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Research article

Development and validation of a nomogram model for predicting 28-day mortality in patients with sepsis

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ABSTRACT

Background: This study aimed to develop and validate a nomogram model for predicting 28-day mortality in patients with sepsis in the intensive care unit (ICU).
Methods: We retrospectively analyzed data from 331 patients with sepsis admitted to the ICU as a training set and collected a validation set of 120 patients. Both groups were followed for 28 days. Logistic regression analyses were performed to identify the potential prognostic factors for sepsis-related 28-day mortality. A nomogram model was generated to predict 28-day mortality in patients with sepsis in the ICU. Receiver operating characteristic (ROC) curve analysis, calibration curves, and decision curve analysis (DCA) were used to evaluate the model's prediction performance and clinical application. In addition, we used ROC curve analysis and DCA to compare this model with the sequential organ failure assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores and further assessed the clinical value of our model.
Results: Logistic multivariate regression analysis revealed that mechanical ventilation, oxygenation index, and lactate and blood urea nitrogen (BUN) levels were independent predictors of 28-day mortality in patients with sepsis in the ICU. We developed a nomogram model based on these results to further predict 28-day mortality. The model demonstrated satisfactory calibration curves for both training and validation sets. Additionally, in the training set, the area under the ROC curve (AUC) for this model was 0.80. In the validation set, the AUC was 0.82. DCA showed that the high-risk thresholds ranged between 0 and 0.86 in the training set and between 0 and 0.75 in the validation set. We compared the ROC curve and DCA of this model with those of SOFA and APACHE II scores in both the training and validation sets. In the training set, the AUC of this model was significantly higher than those of the SOFA ($P = 0.032$) and APACHE II ($P = 0.004$) scores. Although the validation set showed a similar trend, the differences were not statistically significant for the SOFA ($P = 0.273$) and APACHE II ($P = 0.320$) scores. Additionally, the DCA showed comparable clinical utility in all three assessments.

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Conclusion: The present study used four common clinical variables, including mechanical ventilation, oxygenation index and lactate and BUN levels, to develop a nomogram model to predict 28-day mortality in patients with sepsis in the ICU. Our model demonstrated robust prediction performance and clinical application after validation and comparison.

1. Introduction

Sepsis is a severe condition involving systemic multiple organ dysfunction caused by a dysregulated host response to infection. It is one of the most common diseases encountered in the intensive care unit (ICU), resulting in high mortality and economic burden [1–3]. Worldwide, sepsis-related death rates continue to range between 15 % and 56 %, despite advancements in scientific research and therapeutic approaches. This vast difference originates from the lack of discrimination in the severity of sepsis, emphasizing the need for risk stratification and timely individualized interventions to improve outcomes in patients with sepsis [2,4]. Baseline characteristics and laboratory parameters are typically obtained for each patient with sepsis upon admission to the ICU. However, it is difficult for clinicians to accurately evaluate the prognosis of sepsis based on clinical data.

Recent studies have reported that the prognosis of sepsis is linked to age, inflammatory factors, lactate level, complications, and other factors [4–7]. However, accumulating evidence has shown that these prognostic factors are not satisfactory for predicting sepsis-related mortality [8–10]. Several clinical scoring systems have been widely used to predict sepsis-associated prognoses, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores [11–14]. Nevertheless, these prediction tools are complicated and time-consuming for physicians and do not provide an accurate probability of adverse outcomes.

To the best of our knowledge, the nomogram model has been widely applied to predict the diagnosis and prognosis of various diseases and can simplify statistical predictive models into a single numerical estimate of the probability of an event. Therefore, to find a strong clinically practical model for clinicians, we conducted this study to develop and validate a nomogram model and compare its performance with that of APACHE II and SOFA scores for predicting 28-day mortality in patients with sepsis in the ICU.

2. Materials and methods

2.1. Study population

We retrospectively collected data of 331 eligible patients with sepsis hospitalized at the Anhui Provincial Public Health Clinical Center between September 2020 and September 2023. These patients comprised the training set. For the validation cohort, we enrolled 120 patients hospitalized at Anhui Provincial Chest Hospital between September 2022 and September 2023. We divided each cohort into survivor and non-survivor groups based on the study design. The inclusion criteria were (1) age $\geq$18 years, (2) presence of sepsis (according to the definition criteria in Sepsis-3 [1]) caused by a respiratory infection, and (3) admission to the ICU after a diagnosis of sepsis. The exclusion criteria were (1) failure to complete the 28-day follow-up, (2) receiving glucocorticoid or immunosuppressant treatment, and (3) <24-h stay in the ICU. This study was approved by the Anhui Public Health Clinical Center Ethics Committee (approval number: PJ-YX2024-007) and the Anhui Chest Hospital Ethics Committee (approval number: KJ2030-40). The patients were treated and managed according to the international sepsis and septic shock guidelines [15]. The primary observational endpoint was 28-day mortality. Telephonic follow-ups and outpatient reviews were performed to assess the prognosis of patients discharged within 28 days.

2.2. Variable collection

Data for all patients were collected from the medical records of the hospital's computerized database. We collected data on demographic parameters, including age and sex; common comorbidities, including hypertension, diabetes mellitus, chronic lung disease, cardiac disease, cancer, chronic renal disease, and cerebrovascular disease; and intervention strategies, including mechanical ventilation and continuous renal replacement therapy (CRRT). Septic shock was also identified as a complication of sepsis and diagnosed according to the third international consensus definition [1]. In addition, the APACHE II and SOFA scores were calculated to assess disease severity within 24 h of ICU admission based on previously published methods [16,17]. The initial laboratory parameters at ICU admission were evaluated in our clinical laboratory, which included white blood cell (WBC) counts, hemoglobin levels, and platelet (PLT) counts; arterial blood gas analysis of the potential of hydrogen (pH), lactate levels, arterial carbon dioxide partial pressure ($PaCO_2$), and oxygenation index (the ratio of arterial oxygen partial pressure to inspired oxygen fraction); serum inflammatory factors C-reactive protein (CRP) and procalcitonin (PCT); and blood urea nitrogen (BUN), creatinine, uric acid, albumin, alanine aminotransferase (ALT), bilirubin, and glucose levels and the coagulation function of fibrinogen and D-dimer.

2.3. Statistical analysis

Empowerstats (www.empowerstats.cn) and R (http://www.R-project.org) were used for all statistical analyses. Continuous variables are reported as the mean $\pm$ standard deviation (SD) or the median with interquartile range (IQR) presented as the 25th to 75th

percentiles. Categorical variables are expressed as frequencies and percentages. Initially, the Kolmogorov-Smirnov test was employed to evaluate whether continuous variables were normally distributed. The Mann-Whitney *U* test was used to compare continuous variables with non-normally distributed data, and the Student's *t*-test was used to compare normally distributed variables. Chi-square and Fisher's exact tests were used for categorical variable analyses, as appropriate. Subsequently, univariate logistic regression analyses were performed using all variables to investigate possible risk factors for 28-day mortality. Considering the partial overlap of parameters in the SOFA and APACHE II scores with those assessed in our study and to ensure direct comparability with our model, we excluded these scores from the logistic regression analyses. All possible risk factors with P values < 0.05 in the univariate logistic regression analysis were included in the multivariate logistic regression analyses to explore the risk factors related to 28-day mortality. Finally, these risk factors were used to develop a regression model and transformed into a nomogram model. Calibration plots, receiver operating characteristic (ROC) curve analysis, and decision curve analysis (DCA) diagrams were used to assess the model. In addition, the predictive value of this model was further used to compare the SOFA and APACHE II scores according to ROC curve analysis and DCA. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient characteristics

Based on the inclusion and exclusion criteria, 331 patients with sepsis in the ICU were included in the training cohort and 120 in the validation cohort. Table 1 presents the baseline characteristics of the study participants. In the training cohort, 236 patients (71.3 %) were men and 95 (28.7 %) were women. In the validation cohort, 95 (79.2 %) were men and 25 (20.8 %) were women. The 28-day mortality rates were 29.6 % (98/331) and 23.3 % (28/120) in the training and validation cohorts, respectively. Patients with sepsis who died within 28 days after ICU admission were older and had a higher proportion of chronic renal disease, greater frequency of mechanical ventilation and CRRT, and higher APACHE II and SOFA scores than the survivors in the training cohort. In the validation cohort, the percentage of non-survivors requiring mechanical ventilation and experiencing septic shock was remarkably higher than that of the survivors. Additionally, non-survivors exhibited notably higher APACHE II and SOFA scores.

3.2. Laboratory parameters

Table 2 presents a comparison of laboratory parameters between the survivor and non-survivor groups in the training and validation cohorts. In both cohorts, no significant associations with prognosis were observed for WBC count or hemoglobin, $PaCO_2$, PCT, albumin, ALT, glucose, fibrinogen, and D-dimer levels between survivors and non-survivors However, the non-survivor group had higher lactate, CRP, BUN, creatinine, and bilirubin levels than the survivor group. In contrast, patients who died within 28 days had significantly lower pH and oxygenation index than those who survived beyond 28 days. Notably, uric acid levels and PLT counts significantly differed between the two groups in the training cohort, although there were no differences in the validation cohort.

Table 1
Baseline characteristics of patients with sepsis between the survivor and non-survivor groups in training and validation sets.

Parameters	Training set			Validation set		
	Survivors (n = 233)	Non-survivors (n = 98)	P -value	Survivors (n = 92)	Non-survivors (n = 28)	P -value
Age (years)	67.00 (53.00–76.00)	69.50 (58.00–80.00)	0.019*	72.00 (63.00–80.00)	71.50 (63.75–83.00)	0.592
Gender, n (%)	–	–	0.618			0.132
Male	168(72.10 %)	68(69.39 %)	–	70 (76.09 %)	25 (89.29 %)	
Female	65(27.90 %)	30(30.61 %)	–	22 (23.91 %)	3 (10.71 %)	
Comorbidities	–	–	–			
Hypertension, n (%)	76(32.62 %)	37 (37.76 %)	0.368	24 (26.09 %)	7 (25.00 %)	0.908
Diabetes Mellitus, n (%)	71(30.47 %)	28 (28.57 %)	0.730	20 (21.74 %)	4 (14.29 %)	0.388
Chronic lung disease, n (%)	22(9.44 %)	9 (9.18 %)	0.941	10 (10.87 %)	2 (7.14 %)	0.565
Cardiac disease, n (%)	32(13.73 %)	21 (21.43 %)	0.081	16 (17.39 %)	8 (28.57 %)	0.195
Cancer, n (%)	36(15.45 %)	23 (23.47 %)	0.082	28 (30.43 %)	12 (42.86 %)	0.222
Chronic renal disease, n (%)	21(9.01 %)	20 (20.41 %)	0.004*	19 (20.65 %)	6 (21.43 %)	0.929
Cerebrovascular disease, n (%)	64(27.47 %)	21 (21.43 %)	0.251	24 (26.09 %)	11 (39.29 %)	0.178
Mechanical ventilation, n (%)	154(66.09 %)	79 (80.61 %)	0.008*	60 (65.22 %)	25 (89.29 %)	0.014*
CRRT, n (%)	18(7.73 %)	20 (20.41 %)	<0.001*	10 (10.87 %)	3 (10.71 %)	0.982
Septic shock, n (%)	72(30.90 %)	41 (41.84 %)	0.055	15 (16.30 %)	12 (42.86 %)	0.003*
APACHE II score	23.00(17.00–28.00)	28.50 (23.25–35.75)	<0.001*	18.00 (16.00–22.00)	23.50 (19.75–30.50)	<0.001*
SOFA score	7.00(5.00–9.00)	10.00 (8.00–13.00)	<0.001*	5.00 (4.00–7.00)	8.00 (6.00–10.00)	<0.001*

Categorical data were presented as frequency (percentage), parametric continuous data were presented as mean ± (standard deviation), whereas non-parametric continuous data were presented as median (interquartile range). CRRT: Continuous renal replacement therapy; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; *P* values were calculated by chi-square test, Fisher exact test, Student's *t*-test, or Mann–Whitney *U* test, Student's *t*-test, Mann–Whitney *U* test, *$P < 0.05$ indicates statistical significance.

Table 2
Laboratory parameters of patients with sepsis between the survivor and non-survivor groups in training and validation sets.

Parameters	Training set			Validation set		
	Survivors (n = 233)	Non-survivors (n = 98)	*P*-value	Survivors (n = 92)	Non-survivors (n = 28)	*P*-value
WBC (109/L)	10.94 (7.04–15.10)	10.29 (6.76–13.63)	0.774	10.32 ± 4.77	11.13 ± 6.76	0.592
Hemoglobin (g/L)	110.30 ± 33.08	104.92 ± 34.03	0.182	102.08 ± 34.69	96.86 ± 31.96	0.479
PLT (109/L)	167.00 (117.00–233.00)	128.50 (62.00–193.25)	0.001*	173.00 (116.50–237.25)	162.50 (95.50–203.25)	0.338
pH	7.40 (7.33–7.47)	7.36 (7.26–7.44)	0.001*	7.40 (7.36–7.48)	7.35 (7.30–7.42)	0.003*
Lactate (mmol/L)	1.80 (1.20–2.90)	3.64 (1.92–7.75)	<0.001*	1.81 (1.37–2.57)	3.17 (2.58–4.84)	<0.001*
PaCO2 (mmHg)	34.30 (30.20–41.30)	34.65 (27.52–40.75)	0.440	38.00 (30.98–61.05)	43.15 (29.73–52.52)	0.435
Oxygenation index (mmHg)	203.50 (139.00–315.00)	133.50 (95.97–241.25)	<0.001*	147.15 (114.00–182.25)	117.50 (87.72–156.50)	0.009*
CRP (mg/L)	70.87 (10.00–169.30)	103.56 (20.55–211.76)	0.016*	85.76 (38.12–151.97)	172.31 (105.66–272.32)	<0.001*
PCT (ng/mL)	0.67 (0.10–4.47)	1.71 (0.30–12.81)	0.179	0.31 (0.13–1.77)	1.52 (0.43–6.88)	0.641
BUN (mmol/L)	8.20 (5.60–12.50)	12.42 (7.62–20.30)	<0.001*	8.55 (6.25–12.40)	12.50 (8.00–22.63)	0.002*
Creatinine (μmol/L)	76.40 (51.80–117.40)	120.80 (77.43–231.70)	0.003*	78.00 (51.25–102.15)	142.00 (93.08–214.95)	<0.001*
Uric acid (μmol/L)	261.00 (175.00–390.00)	344.50 (241.25–478.75)	<0.001*	334.80 ± 176.21	385.93 ± 119.14	0.154
Albumin (g/L)	30.90 (26.00–35.10)	29.05 (24.45–34.58)	0.313	29.70 (26.77–32.62)	27.75 (25.88–30.50)	0.096
ALT (U/L)	31.00 (20.00–51.00)	38.50 (23.50–66.75)	0.050	37.00 (21.75–70.25)	39.50 (20.00–71.25)	0.835
Bilirubin (mg/dL)	15.00 (9.80–22.60)	21.35 (13.03–35.90)	<0.001*	13.15 (9.00–18.20)	17.30 (12.68–24.27)	0.041*
Glucose (mmol/L)	8.10 (6.50–10.90)	9.20 (6.60–12.30)	0.192	8.13 (6.80–11.37)	9.43 (6.54–12.60)	0.424
Fibrinogen (g/L)	3.67 (2.60–5.17)	3.50 (2.33–4.84)	0.628	4.54 (3.02–5.73)	4.33 (3.15–6.36)	0.607
D-dimer (mg/L)	1.51 (0.68–3.36)	2.53 (0.96–4.74)	0.067	0.94 (0.34–1.81)	1.16 (0.67–1.98)	0.090

Categorical data were presented as frequency (percentage), parametric continuous data were presented as mean ± (standard deviation), whereas non-parametric continuous data were presented as median (interquartile ranges). WBC: white blood cell; PLT: platelet; pH: potential of hydrogen; PaCO2: partial pressure of arterial carbon dioxide; CRP: C-reactive protein; PCT: procalcitonin; BUN: blood urea nitrogen; ALT: alanine aminotransferase; *P* values were calculated by Student's *t*-test or Mann–Whitney *U* test, Student's *t*-test, Mann–Whitney *U* test, $^*P < 0.05$ indicates statistical significance.

Table 3
Risk factors for 28-day mortality in patients with sepsis by univariate and multivariate logistic regression analyses.

Variables	Univariable OR (95 % CI) *P* value	Multivariable OR (95 % CI) *P* value
Age (years)	1.02 (1.00, 1.04) 0.021*	1.02 (1.00, 1.04) 0.073
Gender, (Female)	1.14 (0.68, 1.91) 0.618	
Hypertension, n (yes vs. no)	1.25 (0.54, 1.53) 0.369	
Diabetes Mellitus, n (yes vs. no)	0.91 (0.54, 1.53) 0.730	
Chronic lung disease, n (yes vs. no)	0.97 (0.43, 2.19) 0.941	
Cardiac disease, n (yes vs. no)	1.71 (0.93, 3.15) 0.084	
Cancer, n (yes vs. no)	1.68 (0.93, 3.02) 0.084	
Chronic renal disease, (yes vs. no)	2.59 (1.33, 5.03) 0.005*	1.50 (0.58, 3.88) 0.402
Cerebrovascular disease, n (yes vs. no)	0.72 (0.41, 1.26) 0.252	
Mechanical ventilation (yes vs. no)	2.13 (1.21, 3.77) 0.009*	2.00 (1.03, 3.90) 0.042*
CRRT, (yes vs. no)	3.06 (1.54, 6.09) 0.001*	2.22 (0.81, 6.09) 0.123
Septic shock, (yes vs. no)	1.61 (0.99, 2.62) 0.056	
WBC (109/L)	0.999 (0.995, 1.004) 0.777	
Hemoglobin (g/L)	0.995 (0.988, 1.002) 0.182	
PLT (10^9/L)	0.996 (0.993, 0.999) 0.002*	0.999 (0.996, 1.001) 0.314
pH	0.04 (0.01, 0.29) 0.002*	2.32 (0.16, 33.52) 0.538
Lactate (mmol/L)	1.25 (1.16, 1.35) <0.001*	1.22 (1.11, 1.34) <0.001*
PaCO2 (mmHg)	0.99 (0.97, 1.01) 0.440	
Oxygenation index (mmHg)	0.996 (0.994, 0.998) <0.001*	0.996 (0.993, 0.998) 0.002*
CRP (mg/L)	1.003 (1.001, 1.005) 0.017*	1.000 (0.997, 1.004) 0.763
PCT (ng/mL)	1.01 (1.00, 1.02) 0.190	
BUN (mmol/L)	1.06 (1.03, 1.08) <0.001*	1.06 (1.01, 1.11) 0.021*
Creatinine (μmol/L)	1.002 (1.001, 1.003) 0.004*	0.999 (0.996, 1.002) 0.487
Uric acid (μmol/L)	1.003 (1.001, 1.004) <0.001*	1.000 (0.998, 1.002) 0.649
Albumin (g/L)	0.99 (0.97, 1.02) 0.459	
ALT (U/L)	1.002 (1.000, 1.004) 0.063	
Bilirubin (mg/dL)	1.02 (1.01, 1.03) 0.003*	1.01 (1.00, 1.02) 0.087
Glucose (mmol/L)	1.03 (0.98, 1.08) 0.195	
Fibrinogen (g/L)	0.97 (0.85, 1.10) 0.627	
D-dimer (mg/L)	1.03 (1.00, 1.07) 0.074	

CRRT: Continuous renal replacement therapy; WBC: white blood cell; PLT: platelet; pH: potential of hydrogen; PaCO2: partial pressure of arterial carbon dioxide; CRP: C-reactive protein; PCT: procalcitonin; BUN: blood urea nitrogen; ALT: alanine aminotransferase; HR: hazard ratio; CI: confidence interval; $^*P < 0.05$ indicates statistical significance.

3.3. Risk factors for 28-day mortality

As shown in Table 3, to investigate the possible risk factors for 28-day mortality in patients with sepsis in the ICU, univariate logistic regression analyses were performed using all variables except for the APACHE II and SOFA scores based on the training set data. Univariate logistic regression identified 13 potential prognostic factors ($P < 0.05$) in patients with sepsis, consistent with the differences in variables noted in the training set (Tables 1 and 2). The inclusion of these variables in the multiple regression analysis showed that mechanical ventilation, oxygenation index, lactate level, and BUN level were independent risk factors for 28-day mortality in patients with sepsis in the ICU.

3.4. Development of the nomogram model

Based on the results of the multivariate analysis, we constructed a nomogram model to predict 28-day mortality in patients with sepsis in the ICU (Fig. 1). This model assigns scores to each independent prognostic factor on a corresponding score scale. The total score was derived by summing the specific scores of all the variables. A vertical line was drawn from the total score row and aligned with the probability of the sepsis-related 28-day mortality.

3.5. Validation of the nomogram model

As shown in Fig. 2 A and B, a calibration curve was constructed by plotting the actual probability of sepsis-related 28-day mortality (y-axis) against the predicted occurrence rate (x-axis), demonstrating a favorable agreement between the predicted and observed probabilities in both the training and validation sets. As shown in Fig. 3 A and B and Table 4, this predictive model demonstrated a relatively satisfactory discriminatory ability. In the training set, the area under the ROC curve (AUC) was 0.80 (95 % confidence interval (CI): 0.74–0.84), with a specificity of 69 % and sensitivity of 80 %. In the validation set, the AUC was 0.82 (95 % CI: 0.72–0.92), with a specificity of 80 % and sensitivity of 82 %. In addition, as shown in Fig. 4A and B, to validate the clinical benefits of this model, we plotted the DCA with the net benefit rate as the ordinate and high-risk threshold as the abscissa, with a high-risk threshold between 0 and 0.86 in the training set and between 0 and 0.75 in the validation set.

3.6. Comparison of the nomogram model with SOFA and APACHE II scores

As shown in Fig. 3 and Table 4, to further investigate the effectiveness of the nomogram model in predicting sepsis-related 28-day mortality, we scrutinized the SOFA and APACHE II scores using ROC curves in the training set, with AUCs of 0.72 and 0.71, respectively. We compared the ROC curves of this model with those of the SOFA and APACHE II scores. The AUC of this model was significantly higher than those of the SOFA ($P = 0.032$) and APACHE II ($P = 0.004$) scores. In the validation set, the AUC of both models was 0.75, and our model showed a tendency for the AUC to be higher than those of the SOFA ($P = 0.273$) and APACHE II ($P = 0.320$) scores, although the difference was not statistically significant. Moreover, as shown in Fig. 4, the DCA for this model was juxtaposed with those for the SOFA and APACHE II scores in both the training and validation sets, highlighting comparable clinical applications among the three.

4. Discussion

Our study found that mechanical ventilation, oxygenation index, lactate level, and BUN level were independent predictors of 28-day mortality in patients with sepsis in the ICU, based on logistic regression analysis. Mechanical ventilation is a life-saving procedure. However, previous studies have shown that mechanical ventilation is strongly associated with a poor prognosis, and the main causes are diaphragmatic injury and atrophy due to mechanical ventilation [18]. A retrospective study by Lemay et al. concluded that

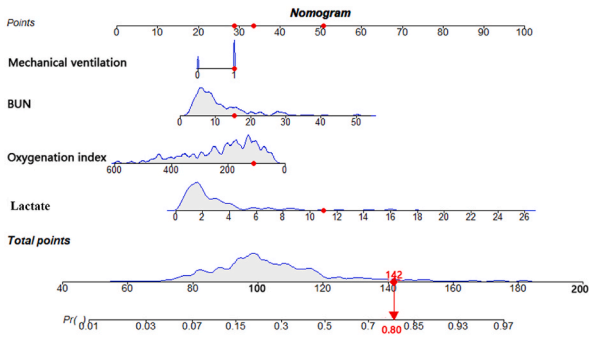

Fig. 1. The nomogram model predicting the probability of 28-day mortality in patients with sepsis in the ICU. When using it, drawing a vertical line to the point axis from each risk factor and scoring the corresponding points. After the points of each variable were added to obtain a total score, draw a vertical line again to the total point axis to correspond the probability of 28-day mortality. BUN: blood urea nitrogen.

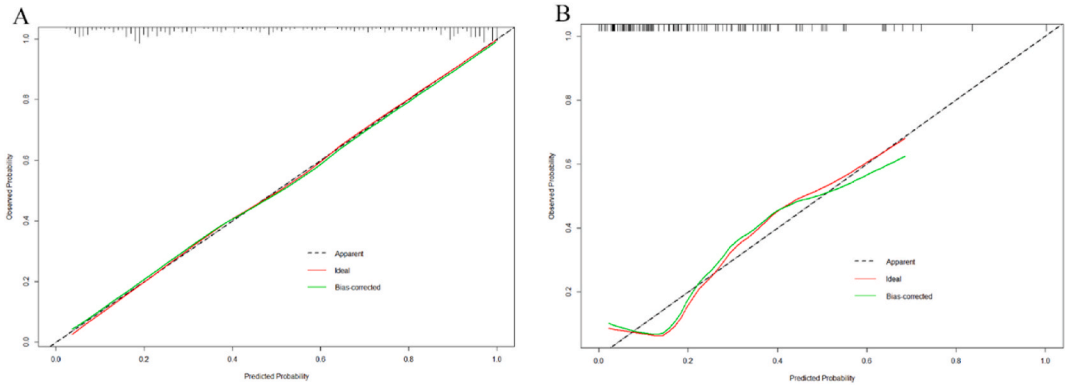

Fig. 2. Calibration curves of the nomogram model. A: Training set, B: Validation set. The calibration of this model in accordance with the agreement between predicted and observed probability of 28-day mortality in patients with sepsis.

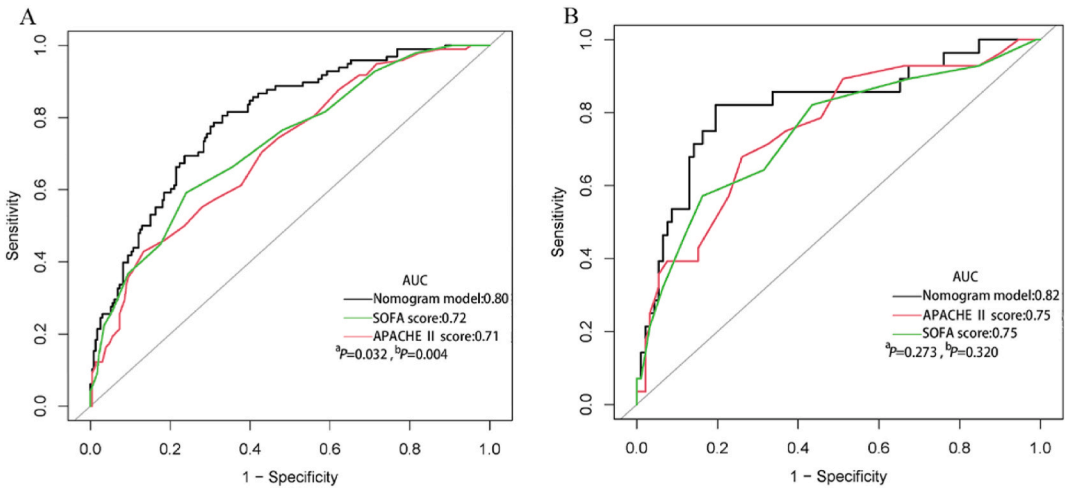

Fig. 3. The ROC curves of the nomogram model, APACHE II score, and SOFA score for the predictive value of 28-day mortality in patients with sepsis. A: Training set, B: Validation set. ROC: receiver operating characteristic; AUC: area under the ROC curve; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; [a]*P*: Nomogram model vs SOFA score; [b]*P*: Nomogram model vs APACHE II score.

Table 4
Predictive value of the nomogram model, APACHE II score, and SOFA score for 28-day mortality in patients with sepsis.

Predictive model	Variables	ROC area (AUC)	95 % CI	Best threshold	Specificity	Sensitivity	*P* value
Training set	Nomogram model	0.80	0.74 ~ 0.84	−1.11	0.69	0.80	
	SOFA score	0.72	0.66 ~ 0.78	9.50	0.76	0.59	[a]$P = 0.032$
	APACHE II score	0.71	0.65 ~ 0.77	30.50	0.86	0.42	[b]$P = 0.004$
Validation set	Nomogram model	0.82	0.72 ~ 0.92	−0.89	0.80	0.82	
	SOFA score	0.75	0.64 ~ 0.86	7.50	0.84	0.57	[a]$P = 0.273$
	APACHE II score	0.75	0.65 ~ 0.86	21.50	0.74	0.68	[b]$P = 0.320$

ROC: receiver operating characteristic; AUC: area under the ROC curve; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; CI: confidence interval; [a]*P*: Nomogram model vs SOFA score; [b]*P*: Nomogram model vs APACHE II score.

mechanical ventilation was closely associated with increased 90-day mortality in patients with sepsis [19], which is similar to our findings.

In our study, the oxygenation index was also an independent prognostic factor for patients with sepsis in the ICU. The oxygenation index is commonly used in clinical practice to assess the extent of lung injury [20], which is a major complication of sepsis [15]. Accumulating evidence has demonstrated that the activation of inflammatory cells and the release of large amounts of cytokines during sepsis create a cytokine storm that leads to lung injury [21,22]. An analysis based on the Medical Information Market for Intensive Care (MIMIC-III) database revealed that oxygenation index was independently associated with prognosis and was included in a predictive

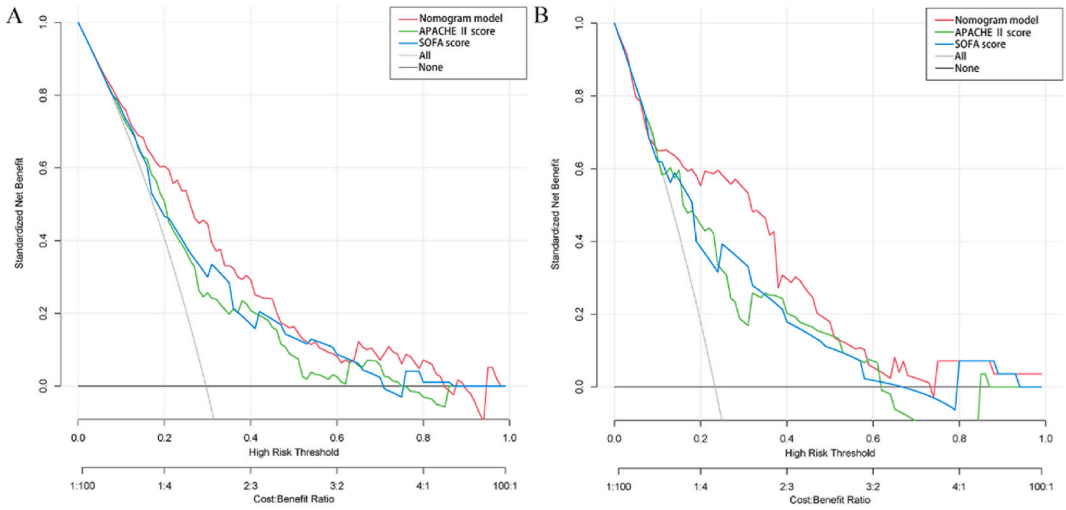

Fig. 4. The DCA curves of the nomogram model, APACHE II score, and SOFA score in patients with sepsis. A: Training set, B: Validation set. APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

model to assess the risk of in-hospital mortality in patients with sepsis in the ICU [12]. Furthermore, a single-center study by Lai et al. reported that the oxygenation index was negatively correlated with poor prognosis in patients with sepsis and therefore used to develop a new scoring system for predicting 28-day mortality that was comparable to SOFA and APACHE II scores [23].

Our study provides evidence that high baseline lactate and BUN levels are significantly associated with an increased 28-day mortality in patients with sepsis in the ICU. Blood lactate, a common clinical indicator of sepsis, is believed to be caused by insufficient tissue perfusion in patients with sepsis [24]. Many retrospective studies have demonstrated that high lactate levels are a well-established factor closely related to higher mortality in patients with sepsis [4,25]. BUN is derived from protein metabolites and is mainly cleared by the kidneys. BUN levels significantly increase in response to markedly increased protein metabolism and acute kidney injury in patients with sepsis [26]. Currently, few studies have used BUN alone as an indicator of prognosis in patients with sepsis. BUN has been combined with an increasing number of additional clinical markers to evaluate the prognosis of patients with sepsis [27,28]. This also demonstrates the significance of urea nitrogen in determining the prognosis of patients with sepsis.

Our study revealed that the use of mechanical ventilation, low baseline oxygenation index levels, and high baseline levels of lactate and BUN can independently increase 28-day mortality in patients with sepsis in the ICU. Our research has shown that the poor prognosis of sepsis can be attributed to a variety of factors. Previous studies have reported a variety of scoring systems for the prognostic assessment of sepsis involving multiple factors, such as the APACHE II and SOFA scores, which are common scoring systems for critically ill patients with sepsis [29,30]. However, it is important to note that APACHE II and SOFA scores do not consistently exhibit optimal performance in predicting sepsis-related mortality [31]. Further investigations are necessary to identify new methods for improving our ability to predict 28-day mortality in patients with sepsis in the ICU.

Recently, the nomogram model has been widely used as a novel prediction model in the survival analysis of patients with various diseases [32,33]. The nomogram model can assist clinicians in thoroughly assessing true mortality based on risk factors and objectively estimating the gain and loss of medical intervention in patients with sepsis. Additionally, it is crucial to improve the ability of medical professionals, patients, and their family members to carefully assess the effects of further treatment measures, support them in making wise medical decisions, and avoid medical disagreements [32]. In our study, four independent risk factors based on the results of the multivariate analysis, including mechanical ventilation, oxygenation index, and lactate and BUN levels, were integrated to generate a nomogram model. To the best of our knowledge, the four factors in our model are routinely and conveniently monitored in the ICU for patients with sepsis, and results can be obtained quickly. Our nomogram model demonstrated a strong predictive performance and visual prediction rates for sepsis-related 28-day mortality, as evidenced by satisfactory calibration curves and relatively high AUC values in both the training and validation sets. In addition, the model has broad clinical applicability in predicting sepsis-associated 28-day mortality, as evidenced by the DCA in both cohorts. In both the training and validation sets, the nomogram model showed higher AUC values than those of the SOFA and APACHE II scores based on the ROC curve and was superior to them in terms of sensitivity, thus further validating the model's good predictive performance for 28-day mortality in patients with sepsis. The DCA of this model demonstrated extensive clinical application for predicting sepsis-related 28-day mortality in patients in the ICU, comparable to the SOFA and APACHE II scores. Furthermore, this model has fewer items and is more convenient for medical staff.

This study had several limitations. First, this was a retrospective analysis with a limited sample size, which may constrain the generalizability of our results. Large-sample multicenter studies are necessary to validate the feasibility and applicability of this nomogram model. Second, the absence of correction for multiple testing implies that the results of the subgroup comparisons should be regarded as preliminary. Last, the follow-up time of our study was too short. Long-term follow-up results should be obtained to evaluate the predictive performance of our model for 28-day mortality in patients with sepsis in the ICU.

5. Conclusion

The present study used four common clinical variables, including mechanical ventilation, oxygenation index, lactate level, and BUN level, to develop a nomogram model to predict 28-day mortality in patients with sepsis in the ICU. In both the training and validation cohorts, our model demonstrated a strong predictive performance and clinical utility comparable to the SOFA and APACHE II scores based on the ROC curve and DCA. Therefore, our model may be more practical and convenient for clinicians to predict the prognosis and develop therapeutic strategies for patients with sepsis in the ICU.

Ethics statement

The participants provided written informed consent following approval from the Anhui Public Health Clinical Center Committee (approval number: PJ-YX2024-007) and the Anhui Chest Hospital Ethics Committee (approval number: KJ2030-40).

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Data availability

The original data supporting the results of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Xiaoqian Wang: Writing – original draft, Conceptualization. **Shuai Li:** Writing – original draft, Methodology, Data curation, Conceptualization. **Quanxia Cao:** Methodology, Data curation. **Jingjing Chang:** Methodology, Data curation. **Jingjing Pan:** Data curation. **Qingtong Wang:** Methodology, Data curation. **Nan Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Nan Wang reports financial support was provided by the Research Fund of the Anhui Institute of Translational Medicine (2022zhyx-C66) and Anhui Medical University Clinical and Pre-discipline Co-Construction Project. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M. Singer, C.S. Deutschman, C.W. Seymour, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801–810.
[2] M. Cecconi, L. Evans, M. Levy, et al., Sepsis and septic shock, Lancet 392 (10141) (2018) 75–87.
[3] C.F. Bi, J. Liu, L.S. Yang, et al., Research progress on the mechanism of sepsis induced myocardial injury, J. Inflamm. Res. 15 (2022) 4275–4290.
[4] S. Li, Y. Shen, B. Chang, et al., Prognostic value of albumin-to-fibrinogen ratio for 28-day mortality among patients with sepsis from various infection sites, Mediat. Inflamm. 2022 (2022) 3578528.
[5] C. Rhee, T.M. Jones, Y. Hamad, et al., Prevalence, underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals, JAMA Netw. Open 2 (2) (2019) e187571.
[6] E.H.A. Michels, J.M. Butler, T.D.Y. Reijnders, et al., Association between age and the host response in critically ill patients with sepsis, Crit. Care 26 (1) (2022) 385.
[7] P. Liang, F. Yu, Value of CRP, PCT, and NLR in prediction of severity and prognosis of patients with bloodstream infections and sepsis, Front Surg 9 (2022) 857218.
[8] J. Silvestre, P. Povoa, L. Coelho, et al., Is C-reactive protein a good prognostic marker in septic patients? Intensive Care Med. 35 (5) (2009) 909–913.
[9] N. Makkar, M. Soneja, U. Arora, et al., Prognostic utility of biomarker levels and clinical severity scoring in sepsis: a comparative study, J. Invest. Med. 70 (6) (2022) 1399–1405.
[10] A.R. Godinez-Vidal, A. Correa-Montoya, D. Enriquez-Santos, et al., Is albumin a predictor of severity and mortality in patients with abdominal sepsis? Cir. Cir. 87 (5) (2019) 485–489.
[11] J. Chen, X. Shi, M. Diao, et al., A retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features and adverse outcomes, BMC Emerg. Med. 20 (1) (2020) 77.
[12] Y. Ren, L. Zhang, F. Xu, et al., Risk factor analysis and nomogram for predicting in-hospital mortality in ICU patients with sepsis and lung infection, BMC Pulm. Med. 22 (1) (2022) 17.
[13] Z. Qu, Y. Zhu, M. Wang, et al., Prognosis and risk factors of sepsis patients in Chinese ICUs: a retrospective analysis of a cohort database, Shock 56 (6) (2021) 921–926.

[14] H. Liu, L. Zhang, F. Xu, et al., Establishment of a prognostic model for patients with sepsis based on SOFA: a retrospective cohort study, J. Int. Med. Res. 49 (9) (2021) 3000605211044892.
[15] L. Evans, A. Rhodes, W. Alhazzani, et al., Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021, Intensive Care Med. 47 (11) (2021) 1181–1247.
[16] W.A. Knaus, E.A. Draper, D.P. Wagner, et al., Apache II: a severity of disease classification system, Crit. Care Med. 13 (10) (1985) 818–829.
[17] J.L. Vincent, R. Moreno, J. Takala, et al., The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine, Intensive Care Med. 22 (7) (1996) 707–710.
[18] E.C. Goligher, M. Dres, E. Fan, et al., Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes, Am. J. Respir. Crit. Care Med. 197 (2) (2018) 204–213.
[19] A.C. Lemay, A. Anzueto, M.I. Restrepo, et al., Predictors of long-term mortality after severe sepsis in the elderly, Am. J. Med. Sci. 347 (4) (2014) 282–288.
[20] A.D.T. Force, V.M. Ranieri, G.D. Rubenfeld, et al., Acute respiratory distress syndrome: the Berlin Definition, JAMA 307 (23) (2012) 2526–2533.
[21] J.A. Englert, C. Bobba, R.M. Baron, Integrating molecular pathogenesis and clinical translation in sepsis-induced acute respiratory distress syndrome, JCI Insight 4 (2) (2019).
[22] F. Zhang, F. Guo, Y. Zhang, et al., Huashibaidu formula attenuates sepsis-induced acute lung injury via suppressing cytokine storm: implications for treatment of COVID-19, Phytomedicine 109 (2023) 154549.
[23] Q. Lai, Y. Xia, W. Yang, et al., Development and validation of a rapid and efficient prognostic scoring system for sepsis based on oxygenation index, lactate and glasgow coma scale, J. Inflamm. Res. 16 (2023) 2955–2966.
[24] G. Wardi, J. Brice, M. Correia, et al., Demystifying lactate in the emergency department, Ann. Emerg. Med. 75 (2) (2020) 287–298.
[25] Y. Xie, D. Zhuang, H. Chen, et al., 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. 42 (1) (2023) 77–85.
[26] X. Li, R. Zheng, T. Zhang, et al., Association between blood urea nitrogen and 30-day mortality in patients with sepsis: a retrospective analysis, Ann. Palliat. Med. 10 (11) (2021) 11653–11663.
[27] T. Han, T. Cheng, Y. Liao, et al., Analysis of the value of the blood urea nitrogen to albumin ratio as a predictor of mortality in patients with sepsis, J. Inflamm. Res. 15 (2022) 1227–1235.
[28] J. Weng, R. Hou, X. Zhou, et al., Development and validation of a score to predict mortality in ICU patients with sepsis: a multicenter retrospective study, J. Transl. Med. 19 (1) (2021) 322.
[29] B. Khwannimit, R. Bhurayanontachai, V. Vattanavanit, Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country, J. Crit. Care 44 (2018) 156–160.
[30] G. Richards, H. Levy, P.F. Laterre, et al., CURB-65, PSI, and Apache II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS, J. Intensive Care Med. 26 (1) (2011) 34–40.
[31] S.H. Chen, Y.C. Wang, A. Chao, et al., Early prediction of survival at different time intervals in sepsis patients: a visualized prediction model with nomogram and observation study, Tzu Chi Med. J. 34 (1) (2022) 55–61.
[32] Y. Yang, S. Liang, J. Geng, et al., Development of a nomogram to predict 30-day mortality of patients with sepsis-associated encephalopathy: a retrospective cohort study, J Intensive Care 8 (2020) 45.
[33] J. Wu, H. Zhang, L. Li, et al., A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: a population-based analysis, Cancer Commun. 40 (7) (2020) 301–312.