Analysis of risk factors affecting the prognosis of patients with sepsis and construction of nomogram prediction model

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Abstract. – **OBJECTIVE:** This study analyzed the clinical data of 200 sepsis patients, exploring the risk factors that affect patient prognosis and providing the basis for clinically targeted intervention to improve patient prognosis.

PATIENTS AND METHODS: 200 septic patients were admitted to Yulin Second Hospital, and they were divided into a survival group of 151 patients and a death group of 49 patients, according to their clinical outcomes on admission. The relevant clinical parameters within 24 h of admission were collected, and the independent risk factors affecting the prognosis of septic patients were analyzed by multivariate Logistic regression. R language 4.21 software was used to construct a nomogram prediction model. The receiver operating characteristic curve was used to evaluate the discrimination of the nomogram model, and decline curve analysis was drawn to evaluate the effectiveness of the model.

RESULTS: In the nomogram prediction model, age, the Acute Physiology and Chronic Health Scoring System Domain (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) score, C-reactive protein (CRP), total bilirubin, albumin (Alb), urea nitrogen, creatinine, and lactate (Lac) were independent risk factors for death in septic patients. The area under the receiver operating characteristic (ROC) curve for predicting the prognosis of septic patients was 0.597-1.000, and the calibration curve tends to be the ideal curve. The model had good discrimination and calibration and had high accuracy in evaluating septic patients. The modeling curves in the decline curve analysis (DCA) were all above the two extreme curves, which had good clinical value.

CONCLUSIONS: Nine clinical variables have been found to be independent risk factors for death in septic patients. The prediction model established based on this has good accuracy, discrimination, and consistency in predicting the prognosis of sepsis patients.

Introduction

With the development of modern society, sepsis is still a disease that seriously threatens human health. The disease is a clinical syndrome caused by the body's out-of-control response to infection. It is characterized by infection complicated by circulatory or organ failure. Its disability and mortality rates are both at a high level. International data show that death cases due to sepsis are approximately 20% of the total number of sepsis cases[1]. Most domestic sepsis cases originate from intensive care units (ICU), and the mortality rate is about 35.5%[2]. Starting targeted anti-infective treatment as soon as possible after sepsis is diagnosed can effectively reduce the mortality rate.

Although sepsis guidelines are constantly updated, its incidence continues to increase[3]. In the past 30 years, due to limited medical resources and limited understanding of the disease, the in-hospital mortality rate for patients with severe sepsis and septic shock has exceeded 80%[4]. Traditional prognostic indicators, such as ICU mortality rate and in-hospital mortality rate, cannot quantify patients' recovery status. While reducing short-term mortality rates, people are paying more and more attention to the long-term recovery status of survivors. Studies[5] have shown that septic patients still have a high risk of death months or even years after being transferred out of the ICU. At the same time, these patients are often prone to cognitive dysfunction and reduced quality of life[6,7].

The latest international sepsis diagnosis and treatment guidelines still use the 2016 sepsis 3.0

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definition[8]. However, this definition is based on large clinical data, and its early identification and management of sepsis is still controversial. As early as 2017, the World Health Assembly (WHA)[9] prompted 194 joint member states to reach a unanimous resolution on improving the prevention, diagnosis, and management of sepsis. Its purpose was to improve the early identification and management capabilities of sepsis. In 2020, China also released the "Expert Consensus on Early Prevention and Emergency Intervention of Sepsis in China[10]". It can be said that early warning of sepsis has become a top priority for international medical workers in sepsis treatment. Sepsis is mainly the result of an imbalance in the interaction between pathogens and hosts.

Lung infection is the most common source of infection in septic patients, accounting for more than 50% of all sepsis cases, followed by abdominal infection and urinary tract infection[2]. Domestic epidemiological studies[2,11] suggest that more than half of sepsis patients are infected with G-bacteria. Studies[2] have shown that the infection rate of G– bacteria even reached 62.5%, while G+ bacteria only accounted for 14.5%. This difference may be due to the lack of national large-scale epidemiological studies in China, and the etiology of different regions and ICUs is different; it may also be related to the changes in the types of etiology caused by the abuse of antibacterial drugs[12].

The short-term mortality of sepsis (including ICU mortality, in-hospital mortality, 28-day mortality, etc.) has always been the focus of intensive care medicine. There are multiple studies in literature showing the mortality rate of sepsis at all levels of the hospital. A study[13] based on global sepsis epidemiological data showed that the ICU incidence rate of sepsis reached 29.5%, and the ICU mortality rate reached 25.8%. The incidence rate of severe sepsis (including septic shock) in domestic ICU is 37.3%, and the ICU mortality rate and in-hospital mortality rate are 28.7% and 33.5%, respectively[2].

Long-term mortality is the most important long-term prognostic indicator of sepsis. Patients with sepsis still have a high risk of death within months to years after being transferred out of the ICU[5], which makes it necessary to prolong the follow-up time for research related to the prognosis of sepsis. Compared with non-septic patients in the ICU, septic patients have a higher long-term mortality rate[14]. The older the patient, the higher the severity of sepsis[14,15], and the higher the long-term mortality rate. As the most common infection in the ICU, pulmonary infection is also a risk factor for long-term mortality in septic patients[16,17].

Compared with healthy people, the long-term quality of life of septic patients is significantly lower[18,19]. Six months after discharge, the physical health of sepsis patients gradually recovers, but their mental health does not improve significantly[20]. After the onset of sepsis, critically ill patients have varying degrees of damage to their social function, energy, emotional role function, and physical health. After being transferred out of the ICU for 6 months, they gradually recover but are still lower than the baseline level before admission[21]. A systematic review by Rochwerg et al[22] showed that septic patients had a significantly reduced quality of life compared with healthy people, which could persist for up to 5 years.

The Acute Physiology and Chronic Health Scoring System Domain (APACHE II) score is a commonly used clinical method to evaluate the condition and prognosis of critically ill patients. However, the calculation method is complex, and the calculation time is long, which may affect the early and effective treatment of patients[23]. The Sequential Organ Failure Assessment (SOFA) score is often used to dynamically track the organ functional status of patients in intensive care units and determine the degree of organ failure[24,25]. The lack of specificity in the clinical manifestations of septic patients leads to a low detection rate and delays the timing of diagnosis and treatment. Therefore, early, timely, and effective diagnosis is meaningful for judging the patient's condition and degree of infection. In view of this, this study retrospectively analyzed the clinical data of 200 sepsis patients admitted to our hospital from June 2020 to June 2023. Explore the risk factors that affect patient prognosis and provide the basis for clinically targeted intervention to improve patient prognosis.

Patients and Methods

Normal Information

The clinical data of 200 patients with positive sepsis admitted to our hospital from June 2020 to June 2023 were retrospectively analyzed. All patients were treated with antibiotics upon admission, and blood culture specimens were taken before anti-infective drugs were administered. The

patients were grouped according to the outcome of their condition when they were transferred out of the ICU or discharged from the hospital.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients meeting the diagnostic Sepsis 3.0 Criteria[26], which included patients with life-threatening organ dysfunction caused by an uncontrolled host response to infection; (2) with at least a 2-point increase in the SOFA score in response to an infection; (3) had two of the following four items: (a) abnormal body temperature (<36.5°C or >38.5°C); (b) changes in respiratory rate (>40 times/min); (c) heart rate changes (<100 times/min or >180 times/min); (d) white blood cell count >19.5 × 10^9 L or <5.0 × 10^9 L; (4) patients older than 12 years; (5) available Superficial Musculo-Aponeurotic System (SMAS) ultrasound within the first 24 h of ICU admission; (6) after admission, the medical records and examination results were complete and intact. The infection basis of this study was selected as the gold standard - positive blood culture.

Exclusion criteria: (1) mental or intellectual developmental disorders; (2) severe liver and kidney insufficiency or heart failure; (3) patients younger than 12 years; (4) pregnant and lactating women; (5) autoimmune or connective tissue disease; (6) patients who received chemotherapy within 6 months before admission; (7) patients receiving corticosteroids or other immunosuppressants and immunomodulators at present or within the previous 3 months; (8) HIV-positivity; (9) patients who stayed in the ICU for less than 48 h.

Grouping

Among the 200 patients, they were divided into 2 groups, according to the outcome of the disease when they were transferred out of the ICU or discharged from the hospital: 1) Death group, with a total of 49 cases, including in-hospital death and unavoidable death who were automatically discharged (death confirmed after follow-up); 2) Survival group, with a total of 151 cases, including improvement, improvement, and discharge, and transfer to the intensive care unit.

Observation Indicators

Inflammatory indicators, organ function indicators, nutritional indicators, and admission scores were collected. The collection was completed within 24 h from the patient's admission:

blood urea nitrogen, serum creatinine, total bilirubin, albumin (Alb), prealbumin, C-reactive protein (CRP), white blood cell count, age, lactate (Lac) level, APACHE II score, SOFA score, neutrophil/lymphocyte ratio (NLR).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 21.0 (IBM Corp., Armonk, NY, USA). Data were expressed as means ± standard deviation (SD). Univariate analysis was performed on the clinical indicators, and two independent sample *t*-tests were performed on the measurement data. Then, the risk factors that might affect the prognosis were gradually introduced into the Logistic regression analysis, and the risk factors with *p*<0.05 were included in the nomogram prediction model. R language 4.21 software (The R Foundation for Statistical Computing, Vienna, Austria) was used to construct a nomogram prediction model. The receiver operating characteristic curve (ROC) was used to evaluate the discrimination of the nomogram model, and the decline curve analysis (DCA) was drawn to evaluate the validity of the model.

Results

Comparison of Clinical Data

We performed a comparative analysis of patient clinical factors. Univariate analysis showed that age, APACHE II, SOFA score, CRP, PCT, total bilirubin, Alb, urea nitrogen, creatinine, and lactic acid were significantly different between the two groups (*p*<0.05, Table I). The two groups of patients were comparable in terms of gender (male/female), history of diabetes, history of hypertension, continuous renal replacement therapy, hemoglobin, and fasting blood glucose (*p*>0.05).

Multivariate Logistic Regression Analysis

Nine variables in Table I were selected for multi-factor Logistic regression analysis (Table II). The results showed that age, APACHE II, SOFA score, CRP, total bilirubin, albumin, urea nitrogen, creatinine, and Lac were independent risk factors for death in septic patients (*p*<0.05). Stepwise regression was used for secondary screening, and a predictive model was established for meaningful variables.

Table I. Comparison of general clinical data of patients.

Index	Death group (n = 49)	Survival group (n = 151)	t/χ²	p
Age	68.79 ± 14.46	64.62 ± 13.34	1.862	0.046
Gender (Male/Female)	30/19	95/56	0.045	0.832
History of diabetes	10 (20.41)	35 (23.18)	0.163	0.687
History of hypertension	20 (40.82)	62 (41.06)	0.001	0.976
CRRT	15 (30.61)	32 (21.19)	1.826	0.177
Hemoglobin (g/L)	119.8 ± 32.2	115.3 ± 24.5	1.030	0.304
APACHE II (points)	23.18 ± 4.16	16.5 ± 4.3	9.523	0.000
SOFA (points)	8.24 ± 3.83	4.82 ± 2.14	7.848	0.000
CRP (mg/L)	159.03 ± 35.21	67.98 ± 13.56	25.406	0.000
PCT (ng/mL)	8.25 ± 2.05	4.46 ± 1.78	12.467	0.000
Total bilirubin (μmol/L)	34.7 ± 14.5	45.2 ± 18.4	-3.642	0.000
Alb (g/L)	29.22 ± 3.5	32.01 ± 4.23	-4.175	0.000
Urea nitrogen (mmol/L)	11.37 ± 5.3	7.15 ± 2.46	7.604	0.000
Creatinine (μmol/L)	178.65 ± 45.31	85.42 ± 27.48	17.337	0.000
Lac (mmol/L)	5.31 ± 1.25	2.07 ± 0.37	28.371	0.000
FBG (mmol/L)	9.69 ± 3.76	9.57 ± 3.76	0.194	0.846

CRRT-continuous renal replacement therapy, PCT - Serum procalcitonin, FBG - Fasting blood glucose, Lac - Lactic acid, Alb-Albumin, CRP - C-reactive protein, APACHE II - Acute Physiology and Chronic Health Scoring System Domain II, SOFA - Sequential Organ Failure Assessment.

Table II. Nomogram of mortality risk after admission to hospital with sepsis.

Index	β	SE	Wald	p	OR	95% CI
Age	0.044	0.036	1.49	0.008	0.957	1.297-2.926
APACHE II	0.135	0.084	2.58	0.012	1.144	1.001-1.105
SOFA	0.641	0.332	3.73	0.028	0.527	1.661-4.321
CRP	0.207	0.051	16.47	0.007	0.813	1.940-12.619
Total bilirubin	0.004	0.001	16.00	0.048	1.004	1.132-9.691
Alb	0.091	0.047	3.75	0.005	1.095	1.356-2.395
Urea nitrogen	0.473	0.275	2.96	0.002	1.605	1.143-1.913
Creatinine	0.04	0.025	2.56	0.001	0.961	0.847-0.974
Lac	0.167	0.095	3.09	0.048	1.052	1.326-2.926
Constant	2.094	1.276	2.69	0.025	0.057	-

APACHE II - Acute Physiology and Chronic Health Scoring System Domain II, SOFA - Sequential Organ Failure Assessment, Lac-Lactic acid, Alb-Albumin, CRP-C-reactive protein.

Construction of Prognostic Nomogram Prediction Model

Based on the results of multivariate Logistic regression analysis, a nomogram prediction model for the prognosis of septic patients was constructed (Figure 1). The relevant area under the curve (AUC) was obtained through the analysis of relevant continuous variables ROC analysis (Figure 2).

Calibration Curve and DCA Curve

the calibration curve of the nomogram model for predicting the prognosis of sepsis patients was then analyzed, and the result was very close to the ideal curve (Figure 3). We also used the DCA to evaluate the clinical effectiveness (Figure 4), and the modeling curves were all above the two extreme curves, which indicated good clinical value.

Discussion

Sepsis is a disease that progresses rapidly and has high mortality. Timely and accurate assessment of the patient's condition and finding
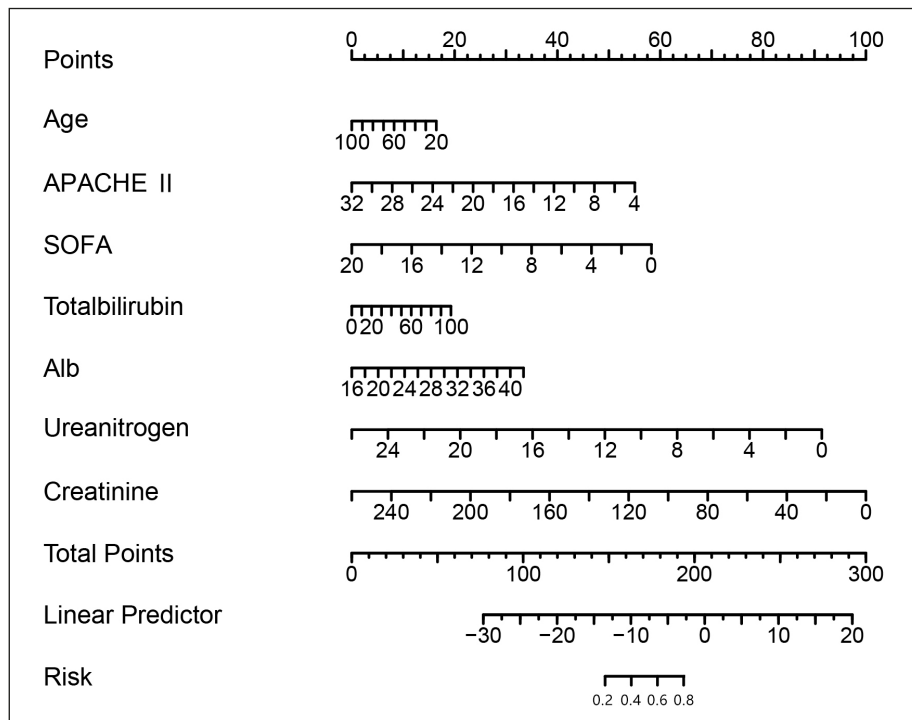
Figure 1. Nomogram of risk of death in patients with sepsis. APACHE II - Acute Physiology and Chronic Health Scoring System Domain II, SOFA - Sequential Organ Failure Assessment, Alb - Albumin.

prognostic indicators of critical illness will help improve the prognosis and reduce mortality[1]. Sepsis-3 strongly recommends the SOFA score as a clinical diagnostic criterion for sepsis. However, there is limited evidence of its prognostic value.

Although the diagnosis and treatment techniques of sepsis have improved significantly in recent years, the incidence and fatality rates remain high. Prediction studies[27] on the susceptibility factors and prognosis of sepsis show that
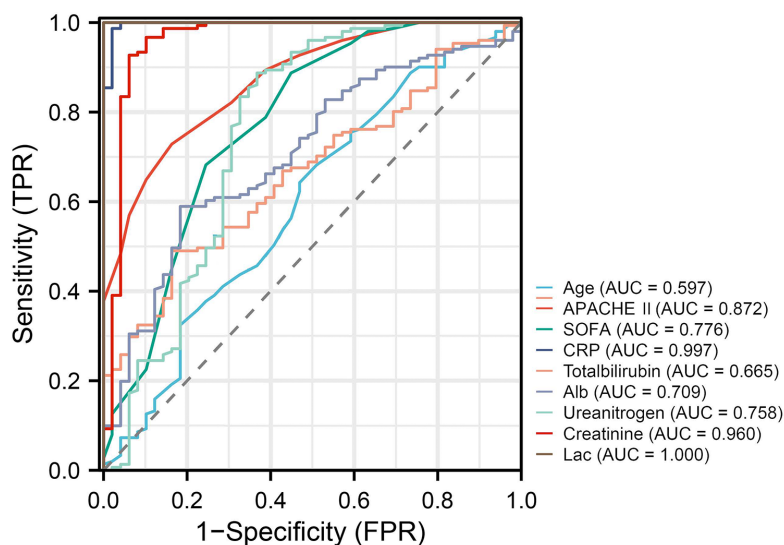

Figure 2. ROC curve of nomogram model for predicting prognosis. APACHE. II - Acute Physiology and Chronic Health Scoring System Domain II, SOFA - Sequential Organ Failure Assessment, Lac - Lactic acid, Alb - Albumin, CRP - C-reactive protein, AUC - Area Under Curve.
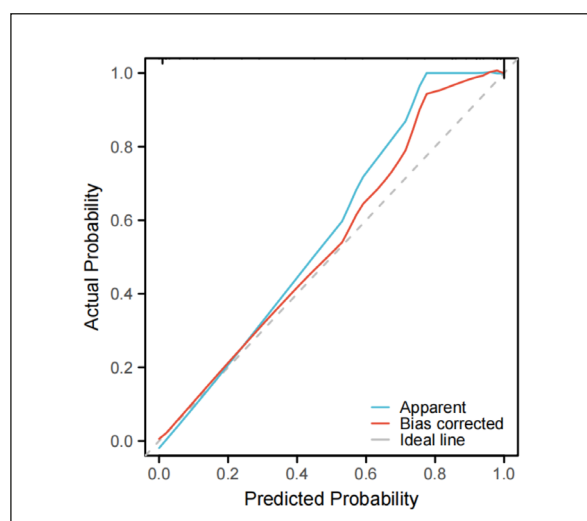
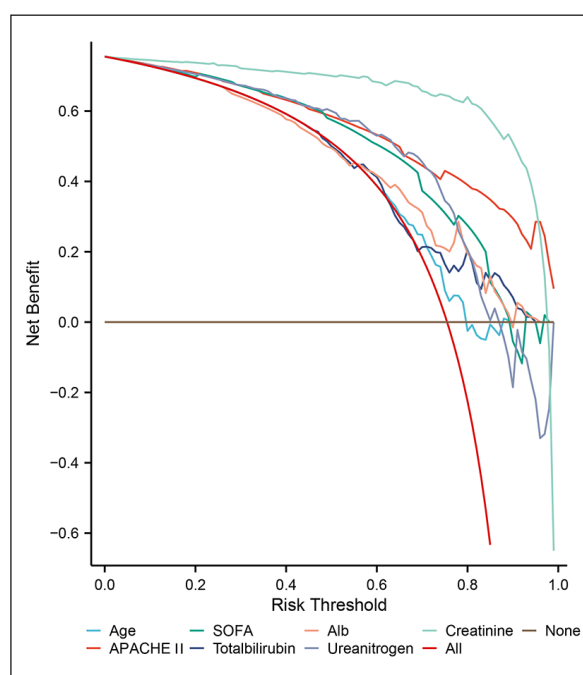**Figure 3.** Calibration curve of nomogram model

Figure 4. DCA curve of nomogram model. APACHE II - Acute Physiology and Chronic Health Scoring System Domain II, SOFA - Sequential Organ Failure Assessment, Alb-Albumin.

the mortality rate of sepsis increases significantly with age, from 10% in childhood to 40% in those over 85 years old.

The APACHE II score is often used clinically to evaluate the condition of sepsis and its clinical effects, while the SOFA score is used to judge organ function in septic patients. The two are used together to better evaluate the prognosis of patients.

Some scholars[28] have shown that age is an independent risk factor affecting the prognosis of sepsis; elderly patients are more likely to develop sepsis because their immune function is weakened, and they often have multiple chronic diseases. This study shows that age is an independent risk factor affecting the prognosis of sepsis, and its sensitivity and specificity as predictive indicators are both high. The reason may be that organ function declines physiologically with age, and combined diseases lead to further reductions in organ reserve function and compensatory capacity. Some minor pathogenic factors can cause organ failure, leading to aggravation of the disease and increased mortality.

C-reactive protein is an acute-phase reaction protein synthesized by the liver. As an acute-phase protein, it rises rapidly within hours after the onset of various acute inflammations, tissue injuries, myocardial infarction, surgical trauma, radiation damage, and other diseases. The increase is positively correlated with the degree of inflammatory response and the severity of the disease[29,30]. The elevated degree of CRP is related to the degree of infection and patient prog-

nosis, but its specificity is not strong and can be used for the exclusionary diagnosis of sepsis[31]. This study shows that CRP has high prognostic sensitivity for sepsis and can, therefore, be used as a valuable screening and efficacy follow-up indicator.

The APACHE II score has been widely used in critical illness assessment and has been proven[32] to have good clinical assessment effects on sepsis and other critically ill patients. Consistently with the results of this study, Mi et al[33] found that the APACHE II score was independently associated with prognosis in a study on the prognosis of septic patients in neuro-ICU.

Urea nitrogen and serum creatinine are indicators that reflect kidney function damage. Early renal decompensation in septic patients can cause internal environment disorders and affect the function of normal organs. Impaired organ function further aggravates the disorder of the body's internal environment, creating a progressive vicious cycle. Multiple organ dysfunction syndrome (MODS) can occur in severe sepsis and progressive deterioration of SIRS, and the mortality rate of sepsis is 30-50%, while the mortality rate of patients with septic shock and MODS can reach 50-100%[16].

This study included 200 septic patients. Multivariate Logistic regression analysis showed that age, APACHE II, SOFA score, CRP, total bilirubin, alb, urea nitrogen, creatinine, and Lac were independent risk factors for death in septic patients after admission. A study by Yang et al[34] confirmed that serum bilirubin levels are related to mortality in patients with severe sepsis. Another study[35] showed that elevated serum bilirubin levels within 72 h of admission are associated with increased mortality in septic patients. Bilirubin can impair the bactericidal properties of neutrophils, inhibit inducible nitric oxide synthase, and inhibit platelet activation and anti-platelet aggregation[36].

The results of this study show that total bilirubin is an independent risk factor affecting the prognosis of septic patients. The results of the study by Xiao et al[36] show that the sensitivity and specificity of bilirubin, creatinine levels, and quick SOFA score (qSOFA) in predicting the progression and prognosis of sepsis are higher. This study shows that creatinine is also an independent risk factor.

Albumin is synthesized in the liver and has various physiological functions, such as expanding blood volume, providing nutrition and transportation, etc. Some studies[10,38] have shown that serum albumin levels are associated with the prognosis of sepsis patients. Pathogenic microorganisms and the various toxins released by albumin can stimulate the immune system, release a large number of inflammatory mediators, damage the function of the vascular endothelial barrier, increase capillary permeability, and reduce the concentration of albumin[39]. The results of this study show that albumin is an independent risk factor affecting the prognosis of septic patients. Therefore, for septic patients with low albumin, albumin infusion, and effective circulating blood volume supplementation can be used to improve the prognosis.

Serum lactate is an important prognostic indicator reflecting decreased oxygen supply and tissue hypoperfusion[40]. A study[41] showed that when the blood lactate level exceeds 2.75 mmol/L, the risk of acute kidney injury (AKI) in septic patients increases by 1.772 times. When the blood lactate level exceeds 5.95 mmol/L, the risk of death in septic patients-related AKI increases by 1.511 times. The results of this study show that lactic acid is an independent risk factor affecting the prognosis of septic patients, suggesting that early detection of lactic acid levels in septic patients and timely intervention, when necessary, can reduce mortality in sepsis patients.

PCT is a protein composed of multiple amino acid residues and belongs to the propeptide protein of calcitonin. When the body is severely traumatized or infected, it will release a large number of inflammatory cytokines, including PCT, which in turn triggers systemic inflammatory response syndrome. Studies[41] have reported that the rise and fall of PCT levels in the early stages of sepsis are correlated with the severity of infection, and increased levels can reflect the severity and prognosis of sepsis to a certain extent. The current research results are enough to remind ICU physicians to pay attention to the research results and combine them with the clinical manifestations of the patients. Taking corresponding measures to check controllable risk factors, being alert to uncontrollable factors, and fully communicating with family members can improve the success rate of rescue of critically ill patients and reduce medical disputes.

In this study, a nomogram prediction model was established for the independent risk factors affecting the death of septic patients. The area under the ROC curve was 0.597-1.000, and the calibration curve tended to the ideal curve. The model had good discrimination and calibration and had high accuracy in evaluating septic patients. The modeling curves in the DCA curves were all above the two extreme curves, which indicated good clinical value.

Limitations

Some limitations can be detected in this study. First, the sample size was small. Second, this was a single-center retrospective study. Third, this study still lacks some relevant evidence about PCT. There are many factors affecting the prognosis of sepsis, which covers a wide range. Affected by sample size limitations, differences in the types of diseases admitted to the ICU, and confounding factors in sepsis patients, the results of sepsis risk factors are slightly different. Moreover, according to our inclusion criteria, some populations were excluded from our study. This may limit the generalization of our model in patients under 12 years old and emergency patients.

Conclusions

This study constructed a nomogram prediction model. It includes 9 clinical variables which can be used to predict mortality in sepsis patients. It helps clinicians to assess the severity of the pa-

tient's condition, adjust the treatment plan in time, and improve the prognosis. In future studies, we should expand the sample size with a multicenter study to conduct external validation of the model based on more data to further verify the robustness and performance of the nomogram.

Authors' Contributions
Yufang Hao conceived the structure of the manuscript. Shaohua Cui did the experiments and made the figures. Chaoyue Liang reviewed and edited the manuscript. All authors read and approved the final manuscript.

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None.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval
This study was approved by the Ethics Committee of Yulin Second Hospital. The approval number is No. 2023010.

Conflict of Interest
The authors declare that they have no competing interests.

Informed Consent
Not applicable, due to the retrospective nature of the study.

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