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ORIGINAL RESEARCH

Early Prediction of Septic Shock in Severe COVID-19 Patients: Development and Validation of a Nomogram Model

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Purpose: Septic shock is a severe complication in critically ill patients with COVID-19, often associated with poor prognosis. Predictive factors for septic shock remain undetermined. Our objective was to develop an early predictive model for septic shock in severe COVID-19 patients to assist emergency and critical care physicians in resource allocation and medical decision-making.

Patients and Methods: The training cohort was sourced from the cases admitted to Northern Jiangsu People's Hospital between December 2022 and February 2023, while the validation cohort was retrieved from the MIMIC-IV dataset. The Least Absolute Shrinkage and Selection Operator (LASSO) analysis was used to screen for predictors. A multivariate logistic regression was employed to build the predictive model, which was then represented as a nomogram. The performance of the nomogram was evaluated using the Receiver Operating Characteristic (ROC) curve, calibration plot, and Decision Curve Analysis (DCA). External validation was conducted by assessing the model's performance in the validation cohort.

Results: A collective of 274 patients and 75 patients were respectively enrolled as the training cohort and the validation cohort in this study. The predictors included in the nomogram were albumin, mean arterial pressure, lactate, and the Sequential Organ Failure Assessment (SOFA) score. The area under the ROC curve (AUC) for the modeling set was 0.800 (95% CI 0.741–0.858), and for the validation set, it was 0.775 (95% CI 0.651–0.899). Additionally, the calibration curve indicated a correlation between predicted and observed outcomes, and DCA highlighted the clinical utility of the nomogram.

Conclusion: We developed and validated a diagnostic nomogram model for septic shock in critically ill COVID-19 patients, incorporating four parameters: SOFA score, albumin, mean arterial pressure, and lactate. This model demonstrates significant potential in predicting septic shock among critically ill COVID-19 patients.

Keywords: severe COVID-19, septic shock, nomogram, predictive model

Introduction

Coronavirus Disease 2019 (COVID-19) was first identified in late 2019. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and can lead to severe manifestations such as acute respiratory distress syndrome.[1]

SARS-CoV-2 infection shows highly heterogeneous clinical phenotypes, ranging from asymptomatic infection to fatal respiratory failure, with considerable variation in severity.[2–4] A substantial proportion of COVID-19 patients progresses to critical illness. These patients need to be admitted to the intensive care unit (ICU) for treatment.[5,6] Among the various complications of COVID-19, sepsis is the most common and is directly associated with high mortality in severe cases.[7] Studies have shown that the in-hospital mortality rate for sepsis patients with COVID-19 is 59%, significantly higher than the 29% for non-COVID sepsis patients.[8] A prospective study in Berlin, Germany, analyzing clinical and autopsy

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data from 26 deceased severe COVID-19 patients, confirmed that septic shock and multiple organ failure were the primary direct causes of death.[9]

Diagnostic scoring systems facilitate clinical decision-making. Examples of common scoring systems used for the clinical management of patients with pneumonia and sepsis include the Quick Sequential Organ Failure Assessment (qSOFA) score and the Systemic Inflammatory Response Syndrome (SIRS) criteria, which are applied to evaluate disease severity.[10] However, relevant studies have demonstrated that in critically ill COVID-19 patients, SIRS or qSOFA performs poorly in predicting in-hospital mortality, early bacterial infection, or intensive care unit (ICU) admission.[11] Similarly, in specific populations with other diseases such as geriatric trauma, traditional scoring systems including the Injury Severity Score (ISS) and Trauma and Injury Severity Score (TRISS) also have limitations such as insufficient predictive accuracy and high misclassification rates, as they fail to fully consider the unique pathophysiological characteristics of the disease.[12,13] In contrast, nomogram models constructed by screening specific risk factors for these particular populations have demonstrated significantly superior predictive performance compared to traditional scoring systems.[14]

This study aims to identify risk factors for septic shock in severe COVID-19 patients using clinical data and develop a clinically applicable nomogram to assist clinicians in formulating individualized intervention strategies.

Materials and Methods

Data Sources and Study Population

The modeling cohort came from a retrospective study at the Northern Jiangsu People's Hospital from December 2022 to February 2023. The dataset for external validation came from the Medical Information Mart for Intensive Care IV version 3.1, abbreviated as the MIMIC-IV database (https://mimic.mit.edu/). This dataset includes information on 94,458 critically ill patients. These patients were admitted to the Beth Israel Deaconess Medical Center in Boston between 2008 and 2022.[15] From this dataset, we extracted patients diagnosed with COVID-19 during hospitalization between 2020 and 2022, with sequence numbers ranging from 1 to 5, and the diagnostic criteria were based on the International Classification of Diseases (ICD) with code = "U071".

The inclusion criteria for this study were as follows: (1) Positive polymerase chain reaction (PCR) test from nasopharyngeal swab or bronchoalveolar lavage fluid for COVID-19; (2) Diagnosis of severe COVID-19 according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection" (Trial Version 10):[16] 1) Dyspnea with respiratory rate ≥30 breaths/min; 2) Oxygen saturation ≤93% at rest while breathing ambient air; 3) Arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg; 4) Progressive worsening of clinical symptoms, with lung imaging showing significant progression (>50%) of lesions within 24–48 hours. (3) Diagnosis of septic shock based on the Sepsis-3.0 definition and criteria: 1) Suspected or confirmed infection, with the Sequential Organ Failure Assessment (SOFA) score ≥2; 2) Sepsis combined with circulatory failure, serum lactate level >2 mmol/L; 3) Requirement for vasopressors to maintain mean arterial pressure ≥65 mmHg.[17] Patients were excluded if they met any of the following criteria: (1) End-stage chronic disease; (2) Incomplete clinical data. The patient selection flowchart is shown in Figure 1.

Data Collection and Preprocessing

The modeling data were collected from electronic medical records, while the validation data were retrieved from the MIMIC-IV dataset using Structured Query Language (SQL), including demographic features (sex, age), medical history, and admission vital signs such as respiratory rate (RR), heart rate (HR), and mean arterial pressure (MAP). Moreover, the admission SOFA score and medication use were also recorded. Laboratory indicators for analysis included blood - related indicators (hemoglobin, white blood cell count, platelets, neutrophils, lymphocytes), liver - related indicators (albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase), kidney - related indicators (blood urea nitrogen, creatinine), electrolyte indicators (serum sodium, serum potassium, serum calcium), coagulation indicators (prothrombin time, activated partial thromboplastin time, international normalized ratio), and arterial blood gas analysis, which included pH and lactate. For missing data in the training cohort, multiple imputation was adopted for processing. For

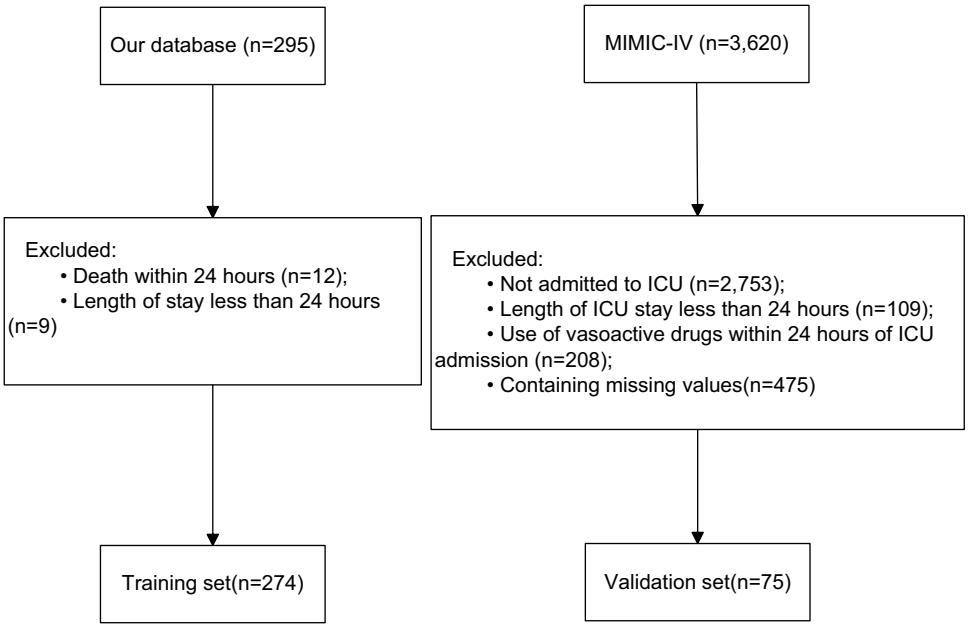

Figure 1 The flowchart of patients' selection.

the external validation cohort, the strategy of directly excluding samples with missing values was implemented. The exact missing rates of specific variables across all cohorts are provided in Supplementary Table 1.

Statistical Analysis

Continuous variables following a normal distribution were expressed as means accompanied by their standard deviations (SD), while non-normally distributed variables were reported as medians with interquartile ranges (IQR). For comparative analyses between groups, parametric data were assessed using Student's *t*-test, whereas non-parametric data were examined through the Wilcoxon rank-sum test. Categorical variables were analyzed using either the Chi-square test or Fisher's exact test, as appropriate. The analytical approach consisted of three sequential phases. Initially, all candidate variables were incorporated into the modeling cohort, and significant predictors associated with septic shock were screened out by the Least Absolute Shrinkage and Selection Operator (LASSO) regression combined with 10-fold cross-validation, where the λ value was set to the minimum (min). Subsequently, these selected variables were incorporated into a multivariate logistic regression framework to construct the predictive model. This model was then translated into a scoring system and graphically represented through a nomogram. Model performance was rigorously evaluated using multiple approaches. Discriminative capacity was quantified by calculating the area under the ROC curve (AUC), with values exceeding 0.75 deemed clinically meaningful. Calibration curves were generated to assess predictive accuracy, while decision curve analysis (DCA) provided insights into clinical utility. External validation was performed using an independent dataset. All statistical computations were conducted using R (version 4.4.3) and SPSS (version 27.0) software packages. A two-tailed significance threshold of $p<0.05$ was applied throughout the analysis to denote statistical significance.

Results

Baseline Characteristics and Outcomes

In the modeling cohort, among 295 severe COVID-19 patients who met the inclusion criteria, 12 were excluded because they died within 24 hours of admission, and 9 were excluded for discontinuing treatment after admission. Ultimately, the training cohort included 274 patients: 205 in the non-septic shock group and 69 in the septic shock group, with a septic shock incidence of 25.1%. The participants had a median age of 82 (IQR 73–88), and 65% of them were male. Significant differences ($P < 0.05$) were found between the two groups in MAP, white blood cells, platelets, neutrophils,

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Table 1 Baseline Characteristics of Training Cohort

	All (N=274)	Non-Septic Shock (N=205)	Septic Shock (N=69)	p
Gender, n (%)				0.051
Male	178 (65.0%)	126 (61.5%)	52 (75.4%)	
Female	96 (35.0%)	79 (38.5%)	17 (24.6%)	
AGE (years)	82.0 [73.0;88.0]	80.0 [72.0;88.0]	85.0 [76.0;88.0]	0.047
Vital signs				
Temperature (°C)	36.7 [36.5;37.4]	36.7 [36.5;37.5]	36.7 [36.5;37.0]	0.718
Heart rate (/min)	92.0 [80.2;106]	92.0 [80.0;104]	90.0 [82.0;109]	0.905
Respiratory rate (/min)	20.0 [18.0;24.8]	20.0 [18.0;24.0]	20.0 [18.0;26.0]	0.069
MAP (mmHg)	90.0 [83.0;100]	93.0 [86.0;103]	85.0 [78.0;91.0]	<0.001
SOFA	3.00 [2.00;5.00]	3.00 [2.00;4.00]	5.00 [3.00;6.00]	<0.001
Comorbidities, n (%)				
Hypertension	155 (56.6%)	114 (55.6%)	41 (59.4%)	0.68
Diabetes	91 (33.2%)	68 (33.2%)	23 (33.3%)	1
COPD	43 (15.7%)	36 (17.6%)	7 (10.1%)	0.203
Malignant tumor	34 (12.4%)	22 (10.7%)	12 (17.4%)	0.215
Coronary atherosclerosis	36 (13.1%)	25 (12.2%)	11 (15.9%)	0.555
Renal disease	19 (6.93%)	13 (6.34%)	6 (8.70%)	0.584
STROKE	32 (11.7%)	22 (10.7%)	10 (14.5%)	0.532
Laboratory data				
Hemoglobin (g/L)	121 [107;140]	121 [108;138]	119 [100;144]	0.54
White blood cell (*10^9)	7.82 [5.70;11.2]	7.57 [5.60;10.4]	9.59 [6.20;13.8]	0.021
Platelet (*10^9)	168 [118;237]	171 [122;252]	143 [108;203]	0.017
Neutrophil (*10^9)	5.86 [4.41;9.10]	5.65 [4.24;8.58]	6.90 [4.66;11.3]	0.025
Lymphocyte (*10^9)	0.66 [0.41;0.98]	0.70 [0.47;1.06]	0.44 [0.28;0.79]	<0.001
Albumin (g/dL)	32.5 [28.9;35.8]	33.5 [29.5;36.1]	30.0 [26.7;34.4]	<0.001
Total bilirubin (mg/dL)	12.6 [7.53;19.3]	12.0 [7.40;18.0]	13.8 [8.30;22.0]	0.125
Alanine aminotransferase (U/L)	23.0 [17.0;33.0]	22.0 [17.0;31.0]	25.0 [16.0;34.0]	0.229
Aspartate aminotransferase (U/L)	36.0 [26.0;53.0]	35.0 [26.0;49.0]	49.0 [28.0;65.0]	0.009
Blood urea nitrogen (mmol/L)	8.75 [6.27;13.4]	8.07 [6.05;11.6]	12.1 [7.47;19.6]	0.001
Creatinine (mg/dL)	92.3 [65.7;128]	87.0 [65.2;121]	113 [69.5;186]	0.008
Potassium (mmol/L)	3.99 [3.52;4.45]	3.98 [3.53;4.40]	4.13 [3.52;4.78]	0.146
Sodium (mmol/L)	135 [131;138]	134 [131;138]	136 [131;140]	0.011
Calcium (mmol/L)	2.08 [1.96;2.23]	2.09 [1.97;2.25]	2.02 [1.92;2.18]	0.026
Prothrombin time (seconds)	13.3 [12.5;14.2]	13.2 [12.4;14.0]	13.8 [13.1;15.2]	0.001
Activated partial thromboplastin time (seconds)	32.2 [29.2;34.7]	31.8 [29.1;34.4]	32.5 [29.7;35.9]	0.122
International normalized ratio (seconds)	1.17 [1.09;1.24]	1.15 [1.08;1.23]	1.22 [1.13;1.34]	0.001
Arterial pH	7.43 [7.37;7.47]	7.43 [7.38;7.47]	7.42 [7.37;7.46]	0.251
Lactic acid (mmol/L)	1.90 [1.40;2.70]	1.80 [1.35;2.50]	2.30 [1.80;3.50]	<0.001
Intervention, n (%)				
Antivirus drug use	106 (38.7%)	74 (36.1%)	32 (46.4%)	0.17
Glucocorticoid use	120 (43.8%)	85 (41.5%)	35 (50.7%)	0.23

lymphocytes, albumin, aspartate aminotransferase, blood urea nitrogen (BUN), creatinine, serum sodium, serum calcium, and SOFA score. As shown in Table 1, in addition, other baseline clinicopathological data were comparable between the two groups. A total of 75 patients were enrolled in the validation cohort, and their baseline characteristics are presented in Supplementary Table 2.

Predictors of Septic Shock

Variables were standardized and normalized through 10 - fold cross - validation (Figure 2A and B). First, LASSO regression was used to preliminarily screen predictors of septic shock. The selected predictors were BUN, albumin, mean arterial pressure (MAP), lactate, and SOFA score. Subsequently, a multivariate logistic regression analysis was conducted on these five variables, leading to the development of a multi-factor risk model through the stepwise backward method (Table 2). Factors with $P < 0.05$ were selected as the final predictors, including albumin (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.86–0.98), lactate (OR 1.22, 95% CI 1.05–1.42), MAP (OR 0.95, 95% CI 0.93–0.98), and SOFA score (OR 1.29, 95% CI 1.09–1.53).

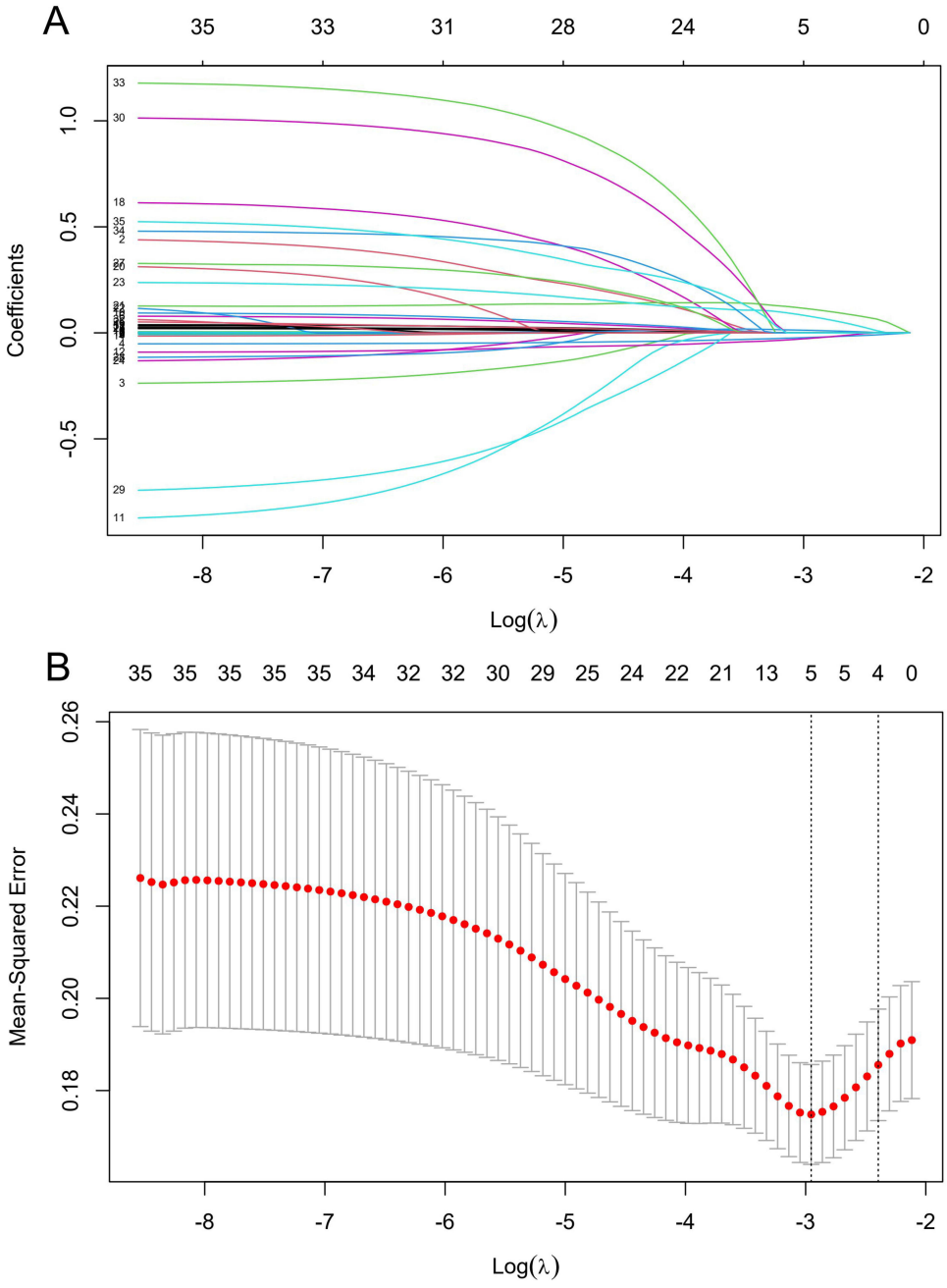

Figure 2 Identification of the risk factors of Septic Shock by LASSO regression. (**A**) Least absolute shrinkage and selection operator coefficient profiles of variables. (**B**) Following verification of the optimal parameter (λ) in the least absolute shrinkage and selection operator model, dashed vertical line was plotted according to the minimum criterion likelihood deviance (binomial) curve and log (λ).

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Table 2 Multivariate Logistic Regression Analysis of the Predictors for Septic Shock

Characteristics	OR	95% CI	P
MAP	0.95	0.93–0.98	0.001
ALB	0.92	0.86–0.98	0.012
SOFA	1.29	1.09–1.53	0.003
LAC	1.22	1.05–1.42	0.010
BUN	1.02	0.98–1.07	0.184

Nomogram Construction and Validation

A risk prediction model for septic shock in severe COVID-19 patients was developed with these four factors, as shown in Figure 3. The model demonstrated strong discrimination in both the training and validation cohorts (Figure 4A and B). In the training set (Figure 4A), the ROC curve showed strong discrimination (AUC 0.800, 95% CI 0.741–0.858). The model's discrimination was further validated in the test set (AUC 0.775, 95% CI 0.651–0.899), as shown in Figure 4B. Calibration curve analysis indicated that the nomogram model was well - calibrated with the observed incidence of septic shock in severe COVID-19 patients (Figure 5A and B). The Hosmer-Lemeshow goodness-of-fit test revealed no statistically significant difference between the model's predictions and actual outcomes in the training group (P = 0.689), as depicted in Figure 5A. Decision curve analysis further demonstrated that the nomogram model provided better net benefits (Figure 6A and B).

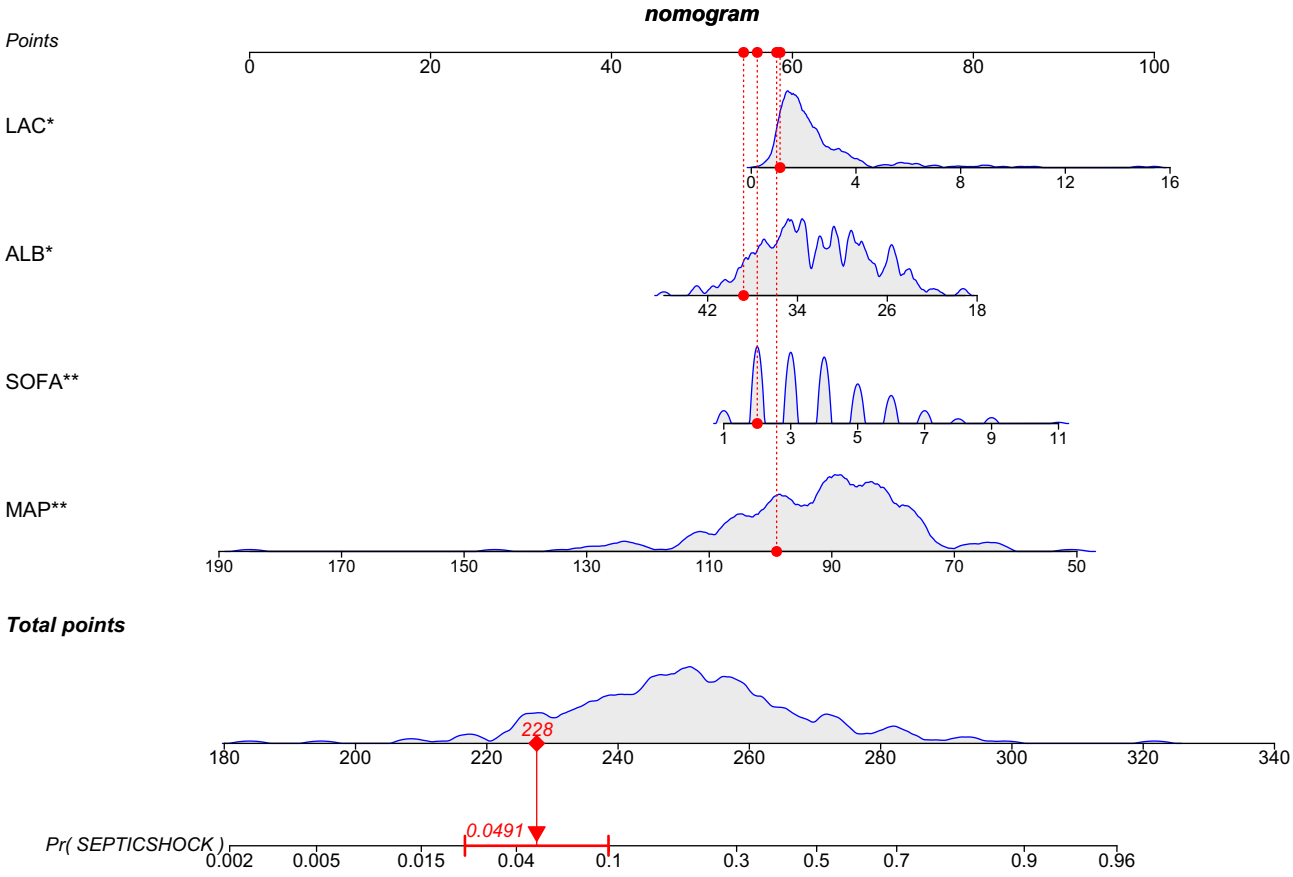

Figure 3 Nomogram for Predicting Septic Shock in Patients with Severe COVID-19. "*": P<0.05; "**": P<0.01.

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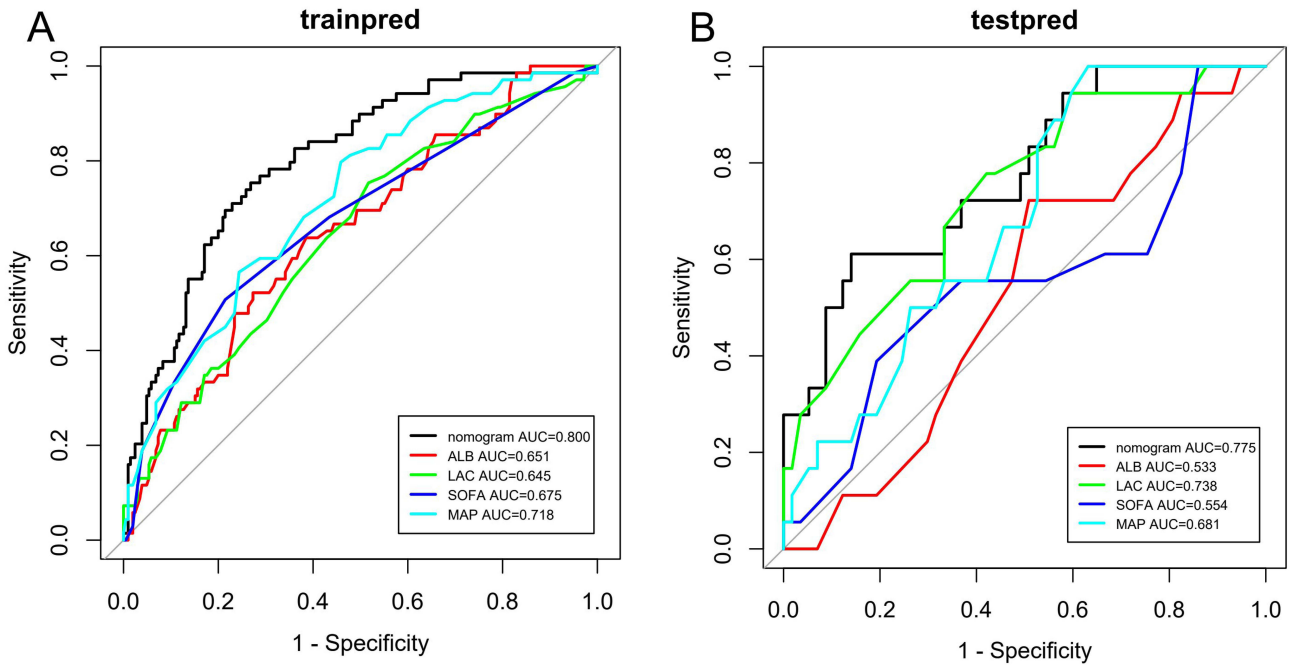

Figure 4 ROC curves. The ROC curves of the training cohort (**A**) and the validation cohort (**B**).
Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the receiver operating characteristic curve.

Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades host cells via the binding of its spike protein to angiotensin-converting enzyme 2 (ACE2) receptors. This process activates immune cells such as monocytes and macrophages, triggering the massive release of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and ultimately inducing a "cytokine storm".[18] This excessive immune response damages the vascular endothelial barrier and causes microcirculatory dysfunction, which in turn leads to sepsis and may progress to septic shock in severe cases. Five years have passed since the initial report of the ancestral SARS-CoV-2 strain in late 2019. Among its variants, Omicron has long been the globally dominant circulating strain and was also the primary strain analyzed in this study.[19–22] The core pathogenic mechanism has not fundamentally changed between the ancestral strain and currently circulating variants. Mutations of the Omicron variant are mainly focused on enhancing viral transmissibility or evading host humoral immunity.[23] Therefore, the pathogenic mechanism described above is also applicable to the pathophysiological process of septic shock induced by different SARS-CoV-2 variants.

Research on septic shock in severe COVID-19 patients is currently limited. A Brazilian prospective study involving 86 severe COVID-19 patients explored the predictive value of Syndecan - 1 (SDC - 1) levels for septic shock and identified an optimal cutoff of 269 ng/mL. Patients with SDC-1 levels above this threshold experienced significantly earlier onset of septic shock.[24] Another retrospective study from Moscow analyzed 1,078 severe COVID-19 patients and found that age >50 years and the presence of ≥3 chronic diseases were associated with higher septic shock risk.[25] Nevertheless, SDC - 1 testing can be challenging in resource - limited settings, and the Moscow study lacked visual or quantitative tools. In our study, we identified albumin, lactate, SOFA score, and MAP as independent predictors of septic shock in severe COVID-19 patients. The nomogram model based on these four factors has high clinical practicality because of its simplicity and accuracy, without the need for complex calculations and using readily available parameters. Importantly, these factors can be modulated through timely clinical interventions, potentially reducing septic shock risk.

Albumin levels, closely linked to nutritional status and inflammatory burden, inversely correlate with septic shock risk. Hypoalbuminemia can potentially promote septic shock as it exacerbates microcirculatory dysfunction and tissue hypoxia.[26] A case-control study of 191 COVID-19 patients and 203 healthy individuals found significantly lower serum albumin levels in COVID-19 patients.[27] Other studies confirmed albumin's association with disease severity and its

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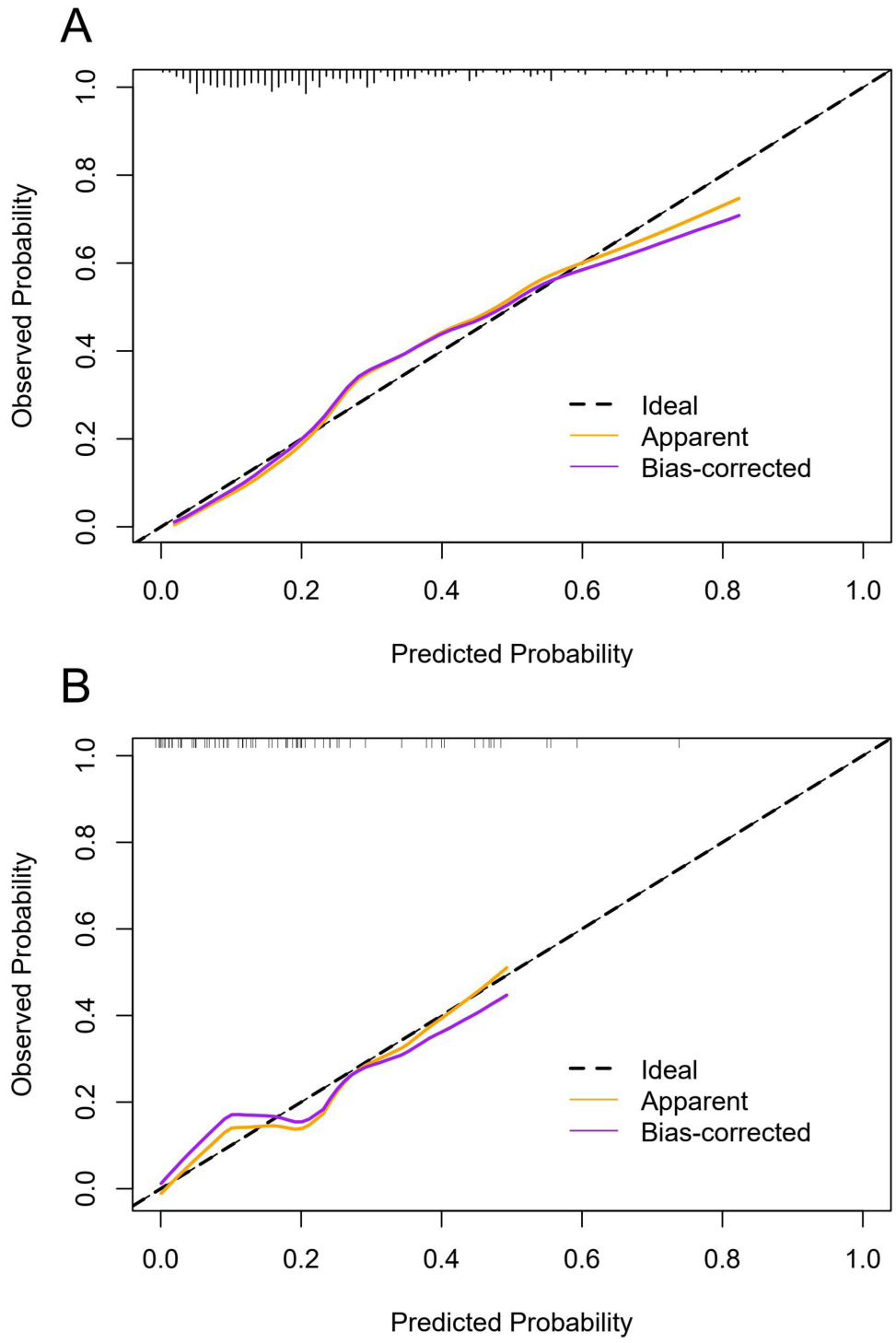

Figure 5 Calibration plots of the nomogram in the training cohort (**A**) and the validation cohort (**B**).

utility in predicting mortality risk in critical COVID-19 cases.[28] Our findings further support these conclusions, suggesting albumin as a key predictor of septic shock in severe COVID-19 patients.

COVID-19 has been identified as a specific trigger for sepsis and is included in current sepsis guidelines.[29] These guidelines suggest that monitoring dynamic indicators like serum lactate levels can guide the evaluation of fluid therapy response in COVID-19 related sepsis patients. In this context, blood lactate levels may serve as a potential indicator for assessing the risk of critical illness and mortality in COVID-19. Kayina et al conducted a study on 235 COVID-19

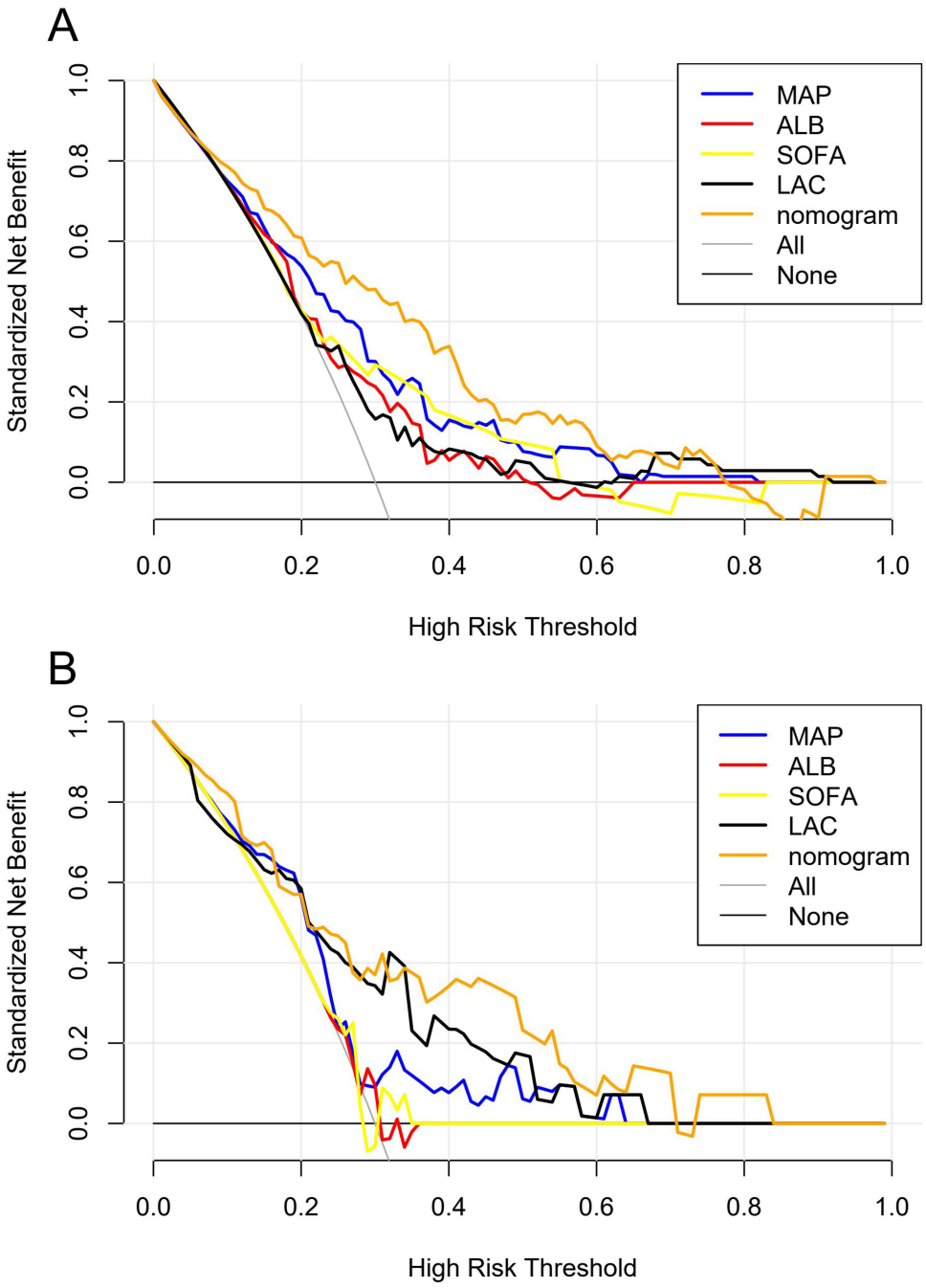

Figure 6 The DCA curves of the nomogram in the training cohort (**A**), and validation cohort (**B**).

patients and found that lactate levels were significantly higher in non - survivors than in survivors [4.1 (2.4–6.4) mmol/L versus 1.8 (1.2–2.7) mmol/L, p = 0.002].[30] Another study of 981 COVID-19 patients demonstrated that high lactate level is a predictor of mortality risk.[31] Our study also showed that lactate level can be an independent risk factor for septic shock in severe COVID-19 patients. Therefore, for severe COVID-19 patients with markedly elevated lactate levels at admission, clinicians should be vigilant for the development of septic shock and implement early clinical interventions.

A retrospective study involving 4,126 patients showed that in COVID-19 positive patients, a low - normal blood pressure (mean arterial pressure 65–86 mmHg) at presentation is associated with an increased risk of mortality.[32] Similarly, our study found that a lower mean arterial pressure at presentation in COVID-19 positive patients may raise the risk of septic shock. Thus, in clinical practice, monitor the mean arterial pressure at admission in COVID-19 positive

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patients, as it may be associated with poorer outcomes. Compared to mean arterial pressure, the SOFA score offers a more detailed and comprehensive assessment of disease severity. Studies have indicated that a high SOFA score at admission is a significant predictor of clinical deterioration during hospitalization in COVID-19 patients,[6] and it has been confirmed as a mortality risk factor in these patients.[33–35] In our study, a high SOFA score was associated with the occurrence of septic shock and could serve as an independent risk factor for septic shock.

Some studies have reported favorable antiviral effects of drugs such as nirmatrelvir/ritonavir (Paxlovid) and azvudine in COVID-19.[36,37] For example, the EPIC-HR trial showed that nirmatrelvir/ritonavir reduced 28-day hospitalization/mortality risk by approximately 89% in high-risk COVID-19 patients.[36] Another retrospective cohort study of 1,505 hospitalized COVID-19 patients showed that the azvudine group had lower all - cause mortality ($P = 0.027$) and reduced disease progression outcomes ($P = 0.041$).[38] However, these drugs showed no significant benefit in our cohort, possibly because our study consisted of severe COVID-19 patients, whereas these treatments are more effective in mild-to-moderate cases.

Our study has several limitations. First, while the pathophysiological mechanism underlying the model supports its generalizability to viral variants, the relatively short and continuous enrollment period—though reducing case heterogeneity—may have limited the total sample size and consequently reduced statistical power. Second, external validation was performed, but the sample size in the external validation cohort was relatively small. To address these issues, future studies should focus on implementing multicenter external validation to ensure that our findings are reliable and generalizable across different clinical settings. Finally, as a retrospective study, the data were limited to routinely monitored clinical and laboratory variables, which may have constrained the model's performance. Prospective studies collecting high-dimensional omics or imaging data and employing machine learning methods could further improve model construction in the future.

Conclusion

This study developed a nomogram model integrating clinical and laboratory parameters measured at admission, which enables accurate prediction of septic shock risk in patients with severe COVID-19. As a practical clinical tool, it provides actionable guidance for clinicians to identify high-risk individuals early, optimize clinical decision-making, and thereby holds great potential for improving patient prognosis.

Abbreviations

ALB, Albumin; AUC, area under the receiver operating characteristic curve; COVID-19, Coronavirus disease 2019; DCA, decision curve analysis; ICU, intensive care unit; LAC, lactate; LASSO, least absolute shrinkage and selection operator; MAP, mean arterial pressure; OR, odds ratio; ROC, receiver operating characteristic curve; SARS-CoV, severe acute respiratory syndrome coronavirus; SOFA, Sequential Organ Failure Assessment.

Data Sharing Statement

The data sets used during the study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Some data in this study were based on a third-party anonymous public database, for which we obtained approval from the Institutional Review Board (Approval No.: 14674232). Therefore, ethical review was not required for this portion of data. To access this database, we completed the online training course and examination on protecting human research participants provided by the National Institutes of Health (ID No: 14674232). This research was approved by the ethics committee of Northern Jiangsu People's Hospital (ID No: 2025ky025). Due to the retrospective nature of the study, written informed consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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