

# Development of a nomogram to predict in-hospital mortality of sepsis-associated encephalopathy: a retrospective cohort study

**Yang Yang**

Department of Neurosurgery, Tangdu Hospital, Air Force Medical University, Xi'an, 710038

**Shengru Liang**

Department of Endocrinology, Xijing Hospital, Air Force Medical University, Xi'an, 710032

**Jie Geng**

Department of Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, 710038

**Qiuhe Wang**

Department of Liver Disease and Digestive Interventional Radiology, National Clinical Research Centre for Digestive Disease and Xijing Hospital of Digestive Diseases, Air Force Medical University, Xi'an, 710032

**Pan Wang**

Institute of Medical Research Northwestern Polytechnical University, Xi'an, 710072

**Yuan Cao**

Department of Neurosurgery, Xijing Hospital, Air Force Medical University, Xi'an, 710032

**Rong Li**

Department of Neurosurgery, The 986th Hospital of Chinese People's Liberation Army, Xi'an, 710054

**Guodong Gao**

Department of Neurosurgery, Tangdu Hospital, Air Force Medical University, Xi'an, 710038

**Lihong Li** (✉ [lihonglifmmu@163.com](mailto:lihonglifmmu@163.com))

Tangdu Hospital, Air Force Medical University

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## Research article

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# Abstract

## Background

Sepsis-associated encephalopathy (SAE) is related to an increased in-hospital mortality in patients with sepsis. We aim to establish a user-friendly nomogram for individual prediction of in-hospital death probability in patients with SAE.

## Methods

Data were retrospectively retrieved from the Medical Information Mart for Intensive Care (MIMIC III) open source clinical database. SAE was defined by a Glasgow Coma Score (GCS) <15 at the presence of sepsis. Prediction model with a nomogram was constructed in the training set by Logistic regression analysis and then internally validated. A decision curve analysis (DCA) was performed to evaluate the net benefit of intervention with the nomogram.

## Results

A total of 669 and 287 patients with SAE were randomly assigned to training set and internal validation set according to an allocation ratio of 7:3, respectively. Parameters eligible for the nomogram included age, Sequential Organ Failure Assessment (SOFA) score, red blood cell distribution width (RDW) and the mean values of heart rate, temperature and respiratory rate at first day of ICU admission. The nomogram exhibited good discrimination with an area under the receiver operating characteristic curve (AUROC) of 0.773 (95%CI: 0.729–0.818) in the training set and 0.741 (95%CI 0.673–0.809) in the validation set, respectively. Calibration of the derived model was also excellent, with Brier score of 0.136 (95%CI: 0.12–0.153) and 0.168 (95%CI: 0.144–0.192) in both sets. The DCA of the nomogram indicated greater net benefit than SOFA. X-tile analysis showed that the nomogram can clearly stratify patients into three subgroups with different risks of in-hospital death.

## Conclusions

The nomogram presents excellent performance in predicting in-hospital mortality of SAE patients, which can guide the prevention of SAE progression and may be more beneficial once specific treatments towards SAE are developed.

## Introduction

Sepsis-associated encephalopathy (SAE) is the dysfunction of brain that develops with the process of sepsis without evidence of the central nervous system infection. It is preferentially associated with deterioration of consciousness, behavior, memory and cognitive function, imposing heavy medical and financial burden on families and society [1–3]. More harmfully, patients with sepsis complicated by encephalopathy tend to have higher short-term mortality than those with sepsis alone. A landmark study conducted by Eidelman LA et al. demonstrated that encephalopathy was associated with increased in-

hospital mortality from 16% when the Glasgow Coma Score (GCS) is 15 to 63% when GCS is between 3–8 [4]. Consistent findings were also reported in another high-quality study performed by Romain Sonneville et al. showing that SAE was related to decreased 30-day survival probability from 67% when GCS is 15 to 32% when GCS is between 3–8, and even mild change of consciousness (defined by GCS of 13–14) is an independent risk factor of 30-day death with an hazard rate (HR) of 1.38 after adjustment for confounding factors [5]. The clinical significance of SAE is further strengthened by several other studies consolidating that SAE was responsible for the increase of short-term mortality, prolongation of hospital staying, or excessive therapeutic activity leading to overmuch assumption of medical resources [6, 7]. However, it is still difficult to identify SAE patients with higher risk of in-hospital death and further stratify them. Therefore, the main objective of the present study by a large clinical database was to develop a predictive nomogram to individually predict the probability of in-hospital death in SAE patients and thereby facilitate clinicians to make timely treatment decision and improve the prognosis of such patients.

## Material And Methods

### Data source

We conducted an observational study by retrieving data from the Medical Information Mart for Intensive Care (MIMIC III) open source clinical database, which contains de-identified health-related data of over forty thousand patients who received treatment in critical care units of the Beth Israel Deaconess Medical Center between 2001.06 and 2012.10 [8, 9]. All data in MIMIC III was classified into 26 tables recording various individual information, such as demographics characteristics, treatment measures, nursing notes and laboratory tests. Besides, it contains survival outcome data obtained from the hospital and laboratory health record systems reporting the in-hospital mortality, or from the Social Security Administration Death Master File recording the out-of-hospital survival data. The MIMIC III database can be freely utilized after successful application and ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). Since all data are de-identified in this database to remove patient information, the requirement for individual patient consent is not indispensable.

### Study population and data extraction

PgAdmin (version 4.1, Bedford, USA) was used to run structure query language (SQL) and then to extract data from the MIMIC III database. Six tables were occupied in our study, including DIAGNOSES\_ICD, ICUSTAYS, PATIENTS, LABEVENTS, MICROBIOLOGYEVENTS and PRESCRIPTIONS. We included adult patients (> 17 years of age) with a diagnosis of sepsis according to the Third International Consensus Definitions for Sepsis (Sepsis 3.0): (1) Patients with infection at ICU admission, and (2) the Sequential Organ Failure Assessment (SOFA) score  $\geq 2$  [10]. Excluded were patients with (1) primary brain injury (traumatic brain injury, ischemic stroke, hemorrhagic stroke, epilepsy or intracranial infection); (2) pre-existing liver or kidney failure affecting consciousness; (3) severe burns and trauma; (4) hypothermia or

malignant hyperthermia; (5) chronic alcohol or drug abuse; (6) pre-existing mental illness, including schizophrenia, depression, anxiety, compulsion and dementia; (7) severe electrolyte imbalances or blood glucose disturbances, including hyponatremia ( $< 120$  mmol/l), hypercapnia ( $PCO_2 > 75$  mmHg), hyperglycemia ( $> 180$  mg/dl) or hypoglycemia ( $< 54$  mg/dl); (8) dying or leaving within 24 hours since ICU admission; (9) without an evaluation of GCS. Eligible patients were included in the final cohort for investigation (Additional file 1: Fig.S1). For the final cohort, we retrospectively collected the following data from the database: (1) demographic data and hospital outcome; (2) comorbidity conditions as coded and defined in the International Classification of Diseases, Ninth Revision (ICD-9); (3) mean value of vital signs during the first 24 hours of ICU stay; (4) the first laboratory data since ICU admission; (5) site of infection and type of micro-organism; (6) use of antibiotic, sedative and analgesic agents. The severity of illness and organ failure was assessed by SOFA on the first day of ICU stay [11].

## **Sepsis-associated encephalopathy**

As GCS had been proved to be an excellent tool for characterizing SAE and distinguishing it from sepsis, we defined SAE in the study as sepsis accompanied by GCS  $< 15$  on the first day of ICU admission [4]. For sedated or postoperative patients, we adopted GCS measured before sedation or surgery. Sepsis with normal consciousness (GCS = 15) but complicated by delirium should also be defined as SAE. However, the Confusion Assessment Method developed for ICU patients (CAM-ICU) to diagnose delirium in ICU patients are scarce in the database [12], thus it is unavailable to include this subgroup of patients in the study. Nevertheless, such patients only account for less than 10% of SAE, and show no significant difference on the short-term mortality comparing with sepsis without encephalopathy according to previous report [5]. Therefore, not including this subgroup may not significantly compromise the reliability of the results in our study.

## **Statistical analysis**

Shapiro-Wilk tests was used to assess the distribution of variables. Data were expressed as mean  $\pm$  standard deviation (SD) for parametric continuous data and as median (interquartile ranges) for non-parametric distribution. Categorical data were expressed as number (percentages).

To enhance the stability and reliability of the conclusion, the patients in the final cohort were randomly distributed to a training set and a validation set without replacement at a ratio of 7:3. Parametric continuous variables were compared between training and validation sets by using unpaired Student' t test and non-parametric continuous variables by Mann–Whitney U test. The Chi-Squared test was adopted to assess the differences in categorical variables between datasets.

Logistic regression analysis was used to identify risk factors independently associated with in-hospital mortality. Specifically, variables significantly related to in-hospital death in univariate analysis ( $p < 0.1$ ) were entered into multivariate Logistic regression analysis to calculate estimated odds ratios (OR) and 95% confidence intervals (95%CI), where significant level for independent risk factors was  $p < 0.05$ . To avoid multicollinearity, the significant variables incorporated into the SOFA score were not included in the multivariate analysis. Moreover, a nomogram was obtained by the training set according to Occam's Law

of Razor, namely the best model should be one that can achieve the aim of study with fewer variables [13]. Missing values were addressed with multiple imputation in the process of Logistic regression and model construction. Then, the performance of the nomogram and SOFA score in predicting the probability of in-hospital death were evaluated in both training and validation sets by an area under the curve of the receiver operating characteristic (AUROC). The performance of the nomogram was also evaluated with calibration by bootstrap method with 1000 resampling, and the calibration results of the nomogram and SOFA score were also compared. Besides, integrated discrimination improvement (IDI) was calculated to compare discrimination slopes and Brier score to evaluate model fitness [14]. DCA analysis was performed to evaluate the net benefit of medical intervention conforming each model at different threshold probabilities in the training and validation sets. To achieve the best sensitivity and specificity, X-tile analysis was used to find out the cut-off values of the total score calculated by the nomogram. Kaplan-Meier analysis was conducted to visualize the probability of hospital survival grouped by the cut-off points in both training and validation sets, and log-rank tests were used to identify between-group difference.

Statistical analyses were performed using R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value of  $< 0.05$  was considered statistically significant. All analyses were reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [15].

## Results

### Characteristics of participants

There were a total of 46467 patients entering into ICU for various causes, and 15847 patients with sepsis were included in the study cohort. After screening by the inclusion and exclusion criteria, a total of 956 patients were diagnosed as SAE by GCS  $< 15$  and were included into the final cohort. Characteristics at baseline and upon ICU admission of the 956 participants (669 from the training set and 287 from the validation set) revealed that both sets had no statistic difference in almost all the variables (Table 1,2). The median age of the two sets were 73 (60, 82) and 72 (58, 82) years, respectively. Male accounted for 52.62% and 56.45% of patients in the two sets. Median hospital stay time was 12.33 (7.52, 21.68) days in the training set and 13.98 (8.03, 23.36) days in the validation set, and nearly half of patients were received into the Medical Intensive Care Unit (MICU). The in-hospital mortalities in the two sets were 143 (21.38%) and 58 (20.21%), respectively, without statistical difference ( $p = 0.75$ ). On the first day of ICU admission, SOFA score were 6 (4, 9) and 6 (4, 8) as well as GCS were 13 (9, 14) and 13 (8, 14) in the training set and validation set, respectively.

### Development of a prediction nomogram in the training set

Missing values were addressed by multiple imputation before Logistic regression analysis. We interpolated 10 times and combined them into one dataset by taking their mean values. Univariate and multivariate Logistic regression results are shown in Table.3. Except for bilirubin, PO<sub>2</sub>, SAPSII, GCS and systolic pressure, which were included in SOFA score, sixteen variables with p value < 0.1 in univariate analysis were entered into multivariate analysis. Finally, age, SOFA, RDW, neutrophil to lymphocyte ratio (NLR), heart rate, respiratory rate, temperature, lung infection and gram-positive bacterium(G+) infection were considered as the independent risk factors for hospital death among patients with SAE. Lung infection and G + infection were not included for model development since these two parameters depended on microbial culture, which took more than 48 hours. Then, the performances of all combination of the remaining seven risk factors were comprehensively evaluated and NLR was then excluded due to its minimal contribution to the improvement of model discrimination. Finally, a model integrating age, SOFA, RDW, heart rate, respiratory rate and temperature was established for it had similar discrimination compared with the combined model integrating all the independent risk factors (Fig. 1A). Based on this model, a nomogram was plotted to predict the probability of in-hospital death (Fig. 1B).

## Validation of the predictive nomogram

Comparison between the nomogram and SOFA score for predicting in-hospital mortality in SAE patients was shown in Table.4. The AUROC of the current model was 0.774 (95%CI: 0.729–0.818) in the training set, which was significant higher than that of SOFA with a value of 0.662 (95%CI: 0.61–0.714; p < 0.01) (Fig. 2A); Similarly, the AUROC of SOFA was 0.599 (95%CI: 0.524–0.674) in the validation set, which can be improved by the nomogram to a value of 0.741 (95%CI: 0.673–0.809; p < 0.01). All these results indicated that the predictive nomogram had better discrimination than SOFA in predicting the in-hospital mortality of patients with SAE and about 77.4% as well as 74.9% of the probability of individual mortality would be correctly predicted by the nomogram in both sets respectively.

Calibration curves were depicted for both training and validation sets and the bias-corrected line is formed using a bootstrap approach. In the training set, the apparent curve, the bias-corrected curve and the ideal reference line were closely aligned, demonstrating good calibration (Fig. 3A). In the validation set, the apparent curve and bias-corrected curve slightly deviated from reference line, but a good conformity between observation and prediction is still observed.(Fig. 3B). The Brier score of the nomogram and SOFA were 0.136 (95%CI: 0.12–0.153) and 0.155 (95%CI: 0.138–0.172), respectively in the training set; and 0.168 (95%CI: 0.144–0.192) and 0.193 (95%CI: 0.169–0.216), respectively in the validation set, indicating that the predictive nomogram had better calibration than SOFA (Additional file 2: Fig.S2). Moreover, when compared with SOFA, the IDI of the nomogram was 0.109 (95%CI: 0.081–0.136, p < 0.001) in the training set and 0.083 (95%CI: 0.049–0.117, p < 0.001) in the validation set, which meant that the nomogram could increase the prediction probability of SOFA by 10.9% and 8.3% in the two sets respectively.

# DCA analysis and performance of the nomogram in stratifying risk of patients

With regard to clinical use, the DCA for nomogram was presented and compared with SOFA in both the training and validation sets. In the training set, medical intervention guided by the nomogram could add more net benefit than SOFA when the threshold probability (PT) was between 0.1 and 0.8 (Fig. 4A). In the validation set, treatment directed by nomogram could gain more net benefit when PT was between 0.25 and 0.8 (Fig. 4B).

The score calculated with the nomogram were then divided into three subgroups based on the cut-off values detected by the X-tile analysis in the training set (Fig. 5A), namely 217 and 258 points. Kaplan-Meier curves in both training and validation sets showed significant difference in the in-hospital survival when SAE patients were stratified into low-risk group ( $\leq 217$ ), middle-risk group (218–257) and high-risk group ( $\geq 258$ ) by the cut-off points (log-rank  $p < 0.001$  and log-rank  $p = 0.0052$ , respectively) (Fig. 5B).

## Discussion

In this retrospective analysis by MIMIC III database, we conducted Logistic regression analysis to recognize the independent risk factors for in-hospital death of SAE patients and then predictors including age, SOFA, RDW, heart rate, respiratory rate and temperature were identified and then integrated into a best-fit prediction model visualized as a prediction nomogram. To the best of our knowledge, this is the first study to evaluate the potentially modifiable factors contributing to the hospital death of SAE and to develop a nomogram to predict its hospital mortality. The prediction performance of the nomogram was then tested by discrimination and calibration in a training set and validation set as well as by the bootstrap method, all exhibiting acceptable and stable predicting performance. Moreover, decision curve analysis was employed to account for both the benefits and the costs of intervention to SAE patient guided by the nomogram to validate its clinical usefulness. The decision curve showed that interventions guided by the current nomogram can add more net benefits than SOFA score.

SOFA system was firstly developed to better describe multiple organ failure or morbidity [16]. Since then, researchers found that SOFA was not only a scoring system to evaluate the severity of organ failure but also a useful tool in predicting the in-hospital mortality of cardiovascular disease, trauma and critically ill patients [17–19]. More recently, the third international consensus definitions for sepsis and septic shock (Sepsis-3) recommended the use of SOFA to diagnose sepsis because it is associated with a 10% higher in-hospital mortality of systemic infection, and recognition of this crisis may promote clinicians to give prompt and appropriate medical intervention [10]. Seymour CW et al. further supported the consensus with the finding that the validity of SOFA in discriminating the in-hospital mortality of systemic infection was acceptable with AUROC of 0.74, which has no statistical difference compared with the more complex LODS score but was obviously greater than qSOFA score [20]. These findings indicated that SOFA score is a useful and simple tool in predicting the in-hospital death of patients with systemic infection, but whether it is applicable to the forecast of the in-hospital mortality of patients with SAE is still unclear. Thus, we evaluated the performance of SOFA in predicting the in-hospital death of patients with systemic

infection alone and those with SAE. Results indicated that in the 15847 patients with systemic infection, the AUROC was 0.724 (Additional file 3: Fig.S3), which was similar to the AUROC (0.74) in the study of Seymour CW, indicating a good performance of the SOFA score in discriminating patients with systemic infection under the risk of in-hospital death. Nevertheless, SOFA score exhibited poor performance in discriminating SAE patients under the risk of in-hospital death with AUROC of 0.599–0.662. Therefore, we developed the current predictive model incorporating SOFA score and clinical parameters, which showed better predictive performance than SOFA and exhibited improved discrimination and calibration. Interestingly, SOFA accounted for the biggest weight in the nomogram, indicating that it is the most important predictor in the best fit model and has the strongest power to predict in-hospital mortality in SAE patients.

RDW is a measure of the size of circulating erythrocytes and was routinely used in the differential diagnosis of anemia. However, studies have revealed that RDW is also useful in estimating the short-term mortality of non-hematologic diseases, such as cardiovascular diseases [21, 22], stroke [23], liver diseases [24, 25], and critical illness [26]. In patients with acute subarachnoid hemorrhage or acute heart failure, RDW is even associated with long-term mortality of patients [27, 28]. Consistently, our study demonstrated that RDW is an independent risk factor and potent predictor for the in-hospital mortality of SAE. Mechanisms under the relationship between RDW and short-term mortality of SAE remain largely unknown, but several studies had revealed that RDW is positively associated with inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), in unselected outpatients, autoimmune diseases and healthy population [29–32]. Thus, we hypothesized that the inflammatory response during sepsis may contribute to the adverse impact of RDW on the prognosis of SAE. Besides, oxidative stress may be another reason to connect RDW with poor in-hospital outcome because studies indicated that oxidative stress can increase anisocytosis by disrupting erythropoiesis, and altering the circulating half-life of red blood cell, ultimately leading to increased level of RDW [33, 34].

To further facilitate clinical use and treatment, patients with SAE was stratified into three risk groups based on the cut-off values calculated by the nomogram. The in-hospital mortality in the three risk groups were 7.4%, 28.71% and 45.57% in the training set as well as 11.49%, 26.14% and 44% in the validation set. Interestingly, the in-hospital mortality of the high-risk group was similar to that of patients with septic shock with a value of 42.3% [10]. As septic shock is characterized by the use of vasopressor to maintain mean arterial pressure (MAP)  $\geq$  65 mmHg and an increased level of lactate ( $>$  2 mmol/L), we further compared the frequency of vasopressor use as well as levels of MAP and lactate in the three groups. Results showed significant higher level of lactate and frequency of vasopressor usage in the high-risk group than in the other two risk groups, simultaneously MAP was over 65 mmHg in all groups (Additional file 4–6: Fig.S4-S6), indicating that septic shock may be an important cause for in-hospital death in high risk group. Based on these, medical interventions towards septic shock, including early investigation for and treatment of infection, fluid resuscitation within 15–30 minutes and repeated assessment of hemodynamics, adoption of vasopressor and corticosteroids, provision of supportive care and so on [35, 36], may reduce the in-hospital mortality of SAE patients in the high-risk group. It is difficult to confirm the exact mechanism for the increased in-hospital mortality in the middle-risk group, but the in-hospital

mortality in the middle-risk group was similar to that of septic patients with fluid-resistant hypotension requiring vasopressors but without hyperlactatemia ( $< 2$  mmol/L) [10]. Consistently, the level of blood lactate was lower than 2 mmol/L in the low- and middle-risk groups and had no difference between them (Additional file 4 Fig.S4). We hypothesized that circulatory failure without obvious abnormality of cell metabolism may be one reason for the increased in-hospital mortality in the middle-risk group. In consequence, fluid resuscitation and rational use of vasoactive drugs to improve circulatory function may be useful to prevent in-hospital death of patients in the middle-risk group [37]. Nevertheless, more studies are needed to ascertain the exact causes of in-hospital mortality in the three risk groups so that targeted therapies can be performed or developed to effectively reduce in-hospital death of SAE patients.

Two points should be noted when using the nomogram. First, as vital signs in our study are the mean values of the first 24 hours of each ICU patient, the nomogram is not applicable to patients dying or leaving within 24 hours since ICU admission. Second, laboratory tests in the nomogram are the first results since ICU admission, thus, all the laboratory tests included in the nomogram should be completed within the first 24 hours of ICU admission.

This study has some limitations: First, as specific therapy for SAE is lacking, the interventions mentioned in the DCA analysis are treatments toward sepsis and septic shock [36, 37]. Therefore, it is urgent to develop specific treatment for the encephalopathy during sepsis, which may further enhance the clinical usefulness of the nomogram and reduce the hospital death of SAE patients. Second, the retrospective nature of this observational study determined that unidentified confounding factors may affect the results if adding to the model. Third, as the database lacks data related to the CAM-ICU, septic patients with GCS = 15 but complicated by delirium were not distinguished in the study. Therefore, whether the nomogram is appropriated to this population need to be further verified. Fourth, as neuroimaging data was not included in the study, we cannot assess the impact of organic lesion of brain on in-hospital outcome. Studies based on the results of brain MRI have revealed that the impairments of cerebral white matter in patients with critical illness are not only related to sequelae of the central nervous system but also associated with increased mortality [38]. Fifth, one of the challenges in studying SAE is that without specific diagnostic method, it remains a rule-out definition, which may lead to a high specificity, but relatively low sensitivity for the diagnosis of SAE. Thus, the current nomogram can only be used in SAE diagnosed by exclusion and may require further modification once specific diagnostic methods are developed. Finally, we only conducted an internal validation by the study cohort from the MIMIC database, external validation should be performed in the future study to further validate the robustness and performance of the prediction model.

## Conclusion

A prediction nomogram based on SOFA score, together with patient's age, RDW, mean values of heart rate, temperature and respiratory rate on the first day of ICU admission can be conveniently used to serve accurate prognostic prediction in the hospital mortality of SAE. This may be particularly beneficial in

preventing the deterioration of SAE once specific treatments towards SAE are developed and finally improve the prognosis of SAE patients.

## **Declarations**

### **Ethics approval and consent to participate**

The MIMIC III database has received ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). All data are de-identified in this database to remove patients' information, the requirement for individual patient consent is not indispensable.

### **Consent for publication**

Not applicable

### **Availability of data and materials**

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

### **Competing interests**

The authors declare that they have no competing interests.

### **Fundings**

None.

### **Authors' contributions**

YY, SL and JG analyzed the data and wrote the paper. QW and PW collected the data. YC and RL checked the integrity of the data and the accuracy of the data analysis. LL and GG designed the study and revised the paper. All authors read and approved the final manuscript.

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None

### **Author information**

Yang Yang, Shengru Liang, and Jie Geng contribute equally to this work and are co-first authors.

Lihong Li and Guodong Gao contributed equally to this work and are co-corresponding authors.

### **Affiliations**

Department of Neurosurgery, Tangdu Hospital, Air Force Medical University, Xi'an, 710038, China.

Yang Yang & Guodong Gao

Department of Endocrinology, Xijing Hospital, Air Force Medical University, Xi'an, 710032, China.

Shengru Liang

Department of Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, 710038, China.

Jie Geng

Department of Liver Disease and Digestive Interventional Radiology, National Clinical Research Centre for Digestive Disease and Xijing Hospital of Digestive Diseases, Air Force Medical University, Xi'an, China

Qiuhe Wang

Institute of Medical Research Northwestern Polytechnical University, Xi'an, 710072, China

Pan Wang

Department of Neurosurgery, Xijing Hospital, Air Force Medical University, Xi'an, 710032, China.

Yuan Cao

Department of Neurosurgery, The 986th Hospital of Chinese People's Liberation Army, Xi'an, 710054, China.

Rong Li

Department of Emergency, Tangdu Hospital, Air Force Medical University, Xi'an, 710038, China

Lihong Li

## **Abbreviations**

SAE

Sepsis-associated encephalopathy

GCS

Glasgow coma score

SOFA

Sequential Organ Failure Assessment

RDW

Red blood cell distribution width

IDI

Integrated discrimination improvement  
AUROC  
Area under the receiver operating characteristic curve  
DCA  
Decision Curve Analysis  
qSOFA  
Quick Sequential Organ Failure Assessment  
LODS  
Logistic Organ Dysfunction System  
MIMIC III  
Medical Information Mart for Intensive Care  
SQL  
Structure Query Language  
ICD-9  
International Classification of Diseases, Ninth Revision  
CAM-ICU  
Confusion Assessment Method developed for ICU patients  
NLR  
Neutrophil to Lymphocyte Ratio  
PT  
Threshold Probability  
CCU  
Coronary Care Unit  
CSRU  
Cardiac Surgical Intensive Care Unit  
MICU  
Medical Intensive Care Unit  
SICU  
Surgical Intensive Care Unit  
TSICU  
Trauma/Surgical Intensive Care Unit  
MAP  
Mean Arterial Pressure  
CRP  
C-reactive Protein  
ESR  
Erythrocyte Sedimentation Rate

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## Tables

**Table 1 Patients' baseline characteristics<sup>a</sup>**

Variable	SAE patients n=956	Training set n=669	Validation set n=287	P value
Age, years	73(59, 82)	73(60, 82)	72(58, 82)	0.42
Gender, male	514(53.77)	352(52.62)	162(56.45)	0.31
<b>Comorbidity, n (%)</b>				
Congestive heart failure	351(36.72)	247(36.92)	104(36.24)	0.30
Arrhythmia	382(39.96)	258(38.57)	124(43.20)	0.20
Valvular heart disease	144(15.06)	99(14.80)	45(15.68)	0.80
Pulmonary circulatory disease	30(3.14)	22(3.29)	8(2.79)	0.84
peripheral vascular disease	111(11.61)	79(11.81)	32(11.15)	0.86
Renal failure	192(20.08)	133(19.88)	59(20.56)	0.88
Hypertension	506(52.93)	345(51.57)	161(56.10)	0.22
Paralysis	37(3.87)	29(4.33)	8(2.79)	0.34
Other Neurological Disease	119(12.45)	81(12.11)	38(13.24)	0.70
Chronic Pulmonary Disease	223(23.33)	161(24.07)	62(21.60)	0.46
Diabetes	214(22.38)	153(22.87)	61(21.25)	0.64
Hypothyroidism	113(11.82)	72(10.76)	41(14.29)	0.15
Liver Disease	67(7.01)	46(6.88)	21(7.32)	0.92
Lymphoma	34(3.56)	22(3.29)	12(4.18)	0.62
Metastatic Cancer	62(6.49)	40(5.98)	22(7.67)	0.41
Solid Tumor	58(6.07)	44(6.58)	14(4.88)	0.39
Coagulopathy	176(19.41)	121(18.09)	55(19.16)	0.76
Anemias	252(26.36)	175(26.16)	77(26.83)	0.89

<sup>a</sup> Continuous data are presented as median (interquartile range), whereas categorical data are presented as frequency (percentage).

**Table 2 Patients' characteristics at ICU admission<sup>a</sup>**

Variable	SAE patients n=956	Training set n=669	Validation set n=287	P value
Hospital deaths, n (%)	201(21.03)	143(21.38)	58(20.21)	0.75
Hospital stay time, days	12.88(7.76, 21.96)	12.33(7.52, 21.68)	13.98(8.03, 23.36)	0.06
ICU stay time, days	3.25(1.94, 7.25)	3.27(1.96, 6.87)	3.22(1.76, 7.87)	0.65
Mechanical ventilation, n (%)	542(56.69)	391(58.45)	151(52.61)	0.11
<b>First care unit<sup>n</sup> (%)</b>				<b>0.81</b>
CCU	83(8.68)	54(8.07)	29(10.10)	
CSRU	159(16.63)	115(17.19)	44(15.33)	
MICU	434(45.40)	305(45.59)	129(44.95)	
SICU	170(17.78)	120(17.94)	50(17.42)	
TSICU	110(11.51)	75(11.21)	35(12.20)	
<b>Severe Score<sup>b</sup></b>				
SOFA	6(4, 9)	6(4, 9)	6(4, 8)	0.33
GCS	13(9, 14)	13(9,14)	13(8, 14)	0.76
<b>Vital signs<sup>c</sup></b>				
Heart rate (min-1)	89.10±16.17	89.20±16.21	88.85±16.12	0.76
Systolic pressure (mmHg)	115.41±15.42	115.09±14.94	116.16±16.47	0.35
Diastolic pressure (mmHg)	57.47±9.40	57.38±9.30	57.70±9.66	0.63
Respiratory rate (min-1)	19.72±4.36	19.79±4.41	19.56±4.25	0.46
Temperature (°C)	36.86±0.64	36.86±0.64	36.88±0.64	0.55
SpO <sub>2</sub> (%)	97.44(96.04, 98.63)	97.40(96.04, 98.6)	97.53(96.04, 98.80)	0.41
<b>Laboratory tests<sup>d</sup></b>				
Lactate (mmol/L)	1.6(1.1, 2.3)	1.6(1.1, 2.3)	1.5(1.1, 2.3)	0.40
PCO <sub>2</sub> (mmHg)	40(35, 45)	40(36, 45)	39(35, 44)	0.19
PO <sub>2</sub> (mmHg)	110(73, 201)	109(72, 197)	113(74.5, 212.5)	0.32
PH	7.372±0.093	7.371±0.093	7.374±0.092	0.77
Creatinine (K/μL)	1.1(0.80, 1.90)	1.1(0.80, 1.80)	1.1(0.75, 1.90)	0.78
BUN (K/μL)	23.5(15.0, 40.0)	24.0(15.0, 38.0)	23.0(15.0, 42.5)	0.74
ALT <sup>e</sup>	1.45(1.18, 1.76)	1.43(1.18,1.76)	1.48(1.17, 1.75)	0.92
AST <sup>f</sup>	1.57(1.36, 1.86)	1.56(1.36, 1.84)	1.60(1.34,1.87)	0.62
Bilirubin (EU/dL)	0.7(0.4, 1.4)	0.6(0.4, 1.4)	0.7(0.4, 1.5)	0.64
Hematocrit (%)	30.81±5.59	30.80±5.72	30.74±5.29	0.92
Hemoglobin (g/dL)	10.29±1.89	10.29±1.94	10.29±1.76	0.99
Platelet (K/μL)	202(142, 281)	199(143,280)	202(139, 285)	0.91
Potassium (K/μL)	4.1(3.7, 4.6)	4.1(3.7, 4.6)	4.0(3.6, 4.5)	0.04
Sodium (K/μL)	138(135, 141)	138(135, 141)	138(135, 141)	0.88

PTT (sec)	32.70(28.70, 39.63)	32.80(28.80, 39.50)	32.20(28.25, 39.85)	0.86
RDW (%)	15.70±2.31	15.70±2.28	15.69±2.40	0.94
WBC (K/ $\mu$ L)	11.7(8.6, 16.3)	11.8(8.6, 16.4)	11.3(8.6, 16.2)	0.64
Lymphocyte (%)	7.0(4.0, 12.8)	7.0(3.9, 12.0)	7.5(4.3, 14.4)	0.20
Neutrophil (%)	83.00(73.68, 89.90)	83.10(74.00, 90.00)	82.50(72.50, 89.65)	0.47
NLR	11.3(6.2, 21.9)	11.7(6.4, 23.0)	10.7(5.4, 20.5)	0.27
MCV (fL)	90(86, 94)	90(86, 94)	90(86, 95)	0.20
<b>Infection site, n (%)</b>				
Urine	349(36.51)	237(35.43)	112(39.02)	0.32
Blood	239(25.00)	173(25.86)	66(23.00)	0.39
Lung	304(31.80)	210(31.39)	94(32.75)	0.73
Catheter	52(5.44)	44(6.58)	8(2.79)	0.03
Gastrointestinal tract	46(4.81)	37(5.53)	9(3.14)	0.16
Abdominal cavity	28(2.93)	17(2.54)	11(3.83)	0.38
Skin/Soft tissue	175(18.31)	120(17.94)	55(19.16)	0.72
Others	28(2.93)	22(3.29)	6(2.09)	0.43
<b>Microorganisms, n (%)</b>				
Gram-positive	395(41.32)	271(40.51)	124(43.21)	0.48
Gram-negative	314(32.85)	221(33.03)	93(32.40)	0.91
Fungus	264(27.62)	186(27.80)	78(27.18)	0.91
<b>Antibiotics, n (%)</b>				
Cephalosporin	337(35.25)	239(35.72)	98(34.15)	0.69
Penicillin	8(0.84)	5(0.75)	3(1.05)	0.94
Fluoroquinolones	366(38.28)	254(37.97)	112(39.02)	0.81
Carbapenems	92(9.62)	66(9.87)	26(9.06)	0.79
Vancomycin	524(54.81)	373(55.75)	151(52.61)	0.41
<b>Sedative/Analgesic, n (%)</b>				
Propofol	332(34.73)	242(36.17)	90(31.36)	0.17
Benzodiazepines	424(44.35)	304(45.44)	120(41.81)	0.33
Other sedatives	189(19.77)	136(20.33)	53(18.47)	0.57
Fentanyl citrate	318(33.26)	225(33.63)	93(32.40)	0.77
Morphine sulfate	388(40.67)	270(40.48)	118(41.11)	0.91
Other analgesics	44(4.60)	34(5.08)	10(3.48)	0.36

<sup>a</sup> Parametric continuous data are presented as mean  $\pm$  standard deviation (SD), non-parametric continuous data are presented as median (interquartile ranges), whereas categorical data are presented as frequency (percentage)

<sup>b</sup> Severe score is calculated on the first day of each ICU patients' stay

<sup>c</sup> Vital signs is calculated on the first 24 hours of each ICU patients' stay

<sup>d</sup> Laboratory tests recorded the first result of each patients' ICU stay

<sup>e</sup> ALT in the table is the value after logarithmic transformation

<sup>f</sup> ALT in the table is the value after logarithmic transformation

CCU, coronary care unit; CSRU, cardiac surgical intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; SOFA, sequential organ failure assessment; GCS, Glasgow coma score; RDW, red blood cell distribution widths; NLR, neutrophil to lymphocyte ratio; MCV, mean corpuscular volume;

**Table 3 Univariate and multivariate Logistic regression analysis of the training cohort.**

Variables	Univariate Logistic regression		Multivariate Logistic regression	
	OR[95%CI]	P value	OR[95%CI]	P value
Age	1.02(1.01, 1.03)	<0.01	1.03(1.02, 1.05)	<0.01
SOFA	1.21(1.14, 1.28)	<0.01	1.16(1.08, 1.25)	<0.01
Lactate	1.32(1.17, 1.49)	<0.01		
BUN	1.02(1.01, 1.03)	<0.01		
ALT <sup>a</sup>	1.64(1.14, 2.34)	<0.01		
AST <sup>b</sup>	1.72(1.18, 2.49)	<0.01		
RDW	1.20(1.11, 1.30)	<0.01	1.11(1.01, 1.22)	0.02
NLR	1.01(1.00, 1.01)	0.03	1.01(1.00, 1.02)	<0.01
Heart rate	1.02(1.01, 1.03)	<0.01	1.02(1.01, 1.04)	<0.01
Respiratory rate	1.12(1.07, 1.17)	<0.01	1.1(1.05, 1.16)	<0.01
Temperature	0.63(0.46, 0.84)	<0.01	0.55(0.38, 0.78)	<0.01
SpO2	0.87(0.80, 0.94)	0.01		
Lung infection	2.55(1.74, 3.73)	<0.01	2.02(1.20, 3.40)	<0.01
Bacteremia	1.76(1.18, 2.62)	<0.01		
Gram positive bacterium	2.07(1.43, 3.02)	<0.01	1.68(1.05, 2.70)	0.03
Fungus	2.48(1.68, 3.65)	<0.01		

<sup>a</sup> ALT in the table is the value after logarithmic transformation

<sup>b</sup> ALT in the table is the value after logarithmic transformation

SOFA, sequential organ failure assessment; RDW, red blood cell distribution widths; NLR, neutrophil to lymphocyte ratio

**Table 4 Comparison of models for predicting in-hospital mortality in patients.**

Predictive Model	AUROC	P value	IDI	P value	Brier index	P value
<b>Training set</b> <b>Nomogram</b>	0.774(0.729-0.818)	<0.01	0.109(0.081-0.136)	<0.01	0.136(0.120-0.153)	<0.01
<b>SOFA</b>	0.662(0.610-0.714)				0.155(0.138-0.172)	
<b>Validation set</b> <b>Nomogram</b>	0.741(0.673-0.809)	<0.01	0.083(0.049-0.117)	<0.01	0.168(0.144-0.192)	<0.01
<b>SOFA</b>	0.599(0.524-0.674)				0.193(0.169-0.216)	

SOFA, sequential organ failure assessment; AUROC, area under the receiver operating characteristic curve; IDI, integrated discrimination improvement.

## Supplementary Information

**Additional file 1: Figure S1:** Flowchart of inclusion and exclusion in the study. A total of 15847 patients meeting the criteria of Sepsis 3.0 were incorporated into the original population. The order of exclusion was consistent with what we performed by the SQL. After excluding patients with comorbidities that may have adverse impact on consciousness, or without a record of GCS, or died within 24 hours since ICU admission, 2489 patients remained in the study. Then, 956 patients with GCS<15 were picked out to make up the final cohort.

**Additional file 2: Figure S2:** (A) The calibration curve, AUROC and Brier score of nomogram (green), SOFA (red) and SAPSII (blue) in predicting the in-hospital death of SAE in the training set. (B) The calibration curve, AUROC and Brier score of nomogram (green), SOFA (red) and SAPSII (blue) in predicting the in-hospital death of SAE in the validation set.

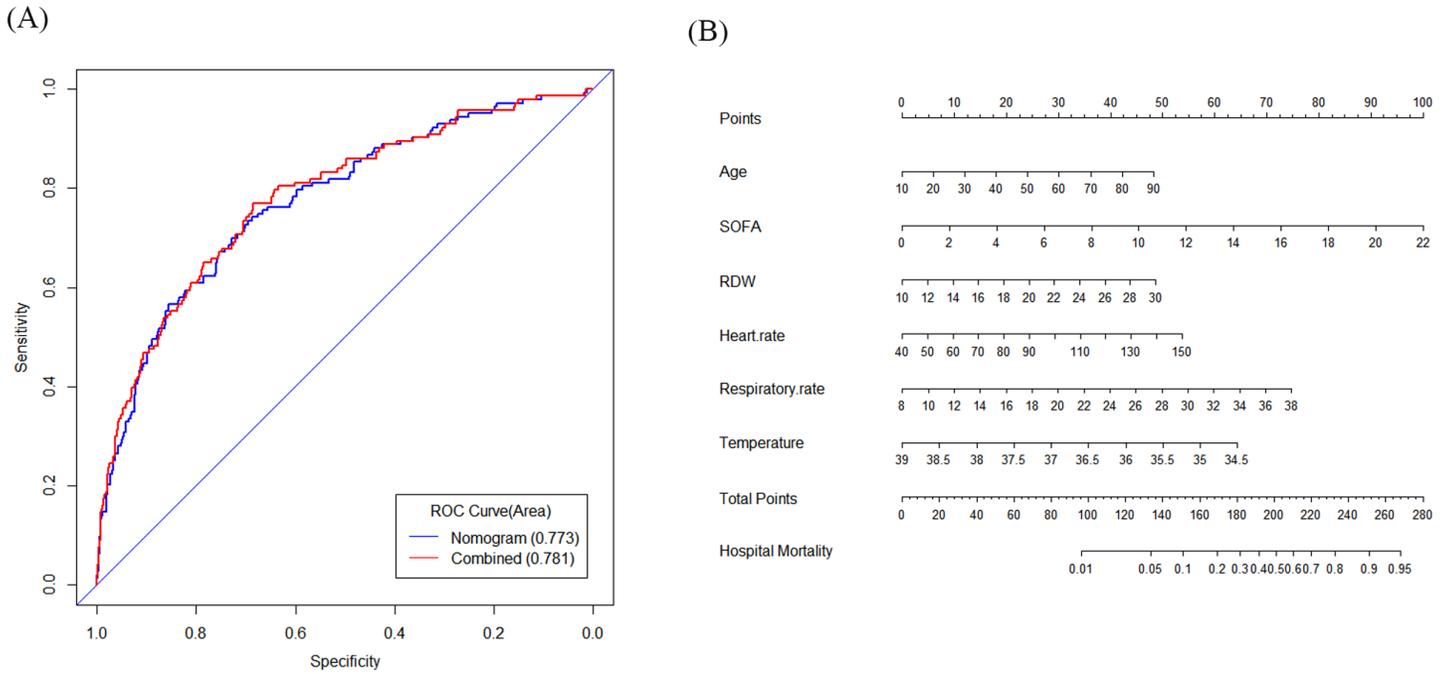
**Additional file 3: Figure S3:** The ROC curve of SOFA in predicting the in-hospital death of patients with sepsis extracted by the criteria of Sepsis 3.0 from the MIMIC III database.

**Additional file 4: Figure S4:** (A) The level of blood lactate in the three risk groups divided by the cut-off values (left) and multiple comparisons among the three groups (right) in the training set. (B) The level of blood lactate in the three risk groups divided by the cut-off values (left) and multiple comparisons among the three groups (right) in the validation set.

**Additional file 5: Figure S5:** (A) The proportion of vasopressor use in the three risk groups divided by the cut-off values in the training set. (B) The proportion of vasopressor use in the three risk groups divided by the cut-off values in the validation set.

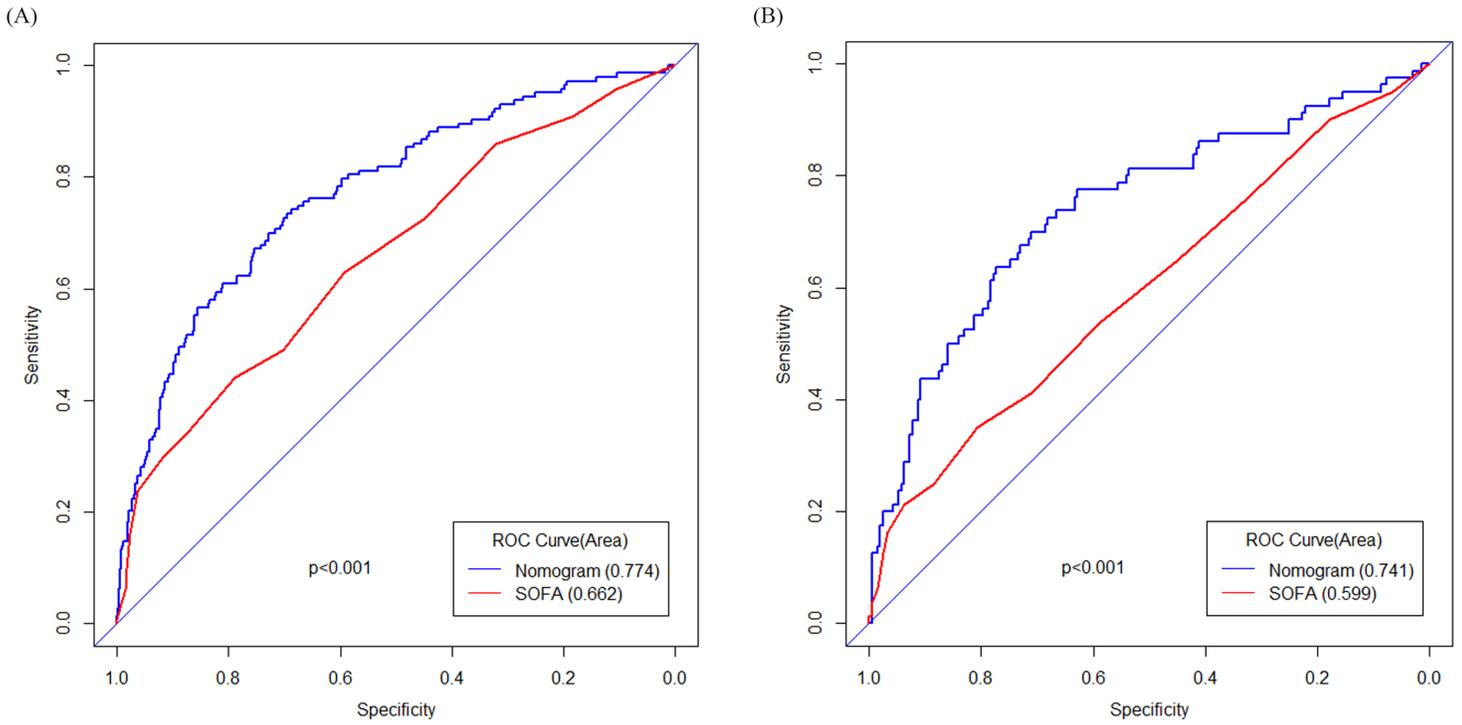
**Additional file 6: Figure S6:** (A) The level of mean arterial pressure (MAP) in the three risk groups divided by the cut-off values (left) and multiple comparisons among the three groups (right) in the training set. (B) The level of MAP in the three risk groups divided by the cut-off values (left) and multiple comparisons among the three groups (right) in the validation set.

# Figures



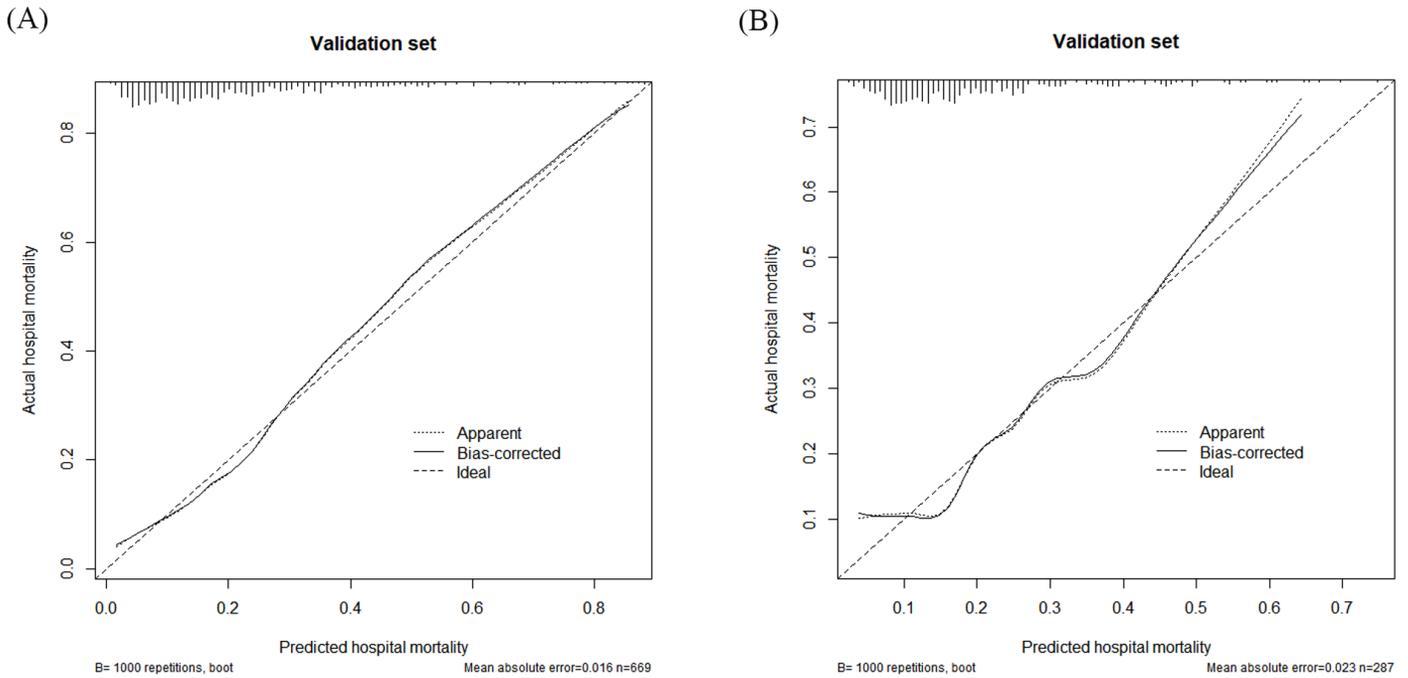
**Figure 1**

(A) The ROC curve of the nomogram and a combined model in predicting the in-hospital mortality of patients with SAE. The combined model is incorporated by variables including age, SOFA, RDW, NLR, heart rate, respiratory rate and temperature. (B) Validated nomogram for predicting in-hospital mortality of SAE; When using it, drawing a vertical line from each variables upward to the points and then recording the corresponding points (i.e. "SOFA=8" = 37 points). The point of each variable was then summed up to obtain a total score that corresponding to a predicted probability of in-hospital death at the bottom of the nomogram.



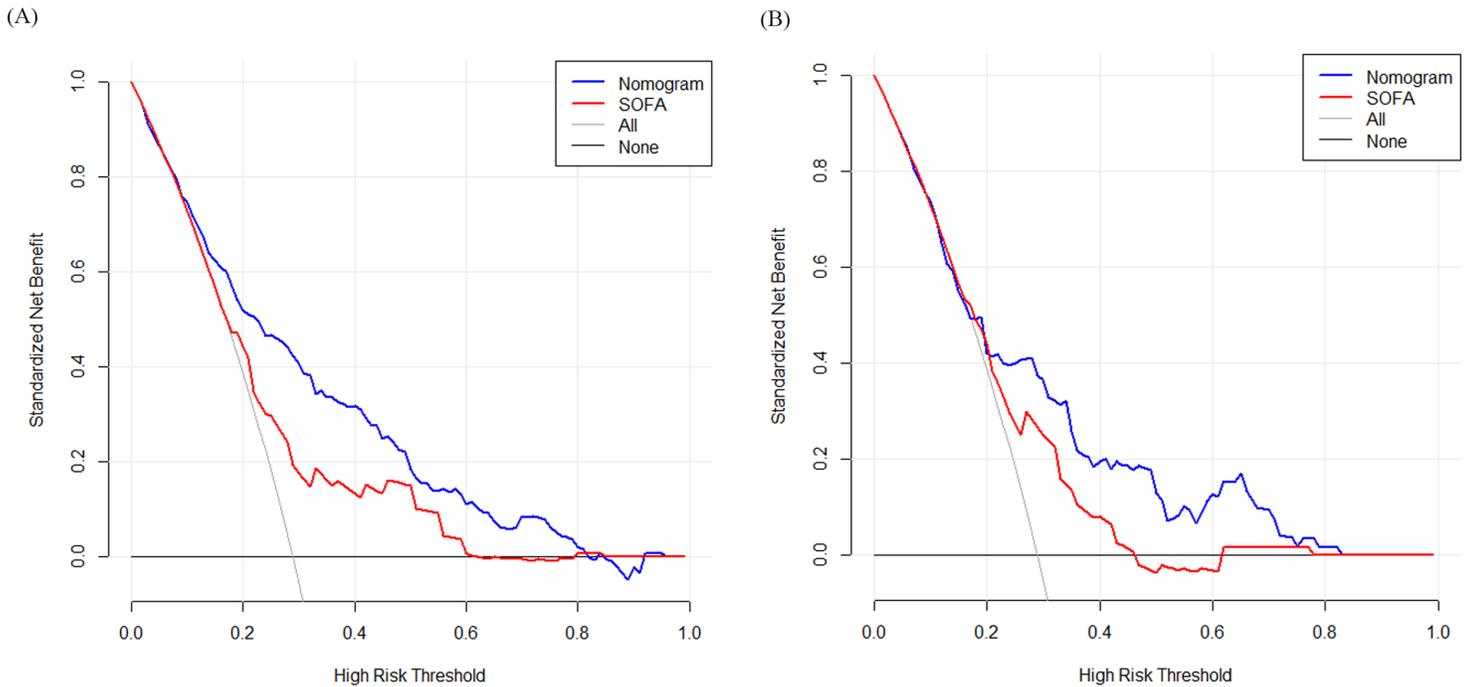
**Figure 2**

(A) The ROC curve of the nomogram (blue) and SOFA (red) in predicting the in-hospital mortality of patients with SAE in the training set. (B) The ROC curve of the nomogram (blue) and SOFA (red) in predicting the in-hospital mortality of patients with SAE in the validation set.



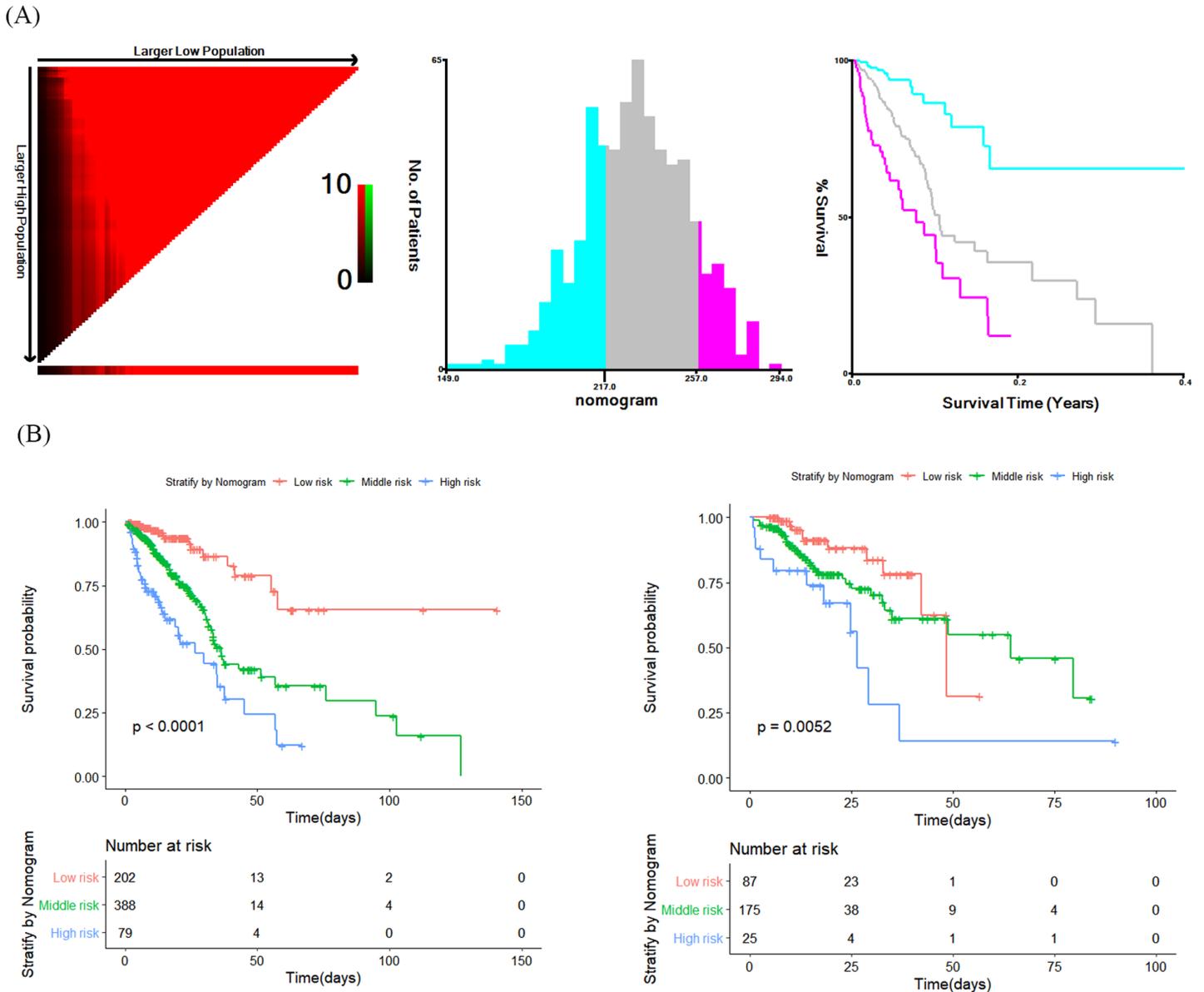
**Figure 3**

(A) Calibration curves constructed by bootstrap approach in the training set. The apparent line, bias-corrected line and the ideal reference line are closely aligned, demonstrating good calibration (B) Calibration curves constructed by bootstrap approach in the validation set. The apparent and bias-corrected lines are well-aligned, but both lines are slightly deviated from the ideal reference line.



**Figure 4**

(A) The DCA curve of medical intervention in patients with the nomogram (blue) and SOFA (red) in the training set. (B) The DCA curve of medical intervention in patients with the nomogram (blue) and SOFA (red) in the validation set.



**Figure 5**

(A) X-tile analysis in the training set to generate the cut-off values of risk score calculated by nomogram and then divide patients into three risk grades: low-risk group ( $\leq 217$ ), middle-risk group (218-257) and high-risk group ( $\geq 258$ ). (B) The Kaplan-Meier curves to show the hospital survival of SAE patients in three risk groups stratified by the cut-off points in the training set (left) and validation set (right).

## Supplementary Files

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