

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

Yang Yang

Tangdu Hospital of Air Force Medical University <https://orcid.org/0000-0002-0090-8970>

Shengru Liang

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

Jie Geng

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

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, China

Pan Wang

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

Yuan Cao

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

Rong Li

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

Guodong Gao

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

Lihong Li (✉ lihonglifmmu@163.com)

<https://orcid.org/0000-0003-4991-9037>

Research

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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 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 SAE 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 Sonnevile 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 II 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) suspected infection, (2) the quick Sequential Organ Failure Assessment (qSOFA) score ≥ 2 , and (3) the Sequential Organ Failure Assessment (SOFA) score ≥ 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, SOFA score and SAPSII 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], and 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. To further evaluate the stability of the nomogram, sensitivity analysis was conducted in the same cohort but did not exclude patients with hypercapnia ($PCO_2 > 75$ mmHg).

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.

Table 2
Patients' characteristics at ICU admission^a

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
First care unit, n (%)				0.81
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)	
Severe Score ^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
Vital signs ^c				
Heartrate (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 ₂ (%)	97.44(96.04, 98.63)	97.40(96.04, 98.6)	97.53(96.04, 98.80)	0.41
Laboratory tests ^d				
Lactate (mmol/L)	1.6(1.1, 2.3)	1.6(1.1, 2.3)	1.5(1.1, 2.3)	0.40
PCO ₂ (mmHg)	40(35, 45)	40(36, 45)	39(35, 44)	0.19

Variable	SAE patients n = 956	Training set n = 669	Validation set n = 287	P value
PO ₂ (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 ^e	1.45(1.18, 1.76)	1.43(1.18,1.76)	1.48(1.17, 1.75)	0.92
AST ^f	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/μL)	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
Infection site, n (%)				
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

Variable	SAE patients n = 956	Training set n = 669	Validation set n = 287	P value
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
Microorganisms, n (%)				
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
Antibiotics, n (%)				
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
Sedative/Analgesic, n (%)				
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
^a Parametric continuous data are presented as mean ± standard deviation (SD), non-parametric continuous data are presented as median (interquartile ranges), whereas categorical data are presented as frequency (percentage)				
^b Severe score is calculated on the first day of each ICU patients' stay				
^c Vital signs is calculated on the first 24 hours of each ICU patients' stay				
^d Laboratory tests recorded the first result of each patients' ICU stay				
^e ALT in the table is the value after logarithmic transformation				

Variable	SAE patients n = 956	Training set n = 669	Validation set n = 287	P value
f 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 1 Patients' baseline characteristics ^a

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
Comorbidity, n (%)				
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
^a Continuous data are presented as median (interquartile range), whereas categorical data are presented as frequency (percentage).				

Table 2 Patients' characteristics at ICU admission (Placed at the end of the document text file)

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. The distribution

of missing values and the effect of imputation were shown in Additional file 2: Fig.S2. Univariate and multivariate Logistic regression results are shown in Table.3. Except for bilirubin, PO₂, 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).

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 ^a	1.64(1.14, 2.34)	< 0.01		
AST ^b	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		
^a ALT in the table is the value after logarithmic transformation				
^b 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				

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.

Validation of the predictive nomogram

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; $p < 0.001$)(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; $p < 0.001$). 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.

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.

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 3: Fig.S3). 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.

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.

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).

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.

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 (≤ 217), middle-risk group (218–257) and high-risk group (≥ 258) by the cut-off points (log-rank $p < 0.001$ and log-rank $p = 0.0052$, respectively) (Fig. 5B).

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 (≤ 217), middle-risk group (218–257) and high-risk group (≥ 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).

Sensitivity analysis in SAE patients without excluding hypercapnia

A total of 1426 patients were incorporated into sensitivity analysis. The AUROC of the nomogram was 0.745 (95%CI: 0.717–0.776), which was significantly higher than that of SOFA (0.64 (95%CI: 0.61–0.68)). The Brier score of the nomogram and SOFA was 0.149 (95%CI: 0.137–0.16) and 0.166 (95%CI: 0.154–0.177), indicating that the nomogram had better calibration than SOFA. Compared with SOFA, the IDI score of the nomogram was 0.094 (95%CI: 0.078–0.11, $p < 0.001$), which meant the nomogram could increase the prediction probability of SOFA by 9.4%. Besides, DCA analysis revealed that medical intervention guided by the nomogram could add more net benefit than SOFA when PT was between 0.1 and 0.76 (Additional file 4: Fig.S4).

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. As one of the decision-making aid, nomogram has become popular because it offers a visual and easy-to-use ruler allowing quick and accurate computation of probability of clinically significant events. Results from a nomogram are reliable and easy to be obtained by merely drawing several lines and calculating a total point. 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, 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 sepsis 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 sepsis, 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 sepsis alone and those with SAE. Results indicated that in the 15847 patients with sepsis, the AUROC was 0.724 (Additional file 5: Fig.S5), 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 sepsis 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, whose in-hospital mortality was 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 and levels of MAP and lactate in the three groups. Results showed that the high-risk group had significant higher level of lactate and frequency of vasopressor usage than the other two risk groups, simultaneously MAP was over 65 mmHg in all groups (Additional file 6–8: Fig.S6-S8), 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. The exact mechanism for the increased in-hospital mortality in the middle-risk group compared with the low-risk group can not be confirmed by the study, but as the level of blood lactate had no difference between the two groups (Additional file 6 Fig.S6), and previous study has demonstrated that the in-hospital mortality was 30.1% in septic patients with fluidresistant hypotension requiring vasopressors but without hyperlactatemia ($<$ 2 mmol/L) [10], which was similar to the in-hospital mortality of patients in the middle-risk group, 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, treatment towards sepsis, especially 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 that result in the increased in-hospital mortality in the middle- or higher-risk groups so that targeted therapies can be performed or developed to effectively reduce in-hospital death of SAE patients.

Several points should be noted when using the nomogram. 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 finally reduce the hospital death of SAE patients. Second, 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. Third, 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. Lastly, the following situations should be considered when recording the respiratory rate of patients supported by mechanical ventilation: (1) If a patient has no spontaneous respiration, respiratory rate should be recorded as the setting rate of controlled ventilation. (2) If a patient has very slow spontaneous breathing, respiratory rate should also be recorded as the setting rate of controlled ventilation. (3) if one's respiratory rate is normal or fast, respiratory rate should be recorded as the spontaneous respiratory rate.

This study has some limitations: First, the retrospective nature of this observational study determined that unidentified confounding factors may affect the results if adding to the model. Second, 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. Third, 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]. Fourth, 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.

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

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

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Figures

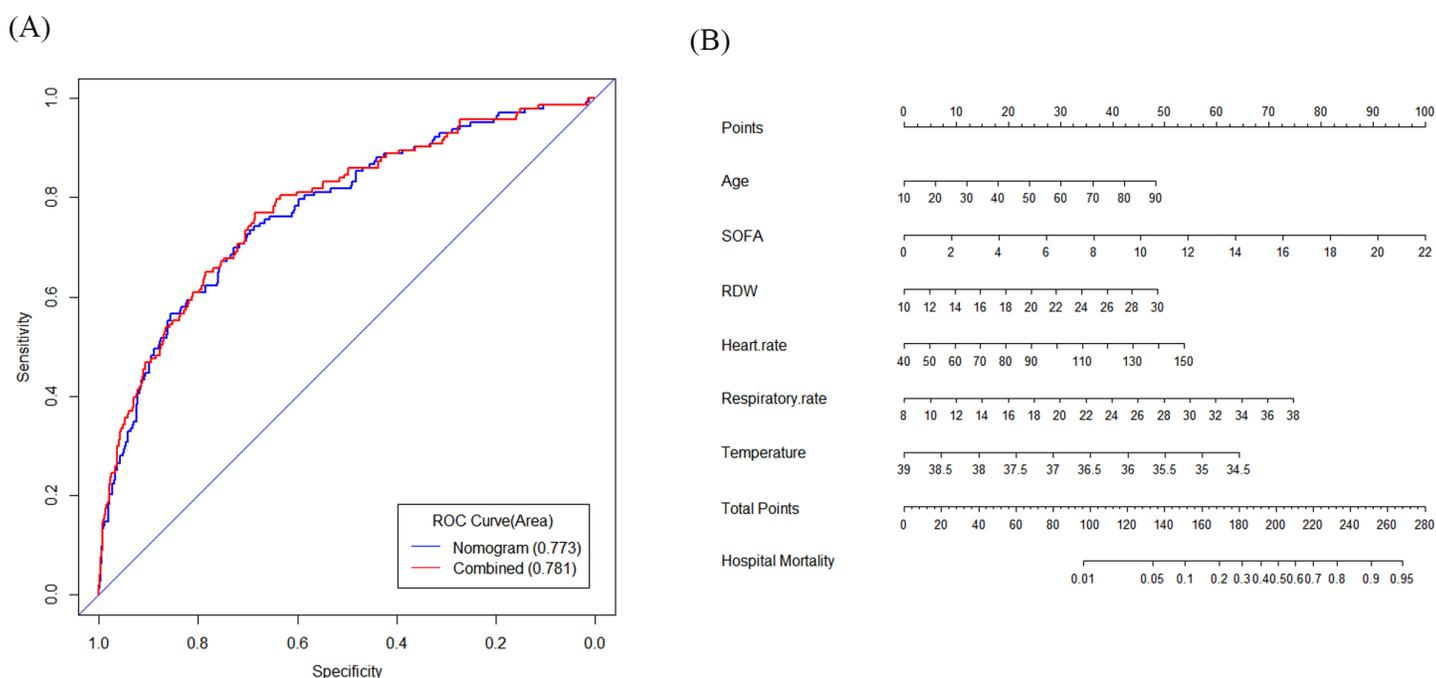


Figure 1

(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.

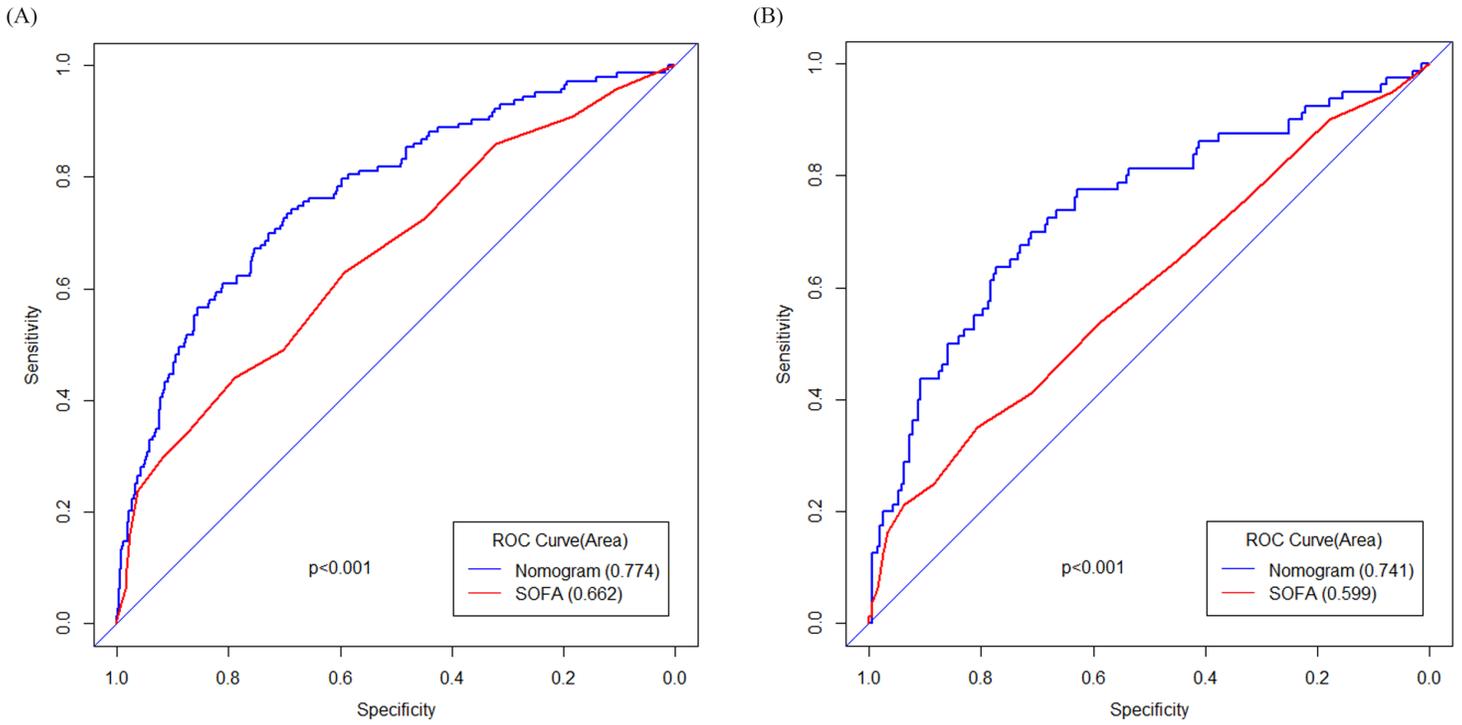


Figure 2

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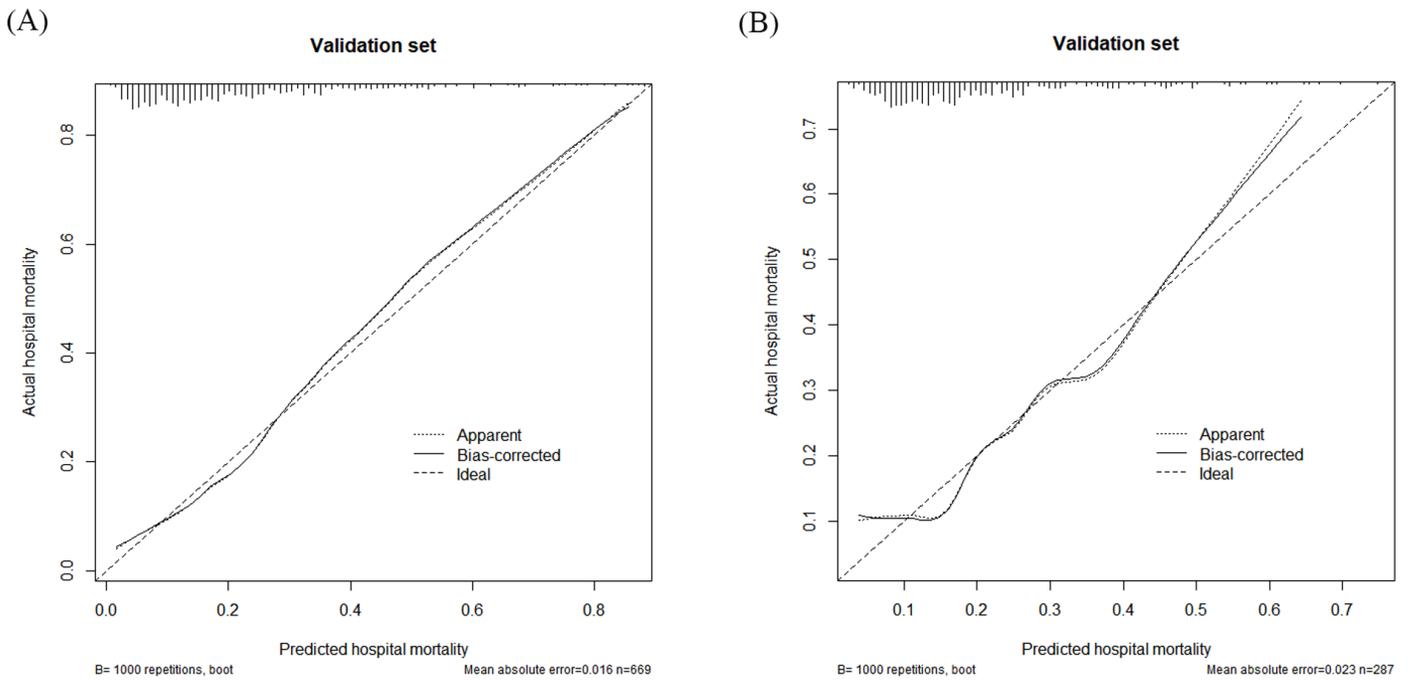


Figure 3

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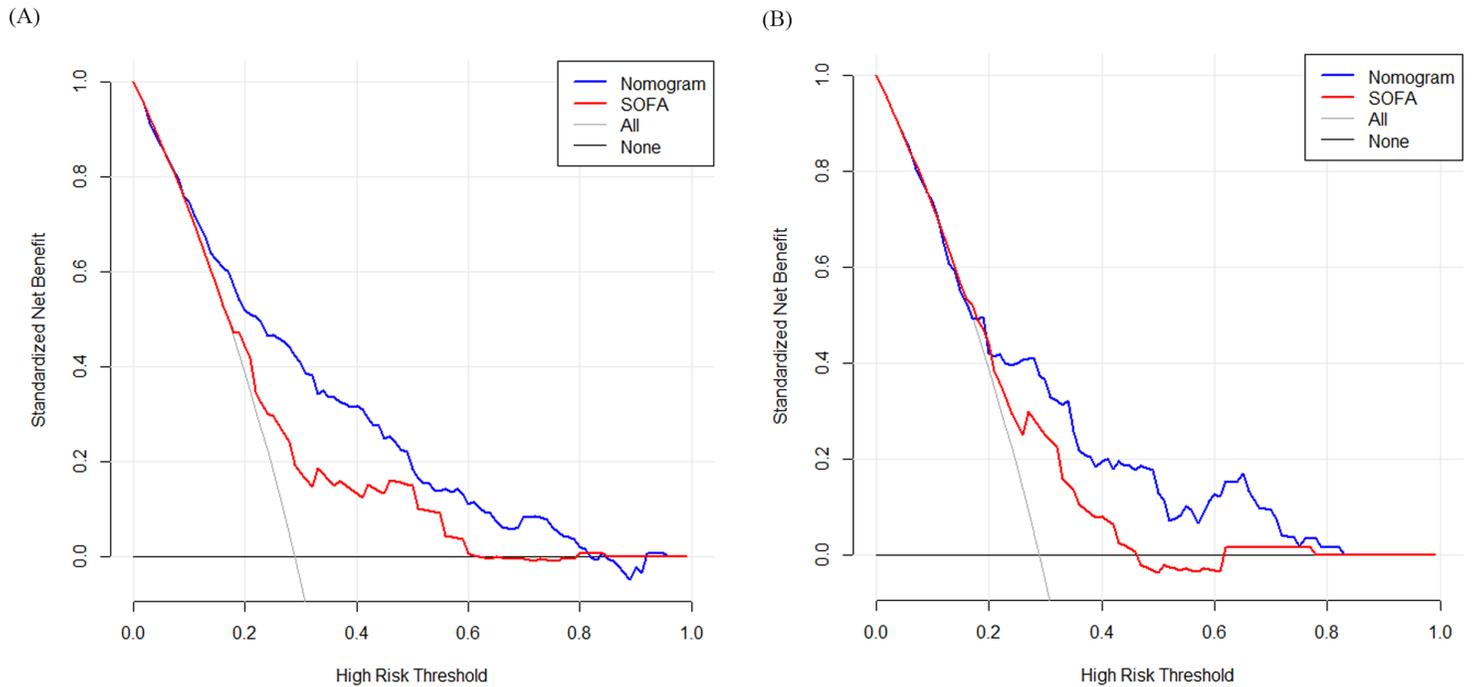


Figure 4

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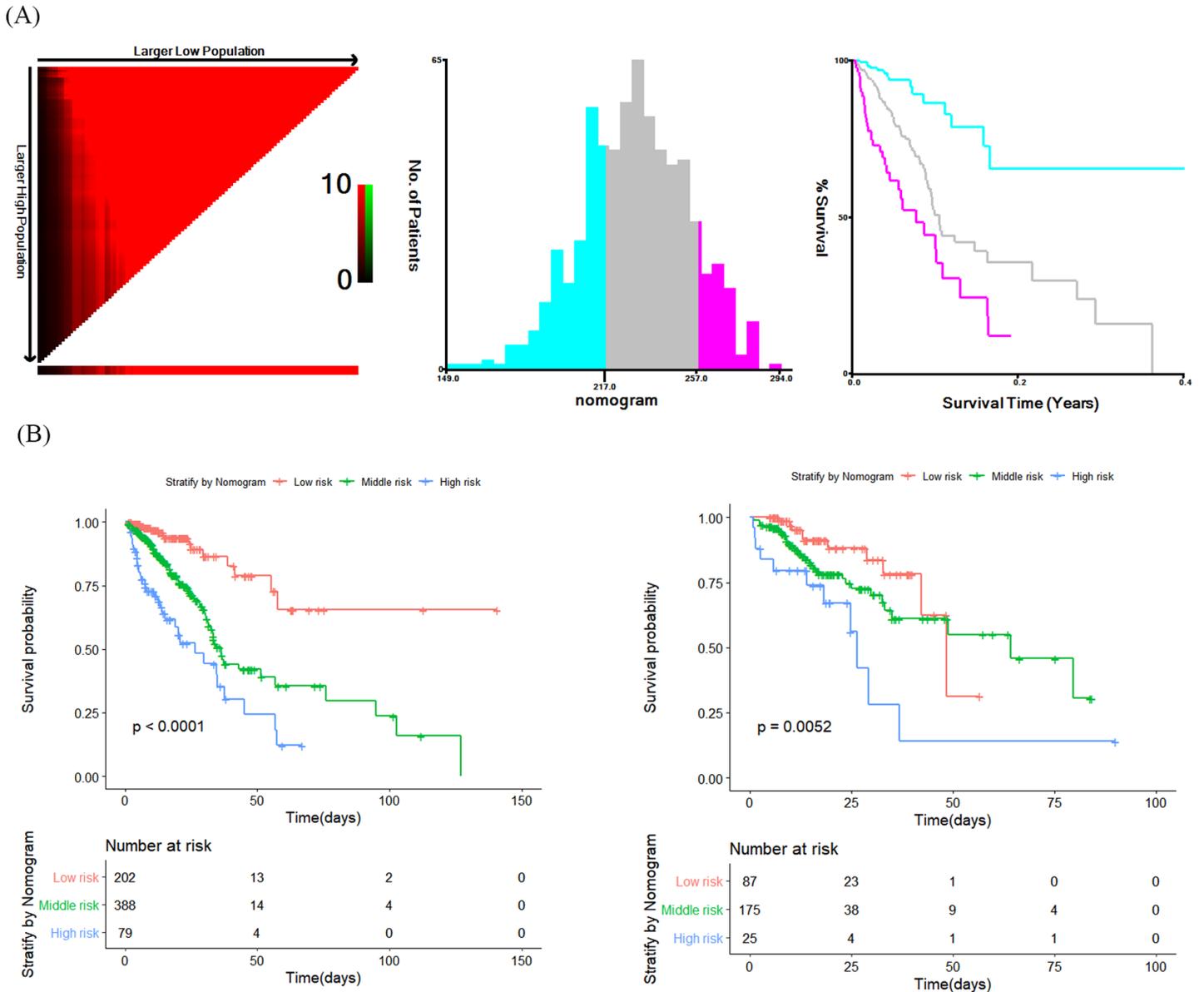


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