Comparison of Two Predictive Models of Sepsis in Critically Ill Patients Based on the Combined use of Inflammatory Markers

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Research

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Abstract

Background: Sepsis is considered to be a systemic inflammatory response due to infection, resulting in organ dysfunction. Timely targeted interventions can reduce mortality and improve prognosis. Therefore, it is important to identify potential sepsis in time. Inflammation plays a crucial role in the process of sepsis. We combined inflammatory markers to develop and validate a nomogram model and a simple risk scoring model for predicting sepsis in critically ill patients. Furthermore, comparing the prediction performance of the two models.

Methods: The medical records of adult patients admitted to our intensive care unit (ICU) from August 2017 to December 2020 were analyzed. The finally included patients were randomly divided into training cohort (70%) and validation cohort (30%). A nomogram model for sepsis was developed through multivariate logistic regression analysis in the training cohort. The continuous variables included in nomogram model were transformed into dichotomous variables. Then a multivariable logistic regression analysis was performed based on these dichotomous variables and the odds ratio (OR) for each variable was used to construct a simple risk scoring model for predicting sepsis. The receiver operating characteristic curves (ROC) were constructed and the area under the curve (AUC) was calculated to evaluate the discrimination performance of the two models.

Results: According to our inclusion and exclusion criteria, 2074 patients were included in study. Finally, white blood cell (WBC), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT) and neutrophil-to-lymphocyte ratio (NLR) were included in our models. The AUC of the nomogram model was 0.854 (95%CI: 0.835-0.872). The AUC of the simple risk scoring model was 0.842 (95%CI: 0.822-0.861). When the cut-off value was 7.5 points, the sensitivity was 77.03% and the specificity was 75.75%. The prediction performance of the two models on sepsis is comparable (p=0.1298) and better than that of Sequential Organ Failure Assessment (SOFA) scores (AUC=0.759).

Conclusions: This study combining five commonly available inflammatory markers (WBC, CRP, IL-6, PCT and NLR) developed a nomogram model and a simple risk scoring model to predict sepsis in critically ill patients. Although the prediction performance of the two models is comparable, the simple risk scoring model may be simpler and more practical for clinicians to identify potential sepsis in critically ill patients at an early stage and make treatment strategies.

Introduction

Sepsis, associated with a dysregulated host response to infection, is an important global health problem and the major cause of death around the world [1]. It is estimated that about 48.9 million patients are diagnosed with sepsis, and 11.0 million patients died due to sepsis every year, accounting for approximately 20% of the global deaths [2, 3]. Although sepsis remains high mortality, it is treatable. Timely targeted interventions, including antibiotics administration, removal of the source of infection, full fluid resuscitation, and other supportive treatments can reduce mortality and improve prognosis [4–7].

Therefore, it is important for clinicians to early identify potential sepsis in time, and conduct adequate and timely interventions.

Sepsis is induced by infection, involving complex inflammatory responses during its progress, which is accompanied by pro-inflammatory and anti-inflammatory mechanisms [8, 9]. Conventional inflammatory markers, such as procalcitonin (PCT), interleukin-6 (IL-6), white blood cell (WBC), and C-reactive protein (CRP), may be served as potential markers to help clinicians identify sepsis early [10–14]. Neutrophil-to-lymphocyte ratio (NLR), an easily accessible biomarker that can be calculated from components of the differential white cell count (dividing neutrophil by lymphocyte count), has shown good predictive and prognostic performance in various disease [15–18]. Emerging evidences suggested that NLR may be used as a predictive marker of sepsis. However, to date, none of these makers has gained unanimous acceptance for identification of sepsis separately. Although some previous studies have combined different markers to predict sepsis, there has not been a combination of WBC, IL-6, PCT, CRP and NLR to develop predictive models of sepsis in critically ill patients.

A nomogram model is widely used to predict diagnosis, staging and prognosis in various situations. Nevertheless, sometimes bedside applications are not so convenient. Therefore, we conducted this study to develop and validate a nomogram model and a simple risk scoring model for prediction of sepsis in critically ill patients. Furthermore, comparing the predictive performance of the two models. Finally, we hope to find a model with strong clinical practicability, which can assist clinicians in identifying potential sepsis at an early stage.

Materials And Methods

Data source and patient selection

This is a retrospective study, which was conducted in the intensive care unit (ICU) of the First Medical Center of the Chinese People's Liberation Army General Hospital, a 3000-bed tertiary teaching hospital in Beijing, China. The medical records of adult critically ill patients admitted to ICU from August 2017 to December 2020 were analyzed. The exclusion criteria were as follows: 1) Younger than 18 years old; 2) Pregnancy; 3) Died or discharged early within 48 hours after ICU admission; 4) ICU readmission; 5) Immunosuppression; 6) Hematological malignancy; 7) Undergoing cardiopulmonary resuscitation before ICU admission.

The sepsis is diagnosed according to the latest Sepsis-3 definitions [1]. All sepsis patients received standard-of-care managements in our ICU following the guidelines of 2016 Surviving Sepsis Campaign [19]. Considering that this is a retrospective observational study, the Institutional Review Committee of our hospital granted a waiver of informed consent for this study.

Data collection

Variables included demographics (age, gender, body mass index (BMI)), vital signs at ICU admission (temperature, systolic blood pressure (SBP), respiratory rate (RR) and heart rate (HR)), Sequential Organ Failure Assessment (SOFA) scores, comorbidities, and the results of the first laboratory test after ICU admission (blood routine tests, blood biochemical tests, arterial blood gas tests, CRP, PCT, IL-6) were collected from hospital electronic medical system.

Statistical analysis

For the continuous variables, the Kolmogorov-Smirnov test was performed to test the normal distribution. The continuous variables were expressed as median (interquartile range) or mean (standard deviation), as appropriate, and compared by Mann-Whitney U test and Student t test for non-normally distributed data and for normally distributed data, respectively. The categorical variables were expressed as frequencies (percentages) and the differences between two groups were compared by using chi-square test.

To find whether the inflammatory markers, including WBC, IL-6, PCT, CRP and NLR, were the independent risk factors for sepsis in ICU patients, both univariate logistic regression analyses and multivariable logistic regression analyses using forward stepwise regression were performed. And the results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The P value less than 0.05 was considered statistically significant.

Development and validation of the nomogram

Patients were randomly divided into training cohort (70%) and validation cohort (30%). Based on the results of the logistic regression, training cohort was used to construct a nomogram by the “rms” package of R software. The receiver operating characteristic curves (ROC) were constructed and the area under the curve (AUC) was calculated to evaluate the discrimination performance of the nomogram model. Internally validated was performed with 1,000 bootstrap resampling and a calibration curve was draw by comparing the predictive probability of the sepsis with the observed incidence of sepsis. The validation cohort was used to assess the generality and stability of the nomogram model. The probability of sepsis of each patient in the validation cohort was calculated according to the established nomogram model, then a ROC curve was constructed, and finally, the AUC was calculated and a calibration curve was plotted.

Development and validation of the simple risk scoring model

We also used the training cohort (70%) and validation cohort (30%) of the nomogram model to develop and validate a simple risk scoring model for early detecting sepsis. In order to make this risk scoring model simpler and more practical for clinical application, all continuous variables included in the model were transformed into dichotomous variables. Considering that either an elevated or a decreased in WBC may indicate infection, it was transformed into a dichotomous variable according to whether its value was within the normal range ($4 \sim 10*10^9$/L). Other continuous variables (IL-6, CRP, PCT, and NLR) were

transformed into dichotomous variables based on their optimal cut-off values for the identification of sepsis alone in the training cohort. For the training cohort, a multivariable logistic regression analysis was performed and the OR for each variable was used to construct the simple risk scoring model [20, 21]. Then, the ROC curve was constructed and the AUC was calculated to evaluate the discrimination performance of this scoring model. The optimal cut-off value of the score for predicting sepsis was determined using the Youden index. Finally, this simple risk scoring model was used to calculate risk scores for each patient in the validation cohort, and the AUC was derived based on the risk scores.

We further compared the ROC curves of the nomogram model and the simple risk scoring model to find whether there is a difference in the predictive ability between the two models. Statistical analyses in this study were performed by SPSS (version 17.0, Chicago, USA), R software (version 4.1.0, Vienna, Austria) and MedCalc (version 19.0.4, Ostend, Belgium).

Results

Patient selection and characteristics

During the study period, 2914 patients were admitted in ICU. According to our inclusion and exclusion criteria, 2074 patients were included in study. And 1451 patients were randomly assigned to the training cohort and 623 to the validation cohort (Fig. 1). The baseline characteristics of the patients in two cohorts were similar, as shown in Table 1. The incidence of sepsis was 688/1451 (47.4%) in the training cohort and 284/623 (45.6%) in the validation cohort. No significant difference was detected (p = 0.444).

Table 1
Baseline characteristics of the training cohort and validation cohort

Variable	Training cohort (n = 1451)	Validation cohort (n = 623)	P value
Demographics			
Age, years (IQR)	64(52, 74)	64(51, 74)	0.562
Male (%)	892(61.5)	390(62.6)	0.629
BMI, Kg/m^2 (IQR)	23.56(21.16, 26.03)	23.53(21.22, 25.95)	0.792
Vital signs (IQR)			
Temperature, ∘C	36.2(36.0, 36.5)	36.2(36.0, 36.5)	0.792
SBP, mmHg	131(113,149)	131(112,149)	0.628
HR, bpm	89(75,102)	88(76,102)	0.669
RR, bpm	16(15,19)	16(15,19)	0.535
Sepsis (%)	688 (47.4)	284(45.6)	0.444
SOFA (IQR)	4(2, 7)	4(2, 6)	0.226
Comorbidities (%)			
Hypertension	586(40.4)	247(39.6)	0.753
Diabetes	290(20.0)	125(20.1)	0.968
CHD	245(16.9)	108(17.3)	0.802
CHF	49(3.4)	22(3.5)	0.859
Cerebral vascular disease	146(10.1)	79(12.7)	0.079
Chronic pulmonary disease	74(5.1)	31(5.0)	0.906
Liver disease	81(5.6)	40(6.4)	0.455
Renal disease	87(6.0)	48(7.7)	0.148
First laboratory tests (IQR)			

IQR interquartile range, BMI body mass index, SBP systolic blood pressure, HR heart rate, RR respiratory rate, CHD coronary heart disease,

SOFA Sequential Organ Failure Assessment, CHF chronic heart failure, WBC white blood cell, IL-6 interleukin-6, Hb hemoglobin, PLT platelet, NLR neutrophil-to-lymphocyte ratio, CRP C-reactive protein, BNP B-type natriuretic peptide, ALT alanine aminotransferase,

AST aspartate aminotransferase, Alb albumin, DBil direct bilirubin, TBil total bilirubin, SCr serum creatinine, PCT procalcitonin, Lac lactic acid.

Variable	Training cohort (n = 1451)	Validation cohort (n = 623)	P value
WBC (*10^9/L)	10.34(7.49, 13.93)	10.56(7.98, 13.88)	0.400
IL-6 (pg/ml)	90.26(36.96, 238.50)	78.35(33.22, 212.80)	0.079
Hb (g/L)	104(89, 119)	103(88, 121)	0.859
PLT (*10^9/L)	172(125, 231)	184(133.252)	0.001
NLR	13.21(7.88, 22.12)	12.96(7.69, 21.65)	0.866
CRP (mg/dl)	1.55(0.27, 5.01)	1.30(0.22,5.08)	0.480
BNP (pg/ml)	242.20(87.20, 918.00)	235.50(87.20, 814.00)	0.544
ALT(u/L)	18.80(11.00, 38.80)	19.30(11.00, 39.50)	0.924
AST(u/L)	24.50(16.00, 47.70)	24.20(16.10, 47.20)	0.988
Alb (g/L)	30.90(27.00, 34.50)	31.20(27.70, 35.00)	0.086
DBil (μmol/L)	5.90(3.60, 10.10)	5.60(3.50, 8.90)	0.064
TBil(μmol/L)	13.00(8.30, 19.80)	12.40(8.40, 19.00)	0.297
SCr (μmol/L)	70.40(54.50, 93.70)	70.30(55.50, 92.10)	0.844
PCT (ng/ml)	0.20(0.06, 0.97)	0.15(0.06, 0.82)	0.080
Lac (mmol/L)	1.60(1.10, 2.70)	1.60(1.00,2.50)	0.168
IQR interquartile range, BMI body mass index, SBP systolic blood pressure, HR heart rate, RR respiratory rate, CHD coronary heart disease,			
SOFA Sequential Organ Failure Assessment, CHF chronic heart failure, WBC white blood cell, IL-6 interleukin-6, Hb hemoglobin, PLT platelet, NLR neutrophil-to-lymphocyte ratio, CRP C-reactive protein, BNP B-type natriuretic peptide, ALT alanine aminotransferase,			
AST aspartate aminotransferase, Alb albumin, DBil direct bilirubin, TBil total bilirubin, SCr serum creatinine, PCT procalcitonin, Lac lactic acid.			

Results of Logistic regression analyses in the training cohort

After univariate logistic and multivariable logistic regression analyses, all of these five markers (WBC, CRP, IL-6, PCT, and NLR) were the independent risk factors for sepsis. The optimal cut-off values for CRP, IL-6, PCT and NLR identifying sepsis alone were 1.3 mg/dl, 90 pg/ml, 0.5 ng/ml and 15, respectively. Then, they were transformed into dichotomous variables according to the cut-off values. Furthermore, another multivariable logistic regression analysis was conducted based on dichotomous variables. And

the ORs for WBC, CRP, IL-6, PCT and NLR were 2.13 (95% CI: 1.63–2.78), 2.32 (95% CI: 1.76–3.05), 2.82 (95% CI: 2.17–3.67), 4.74 (95% CI: 3.52–6.39) and 4.66 (95% CI: 3.56–6.10), respectively (Table 2).

Table 2
Univariate and multivariable logistic regression analyses of inflammatory markers related to sepsis in the training cohort

Variables	Univariate analysis		Multivariate analysis				
	OR (95%CI)	P value	Continuous variables		Dichotomous variables		
			OR (95%CI)	P value	Cut-off	OR (95%CI)	Scores
CRP (mg/dl)	1.206 (1.169, 1.243)	P < 0.001	1.130 (1.089, 1.173)	P < 0.001	≥ 1.3 < 1.3	2.317 (1.761, 3.049)	2.5 0
IL-6 (pg/ml)	1.002 (1.001, 1.002)	P < 0.001	1.001(1.001,1.002)	P < 0.001	≥ 90 < 90	2.821 (2.171, 3.665)	3 0
PCT (ng/ml)	1.582 (1.426, 1.755)	P < 0.001	1.249(1.137,1.371)	P < 0.001	≥ 0.5 < 0.5	4.740 (3.518, 6.387)	4.5 0
NLR	1.071 (1.059, 1.084)	P < 0.001	1.064(1.050,1.078)	P < 0.001	≥ 15 < 15	4.658 (3.558, 6.098)	4.5 0

WBC white blood cell, CRP C-reactive protein, IL-6 interleukin-6, PCT procalcitonin, NLR neutrophil-to-lymphocyte ratio, OR odds ratio, CI confidence interval.

Performance of the nomogram

According to the results of logistic regression analyses, the first laboratory test results of WBC, CRP, IL-6, PCT and NLR after ICU admission were used to construct nomogram (Fig. 2). In the training cohort, the nomogram showed a good discrimination for sepsis, with an AUC 0.854 (95%CI: 0.835–0.872). At the optimal cut-off value, the sensitivity and specificity were 82.0% and 73.7%, respectively (Fig. 3A). In the validation cohort, the AUC was 0.857 (95%CI: 0.827–0.883). There was no significant difference between two cohorts in terms of the discrimination (P = 0.879; Fig. 3A). Furthermore, we compared the discrimination between nomogram and SOFA scores, and nomogram showed a better discrimination (P < 0.0001; Fig. 3C). The calibration curves presented a good agreement between the nomogram prediction and actual observed for incidence of sepsis (Fig. 4).

Performance of the simple risk scoring model

According to the result of multivariable logistic regression based on dichotomous variables, we developed a simple risk scoring model, which was composed of five inflammatory markers, and the total scores range from 0 to 16.5 points (Table 2). The model showed good discrimination for sepsis in both the training cohort and the validation cohort, with an AUC 0.842 (95%CI: 0.822–0.861) and 0.847 (95%CI: 0.816–0.874). No significant difference was detected between two cohorts in terms of the discrimination ($p = 0.7941$; Fig. 3B). In training cohort, the optimal cut-off value was 7.5 points, with a sensitivity 77.03% and specificity 75.75%. Then, we compared the simple risk scoring model with nomogram and SOFA scores for sepsis discrimination. Results indicated the simple risk scoring model was comparable with nomogram in the discrimination of sepsis ($p = 0.1298$; Fig. 3C), and the simple risk scoring model performed better than SOFA scores in the discrimination of sepsis ($p < 0.0001$; Fig. 3C).

Discussion

Sepsis is a complex disorder with high morbidity and mortality, and remains a global health priority [22]. Early identification of sepsis can facilitate timely clinical interventions and may improve prognosis [23]. Our study indicated that inflammatory markers, including WBC, CRP, IL-6, PCT and NLR, were independent risk factors for sepsis in critically ill patients admitted to ICU. Furthermore, a nomogram and a simple risk scoring model were constructed. The prediction performance of the two models on sepsis is comparable and better than that of SOFA scores.

To our knowledge, early detection of sepsis is necessary to initiate specific goal-directed therapy bundles to minimize complications; hence, many studies have focused on early sepsis detection. According to the consensus definition paper, quick SOFA (qSOFA) score is highly recommended to raise suspicion of sepsis [1]. Although qSOFA is clinically valuable, it may be suitable for non-ICU patients rather than ICU patients [24–27]. Microbial cultures are still the gold standard for diagnosing sepsis, but the results are generally available after several days. In addition, in patients receiving antimicrobial treatment, the results sometimes may be false negative.

Sepsis is considered to be a systemic inflammatory response due to infection, resulting in organ dysfunction. Inflammation plays a crucial role in the process of sepsis. Our study combined inflammation makers, including

WBC, CRP, IL-6, PCT and NLR, to predict sepsis. WBC is the most commonly inflammatory marker in clinic, and WBC count greater than 12000 or less than 4000 /microliters is one of the criteria for the diagnosis of systemic inflammatory response syndrome (SIRS) [28]. It is well established that CRP is an acute inflammatory marker that acts as part of the acute-phase reaction in sepsis, and its concentration increases during infection [29, 30]. CRP has a half-life of 19 hours, and it is produced within 4–6 hours after inflammation onset and peaks at 36–48 hours [31, 32]. IL-6 is an important proinflammatory cytokine produced early in inflammation and plays a role in the complex pathophysiology process of

sepsis [33, 34]. IL-6 levels begin to rise within 1 hour of the infectious stimulus and peaked at 2 hours [35]. PCT has attracted much attention due to its high accuracy in sepsis diagnosis and prognosis [36]. PCT is secreted by many cell types during systemic inflammation of infectious origin, and the level is generally low in nonbacterial origin systemic inflammation [37]. The half-life of PCT is 24 hours, and its level begin to rise within 2–4 hours after systemic inflammation and peaks at 12–48 hours, making it valuable in the early detection of sepsis [38]. During the progress of sepsis, apoptosis-induced lymphopenia is a prominent feature of sepsis, and neutrophils are recruited to control infection [39–42]. A dramatical increase in NLR can be observed in sepsis. These makers are readily available and routinely measured at admission to our ICU. However, using any of above-mentioned markers alone to identify sepsis may lack sensitivity and specificity. Therefore, we developed and validated a nomogram model including all of the above markers to predict sepsis in critically ill patients.

Although some previous studies have constructed nomogram models in predicting sepsis, there has been no study combining the results of WBC, CRP, IL-6, PCT and NLR measured at ICU admission to predict sepsis [43–46]. Our nomogram model showed good prediction performance as indicted by the AUC value. The calibration curves presented a good agreement between the nomogram prediction and actual observed for incidence of sepsis. Nomogram is a visualized, reliable and intuitive graphical tool for predicting and quantifying risk of individual experiencing a clinical event based on relevant factors, however, sometimes bedside applications are not so convenient. Therefore, a simple risk scoring model based on dichotomous variables is developed and its prediction performance is comparable to that of the nomogram, which can somewhat help clinicians quickly determine the risk of sepsis at an early stage.

This is the first study to construct a nomograph predictive model of sepsis in ICU using five commonly available inflammatory markers. Furthermore, a simple risk scoring model with good prediction performance is constructed. This study also has some limitations. First, this is a single-center retrospectively study and without external validation. The model needs other centers to further evaluate. Secondly, the study mainly focused on ICU patients, which may not be suitable for emergency patients. Thirdly, to make the model simple and practical, we did not include other laboratory tests other than inflammatory markers, which may potentially reduce the performance of the model.

Conclusion

This study using five commonly available inflammatory markers, including WBC, CRP, IL-6, PCT and NLR, developed a nomogram model and a simple risk scoring model to predict sepsis in critically ill patients. Although the prediction performance of the two models is comparable, the simple risk scoring model may be more practical for clinicians to identify potential sepsis in critically ill patients at an early stage and make treatment strategies.

Abbreviations

AUC

area under the curve; BMI:body mass index; CRP:C-reactive protein; CIs:confidence intervals; HR:heart rate; ICU:intensive care unit; IL-6:interleukin-6; NLR:neutrophil-to-lymphocyte ratio; OR:odds ratio; PCT:procalcitonin; RR:respiratory rate; ROC:receiver operating characteristic curves; SOFA:Sequential Organ Failure Assessment; SBP:systolic blood pressure; SIRS:systemic inflammatory response syndrome; WBC:white blood cell.

Declarations

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Ethics approval and consent to participate

Considering this is a retrospective observational study, the Institutional Review Committee of our hospital granted a waiver of informed consent for this study.

Consent for publication

Not applicable.

Availability of data and materials

The cohorts generated and/or analyzed during this study are not publicly available, due to currently ongoing research studies, but the data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XML conceived of the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. CL participated in the design, performed statistical analyses, and helped to draft the manuscript. XLW participated in the design and performed statistical analyses. ZM participated in the design and coordination. HYY participated in data collection and statistical analyses. FHZ conceived of the study, participated in the design, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Figures

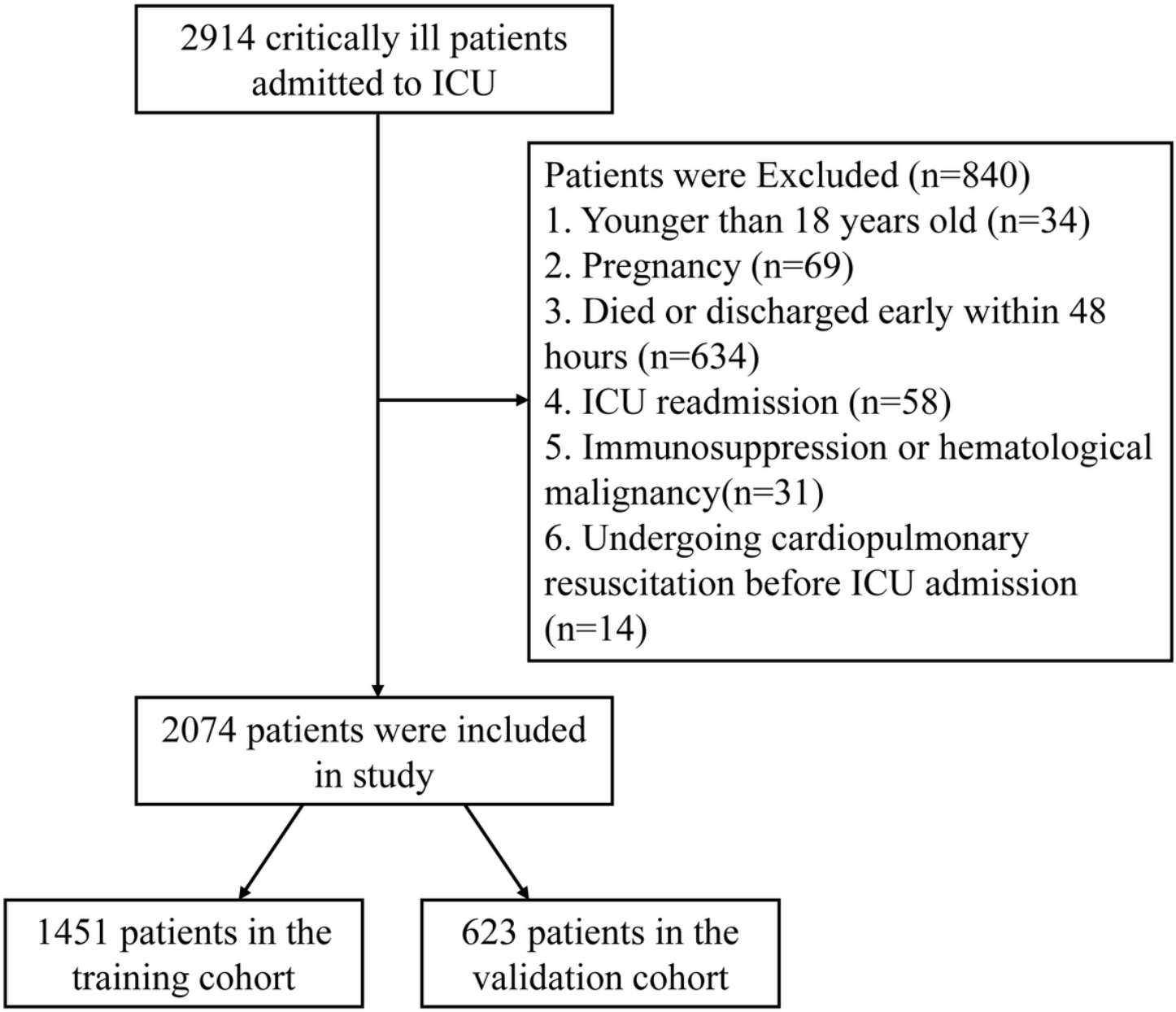

Figure 1

Flowchart of the enrolled patients.

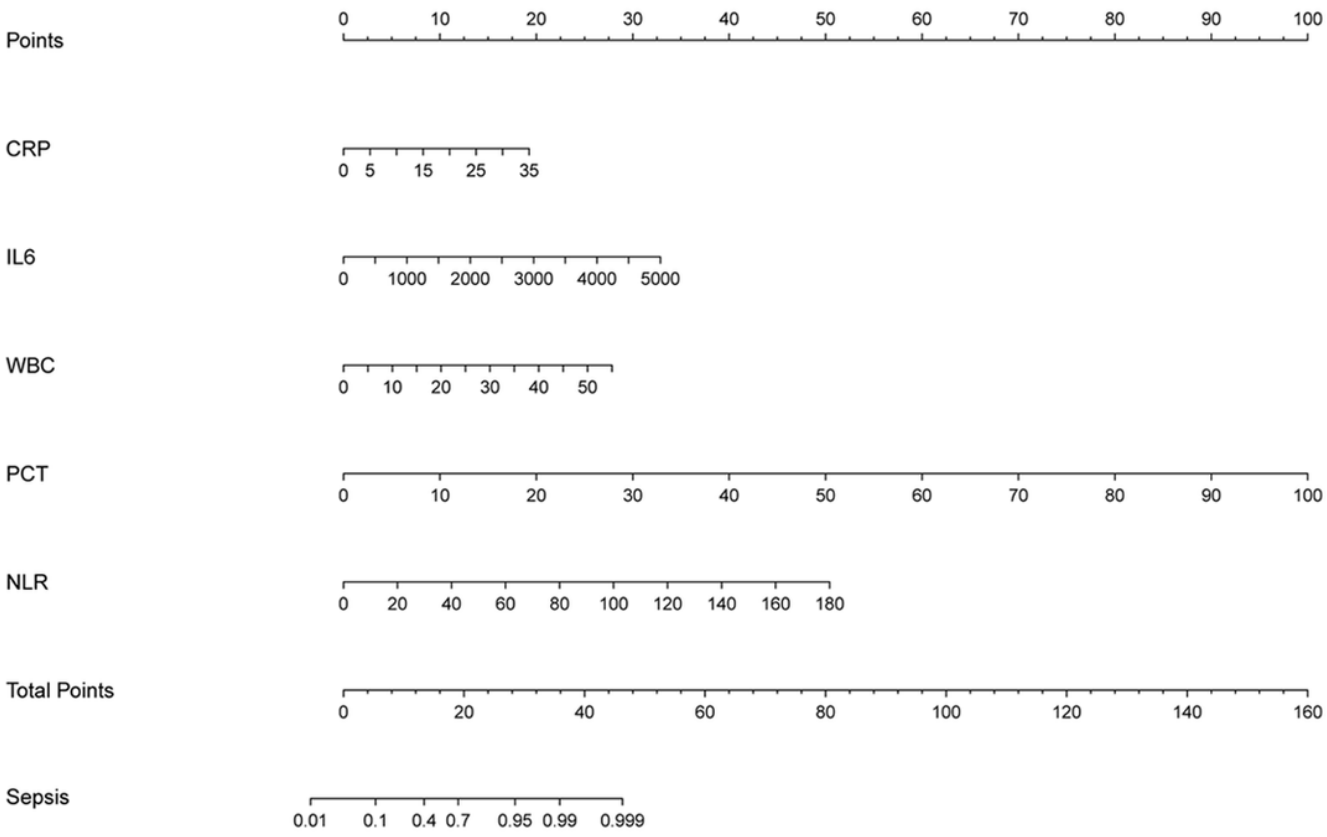

Figure 2

Nomogram predicting the probability of sepsis in critically ill patients of training cohort.

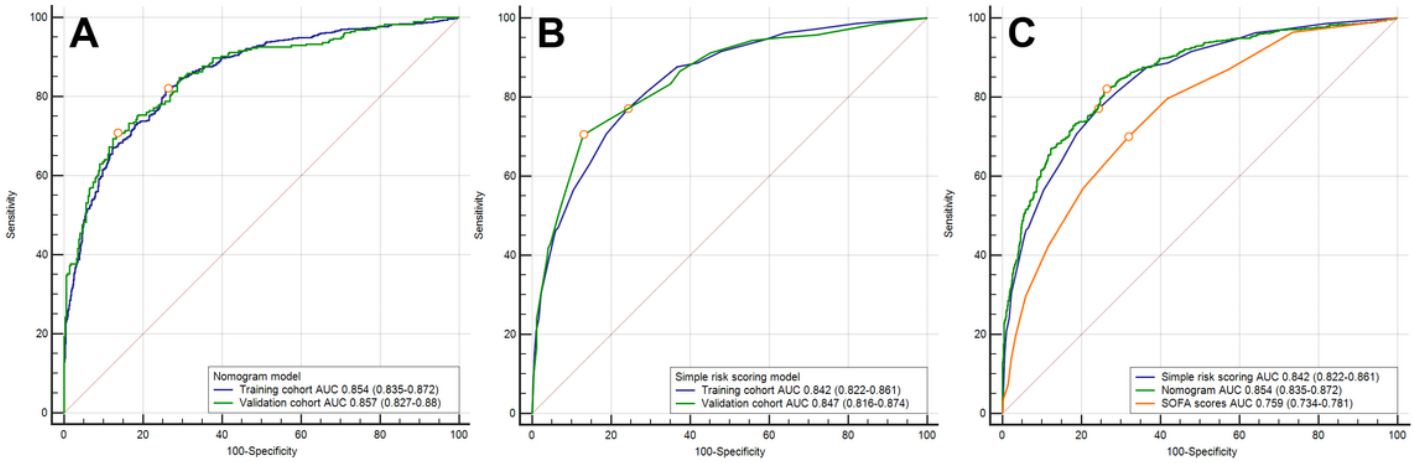

Figure 3

Receiver operating characteristic curve analyses of models for predicting sepsis. (A) Nomogram model; (B) The simple risk scoring model; (C) Nomogram model, simple risk scoring model and SOFA scores.

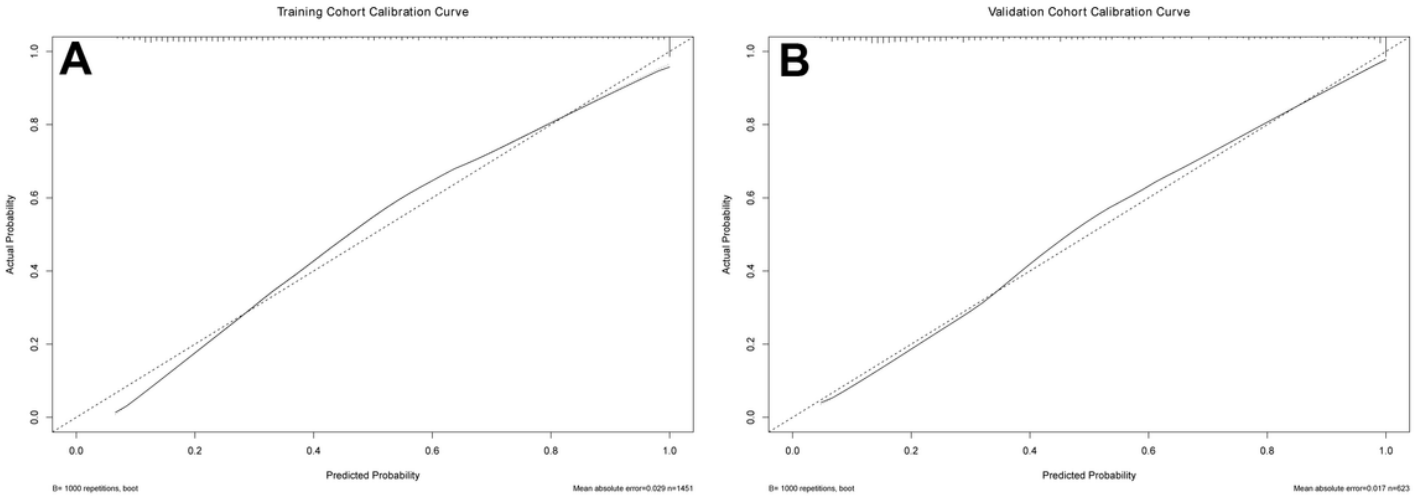

Figure 4

Calibration curves for nomogram model in the training cohort (A) and validation cohort(B). In the calibration curve, the X-axis represents the predicted probability of sepsis, and the Y-axis represents the actual sepsis incidence rate. The 45º diagonal dotted line represents ideal predictions. The solid line represents the performance of the nomogram model, of which a closer fit to the diagonal dotted line represents a better prediction.