Development of a nomogram to predict hospitalized mortality of patients with sepsis

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Abstract

Background

Sepsis is a severe organ dysfunction caused by infection, which is a leading cause of morbidity and mortality in critically ill patients. We developed a novel risk-predicted nomogram of hospitalized mortality for this retrospective study.

Methods

The study involved a retrospective analysis of sepsis patients diagnosed between January 2013 and December 2019. Based on clinical outcomes, patients were categorized into a survival group and a death group. Using logistic regression analysis, a predictive model with a nomogram was formulated in the training set, after which internal validation and sensitivity analysis were performed. C-index and calibration curves were used in the training and validation cohorts to evaluate nomogram discrimination and calibration. Utilizing decision curve analysis, an assessment of the clinical utility of the final nomogram was conducted.

Results

A total of 494 patients were enrolled for analysis. In the multivariate analysis, cardiac function (OR: 1.58, P = 0.039) stood out as an independent sepsis risk factor, whereas hemoglobin (OR: 0.98, P = 0.025) served as a protective factor. Although the multivariate regression analysis did not detect any significant differences in AKI staging, in light of the previous studies, a nomogram for the prediction of hospitalized sepsis mortality was constructed by taking into account these three factors. Based on this model's C-index of 0.626, it suggested moderate predictive power.

Conclusions

Our study indicates that patients with sepsis in combination with anemia, cardiac dysfunction, and AKI are associated with significantly high mortality. To some extent, this may contribute to the determination of risk assessments and treatment strategies.

Introduction

Sepsis is a dysregulated response to infection that causes potentially fatal organ damage and is taking a heavy financial and medical toll on families and society as a whole, which remains the main cause of admission to intensive care unit (ICU)[1]. The current treatment for sepsis includes treating the septic foci with antibiotics, and optimization of organ perfusion, which includes fluid resuscitation and vasopressors[2]. The heart is one of the most commonly involved organs in sepsis which significantly

increases the mortality rate of sepsis. Systolic and diastolic dysfunction appear frequently in severe sepsis and septic shock[3]. During resuscitation, fluid administration and elevated left ventricular filling pressure are associated with cardiac dysfunction. SA-AKI is a widespread and severe complication of sepsis that meets both consensus criteria for sepsis and AKI[4], which is indicative of multiorgan dysfunction and significant adverse outcomes[5]. Thus, developing a predictive model, particularly in early hospitalization stages, is essential for helping to develop prevention strategies.

Echocardiography and tissue Doppler imaging are noninvasive alternatives for hemodynamic monitoring. Diastolic dysfunction can be classified by several echocardiographic measures based on American Society of Echocardiography (ASE 2009) guidelines [6], but it has limitations due to the complexity of measurement and the frequent presence of tachycardia or atrial fibrillation in critically ill patients. The ratio of early transmitral flow velocity to early diastolic mitral annulus velocity (E/e') is often used to reflect the increase in left atrial pressure[7], and it is easy to be measured.

Noteworthy, the nomogram is a reliable tool that has demonstrated the ability to quantify the risk to create a visualized graph of the predictive model by combining and clarifying significant relevant factors[8]. Thus, the primary aim of this study is to investigate the impact of sepsis on hospitalized mortality and to develop a prognostic model for critically ill patients during hospitalization.

Material And Methods

Patient Selection

The retrospective study was approved by the Ethics Committee of Fujian Provincial Hospital (Ethics Code: K2020-05-014) and Fujian Medical University Union Hospital (Ethics Code: 2019KJCX006) from January 2013 to December 2019. Transthoracic echocardiography was performed within 24 hours of admission on all participants enrolled in the study. The study involved a total of 494 patients. The study included adult patients (> 18 years of age) diagnosed with sepsis based on Sepsis-3 (Third International Consensus Definitions for Sepsis): (1) the presence of infection confirmed by microbiological culture or clinical diagnosis and (2) Sequential Organ Failure Assessment (SOFA) score ≥ 2. Exclusion criteria included age less than 18 years old, hemodialysis or end-stage renal disease, acute coronary syndrome, post-renal causes of renal injury, valvular heart disease, heart failure, cardiopulmonary resuscitation before ICU admission, active malignancy, survival time less than 24 hours, pregnant women, and poor quality echocardiographic images. The grouping was determined using a pre-seeded random number generator in R software (version 4.1.0). After random assignment, patients were split into two cohorts: training (n = 371) and validation (n = 123) according to a 3:1 ratio.

Data collection

Demographic and clinical data, physiological parameters, transthoracic echocardiographic parameters, the laboratory data including leukocyte counts, hemoglobin, platelet counts, serum creatinine, urea nitrogen, creatine kinase isoenzyme, and albumin measured within the first 24 hours of ICU admission,

site of infection and type of microorganism, chronic conditions, comorbidities, and the use of invasive mechanical ventilation and continuous renal replacement therapy (CRRT). According to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score, the severity of illness and organ failure was evaluated on the first day of ICU admission.

Echocardiography

Transthoracic echocardiography was performed exclusively by sonographers. Parameters were obtained from long-axis and short-axis parasternal views; apical four-chamber, two-chamber, and long-axis views; and subcostal views using two-dimensional Doppler echocardiography. Data were collected on early transmitral flow velocity (E), late diastolic velocity of mitral inflow (A), early diastolic mitral annulus velocity (e'), E/A ratio, and E/e' ratio. The patients were classified according to American Society of Echocardiography (ASE 2009) guidelines [9] and the simplified definition[10] based on the echocardiographic parameters.

Definitions and outcomes

As defined by Kidney Disease Improving Global Outcomes (KDGIO), AKI is a condition associated with renal decline[11]. The level of anemia is assessed by the reference standard set by the World Health Organization (WHO). Based on the simplified definition of diastolic function in sepsis and septic shock, we classified cardiac functions into the following two categories: normal cardiac function and unnormal cardiac function which includes systolic dysfunction (ejection fraction of <50%), and or diastolic dysfunction. The diastolic dysfunction was classified into three grades (grades I, II, and III) as suggested by Lanspa et al[10].

Statistical analysis

To assess the distribution of variables, Shapiro-Wilk tests were used. Continuous parametric data were expressed as mean±standard deviation (SD), while nonparametric distributions were expressed as median (interquartile range). Numbers (percentages) were used to express categorical data. Unpaired Student t-tests were used to compare parametric continuous variables and Mann-Whitney U tests to compare non-parametric continuous variables. An analysis of categorical variables was conducted using the chi-squared test. In the training cohort, univariate and multivariate factors were analyzed using logistic regressions. A multivariate logistic regression based on forward stepwise selection was conducted on all variables with $P<0.05$ in the univariate logistic analyses. Nomogram predicting the hospitalized mortality was determined using the independently selected significant variables. The C-index was used to measure the discrimination ability of the nomogram. A C-index of 0.5 showed no discrimination, while a C-index of 1.0 implied good discrimination. Additionally, we used a calibration curve to determine the relationship between observed frequency and assumed probability, with a 1000-bootstrapped sample of the training cohort. We evaluated the accuracy of the model by measuring the area under the receiver-operating characteristic (ROC) curve (AUC). The nomogram was assessed in the validation cohort to determine if it was stable and general. Furthermore, we evaluated the clinical utility of

the final nomogram with a decision curve analysis by calculating the net benefit at various threshold probabilities.

Results

Participant Characteristics

From January 2013 to December 2019, a total of 494 patients with sepsis were enrolled in this study, of whom a majority (55.8%) were male. The mean age of patients was (61.69 ± 8.78) years, ranging from 30 to 87 years. Patients were randomly assigned to training (371 patients) or validation (123 patients) cohorts. The patient characteristics were summarized in Table 1, which was shown in supplemental material for details. Both primary and validation cohorts displayed similar baseline clinical characteristics, with survival percentages of 58.5% and 60.2%, respectively.

Table 1
Characteristics of Patients in the Training and Validation Cohorts after randomization

Variable	Training Cohort	Validation Cohort
LVEDD (mm)	49.29 ± 3.48	48.95 ± 3.49
LVESD (mm)	33.97 ± 3.38	33.92 ± 3.55
LVEF(%)	63.90(55.20,67.60)	64.20(53.10,67.70)
E(m/s)	0.81(0.64,1.02)	0.89(0.67,1.09)
A(m/s)	0.75(0.61,0.90)	0.75(0.62,0.91)
E/e'	8.70(7.00,11.50)	8.80(7.20,12.40)
e'(m/s)	0.09(0.07,0.11)	0.09(0.07,0.10)
Age(years)	61.5 ± 8.52	62.25 ± 9.56
BMI	24.93 ± 3.24	24.45 ± 3.21
Leukocyte count (×109/L)	14.75 ± 3.51	14.32 ± 3.49
Platelet count(×109/L)	173(134,208)	169(132,216)
Creatinine at admission (mg/dl)	0.89 (0.68,1.14)	0.89 (0.69,1.23)
Maximum creatinine (mg/dl)	1.54 (0.99,2.56)	1.45 (1.01,2.18)
Serum potassium(mmol/L)	4.78 ± 0.61	4.69 ± 0.60
BUN (umol/L)	15.57 ± 2.61	15.97 ± 2.63
CK-MB(U/L)	16(11,24)	17(10,23)
Total bilirubin (umol/L)	1.02 (0.64,1.26)	0.98 (0.74,1.27)
ALT(U/L)	34(25,43)	35(25,54)
Hb(g/L)	132.02 ± 11.86	133 ± 10.24
Lactate (mg/dl)	51.88 (38.43,73.98)	56.69 (44.20,79.75)
SOFA score	12.28 ± 1.96	12.24 ± 1.93

Variable	Training Cohort	Validation Cohort
APACHE II score	24.49 ± 3.21	24.09 ± 3.16
MAP(mmHg)	82(78,86)	83(77,87)
LOS in ICU (days)	20.3 ± 6.71	19.76 ± 7.77
CRRT free days	17(12,21)	16(11,21)
Cardiac function		
(NEW grading)		
Normal	200(53.9%)	67(54.5%)
Unnormal	171(46.1%)	56(45.5%)
AKI grading		
Normal	116(31.3%)	39 (31.7%)
AKI I	90(24.3%)	35 (28.5%)
AKI II	97(26.1%)	32 (26.0%)
AKI III	68(18.3%)	17 (13.8%)
Sex		
Male	209(56.3%)	66(53.7%)
Female	162(43.7%)	57(46.3%)
Site of infection, n(%)		
Pneumonia	106(28.6%)	37(30.1%)
Urosepsis	38(10.2%)	9(7.3%)
Abdominal sepsis	107(28.8%)	36(29.3%)
Positive blood cultures	153(41.2%)	51(41.5%)
Mechanical ventilation	188(50.7%)	65(52.8%)
Noradrenaline	293(79.0%)	91(74.0%)
CRRT	200(53.9%)	54(43.9%)
Comorbidities		
Hypertension	96(25.9%)	25(20.3%)
Diabetes mellitus	51(13.7%)	22(17.9%)
Coronary artery disease	19(5.1%)	6(4.9%)
Postoperative	60(16.2%)	17(13.8%)

Model specifications and predictors of prognosis during hospitalization

The model was constructed using identified risk factors and demographic characteristics of clinical relevance. Analysis of univariate and multivariate regressions were conducted for variables relevant to death during hospitalization in the training set, and the results are shown in Tables 2 and 3. Three predictors of hospitalized mortality were identified in the final analysis, including hemoglobin levels, AKI grading, and cardiac function.

Table 2
Univariate Logistic Regression Analysis of Factors relating to Hospitalized Mortality in Training Cohort

Variable	OR	95%CI	P-value
LVEDD	0.97	0.92–1.03	0.37
LVESD	1.02	0.96–1.09	0.48
LVEF	0.98	0.96–0.99	0.03
E	0.32	0.12–0.84	0.02
A	0.41	0.14–1.21	0.11
E/e’	1.02	0.98–1.07	0.33
e’	0.00	0.00-0.17	0.02
Age	0.99	0.97–1.02	0.52
BMI	0.99	0.93–1.05	0.67
Sex	1.33	0.87–2.02	0.19
Leukocyte count	1.00	0.95–1.07	0.89
Platelet count	0.99	0.99-1.00	0.49
Creatinine at admission	1.23	0.63–2.42	0.55

Variable	OR	95%CI	P-value
Maximum creatinine	1.08	0.91–1.30	0.38
Serum potassium	1.29	0.91–1.81	0.15
BUN	0.98	0.90–1.06	0.56
CK-MB	1.00	0.99–1.02	0.56
Total bilirubin	0.96	0.68–1.34	0.79
ALT	0.99	0.99-1.00	0.55
Hb	0.98	0.96–0.99	0.03
Lactate	1.00	0.99–1.01	0.59
SOFA	0.98	0.88–1.09	0.72
APACHE II	0.97	0.91–1.04	0.38
MAP	1.02	0.98–1.06	0.30
LOS in ICU	0.99	0.96–1.03	0.72
RRT free days	0.99	0.96–1.02	0.43
Cardiac function (NEW grading)	1.71	1.13–2.60	0.01
AKI grading			0.04
AKI I	1.05	0.59–1.87	0.87
AKI II	1.86	1.07–3.23	0.03
AKI III	1.90	1.03–3.50	0.04
Pneumonia	1.38	0.88–2.18	0.16
Urosepsis	0.80	0.40–1.61	0.54
Abdominal sepsis	0.70	0.44–1.12	0.14
Positive blood cultures	1.47	0.97–2.24	0.07
Mechanical ventilation	1.25	0.82–1.89	0.30
Noradrenaline	0.74	0.45–1.22	0.23
CRRT	1.05	0.69–1.58	0.84
Hypertension	1.27	0.80–2.03	0.32
Diabetes mellitus	1.30	0.72–2.35	0.39
Coronary artery disease	1.61	0.64–4.05	0.32
Postoperative	1.01	0.58–1.77	0.98

Table 3
Results of the multivariate logistic regression analysis of factors relating to Hospitalized Mortality in Training Cohort

Variable	OR	95%CI	P-value
Hb	0.98	0.96–0.99	0.025
Cardiac function (NEW grading)	1.58	1.02–2.44	0.039
AKI grading			
Normal	Ref		
AKI I	1.05	0.58–1.89	0.869
AKI II	1.68	0.95–2.97	0.073
AKI III	1.72	0.92–3.22	0.090

Nomogram for Hospitalized Mortality in the training cohort

The nomogram was developed to predict the probability of death for sepsis patients on multivariate logistic regression analysis (Fig. 1). By adding together all of the factors, the total points were calculated. The ROC curves of the predictive model were shown in the following figure (Fig. 2A and B). The C-index value of this model was 0.626 in the training group (Fig. 2A) and 0.560 in the validation group (Fig. 2B), which meant moderate predictive ability. Furthermore, calibration curves were generated to assess calibration. A general consistency was observed in both the training and validation groups between predicted probability and observed probability (Fig. 3A and B). Clinical utility was quantified by applying decision curve analysis to the training and validation data, which was shown in supplemental material for details (Fig. 4A and B). DCA showed that when the threshold probability was 20%-58% in the training cohort and 25–78% in the validation cohort respectively, the nomogram provided an overall benefit over an all-intervention or no-intervention strategy, suggesting that the nomogram was effective.

Discussion

Numerous studies have already been carried out on the feasibility and benefits of applying nomograms to various fields. The potential strength of this alternative is a more visual assessment of the risk and prognosis of the disease, allowing for early countermeasures. Sepsis is an organ dysfunction caused by infection. When the infection worsens without prompt detection and treatment, it may cause life-threatening complications, such as sepsis shock and organ dysfunction. According to a recent estimate of the worldwide burden of sepsis, there were 194 million patient admissions for sepsis annually and 5.3 million deaths related to sepsis[12]. Therefore, identifying relevant risk factors early is essential to prevent serious adverse outcomes. Our study focused on creating a nomogram based on a multivariate

analysis of three preoperative characteristics: Hb, AKI grading, and cardiac function. This predictive model incorporates comorbidity and complication to assess the in-hospital mortality of sepsis.

Previous studies have indicated acute kidney injury leads to alarming mortality rates in critically ill patients[13]. AKI plays a significant role in increased risk of death in septic patients since it is one of the most commonly involved organs in sepsis[14]. Although sepsis is one of the main causes of AKI, the two syndromes can interweave in the condition of sepsis-associated AKI[15]. The incidence of Sepsis Associated Acute Kidney Injury (SA-AKI) is greater among critically ill patients, and is associated with a higher likelihood of in-hospital death and longer hospital stay than AKI caused by other conditions[16]. There has yet to be reported a single effective treatment for SA-AKI. There has been no report of a single treatment that can significantly change the outcome of SA-AKI to date[17]. It is noteworthy that early diagnosis and treatment can have a positive impact on patient outcomes. A recent study suggests that increased AKI staging and septic AKI are associated with higher mortality[18]. AKI III was correlated with a high rate of hospital mortality in septic patients[19]. Our study shows that mortality rates are significantly higher in AKI II and III than in stage I. Although there is no statistically significant difference, given that this study is limited by the inadequate sample size to reflect the relationship.

The presence of cardiac dysfunction is common in patients suffering from sepsis or septic shock, which is a major cause of death. It has been reported mortality rate of 70–90% in sepsis patients with cardiac dysfunction, compared to 20% without cardiac dysfunction[20]. Septic shock and severe sepsis involve the entire cardiovascular system[21]. A dysfunctional microvascular system results in capillary leakage, tissue edematous, and hypoxia. Hemodynamic disturbances can further be significantly exacerbated by myocardial dysfunction[22]. Accurate identification of cardiac dysfunction and prediction of patients at risk of developing death is essential to improve treatment in practice. According to studies, patients who have only systolic dysfunction (left ventricular ejection fraction ≤ 50%), diastolic dysfunction only, or combined systolic and diastolic dysfunction have poor prognoses[3]. Yu et al. have found that there is a positive association between left ventricular diastolic dysfunction grade and the risk of septic AKI[23]. Cardiac and renal functions are closely related and interact with each other to increase mortality in sepsis patients. Sepsis patients' mortality is increased by both cardiac and renal impairments, which closely interrelate. Therefore early recognition of cardiac dysfunction in sepsis is crucial.

Erythropoiesis has been shown to be severely affected by inflammation and inflammation-related abnormalities in erythropoiesis lead to early-onset anemia, which has been found in critically ill patients[24]. A common complication of severe sepsis is anemia, characterized by decreased hematocrit and hemoglobin[25], which occurs as a result of iatrogenic blood loss, reduced iron and erythropoietin levels, and a decrease in the lifespan of red blood cells. In addition, fluid sequestration, renal failure, and increased intravascular space may additionally affect changes in hemoglobin concentration when administering intravenous fluids during the acute period of sepsis[26]. Sepsis-associated anemia has been shown to be primarily associated with inflammation[27]. In recent research, study findings suggest that severe anemia can have adverse effects on patients with critical illnesses, decreased plasma iron is part of the natural defense against pathogens. The specific mechanisms are complex and involve iron

metabolism affected by inflammation[28]. Although hematocrit is not a recognized marker of sepsis, an association between sepsis and anemia has been established[29]. Pierce et al[30]. have shown that proinflammatory cytokines can inhibit erythropoietin induced maturation erythroid. Anemia was more prevalent in sepsis patients than in controls in females[26], however, in our study, gender differences were not statistically significant with anemia.

Although the study has several positive results, it has several limitations as well. Firstly, the sample size of this study was small and it was performed in two institutions and different investigators performing ultrasound examinations, so some measurement error is inevitable. Results may be skewed by ignoring some differences among the groups as a result. Secondly, this observational study was retrospective, so it is possible that confounding factors may influence the results if included in the model. Thirdly, we have only conducted internal validation with this database, so external validation is needed in future studies to verify the robustness and performance. Furthermore, these disadvantages are inevitable in a retrospective study. However, this nomogram may help clinicians make reasonable risk assessments and treatment decisions.

Conclusion

An accurate prognostic prediction of hospitalized mortality related to sepsis can be accomplished using a prediction nomogram based on hemoglobin, AKI grading, and cardiac function. This is particularly beneficial in preventing the progression of condition and ultimately improving the prognosis of septic patients.

Abbreviations

LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; E: early diastolic velocity of mitral inflow; A: late diastolic velocity of mitral inflow; e': early diastolic mitral annular velocity; E/e': early diastolic velocity of mitral inflow to early diastolic mitral annular velocity; BMI: body mass index; MAP: mean arterial pressure; BUN: Blood Urea Nitrogen; CK-MB: creatine kinase-MB; ALT: Alanine aminotransferase; LOS in ICU: length of stay in intensive care unit; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; CRRT: continuous renal replacement treatment; AKI: acute kidney injury; Hb: hemoglobin.

Declarations

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Author's contributions

Conception and design: K Cheng, GW Yu, XF Zhou, FH Lin; Provision of study materials or patients: K Cheng, GW Yu, XF Zhou, FH Lin; Collection and assembly of data: K Cheng, GW Yu; Data analysis and interpretation: K Cheng, GW Yu; The first draft of the manuscript was written by K Cheng. All authors contributed to the interpretation of the results and critical revision of the manuscript. The authors have approved the final manuscript before submission. K Cheng, and GW Yu contributed equally to this work.

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Availability of data and materials

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent for participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Fujian Provincial Hospital (Ethics Code: K2020-05-014) and Fujian Medical University Union Hospital (Ethics Code: 2019KJCX006). The use of these data was approved by two hospitals. The ethics committees of both hospitals waived informed consent because of the study's retrospective, noninterventional, and observational nature.

Consent for publication

Not applicable.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Figures

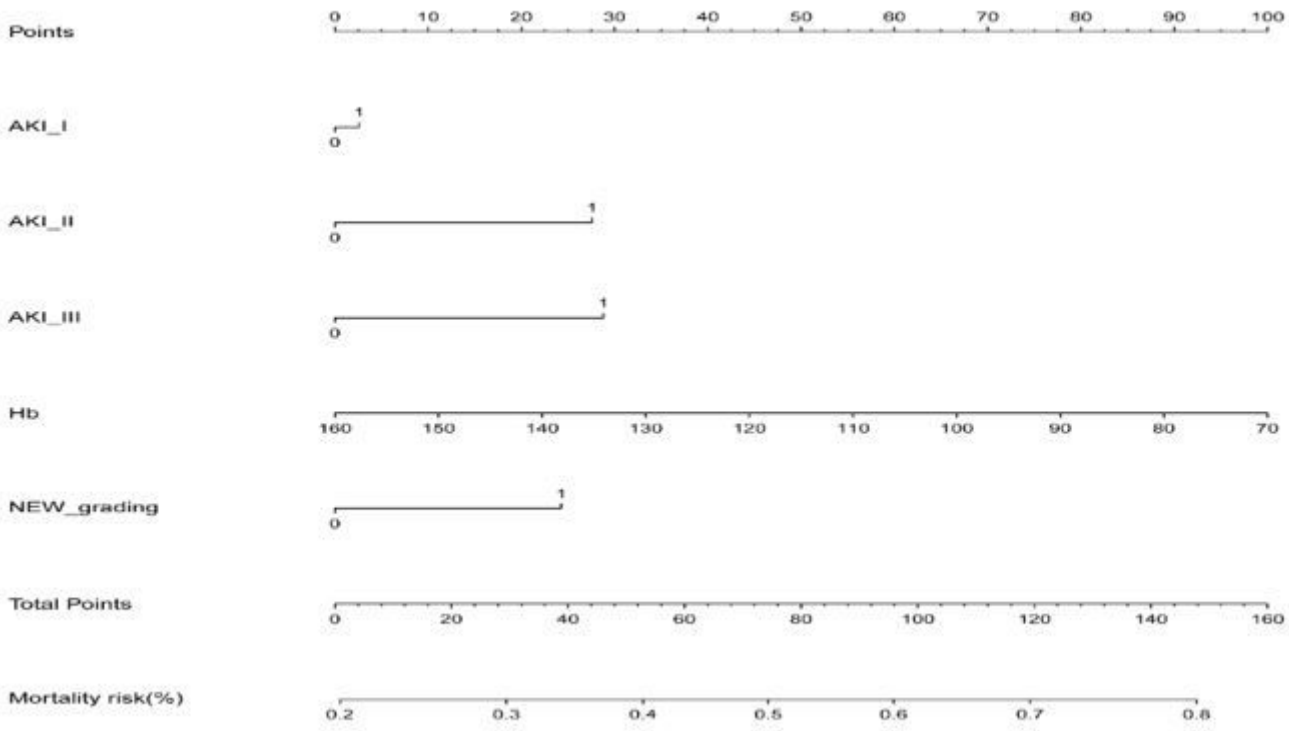

Figure 1

Nomogram for sepsis patients predicting hospitalized mortality

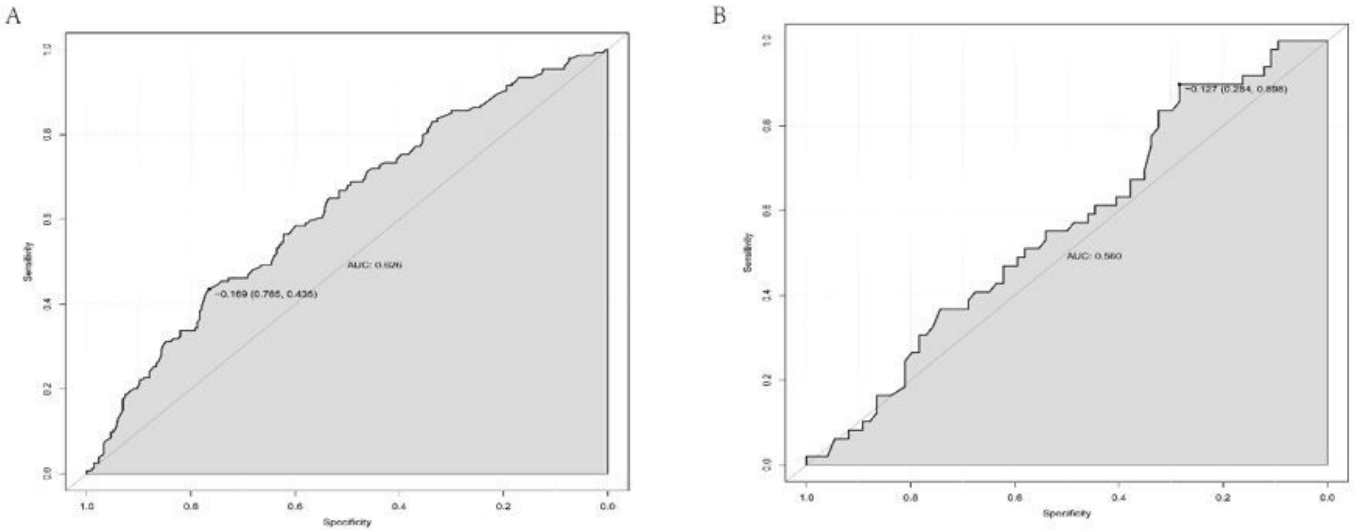

Figure 2

(A) ROC curve of the constructed nomogram in the training Cohort. **(B)** ROC curve of the constructed nomogram in the validation Cohort.

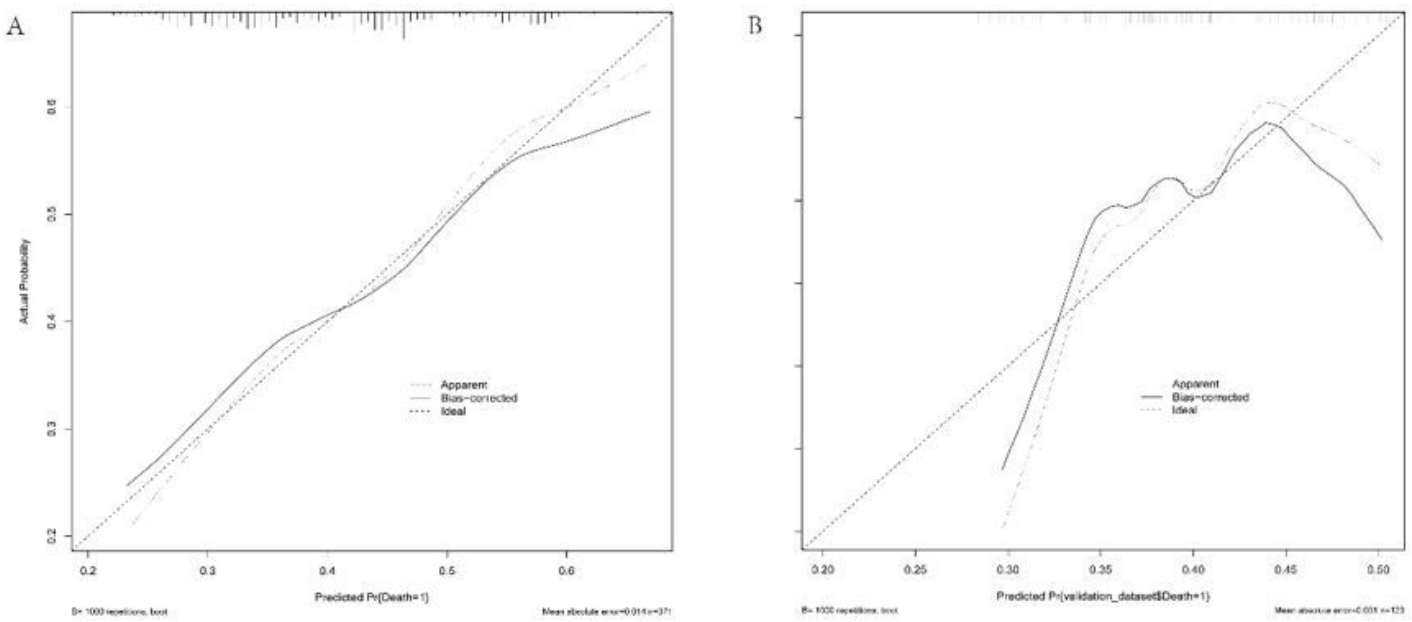

Figure 3

(A) Calibration curve in the training cohort. **(B)** Calibration curve in the validation cohort. The long-dashed line represents a perfect prediction through the use of an ideal model. The short-dashed line and the black line indicate the performance of the apparent and bias-corrected model, respectively.

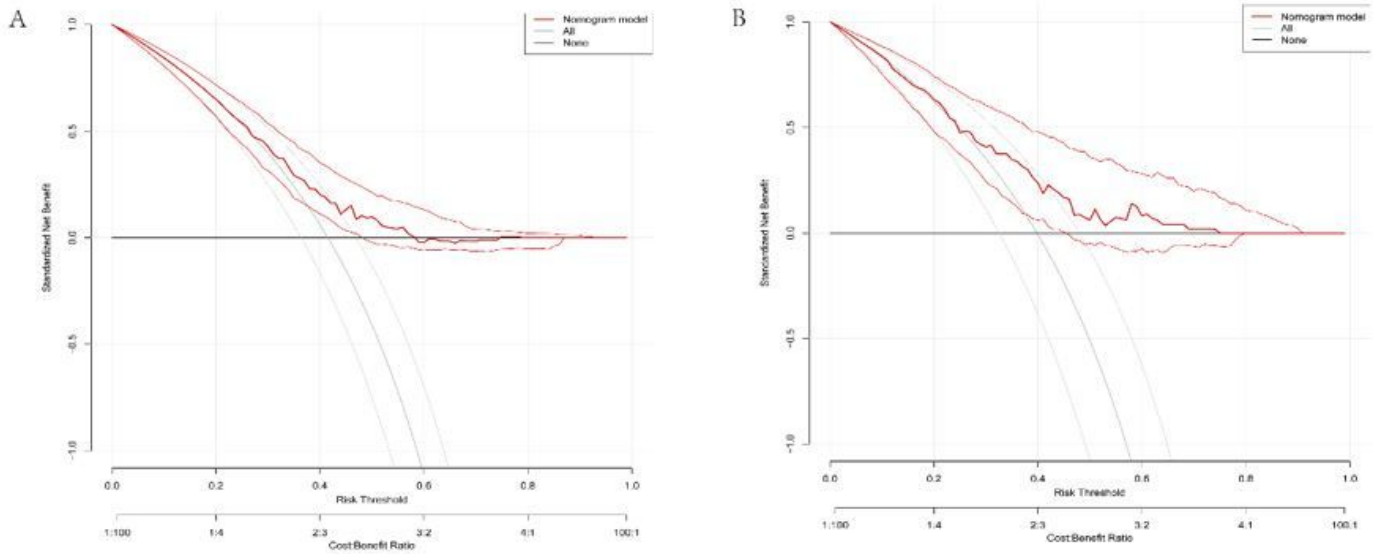

Figure 4

Decision curve analysis (DCA). When the risk threshold is around 20–58% in the training cohort and 25–78% in the validation cohort respectively, the net benefit of application of the model on taking measures is greater than “treat-all-patient” or “treat-none” scheme.