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ORIGINAL RESEARCH

Establishment and Validation of a Risk Prediction Model for Sepsis-Associated Liver Injury in ICU Patients: A Retrospective Cohort Study

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Purpose: Sepsis-associated liver injury (SALI) leads to increased mortality in sepsis patients, yet no specialized tools exist for early risk assessment. This study aimed to develop and validate a risk prediction model for early identification of SALI before patients meet full diagnostic criteria.

Patients and Methods: This retrospective study analyzed 415 sepsis patients admitted to ICU from January 2019 to January 2022. Patients with pre-existing liver conditions were excluded. Using LASSO regression and multivariate logistic analysis, we developed a predictive nomogram incorporating clinical variables. Model performance was evaluated through internal validation using bootstrapping method.

Results: Among the cohort, 97 patients (23.4%) developed SALI. The final model identified five key predictors: total bilirubin, ALT, γ-GGT, mechanical ventilation, and kidney failure. The model demonstrated good discrimination (AUC=0.841, 95% CI: 0.795–0.887) and calibration. Decision curve analysis showed clinical utility across a threshold probability range of 4–87%. The model outperformed traditional scoring systems (SOFA and SAPS II) in predicting SALI risk.

Conclusion: This novel nomogram effectively predicts SALI risk in sepsis patients by integrating readily available clinical parameters. While external validation is needed, the model shows promise as a practical tool for early risk stratification, potentially enabling timely interventions in high-risk patients.

Keywords: SALI, variable, nomogram, risk, probability

Introduction

In intensive care units (ICUs), sepsis, which is globally prevalent and potentially fatal, is a leading contributor to elevated morbidity and mortality rates.[1] The International Surviving Sepsis Campaign defines sepsis as a life-threatening condition where the body's response to infection leads to organ dysfunction, often accompanied by extensive inflammation and organ failure.[2]

The liver has a crucial role in the body's defense against infections due to abundant phagocytic cells and a diverse array of lymphocytes in the liver sinusoids. Additionally, the liver is responsible for maintaining the microbial barrier of the gastrointestinal tract, along with the intestinal flora via the hepato-enteric axis and bile acid secretion.[3–5] In sepsis, the body's inflammatory response can disrupt the integrity of the intestinal barrier, increasing its permeability, thereby allowing intestinal microbes to enter the bloodstream and reach the liver via the portal vein, causing further liver injury.[6] Moreover, while the liver's robust immune system helps eradicate microbes, it also contributes to liver injury as a result of excessive systemic inflammation.[7]

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Sepsis-associated liver injury (SALI) occurs through various mechanisms, such as disturbances in microcirculation, immune dysregulation, and systemic inflammation.[8] SALI mainly presents as cholestasis or hypoxic hepatitis.[9] The prevalence of SALI was reported to be 34.7% by Kobashi et al.[10] However, well-defined diagnostic criteria for sepsis-associated hypoxic hepatitis are currently lacking, leading to varying incidence rates being reported. In ICU settings, several factors contribute to the high mortality rate associated with severe sepsis, such as uncontrolled inflammation causing multiple organ injuries and dysfunctions, bacterial infections that are resistant to multiple drugs, and the ineffectiveness of anti-infection treatments.[2] In addition to the inherent risks of sepsis, hypoxic hepatitis introduces additional hazards, such as concurrent organ injuries that worsen liver conditions and increased drug toxicity due to impaired liver function, all of which collectively contribute to the high mortality rate.

The mortality rate of Hepatic hemophagocytic syndrome (HH), cholestasis, or SALI has consistently been reported to be high (53.0–61.5%).[11–13] Early identification and timely intervention have been shown to significantly improve patient outcomes, with studies reporting mortality reduction of up to 20–30% when SALI is diagnosed and treated in its early stages.[14,15] Several therapeutic strategies, including early goal-directed therapy, appropriate antimicrobial treatment, and organ support, have demonstrated effectiveness in improving survival rates.[7] Moreover, prompt initiation of liver-protective measures and careful medication adjustment based on liver function have been associated with better prognosis.[16] Hence, patients at high risk of SALI must be identified for effective and timely management of sepsis in ICU settings.

Despite the Simplified Acute Physiology Score (SAPS) II score and the Sequential Organ Failure Assessment (SOFA) score being recognized as effective tools for predicting the prognosis of patients with sepsis, their predictive accuracy remains limited for individuals with SALI.[17] The lack of diagnostic methods that accurately incorporate predictive factors linked to sepsis and early-onset liver injury may lead to a high mortality rate among patients with SALI.[17] Presently, there is no established model for risk prediction of SALI in sepsis patients.

Given the critical need for early identification of SALI risk in sepsis patients and the current lack of specialized predictive tools, our study aimed to develop and validate a comprehensive nomogram for SALI risk prediction. This predictive model was designed to integrate liver enzymes, clinical parameters, and demographic factors to identify patients at high risk for developing SALI before they meet the full diagnostic criteria. Unlike existing classification approaches that focus on current liver status or mortality prediction, our model provides an early risk stratification tool to guide preventive interventions and optimize patient outcomes. The development of such a prediction model represents a crucial step toward improving the management of sepsis patients who may develop SALI, potentially reducing morbidity and mortality through early intervention.

Materials and Methods

Selection of Patients and Ethics

Patients admitted to the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University with a diagnosis of sepsis from January 2019 to January 2022 were enrolled in this retrospective cohort study. The inclusion criteria were as follows: (I) patients diagnosed with sepsis according to the Sepsis 3.0 guidelines; (II) patients aged ≥18 years; (III) minimum ICU stay of 48 hrs; and (IV) SALI occurred 24 hours after entering the ICU. Only the initial record was examined for patients who had several ICU admissions during hospitalization, the laboratory examinations within 24 hours after admission are included for analysis. The exclusion criteria were:[18–21] (I) patients not presenting with liver injury; (II) patients with liver trauma, toxic hepatitis, or primary liver disorders including viral hepatitis (either acute or chronic types), liver necrosis, liver failure (acute or chronic), chronic liver disease, hepatic steatosis and cirrhosis; (III) patients with cholangitis and acute cholecystitis with biliary obstruction (IV) those with bile duct and ampullary tumors; (V) autoimmune hepatitis; (VI) hepatic vascular infarction; (VII) occurrence of SALI within 24 hours of admission; (VIII) and <48 hours of ICU stay. Of the 472 participants enrolled in the study, 57 were determined to not meet the requirements and were excluded (Figure 1). The hospital's ethical review board approved the study's planned procedures (approval number: KY-2023-156-01). Signed informed consent was not required since the data were anonymized.

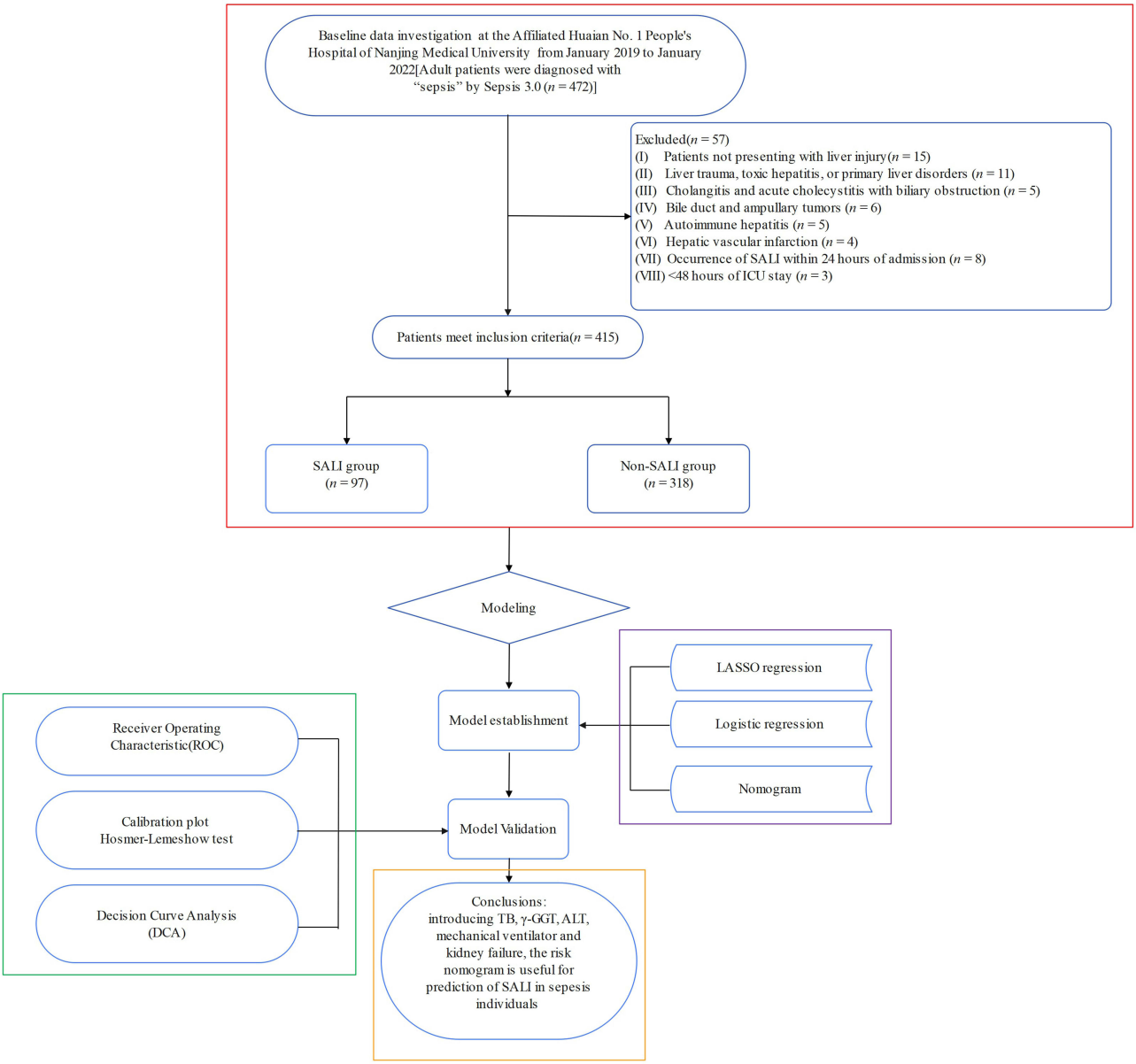

Figure 1 Flowchart of data extraction and study design.
Notes: red boxes (Initial screening population and exclusion criteria); purple boxes (The process of model establishment); green boxes (The process of model validation); yellow box (Included variables and conclusions).
Abbreviations: SALI, sepsis-associated liver injury; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; TB, total bilirubin; ALT, alanine aminotransferase.

Data Collection

Data were obtained retrospectively and included demographic details like age and sex. Furthermore, comorbidities including cardiac insufficiency, chronic pulmonary disease, hypertension, hyperlipidemia, diabetes (with and without complications), malignant cancer and atrial fibrillation, complication including septic shock, acute organ injury including coagulation disorder, acute respiratory failure, kidney failure, respiratory and cardiac arrest and MODS, which were defined per the International Classification of Diseases (ICD-9 and ICD-10). Cases of infection sites and the presence of pathogenic microorganisms were also documented. Moreover, the results of the initial laboratory examinations conducted upon ICU hospitalization and the administration of supportive treatments, including vasoactive drugs, tracheotomy, mechanical ventilation, tracheal intubation, difficulties in weaning off the ventilator, and anticoagulants were recorded. Furthermore, the first SAPS II and SOFA scores during the patient's ICU stay were also recorded. The performance of

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the predictive model was assessed using the SOFA and SAPS II scores, which are often employed in ICUs to determine disease severity and anticipate patient prognosis.

Sali

Previously, researchers have separated SALI into two categories: HH and cholestasis. HH is characterized by elevated levels of alanine aminotransferase (ALT), indicative of HH, are more than ten times higher than the upper limit of the normal range (400 U/dL).[18] Conversely, patients with cholestasis have serum bilirubin levels of > 2 mg/dL.[20,21]

Statistical Analysis

To determine whether the distributions within the sample are normal, the Shapiro–Wilk test was carried out. The format of mean ± standard deviations (SD) was used to present variables conforming to a normal distribution, whereas non-normally distributed variables were reported as median (interquartile range), Categorical variables were presented as frequencies and percentages. The non-parametric Mann–Whitney *U*-test was employed for data with non-normally distributed or heterogeneously distributed variances, while the Pearson's or chi-square test was employed for categorical variables.

Selection of Features and Establishment of the Model

In clinical practice, the SAPS II and SOFA scores are widely applied to assess patients' outcomes. The accuracy of predictive models can be enhanced by integrating these scores as predictor variables; however, recording accurate scores requires comprehensive information about their components. In certain scenarios, the inclusion of the score in the model may reduce its usefulness. Hence, in this study, these scores were not employed for variable screening and model construction; instead, they were used as a benchmark for model comparison. The multiple imputation technique was utilized to estimate the values of missing data. Predictor selection and regularization were conducted utilizing the least absolute shrinkage and selection operator (LASSO) regression analysis. Subsequently, a multivariate logistic regression analysis was conducted to formulate a predictive model capable of discriminating between SALI and non-SALI patients. The created model served as the basis for the development of a nomogram. Then, the discriminative performance of the model was evaluated by computing the area under the curve (AUC). Subsequently, bootstrapping analysis with 500 iterations was performed for internal validation.[22] The Hosmer-Lemeshow test was conducted to evaluate the model's calibration. Furthermore, Decision curve analysis (DCA) was performed to ascertain the clinical effectiveness of the model.[23] Data were statistically analyzed using the R software (v3.6.3). The significance level was established at $P < 0.05$.

Results

Baseline Characteristics and SALI-Related Risk Factors

This study initially screened 472 sepsis patients, with 415 meeting the inclusion criteria after excluding 57 patients based on predefined criteria (Figure 1). Among the included patients, 97 (23.4%) developed SALI during their ICU stay. Comparative analysis of baseline characteristics between SALI and non-SALI groups revealed significant differences in liver function parameters, organ failure indicators, and disease severity scores (Table 1).

Predictors Entering the Model

Initial LASSO regression analysis of 61 potential variables identified 11 predictors with non-zero coefficients, including total bilirubin (TB), BNP, ALT, γ-glutamyl transferase (γ-GGT), LDH, MODS, mechanical ventilation, kidney failure, respiratory and cardiac arrest, septic shock, and coagulation disorder (Figure 2). Subsequent multivariate logistic regression refined these to five independent predictors significantly associated with SALI development: total bilirubin (coefficient: 0.123), ALT (0.003), γ-GGT (0.004), mechanical ventilation (1.017), and kidney failure (1.200). These variables demonstrated both statistical significance (all $P < 0.05$) and strong clinical relevance (Table 2).

Table 1 Patient Demographic and Clinical Characteristics

Variables	ALL (n = 415)	Non-SALI (n = 318)	SALI (n = 97)	*P* value
Demography				
Age (>60 years)	297 (71.6%)	235 (73.9%)	62 (63.9%)	0.075
Sex (Male)	236 (56.9%)	187 (58.8%)	49 (50.5%)	0.185
Laboratory results				
PT (s)	15.6(13.6,17.7)	15.4(13.5,17.3)	16.6(14.1,20.6)	0.003
INR	1.27(1.12,1.49)	1.25(1.12,1.45)	1.38(1.14,1.83)	0.002
APTT (s)	37.9(31.0,47.1)	37.4(30.8,45.7)	41.6(31.7,51.2)	0.047
TT (s)	16.9(15.8,18.6)	16.8(15.8,18.4)	17.4(15.9,19.9)	0.027
Fibrinogen (g/L)	4.34(2.97,5.91)	4.63(3.17,6.24)	3.87(2.69,5.02)	<0.001
D-dimer (μg/mL)	4.42(2.30,7.94)	4.15(2.22,7.80)	5.27(2.44,10.1)	0.122
PH	7.42(7.34,7.47)	7.42(7.35,7.47)	7.42(7.34,7.46)	0.154
PCO_2 (mmHg)	34.5(29.6,39.1)	33.9(30.1,38.6)	34.8(28.7,40.6)	0.695
PO_2 (mmHg)	83.4(64.2,109)	83.4(64.1,108)	87.1(65.2,111)	0.751
BE (mmol/L)	−3.009(−7.45,1.80)	−3.00(−7.77,1.80)	−3.10(−6.60,1.80)	0.907
HCO_3^- (mmol/L)	21.2(16.9,25.0)	21.2(17.3,25.1)	21.2(16.6,24.2)	0.586
SO_2 (%)	96.3(92.8,98.4)	96.3(93.1,98.7)	96.2(92.5,98.2)	0.544
Blood lactate (mmol/L)	2.50(1.60,4.40)	2.40(1.50,4.20)	3.10(1.70,6.00)	0.005
White blood cell (K/UL)	10.6(6.21,17.1)	10.4(6.01,17.1)	11.6(6.89,16.8)	0.673
Neutrophils (K/UL)	9.29(4.67,15.3)	8.89(4.61,15.6)	10.3(5.07,14.1)	0.88
Lymphocytes (K/UL)	0.77(0.46,1.19)	0.80(0.46,1.18)	0.70(0.45,1.29)	0.946
Platelet (K/UL)	141(79.5,214)	151(90.5,218)	95.0(46.0,178)	<0.001
Total bilirubin (mg/dL)	16.1(9.91,29.7)	14.5(9.17,25.2)	28.2(13.6,80.8)	<0.001
BNP (pg/mL)	3063(1106,10,684)	2556(1062,8262)	7600(2047,25,000)	<0.001
Albumin (g/L)	29.8(25.9,34.0)	29.4(25.8,33.8)	30.2(26.2,34.2)	0.34
Creatinine (μmol/L)	98.0(66.0,171)	95.3(66.0,162)	117(65.5,197)	0.279
BUN (mmol/L)	10.6(6.85,15.6)	9.61(6.40,15.3)	12.2(8.69,16.2)	0.023
ALT (IU/L)	26(15.5,64.6)	21.00(13.8,45.0)	121.40(41.3,402)	<0.001
AST (IU/L)	43.0(25.0,105)	36.8(22.0,62.8)	151(59.4,487)	<0.001
γ-GGT (IU/L)	39.0(18.0,79.0)	33.5(16.0,66.0)	55.0(29.0,161)	<0.001
LDH (IU/L)	290(217,450)	280(202,374)	475(276,1544)	<0.001
PCT (ng/mL)	11.6(1.58,52.6)	11.5(1.60,51.6)	11.6(1.30,66.0)	0.707
Treatment, n (%)				
Vasoactive drug	92 (22.2%)	68 (21.4%)	24 (24.7%)	0.577
Tracheotomy	35 (8.43%)	26 (8.18%)	9 (9.28%)	0.894
Mechanical ventilation	275 (66.3%)	194 (61.0%)	81 (83.5%)	<0.001
Tracheal intubation	168 (40.5%)	116 (36.5%)	52 (53.6%)	0.004
Difficulties in weaning off the ventilator	99 (23.9%)	69 (21.7%)	30 (30.9%)	0.083
Anticoagulants	89 (20.4%)	65 (24.7%)	24 (21.4%)	0.366
Comorbidity, n (%)				
Cardiac insufficiency	90 (21.7%)	59 (18.6%)	31 (32.0%)	0.008
Chronic pulmonary disease	8 (1.93%)	7 (2.20%)	1 (1.03%)	0.687
Hypertension	177 (42.7%)	135 (42.5%)	42 (43.3%)	0.976
Hyperlipidemia	182 (42.7%)	132 (42.5%)	50 (43.3%)	0.976
Diabetes	119 (27.7%)	88 (32.0%)	31 (28.7%)	0.414
Diabetes with complication	15 (3.61%)	12 (3.77%)	3 (3.09%)	1.000
Malignant cancer	90 (21.7%)	77 (24.2%)	13 (13.4%)	0.034
Atrial fibrillation	60 (14.5%)	48 (15.1%)	12 (12.4%)	0.615
Complication, n (%)				
Septic shock	72 (17.3%)	45 (14.2%)	27 (27.8%)	0.003

(*Continued*)

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Table 1 (Continued).

Variables	ALL (n = 415)	Non-SALI (n = 318)	SALI (n = 97)	*P* value
Acute organ injury, n (%)				
Coagulation disorder	73 (17.6%)	42 (13.2%)	31 (32.0%)	<0.001
Acute respiratory failure	209 (50.4%)	146 (45.9%)	63 (64.9%)	0.002
Kidney failure	195 (47.0%)	123 (38.7%)	72 (74.2%)	<0.001
Respiratory and cardiac arrest	26 (6.27%)	15 (4.72%)	11 (11.3%)	0.034
MODS	46 (11.1%)	21 (6.60%)	25 (25.8%)	<0.001
Infection site, n (%)				
Lung	203 (48.9%)	149 (46.9%)	54 (55.7%)	0.160
Abdominal cavity	132 (31.8%)	112 (35.2%)	20 (20.6%)	0.010
Urinary tract	70 (16.9%)	61 (19.2%)	9 (9.28%)	0.034
Cerebrovascular disease	52 (12.5%)	35 (11.0%)	17 (17.5%)	0.128
Blood culture results, n (%)				
Multidrug-resistant bacteria	27 (6.51%)	18 (5.66%)	9 (9.28%)	0.303
Klebsiella pneumoniae	29 (6.99%)	22 (6.92%)	7 (7.22%)	1.000
Pseudomonasaeruginosa	5 (1.20%)	3 (0.94%)	2 (2.06%)	0.333
Escherichia coli	40 (9.64%)	34 (10.7%)	6 (6.19%)	0.263
Enterococcus	8 (1.93%)	6 (1.89%)	2 (2.06%)	1.000
Staphylococcus	35 (8.43%)	28 (8.81%)	7 (7.22%)	0.776
Acinetobacter baumannii	12 (2.89%)	8 (2.52%)	4 (4.12%)	0.487
Severity score				
SOFA	9.00(6.00,12.0)	9.00(6.00,12.0)	9.00(7.00,12.0)	0.230
SAPS II	45.0 (39.0,51.0)	45.0(39.0,50.8)	46.0(39.0,52.0)	0.135

Notes: Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables and as N (%) for categorical variables.
Abbreviations: PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; PH, potential of hydrogen; PCO2, partial pressure of carbon dioxide; PO2, partial pressure of oxygen; BE, base excess; HCO3-, Bicarbonate; SO2, oxygen saturation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; PCT, procalcitonin; MODS, multiple organ dysfunction syndrome; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II.

Establishment of the Model and Nomogram

Using these five independent predictors, we constructed a predictive nomogram for individualized SALI risk assessment. The model's formula integrated the weighted contributions of each predictor: logistic (risk score) = −3.550 + 0.123× TB

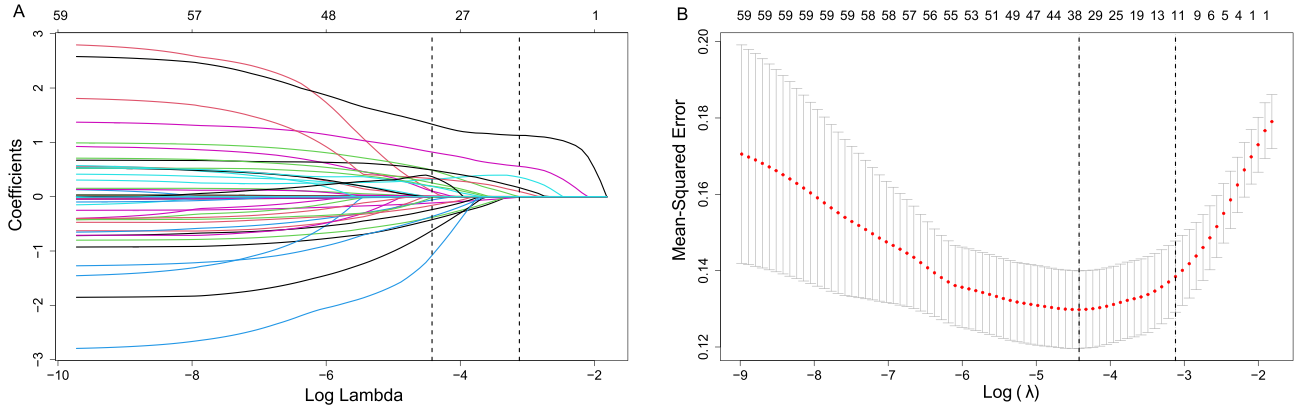

Figure 2 LASSO regression analysis was performed to select the predictors. (**A**) Ten-fold cross-validation was performed to determine the optimal value of the LASSO regression-related tuning parameter (lambda). The binomial deviance was plotted against the logarithm of lambda. The optimal values, determined per the 1-SE (one standard error) criteria, were indicated by vertical dotted lines. (**B**) The coefficient profiles of the variables incorporated in the LASSO regression analysis were plotted against the logarithm of the lambda sequence. The predictive model was established using five detected non-zero coefficients.
Abbreviations: LASSO, least absolute shrinkage and selection operator; SE, standard error.

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Table 2 Multivariate Logistic Regression Analysis of Predictors Selected by LASSO Regression Procedure

Independent Variables	B	SE	OR	95% CI		*P*-value
				Lower	Upper	
TB	0.123	0.052	1.131	1.021	1.26	0.018
ALT	0.003	0.001	1.003	1.001	1.005	<0.001
γ-GGT	0.004	0.001	1.004	1.001	1.006	0.006
Mechanical ventilator	1.017	0.343	2.765	1.449	5.601	0.003
Kidney failure	1.200	0.295	3.319	1.881	6.011	<0.001

Abbreviations: LASSO, least absolute shrinkage and selection operator; TB, total bilirubin; ALT, alanine transaminase; γ-GGT, γ-glutamyl transpeptidase; SE, standard error OR, odds ratio; CI, confidence interval.

+ 0.003× ALT + 0.004 × γ-GGT + 1.017 × mechanical ventilation + 1.200 × kidney failure (Figure 3 and Table 2). This nomogram enables straightforward risk calculation and interpretation in clinical settings.

Comprehensive validation demonstrated the model's robust performance. The nomogram achieved excellent discrimination with an AUC of 0.841 (95% CI: 0.795–0.887), confirmed through bootstrap resampling with 500 iterations (Figure 4A). The model showed strong calibration, evidenced by close alignment between predicted and observed probabilities (Figure 4B) and confirmed by the Hosmer-Lemeshow test (P = 0.881). Decision curve analysis revealed consistent net benefit across a broad threshold probability range (4–87%), outperforming both "screen-none" and "screen -all" strategies (Figure 4C).

Model Comparison

Further comparative analysis revealed our model's superior predictive performance over existing scoring systems. When compared with individual predictors, the nomogram (AUC = 0.841) demonstrated superior discrimination to TB (AUC = 0.694), ALT (AUC = 0.619), γ-GGT (AUC = 0.670), mechanical ventilation (AUC = 0.612), and kidney failure (AUC = 0.678) (all P < 0.05, Figure 5A). Decision curve analysis further confirmed the model's clinical utility. The nomogram showed greater net benefit across a wide range of threshold probabilities compared to individual predictors (Figure 5B). The nomogram significantly outperformed both SOFA (AUC = 0.540, 95% CI: 0.478–0.601) and SAPS II scores (AUC = 0.550,

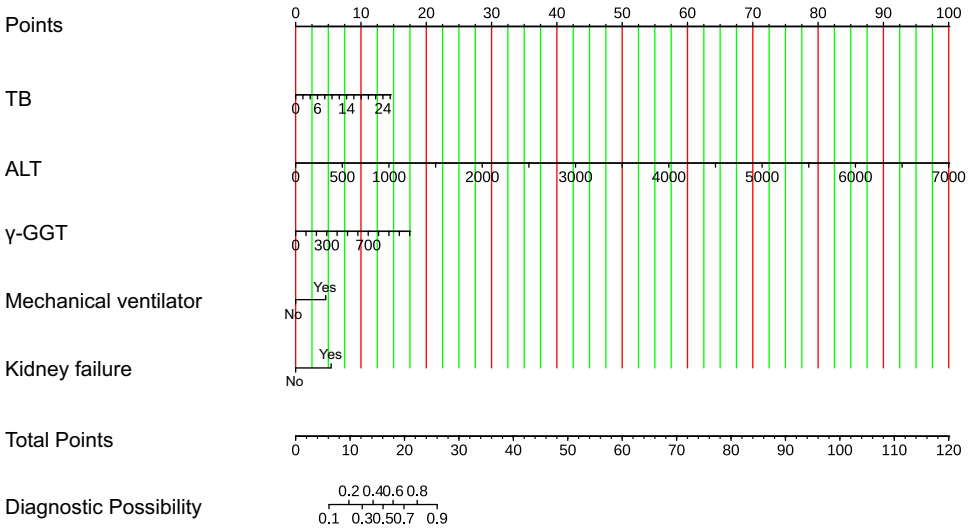

Figure 3 The predictive nomogram can evaluate the risk of SALI in patients with sepsis. To make use of it, one needs to ascertain the points corresponding to each predictor (variable) for a patient along the topmost guideline. Subsequently, the sum of all of these points is used to calculate the total score. Finally, the corresponding predicted probability of SALI provided on the lowermost guideline is checked.
Abbreviations: TB, total bilirubin; ALT, alanine aminotransferase; γ-GGT, γ-glutamyl transpeptidase.

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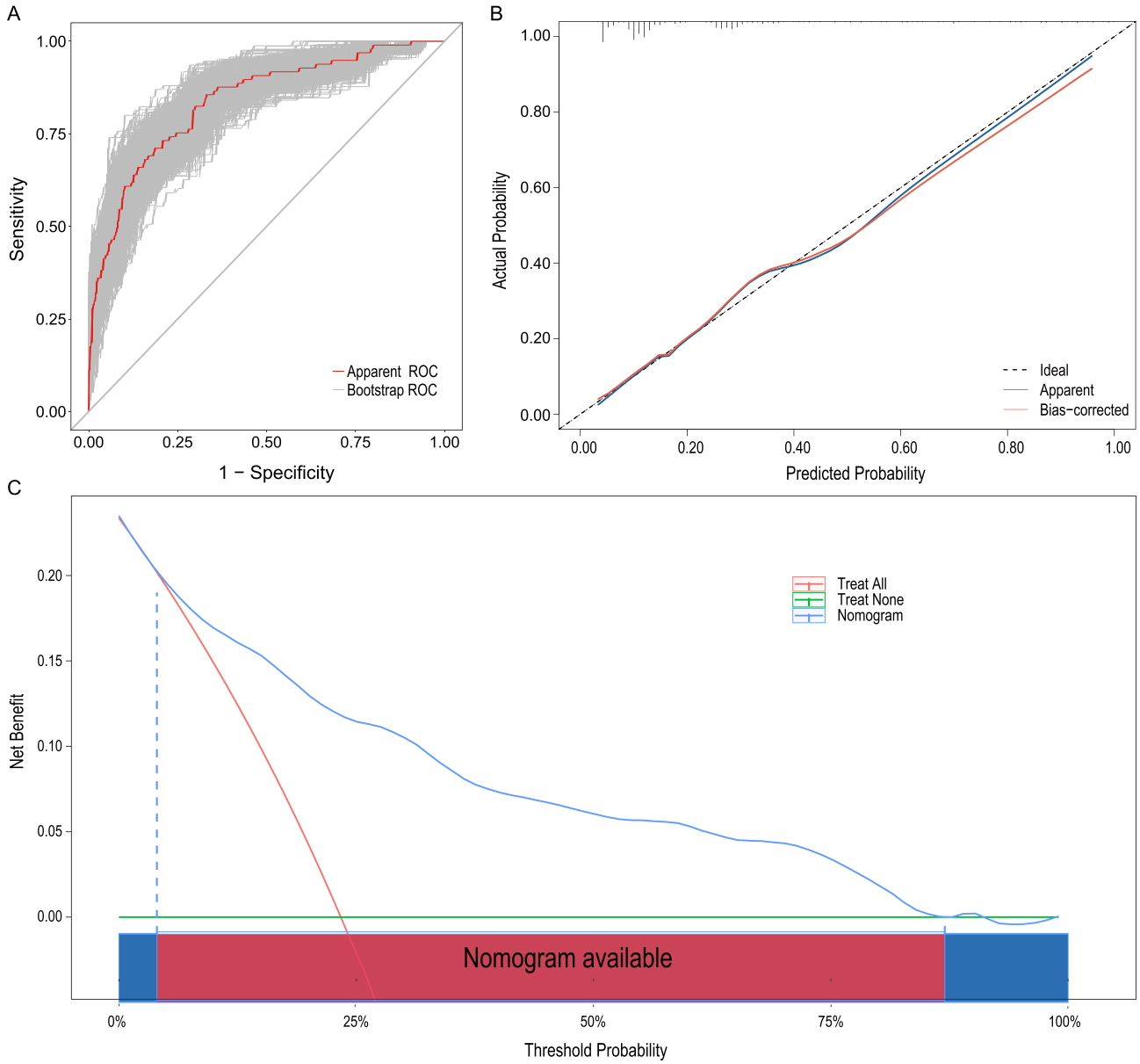

Figure 4 The nomogram model was verified through the following analyses. (**A**) The nomogram-related ROC curve was constructed by bootstrap resampling (500 iterations). (**B**) The predictive accuracy of the nomogram was evaluated using a calibration plot. The solid line, representing the nomogram's performance, was compared to the dotted line, representing an ideal model. To verify the accuracy of the nomogram, a calibration plot was established. (**C**) DCA was performed for the nomogram, and it illustrates the expected net benefit per patient based on the nomogram's prediction of SALI risk. The solid horizontal line corresponds to patients without SALI, while the gray line represents those with SALI. As the model curve extends, the net benefit increases.
Abbreviations: ROC, receiver operating characteristic; DCA, decision curve analysis; SALI, sepsis-associated liver injury.

95% CI: 0.486–0.621) in SALI risk prediction (both $P < 0.05$, Figure 6A) and showed greater clinical utility when the probability threshold exceeded 0.05 (Figure 6B). This comprehensive superiority in both discrimination and clinical utility supports the potential value of our nomogram in guiding clinical decision-making for sepsis patients at risk of SALI.

Discussion

Our study design ensured a clear temporal sequence, with predictive factors collected within the first 24 hours of ICU admission, while SALI diagnosis was made subsequently. This approach reinforces the predictive nature of our model. In the present study, a nomogram incorporating five variables, namely TB, ALT, γ-GGT, mechanical ventilation, and kidney failure, was constructed to identify sepsis patients at risk for SALI. This nomogram demonstrated excellent

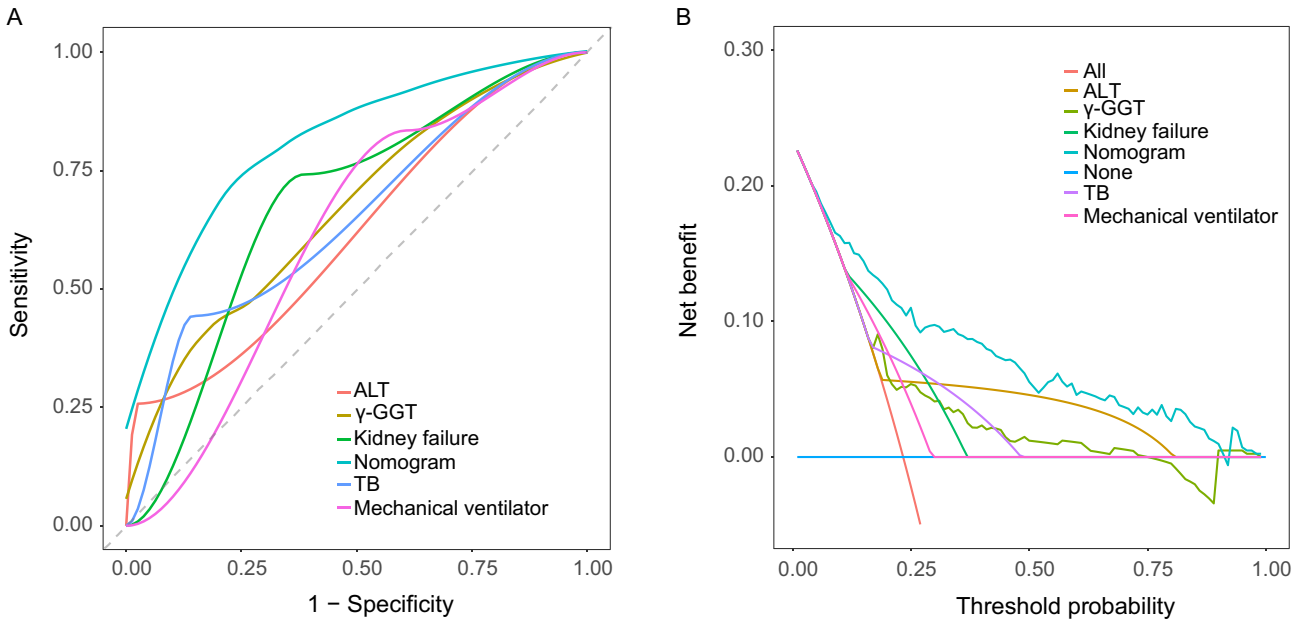

Figure 5 Comparison of models in the entire study cohort. (**A**) ROC curves of various models. (**B**) DCA curves of various models.
Abbreviations: ALT, alanine aminotransferase; γ-GGT, γ-glutamyl transpeptidase; TB, total bilirubin; ROC, receiver operating characteristic curve; DCA, decision curve analysis.

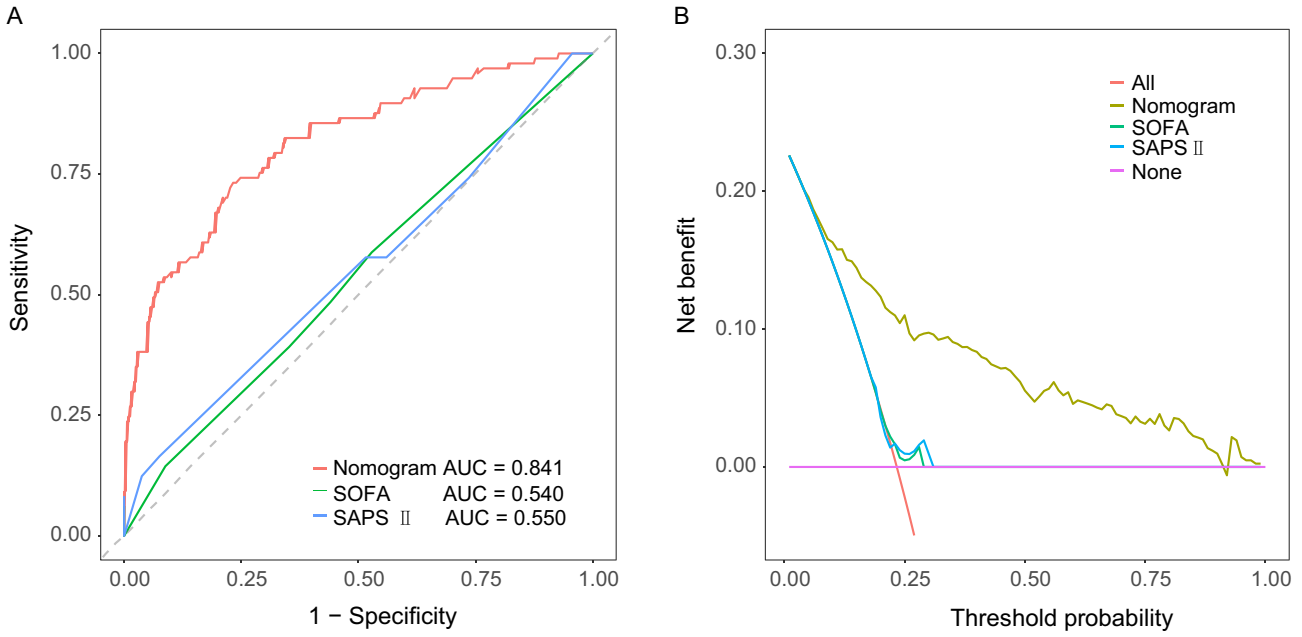

Figure 6 Comparison of ROC and DCA curves between the Nomogram and the SOFA and SAPS II scoring methods. (**A**) ROC Curves; (**B**) DCA Curves.
Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the curve; DCA, decision curve analysis; SOFA, sequential organ failure assessment score; SAPS II, simplified acute physiology score II.

discriminatory performance, calibration, and clinical applicability, empowering clinicians to identify high-risk patients early. Such early identification facilitates timely interventions, potentially improving outcomes in sepsis-associated liver injury.

Currently, there is a dearth of research on the diagnosis of SALI in patients, and healthcare professionals would benefit from a predictive model that can provide an accurate assessment of the risk of SALI in patients with sepsis at an

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early stage. Such a model would empower clinicians to conduct a comprehensive evaluation of the genuine risk associated with SALI and offer families of patients with SALI with clear and informative insights about the condition.

Research evidence suggests that the mortality risk in patients with SALI is linked to several factors, like acute renal failure, acute myocardial infarction, acute respiratory failure, and other conditions leading to hypoxia, inflammatory responses, and metabolic disorders.[17] Previous studies have formulated various models to forecast mortality in patients with SALI and have also reported that these models can prompt physicians to prioritize patients with elevated mortality risks, thereby enhancing the prognosis of patients with SALI.[17,24,25] Compared to existing models focusing on mortality in SALI, our model uniquely addresses the risk of SALI development in sepsis patients, filling a critical gap in early risk assessment. In the present study, a nomogram to anticipate SALI, leveraging five sepsis patient-specific variables, was constructed. The selection of these five variables was performed using LASSO regression analysis, recognized for its advanced predictive predictor selection compared to univariate analysis.[26]

The dynamic changes in liver enzymes during early sepsis may precede clinically evident SALI. Our model captures these early alterations, potentially identifying patients at risk before overt liver dysfunction occurs. With regard to the markers TB, ALT, and γ-GGT, it is essential to recognize the liver's pivotal role in bilirubin metabolism and excretion. Consequently, any liver injury or biliary obstruction can significantly affect bilirubin's metabolic and excretory processes, leading to elevated overall bilirubin levels.[27] ALT is a critical marker employed for assessing liver function and diagnosing liver injuries. In essence, elevated ALT levels indicate the degree of hepatocyte damage and the accompanying inflammatory response. Typically, heightened serum ALT levels are an early indicator of liver injury, often manifesting before the elevation of other liver function enzymes, such as aspartate transaminase(AST).[28] Of note, increased levels of γ-GGT, which is predominantly found in the biliary system of hepatocytes, including bile cells and bile ducts,[29] typically indicate liver injury or biliary tract obstruction.[30] Hence, elevated γ-GGT levels may indicate underlying conditions, such as biliary tract disease, cholestasis, alcoholic liver disease, and hepatobiliary disease. Furthermore, we evaluated the clinical relevance of mechanical ventilation and kidney failure. The requirement of mechanical ventilation indicates an inability to achieve proper gas exchange through natural respiration, leading to hypoxia. Previous studies have documented that hypoxia can be a contributing factor to liver injury.[31] Renal insufficiency impairs the kidneys' capacity to effectively eliminate metabolites and toxins from the body, resulting in their buildup and adversely affecting the liver.[32,33] A prominent illustration is hyperammonemia, a condition commonly found in individuals with uremia (end-stage renal failure), which can lead to hepatocellular damage and hepatic encephalopathy.[34,35] The aforementioned five predictors are frequently utilized clinically. As per the results of the DCA, the nomogram had outstanding discriminative ability and calibration, underscoring its clinical utility. Short-term mortality in sepsis patients can be predicted by the SOFA and SAPS II scoring systems, which are widely used in both general internal medicine wards and ICUs.[36,37] Notably, we found the predictive performance of the SOFA and SAPS II scores to be unsatisfactory in patients with SALI. These scores demonstrated reduced effectiveness, indicating their unsuitability for risk assessment within this specific subgroup of patients with sepsis. Early prediction is crucial for preventing SALI in patients with sepsis, and the establishment of a dependable predictive model for SALI in these patients is an ongoing process. Therefore, the establishment of a model that can aid clinicians in accurately foreseeing the likelihood of SALI is crucial. By utilizing this model, clinicians can ascertain the individual risk of SALI and implement appropriate interventions. For patients identified as high-risk by the nomogram, we recommend the following specific interventions: (1) more frequent monitoring of liver function parameters (every 6–8 hours), (2) early optimization of hemodynamics to improve liver perfusion, (3) careful medication adjustment with special attention to hepatotoxic drugs, (4) prophylactic liver-protective therapy, and (5) early consultation with hepatology specialists. While our model was developed excluding patients with pre-existing liver conditions to ensure precise identification of sepsis-induced liver injury, this may limit its generalizability to patients with underlying liver diseases. Additionally, while our nomogram effectively predicts SALI risk, it was not specifically designed to predict mortality. Future studies should focus of developing integrated models that can predict both SALI risk and subsequent mortality, particularly in patients with pre-existing liver conditions.

There were a few limitations to this research. First, the nomogram was constructed using data from a 3-year prospective study conducted at the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. Since there may be regional variations in the prevalence of SALI, further multicenter validation is essential to assess the nomogram's applicability in other regions or countries. Second, only clinical and laboratory data from the first 24 hours of admission were evaluated, and subsequent serum marker assessment, which would have allowed for a dynamic assessment of changes in the patient's condition, was not performed. Nevertheless, to our knowledge, this is the first research attempting to create a nomogram for predicting the risk of SALI in patients with sepsis, in future work, we will focus on integrating this risk prediction model into clinical decision support systems. This integration aims to facilitate real-time risk assessment and guide the development of personalized management strategies for sepsis patients at risk of SALI.

In conclusion, we have developed and validated a novel nomogram incorporating five clinical parameters that effectively predicts SALI risk in sepsis patients. The model's excellent discrimination and calibration performance, along with its practical clinical utility, provide clinicians with a valuable tool for early risk assessment and intervention. While external validation is needed, this predictive model represents an important advance in the early identification and management of sepsis patients at risk for liver injury.

Data Sharing Statement

The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University (approval number: KY-2023-156-01). The requirement for informed consent was waived due to the retrospective nature of the study and the use of anonymized data. Patient data confidentiality was strictly maintained throughout the study process.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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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 report no conflicts of interest in this work.

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