tanigawa T and Levy JH. Risk stratification utilizing sequential organ failure assessment (SOFA) score, antithrombin activity, and demographic data in sepsis-associated disseminated intravascular coagulation (DIC). Sci Rep 2023; 13: 22502.
[20] Nazer L, Lopez-Olivo MA, Cuenca JA, Awad W, Brown AR, Abusara A, Sirimaturos M, Hicklen RS and Nates JL. All-cause mortality in cancer patients treated for sepsis in intensive care units: a systematic review and meta-analysis. Support Care Cancer 2022; 30: 10099-10109.
[21] Liu MA, Bakow BR, Hsu TC, Chen JY, Su KY, Asiedu EK, Hsu WT and Lee CC. Temporal trends in sepsis incidence and mortality in patients with cancer in the US population. Am J Crit Care 2021; 30: e71-e79.
[22] Wardi G, Tainter CR, Ramnath VR, Brennan JJ, Tolia V, Castillo EM, Hsia RY, Malhotra A, Schmidt U and Meier A. Age-related incidence and outcomes of sepsis in California, 2008-2015. J Crit Care 2021; 62: 212-217.
[23] Liu X, Tang AL, Cheng J, Gao N, Zhang G and Xiao C. RIPK1 in the inflammatory response and sepsis: recent advances, drug discovery and beyond. Front Immunol 2023; 14: 1114103.
[24] Ling H, Chen M, Dai J, Zhong H, Chen R and Shi F. Evaluation of qSOFA combined with inflammatory mediators for diagnosing sepsis and predicting mortality among emergency department. Clin Chim Acta 2023; 544: 117352.
[25] Yang Y, Dong J, Chen X, Chen R and Wang H. Incidence, risk factors and clinical outcomes

of septic acute renal injury in cancer patients with sepsis admitted to the ICU: a retrospective study. Front Med (Lausanne) 2022; 9: 1015735.
[26] Chen C, Wu X, Zhang W, Pu Y, Xu X, Sun Y, Fei Y, Zhou S and Fang B. Predictive value of risk factors for prognosis of patients with sepsis in intensive care unit. Medicine (Baltimore) 2023; 102: e33881.
[27] Zhang G, Wang T, An L, Hang C, Wang X, Shao F, Shao R and Tang Z. U-shaped correlation of lymphocyte count with all-cause hospital mortality in sepsis and septic shock patients: a MIMIC-IV and eICU-CRD database study. Int J Emerg Med 2024; 17: 101.
[28] Calças Marques R, Reis M, Pimenta G, Sala I, Chuva T, Coelho I, Ferreira H, Paiva A and Costa JM. Severe acute kidney injury in hospitalized cancer patients: epidemiology and predictive model of renal replacement therapy and in-hospital mortality. Cancers (Basel) 2024; 16: 561.
[29] Wang J, Li J and Wang Y. Clinical characteristics and prognosis of acute kidney injury in elderly patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019; 31: 837-841.
[30] Liu Y, Yang W and Wei J. Guiding effect of serum procalcitonin (PCT) on the antibiotic application to patients with sepsis. Iran J Public Health 2017; 46: 1535-1539.
[31] Yang J, Peng H, Luo Y, Zhu T and Xie L. Explainable ensemble machine learning model for prediction of 28-day mortality risk in patients with sepsis-associated acute kidney injury. Front Med (Lausanne) 2023; 10: 1165129.
[32] Zhou S, Lu Z, Liu Y, Wang M, Zhou W, Cui X, Zhang J, Xiao W, Hua T, Zhu H and Yang M. Interpretable machine learning model for early prediction of 28-day mortality in ICU patients with sepsis-induced coagulopathy: development and validation. Eur J Med Res 2024; 29: 14.

Table S1. Comparison of LAC clearance rate

Variable	Total	Death group (n = 112)	Survival group (n = 281)	t/Z	P
Lac 0h (mmol/L)	2.70 [1.90, 3.40]	2.70 [2.08, 3.60]	2.59±1.08	1.836	0.066
Lac 24h (mmol/L)	2.00 [1.50, 2.50]	2.46±0.72	1.80 [1.40, 2.20]	7.505	<0.001
24h LCR	0.29 [-0.16, 0.47]	0.18 [-0.28, 0.40]	0.33 [-0.05, 0.48]	-3.135	0.002

Note: LAC, lactic acid; Lac 0h, lactic acid at 0 hour; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate.

Table S2. Comparison of PCT clearance rate

Variable	Total	Death group (n = 112)	Survival group (n = 281)	t/Z	P
PCT 0h (ng/mL)	3.32±1.39	3.27±1.38	3.44±1.40	1.109	0.265
PCT 24h (ng/mL)	2.80 [2.00, 3.20]	3.10 [2.80, 3.50]	2.60 [1.66, 3.00]	6.898	<0.001
24h PCTc	0.25 [0.19, 0.33]	0.19 [-0.10, 0.24]	0.28 [0.22, 0.34]	-8.85	<0.001

Note: PCT, procalcitonin; PCT 0h, procalcitonin at 0 hour; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

Table S3. ROC curve parameters for various measurement data

Marker	AUC	Specificity	Sensitivity	Youden_index	Accuracy	Precision	F1_Score
Age	0.581	38.43%	74.11%	12.54%	48.60%	74.11%	45.11%
NEUT ($\times 10^9$/L)	0.688	56.23%	74.11%	30.33%	61.32%	74.11%	52.20%
PLT ($\times 10^9$/L)	0.716	48.40%	90.18%	38.58%	39.69%	9.82%	8.49%
LYC ($\times 10^9$/L)	0.687	50.53%	82.14%	32.68%	40.46%	17.86%	14.60%
SII	0.588	35.59%	82.14%	17.73%	48.85%	82.14%	47.79%
PaO_2/FiO_2 (mmol/L)	0.571	36.30%	80.36%	16.66%	51.15%	19.64%	18.64%
ALT (U/L)	0.704	68.33%	66.96%	35.29%	67.94%	66.96%	54.35%
SOFA score	0.704	73.31%	58.04%	31.35%	68.96%	58.04%	51.59%
APACHE II score	0.776	77.94%	64.29%	42.22%	74.05%	64.29%	58.54%
Lac 24h (mmol/L)	0.742	79.00%	60.71%	39.72%	73.79%	60.71%	56.90%
24h LCR	0.601	51.60%	66.96%	18.57%	44.02%	33.04%	25.17%
PCT 24h (ng/mL)	0.723	66.55%	73.21%	39.76%	68.45%	73.21%	56.94%
24h PCTc	0.786	67.26%	81.25%	48.51%	28.75%	18.75%	13.04%

Note: AUC, area under the curve; NEUT, neutrophil count; PLT, platelet count; LYC, lymphocyte count; SII, systemic inflammatory index; PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.

Table S4. Assignment table

Variable	Type	Assignment content
Age	X	<62.5 = 0, ≥62.5 = 1
NEUT (×10^9/L)	X	<12.65 = 0, ≥12.65 = 1
PLT (×10^9/L)	X	<209.5 = 0, ≥209.5 = 1
LYC (×10^9/L)	X	<1.215 = 0, ≥1.215 = 1
SII	X	<1438.2 = 0, ≥1438.2 = 1
PaO_2/FiO_2 (mmol/L)	X	<259.1 = 0, ≥259.1 = 1
ALT (U/L)	X	<31.55 = 0, ≥31.55 = 1
SOFA score	X	<8.5 = 0, ≥8.5 = 1
APACHE II score	X	<22.5 = 0, ≥22.5 = 1
Lac 24h (mmol/L)	X	<2.35 = 0, ≥2.35 = 1
24h LCR	X	<0.317 = 0, ≥0.317 = 1
PCT 24h (ng/mL)	X	<2.85 = 0, ≥2.85 = 1
24h PCTc	X	<0.247 = 0, ≥0.247 = 1
Survival status	Y	Death = 1, survival = 0

Note: X, independent variable; Y, dependent variable; NEUT, neutrophils; PLT, platelets; LYC, lymphocytes; SII, systemic inflammatory index; PaO_2/FiO_2, partial pressure of oxygen/fraction of inspired oxygen; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; Lac 24h, lactic acid at 24 hours; 24h LCR, 24-hour lactic acid clearance rate; PCT 24h, procalcitonin at 24 hours; 24h PCTc, 24-hour procalcitonin clearance rate.