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## EDITED BY

You Shang,  
Huazhong University of Science and  
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## REVIEWED BY

Sunil Swami,  
Cigna, United States  
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Beijing Tiantan Hospital, Capital Medical  
University, China  
Jun Lyu,  
First Affiliated Hospital of Jinan  
University, China

## \*CORRESPONDENCE

Hui Liu  
✉ m13366223706@163.com

†These authors have contributed equally to this  
work

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# The nomogram to predict the occurrence of sepsis-associated encephalopathy in elderly patients in the intensive care units: A retrospective cohort study

Qing Zhao<sup>1†</sup>, Jianguo Xiao<sup>2†</sup>, Xiaoli Liu<sup>3</sup> and Hui Liu<sup>2\*</sup>

<sup>1</sup>Department of Diagnosis and Treatment of Cadres, First Medical Center, Chinese PLA General Hospital, Beijing, China, <sup>2</sup>Department of Critical Care Medicine, The First Medical Center, Chinese PLA General Hospital, Beijing, China, <sup>3</sup>Key Laboratory for Biomechanics and Mechanobiology of Ministry of Education, Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing, China

**Background:** Sepsis-associated encephalopathy (SAE) is a critical and common problem in elderly patients with sepsis, which is still short of efficient predictive tools. Therefore, this study aims to screen the risk factors and establish a useful predictive nomogram for SAE in elderly patients with sepsis in the intensive care unit (ICU).

**Patients and methods:** Elderly patients (age  $\geq 65$  years) with sepsis were selected from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Data from demographics and laboratory examinations were collected on the first day of admission to the ICU. SAE was defined by two criteria in the presence of sepsis: ① a Glasgow Coma Scale (GCS) score of  $< 15$  or ② delirium. Differences in demographics and laboratory tests were calculated between SAE and non-SAE groups. Participants were randomly divided into a training set and a validation set without replacement at a ratio of 6:4. A predictive nomogram was constructed in the training set by logistic regression analysis and then validated. The predictive capability of the nomogram was demonstrated by receiver operating characteristic (ROC) analysis and calibration curve analysis.

**Results:** A total of 22,361 patients were selected, of which 2,809 patients (12.7%) died in the hospital and 8,290 patients (37.1%) had SAE. In-hospital mortality in the SAE group was higher than that in the non-SAE group (18.8 vs. 8.9%,  $p < 0.001$ ). Based on the results of logistic regression analysis, a nomogram integrating age,  $\text{Na}^+$ , Sequential Organ Failure Assessment (SOFA) score, heart rate, and body temperature were constructed. The area under the curve (AUC) of the nomogram was 80.2% in the training set and 80.9% in the validation set. Calibration curve analysis showed a good predictive capacity of the nomogram.

**Conclusion:** SAE is an independent risk of in-hospital mortality in elderly patients in the intensive care unit. The nomogram has an excellent predictive capability of SAE and helps in clinical practice.

## KEYWORDS

SAE, nomogram, elderly patients, mortality, SOFA

## 1. Introduction

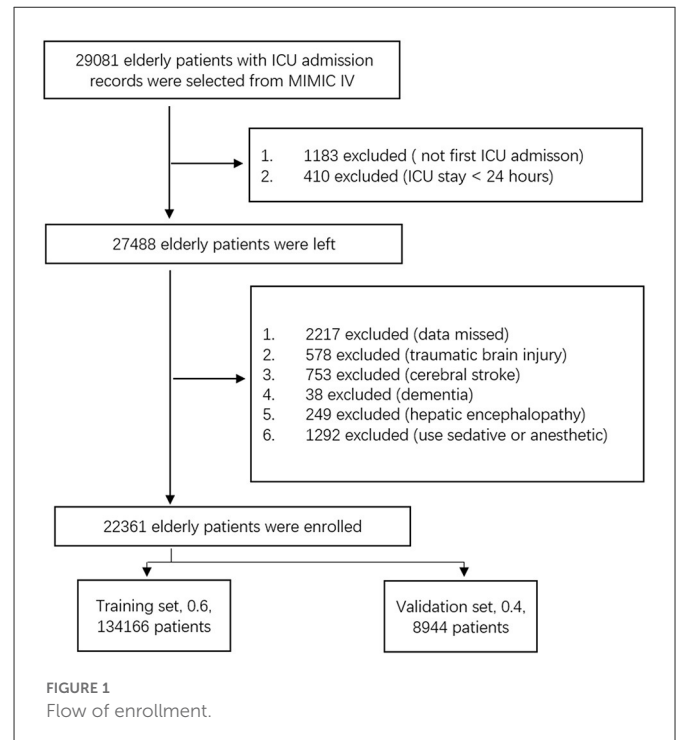
Sepsis-associated encephalopathy (SAE) is a critical complication of patients with sepsis, especially in the elderly population. The clinical manifestation of SAE comprises impairment of awareness, delirium, and coma (1). Patients with SAE suffer from deteriorative cognitive function, bad memory, attention loss, and a decrease in verbal fluency. Sepsis-related delirium is mostly hypoactive, and only a few cases are hyperactive or mixed. Hypoactive delirium is characterized by slowed motor function, confusion, sedation, impaired response, withdrawn attitude, and drowsiness. Hyperactive delirium is commonly characterized by agitation, emotional lability, restlessness, and other positive psychotic manifestations. Patients with sepsis are weak with severe complications, such as shock, infection, and hypoxia. Sedatives are often used in critical patients with sepsis, which also lead to hypoactive delirium. Hypoactive delirium is more often observed in patients with sepsis than in hyperactive delirium. The exacerbation of SAE is associated with focal deficits, seizures, tremors, or nonepileptic myoclonus (2–4). Psychological disorders are common in patients with SAE, such as anxiety or post-traumatic stress disorder (PTSD) (5, 6). SAE is associated with increased mortality and poor long-term outcomes. Its incidence varies from no more than 10% to over 70% according to the severity of sepsis in critical patients in the ICU (7). Early recognition of risk factors related to SAE is important for timely clinical treatment. Elderly patients are more vulnerable to the dysfunction of the central nervous system and develop SAE. However, there are few studies on the epidemic of SAE and relevant risk factors in the elderly population. In this study, we examined the morbidity of SAE and developed an SAE prediction model in critical elderly patients.

## 2. Patients and methods

### 2.1. Study design and participants' enrollment

This was a retrospective cohort study. In this retrospective study, we selected elderly ( $\geq 65$  years) patients between 2008 and 2019 from the MIMIC-IV database (8, 9). Demographics and laboratory examination data of elderly patients ( $\geq 65$  years) were collected on the first day of ICU admission. The incidence of SAE was demonstrated. Risk factors of SAE were screened, and the nomogram model was established. Enrolled patients were divided into a training set and a validation set. The efficiency of the nomogram was validated. The inclusion criteria were as follows: (1) age  $\geq 65$  years, (2) first admission to the ICU, and (3) a length of ICU stay of  $\geq$

Abbreviations: SAE, sepsis-associated encephalopathy; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care–IV database; GCS, Glasgow Coma Score; ROC, receiver operating characteristic analysis; SOFA, Sequential Organ Failure Assessment; AUC, area under the curve; PTSD, post-traumatic stress disorder; RASS, Richmond Agitation Sedation Scale; CAM-ICU, confusion assessment method for the intensive care unit; DSM-5, Diagnostic and Statistical Manuals of Mental Disorders 5; ICD-10, International Classification of Diseases 10; WBC, white blood cell; MBP, mean artery pressure; RR, respiratory rate; PaO<sub>2</sub>, oxygen pressure of artery; SpO<sub>2</sub>, pulse oxygen saturation; HR, heart rate; SD, standard deviation; OR, odds ratio; CI, confidence interval; CNS, central nervous system; DCA, decision curve analysis.



24 h. The exclusion criteria were as follows: (1) data missing, without records of delirium and Glasgow score; (2) traumatic brain injury; (3) cerebral stroke; (4) dementia; (5) hepatic encephalopathy, and (6) use of sedatives or anesthetics. The enrollment workflow is shown in Figure 1.

### 2.2. Terms and definitions

- Sepsis: Organ dysfunction, hypoperfusion, or hypotension caused by systemic infection based upon the sepsis 3.0 definition. Patients with infection and a SOFA score of  $\geq 2$  were regarded as cases with sepsis 3.0 (11).
- Delirium: Patients were identified using the Richmond Agitation Sedation Scale (RASS) and the confusion assessment method for the intensive care unit (CAM-ICU) (12). RASS is graded into unarousable, deep sedation, moderate sedation, light sedation, drowsy, alert and calm, restless, agitated, very agitated, and combative, which are numbered between  $-5$  and  $+4$ . According to the CAM-ICU procedure, delirium is confirmed if (i) the RASS score is  $\geq -3$ ; (ii) there is an acute change in the mental status baseline; (iii) there are  $>2$  errors in the attention test; and (iv) either the RASS score is not 0, or the combined number of errors in the cognitive test is  $>1$ .
- SAE: Patients with sepsis who met the inclusion and exclusion criteria were screened. Patients with sepsis who had a Glasgow Coma Scale (GCS) score of  $< 15$  or had manifestations of delirium (diagnosed by the method mentioned earlier) were identified as having SAE (10, 13, 14). GCS is a common tool for assessing the severity of brain injury. The GCS score ranges from 3 to 15. A GCS score  $\leq 8$  indicates severe brain injury, the GCS scores of 9–12 represent moderate injury, and a GCS score  $\geq 13$  represents mild injury.

- Shock: Shock was assumed when any vasopressor therapy was administered, which included norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine, and milrinone.

### 2.3. Baseline data and outcome data

Baseline data were collected on the first day of ICU admission, including sex, age, hemoglobin, white blood cell (WBC), platelet count, creatinine, blood glucose, Na<sup>+</sup>, oxygen pressure of artery (PaO<sub>2</sub>), heart rate (HR), mean artery pressure (MAP), respiratory rate (RR), body temperature, Sequential Organ Failure Assessment (SOFA) score, diagnosis of sepsis, diagnosis of delirium, and diagnosis of shock. Outcome data included in-hospital mortality, length of hospital stay, and length of ICU stay.

### 2.4. Source of data and ethics approval

Medical Information Mart for Intensive Care IV (MIMIC-IV) is an updated version of MIMIC-III with approval from the institutional review board. MIMIC-IV remarkably evolves in structure, includes new data elements, and improves the usability of previous data elements. Up to now, the clinical data in the MIMIC-IV between 2008 and 2019 contain comprehensive and high-quality data of patients admitted to intensive care units (ICUs) at the Beth Israel Deaconess Medical Center. One author (XLL) obtained access to the database and was responsible for data extraction. This project was approved by the Research Ethics Committee of Chinese PLA General Hospital (S2017-054-01).

### 2.5. Statistics

R version 4.1.1 was used. The continuous variables were expressed as mean  $\pm$  standard deviation (SD). Enumeration data were expressed as numbers and percentages. Categorical variables were analyzed using the odds ratio (OR) and the Chi-square ( $\chi^2$ ) test. Two groups of continuous variables were assessed using the Mann-Whitney *U*-test. The Kaplan-Meier survival analysis and the log-rank test were used to demonstrate the mortality in elderly patients with or without SAE. The determinant of SAE was evaluated using logistic regression analyses through independent variables. The risk factors in the nomogram were chosen based on the results of logistic regression analysis, previous comparable reports, and clinical knowledge of medicine. Enrolled participants were divided into a training set and a validation set in a ratio of 6:4. All verifications of the nomogram were performed in both the training set and the validation set. Receiver operator characteristic (ROC) curve analysis was used to demonstrate the predictive capacity of the nomogram. Calibration curve analysis and decision curve analysis were also implemented. All statistical tests were two-sided and a *p*-value of  $< 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Demographic and clinical data of the enrolled patients

A total of 22,361 elderly patients ( $\geq 65$  years) in the intensive unit were enrolled, of which 2,809 patients died in the hospital (the mortality was 12.7%). The proportion of patients with SAE was approximately 37.1% (8,290 persons). Between the SAE and the non-SAE groups, there was a significant difference in age, WBC, platelet, glucose, Na<sup>+</sup>, PaO<sub>2</sub>, heart rate, MBP, respiratory rate, delirium, hemoglobin, SOFA, sepsis, shock, and creatinine. The SOFA of the SAE group was  $6.64 \pm 3.32$ , and the SOFA of the non-SAE group was  $4.26 \pm 3.07$ . The difference was significant ( $p = 0.000$ ). Compared with patients without SAE, patients with SAE had a longer length of ICU stay ( $4.94 \pm 5.50$  vs.  $3.30 \pm 4.30$  days,  $p < 0.001$ ) and hospital stay ( $12.05 \pm 12.37$  vs.  $9.06 \pm 8.97$  days,  $p < 0.001$ ). As data shown in [Table 1](#), there were 8,290 patients with SAE and 10,694 patients with sepsis. The incidence of SAE in patients with sepsis was 77.5%.

### 3.2. SAE was an independent risk factor of mortality in elderly patients in the ICU

A total of 18.8% of patients died in the SAE group, which was significantly higher than that (8.9%) in the non-SAE group ( $p < 0.001^{**}$ ) ([Table 1](#)). To confirm this, the Kaplan-Meier survival analysis was applied to demonstrate the difference in mortality between SAE and non-SAE groups. The results showed that there were more patients who survived in the non-SAE group. The survival probability in non-SAE was significantly higher than that in the SAE group ( $p < 0.001^{**}$ ) ([Figure 2](#)).

### 3.3. Logistic regression analysis to explore risk factors of SAE

Based on the results of univariable analysis ([Table 1](#)), logistic regression analysis was used to identify risk factors of SAE. Sepsis and delirium were not included in the logistic analysis because they were involved in the definition of SAE. Shock and creatinine were excluded because of their collinearity effect with SOFA. SOFA was selected in the logistic regression analysis. Results showed that the significant risk factors were age, SOFA, platelet, Na<sup>+</sup>, heart rate, respiratory rate, and temperature ( $p < 0.05$ ) ([Table 2](#)).

### 3.4. Development of the prediction nomogram

The enrolled participants were divided into a training set and a validation set in a ratio of 6:4. Baseline characteristics between these two sets were demonstrated to be statistically similar ( $p < 0.05$ ) ([Supplementary material 1](#)). The risk factors related to SAE are shown in [Table 2](#). Platelet and respiratory rate were removed due to their weak impact on SAE. The effect of the remained risk factors was thoroughly evaluated, and finally, a model

TABLE 1 Baseline characteristics and outcome data in SAE and non-SAE groups.

Characteristics	All	Non-SAE	SAE	<i>p</i> -value
Number	22,361	14,071	8,290	
Age (year)	77.25 ± 8.05	76.91 ± 7.99	77.93 ± 8.12	0.000**
Female/male	10,341/12,020	6,478/7,593	3,863/4,427	0.425
Hemoglobin (g/dL)	10.05 ± 2.11	10.19 ± 2.14	9.79 ± 2.02	0.000**
WBC (10 <sup>9</sup> /L)	14.28 ± 11.83	13.47 ± 10.70	15.91 ± 13.69	0.000**
Platelet (10 <sup>9</sup> /L)	186.92 ± 94.91	187.94 ± 91.63	184.87 ± 101.14	0.023*
Creatinine (mg/mL)	1.49 ± 1.35	1.38 ± 1.28	1.70 ± 1.46	0.000**
Glucose (mg/dL)	165.10 ± 91.30	159.21 ± 81.24	176.91 ± 107.77	0.000**
Na <sup>+</sup> (mmol/L)	139.81 ± 4.95	139.51 ± 4.52	140.42 ± 5.66	0.000**
PaO <sub>2</sub> (mmHg)	115.13 ± 50.74	117.55 ± 51.37	110.26 ± 49.10	0.000**
Heart rate (beat/minute)	82.40 ± 14.93	81.09 ± 14.46	85.01 ± 15.50	0.000**
Mean artery pressure (mmHg)	76.89 ± 10.20	77.79 ± 10.46	75.11 ± 9.40	0.000**
Respiratory rate (time/minute)	19.17 ± 3.57	18.93 ± 3.42	19.66 ± 3.81	0.000**
Body temperature (°C)	36.77 ± 0.48	36.75 ± 0.45	36.83 ± 0.53	0.000**
SOFA	5.04 ± 3.35	4.26 ± 3.07	6.64 ± 3.32	0.000**
Sepsis (count/percent)	10,694/47.8%	2,404/17.1%	8,290/100%	0.000**
Delirium (number/percent)	5,453/24.4%	2,248/16.0%	3,205/38.7%	0.000**
Shock (count/percent)	4,370/19.5%	1,767/12.6%	2,603/31.4%	0.000**
<b>Outcome data</b>				
ICU days (day)	3.85 ± 4.79	3.30 ± 4.30	4.94 ± 5.50	0.000**
Hospital days (day)	10.06 ± 10.32	9.06 ± 8.97	12.05 ± 12.37	0.000**
In-hospital mortality (count/percent)	2,809/12.7%	1,248/8.9%	1,561/18.8%	0.000**

\**p* < 0.05, \*\**p* < 0.01.

The values were shown as mean ± SD.

integrating age, Na<sup>+</sup>, SOFA, heart rate, and body temperature was established. The nomogram was plotted to predict the probability of the incidence of SAE (Figure 3). The predictive capacity of the nomogram model was demonstrated through ROC analysis in both the training set and the validation set. The AUCs were 80.2% in the training set and 80.9% in the validation set (Figures 4A, B).

### 3.5. Validation of the prediction nomogram

A calibration curve analysis was used to demonstrate the clinical accuracy of the prediction nomogram. Calibration curves were plotted in both the training and validation sets, and the bias-corrected line was formed using a bootstrap method. In both sets, the bias-corrected curve and apparent curve slightly deviated from the reference line, but a good consistency between observation and ideal reference was still observed (Figures 5A, B). A decision curve analysis (DCA) was performed to demonstrate the net benefit achieved through the clinical use of the nomogram. The results showed the nomogram gained clinical net benefit both in the training set and validation set (Supplementary material 2A, B).

### 3.6. Patients with higher SOFA or more advanced age had a higher incidence of SAE

To demonstrate the influence of age and SOFA on the incidence of SAE, patients were divided into different groups according to age or SOFA. Data showed that the incidence of SAE increased statistically as the age of patients became greater (Figure 6, Supplementary material 3) (*p* = 0.032 between 65~69 and 70~79; *p* = 0.000 between 70~79 and 80~89; *p* = 0.039 between 80~89 and 90~105). In the other results, patients were divided into four groups in terms of SOFA (0~3, 4~8, 9~14, and 15~23). The incidence of SAE increased steadily from 14.3, 44.1, and 72.3 to 87.0%. There was a significant difference between groups of SOFA (*p* < 0.001) (Figure 7, Supplementary material 4).

## 4. Discussion

Currently, there is a shortage of data concerning SAE in elderly patients. The present study provides data about the morbidity of SAE and demonstrates that SAE is an independent risk factor of in-hospital mortality in elderly patients in the ICU. Furthermore, this study identifies relevant risk factors of SAE and develops a prediction

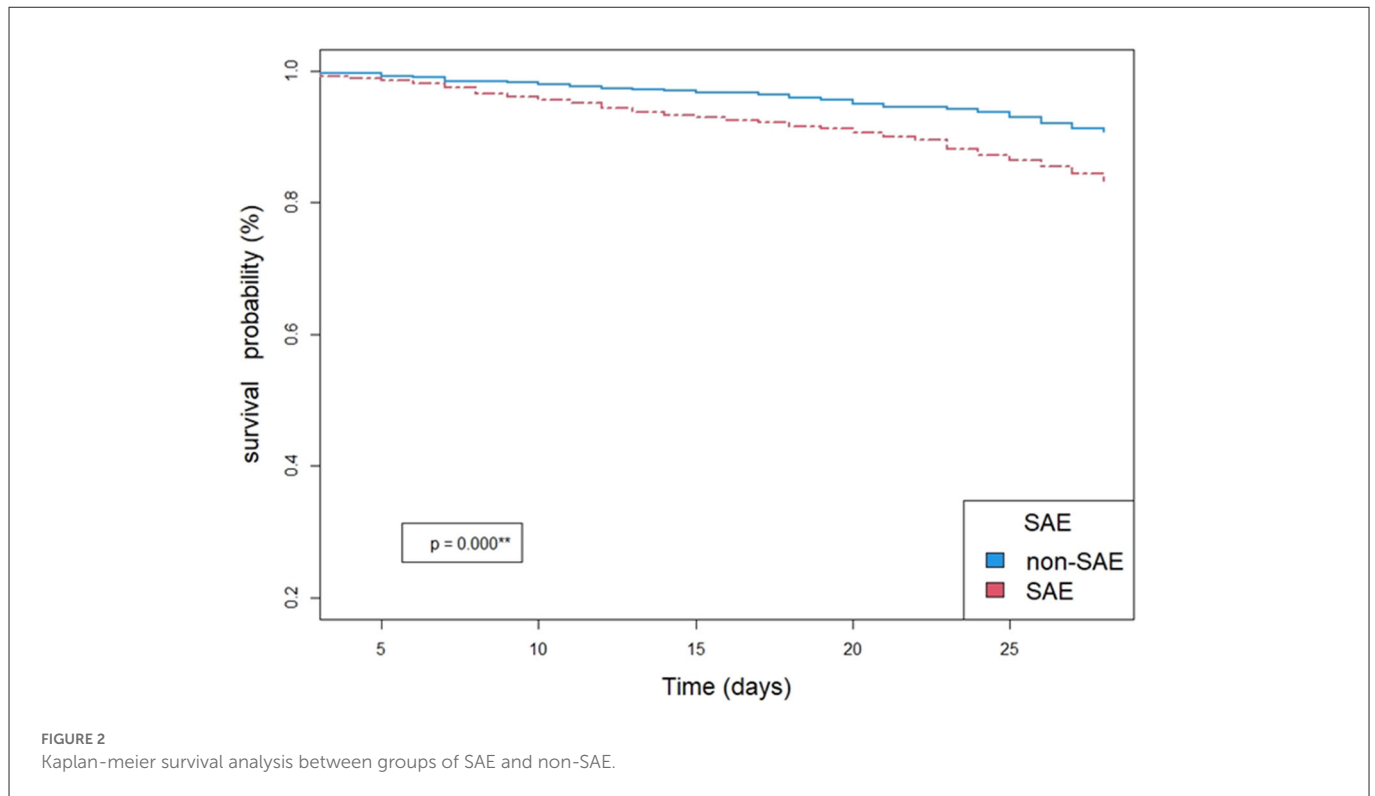


FIGURE 2 Kaplan-meier survival analysis between groups of SAE and non-SAE.

TABLE 2 Logistic regression analysis of risk factors for SAE.

Variable	$\beta$	OR	95% CI	Z-value	$p$
Gender	-0.058	0.943	-0.121-0.004	-1.838	0.066
Age	0.018	1.018	0.014-0.022	9.185	0.000**
SOFA	0.220	1.246	0.209-0.231	38.562	0.000**
Platelet	0.002	1.001	0.001-0.002	9.610	0.000**
WBC	0.002	0.998	-0.007-0.002	-1.010	0.313
Glucose	0.001	1.001	0.000-0.001	1.705	0.089
Hemoglobin	-0.015	0.985	-0.031-0.000	-1.932	0.053
Na <sup>+</sup>	0.027	1.028	0.021-0.034	8.549	0.000**
PaO <sub>2</sub>	-0.001	1.000	-0.001-0.000	-0.925	0.355
Heart rate	0.011	1.011	0.008-0.013	9.215	0.000**
MBP	-0.002	1.002	-0.003-0.007	0.671	0.502
Respiratory rate	-0.014	0.986	-0.027--0.002	-2.194	0.028*
Temperature	0.380	1.462	0.316-0.444	11.713	0.000**

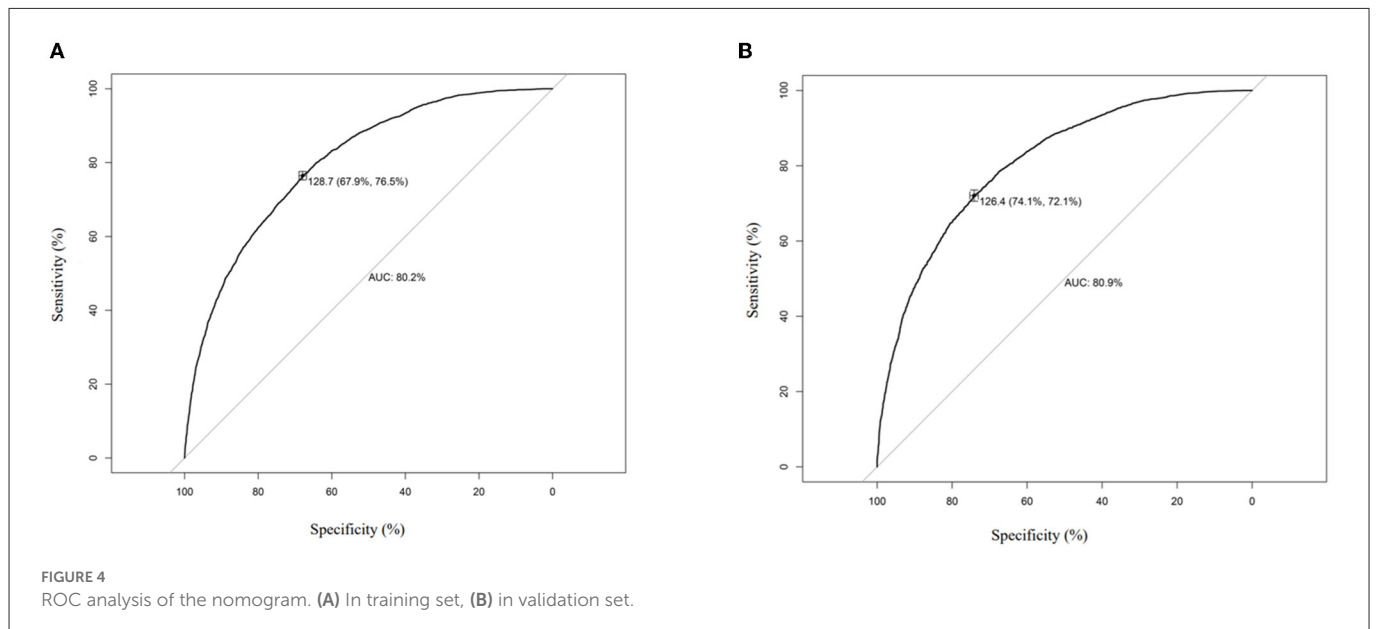
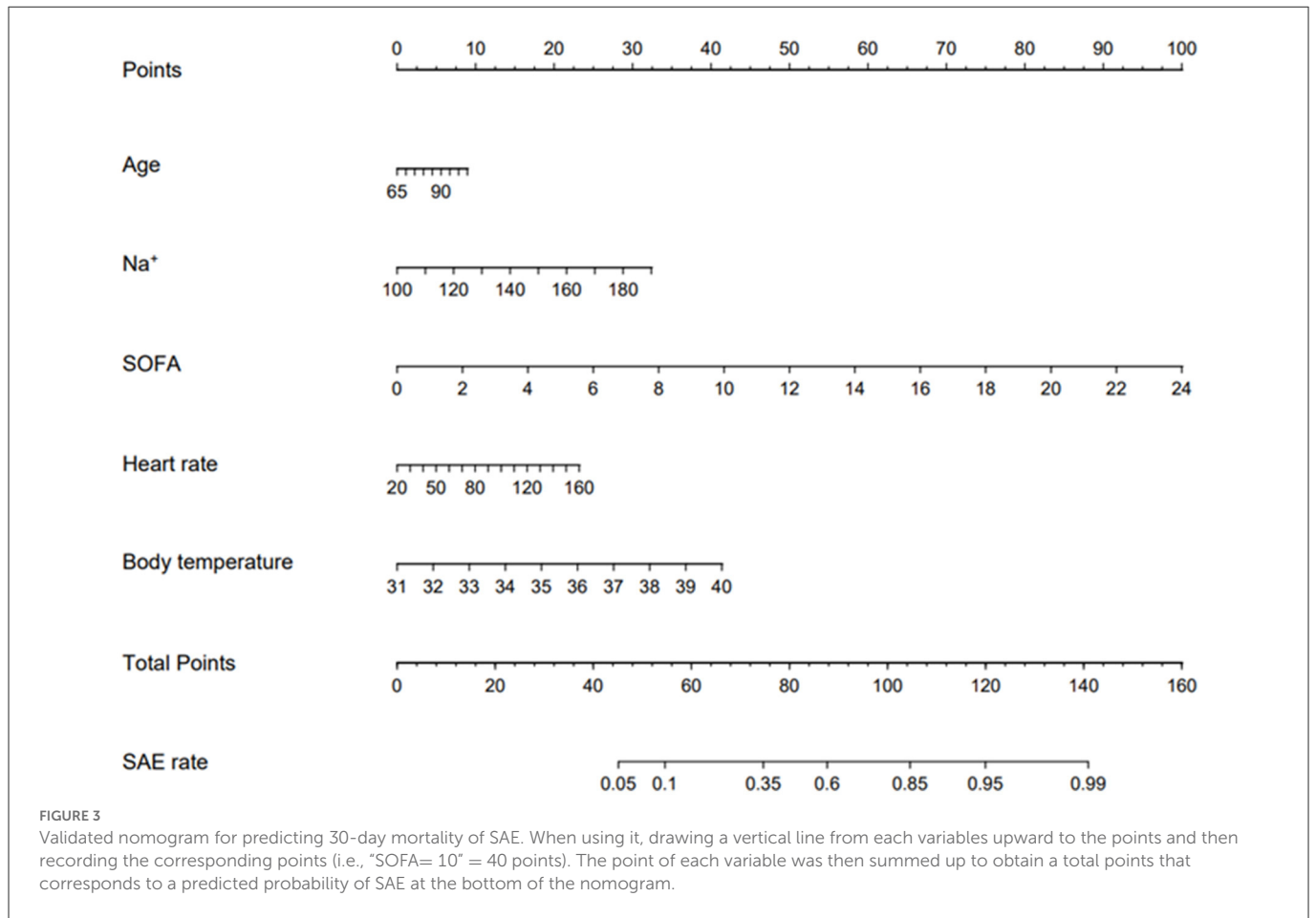
\* $p < 0.05$ , \*\* $p < 0.01$ .  
OR, odds ratio; CI, confidence interval.

nomogram as a useful tool for the clinical management of SAE in elderly patients.

Sepsis is still a crucial cause of death in critical illnesses. More than 19 million patients with sepsis were diagnosed and approximately 5.3 million patients died of it globally every year (15). It is important to note that cognitive impairment is a common clinical syndrome in patients with sepsis, especially in the elderly population. SAE is a neurological dysfunction of the central nervous system induced by sepsis (16). Previous studies reported that 30–70% of

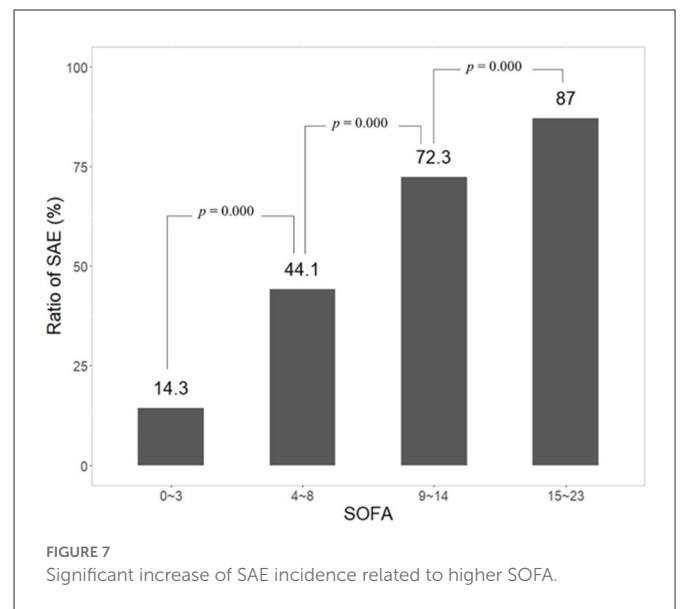
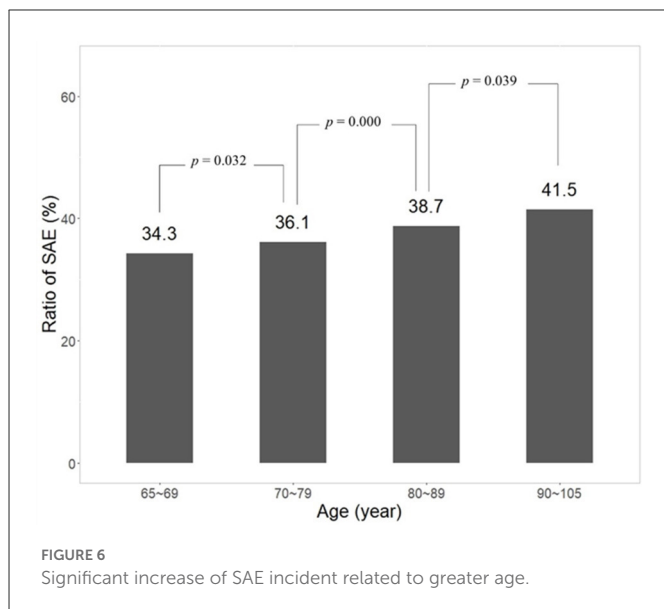
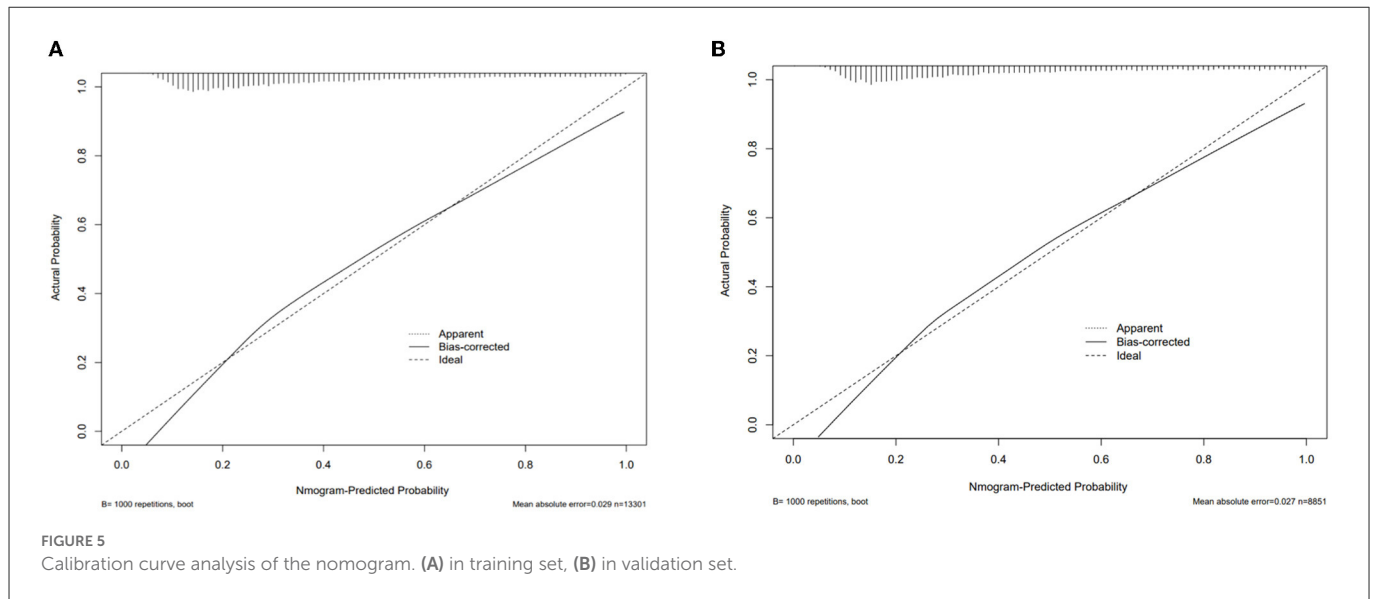
patients with sepsis developed SAE (17). A study enrolled 821 patients with respiratory failure or shock in the medical or surgical intensive care unit (ICU). The median of SOFA was 9 (7, 12) (expressed as median and quartile). A total of 74% of patients developed delirium, which indicated that patients in the ICU were at high risk of cognitive impairment (18). The other study enrolled 175 patients with sepsis, of which 74 patients (42.3%) were diagnosed with SAE. The average age was approximately  $56.2 \pm 15$  years in this study (19). In the present study, as shown in Table 1, there were 8,290 patients with SAE and the incidence of SAE in patients with sepsis was 77.5%. This result (77.5%) was much higher than the data reported previously concerning the less elderly population, which indicated that elderly patients were more vulnerable to developing SAE.

SAE is a reflection of critical illness in the central nervous system. It is the neurological dysfunction induced by the combination of extracranial infection. Different peripheric cytokines, immune cells, or even bacteria infiltrate the cerebrum and take part in the inflammation injury process of the brain. Inflammatory and immunologic injuries play important roles in it. Astrocytes and microglial cells in the brain are activated and also contribute to the development of SAE (7, 20). The decrease in consciousness level is the most common result of SAE. GCS evaluation is reported to be a validated pragmatic way to assess neurological injury in the brain. This was why the definition of SAE in the present study was based on GCS evaluation at ICU admission (21). Delirium is also an important clinical manifestation of SAE and is taken as the other factor in SAE's definition. Therefore, the definition of SAE in the present study was based on GCS and delirium, which was also reported in previous studies (10, 14). SAE is reported to be associated with increased mortality, prolonged length of ICU stay, and hospital stay. These were compared with the results in the present study. The mortality in patients with SAE was much higher than that in patients without



SAE (18.8 vs. 8.9%,  $p < 0.001$ ). Patients with SAE had a longer length of ICU stay ( $4.94 \pm 5.50$  vs.  $3.30 \pm 4.30$  days,  $p < 0.001$ ) and hospital stay ( $12.05 \pm 12.37$  vs.  $9.06 \pm 8.97$  days,  $p = 0.000$ ). A previous study [16] reported the 28-day mortality in SAE and non-SAE groups ( $45.95$  vs.  $17.82\%$ ,  $p < 0.01$ ). The average of SOFA was approximately

$9.1 \pm 4.8$  in this study. However, in our study, the average of SOFA was  $5.04 \pm 3.35$ . It may be the reason why the mortality in our study is lower. The other study based on MIMIC-IV reported 17.62% of patients with SAE died in 30 days which was comparable with our results (22).



SOFA is a classical tool in the evaluation of the severity of illnesses and has a good capability in the prediction of prognosis (23). SOFA was proven to be positively related to the occurrence of delirium (24, 25). In the present study, SOFA was associated with the occurrence of SAE significantly ( $p < 0.001$ ) and showed a strong influence in the nomogram model. The incidence of SAE rose steadily as SOFA increased ( $p < 0.001$ ) (Figure 7). Age is also an independent risk factor of SAE. In elderly patients in ICU, delirium was reported to be more prevalent (26, 27). Our data showed that the incidence of SAE increased statistically from 34.3 to 41.5% as the age of patients rose from 65~69 to 90~69 years ( $p < 0.05$ ). Hyponatremia is a common metabolic disturbance. A previous study showed hyponatremia was associated with SAE significantly (hyponatremia  $>145$  mmol/l, OR = 2.30, 95% CI: 1.48–3.57 by logistic regression analysis) [10]. In the present study, hyponatremia was related to SAE significantly which was proved through logistic

regression analysis (OR = 1.028, 95%CI: 0.021–0.034). So,  $\text{Na}^+$  was adopted in the nomogram model. Platelet was not included in the nomogram because there was little clinical correlation between it and delirium. Tachycardia and high body temperature were also reported to be associated with delirium and impairment of cognition. A multi-centric benchmark study from Lebanon reported the prevalence and incidence of delirium in elderly patients (over 65 years). Tachycardia is a common clinical manifestation induced by fever, hypoxia, and shock. According to this consideration, many patients with delirium were accompanied by tachycardia. Tachycardia is related to cognitive impairment indirectly. Fever usually indicates systemic infection and is a criterion of sepsis. Fever itself could disturb the metabolism of the brain and results in neurological disorder (28). Heart rate and body temperature were integrated into the nomogram and affected the prediction of the nomogram significantly in the present study. Tachycardia and fever usually indicate a

severe condition of illnesses, which are associated with a higher risk of SAE.

All the laboratory tests adopted in the nomogram were taken from the elderly patients at admission to the ICU, as well as the vital signs and SOFA score. Clinicians need to collect the data in the first 24 h after ICU admission to carry on the calculation of the nomogram. This is time-consuming for busy clinical work. Next, the nomogram will be integrated into the hospital information system. The risk of SAE occurrence could be calculated and shown automatically.

The present study has several limitations. First, data were extracted from MIMIC-IV, which made this study a retrospective cohort study from a single center. Therefore, bias could not be avoided. In the real world, it is unavoidable to have occurrence bias in the epidemic investigation of some particular disease in a selected population. The setting is based on the elderly population in ICU. However, there was no intentional intervention in the enrollment, and a total of 22,361 patients were enrolled. The large sample size helped to decrease the occurrence bias to an acceptable level. The other limit is that the definition of SAE was based on delirium and GCS scores. This definition is not as strict as the diagnosis of SAE based on particular clinical evaluation or physico-chemical inspection. All these may reduce the generalizability of the results. A prospective, multiple-center, randomized control trial based on specialized examination is needed in future.

## 5. Conclusion

Sepsis-associated encephalopathy is a high-incidence complication of sepsis in elderly patients in the ICU. SAE is an independent risk of in-hospital mortality. The nomogram integrating several key clinical symptoms and scores is efficient in predicting SAE, which helps in optimizing the management of SAE for elderly patients in the ICU.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

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## Ethics statement

This study has been approved by the Ethics Committee of the Chinese PLA General Hospital (number: S2017–054-01).

## Author contributions

QZ and JX took part in the study design, performed statistical analyses, and drafted the manuscript. XL had access permission to MIMIC-IV and extracted data for the present study. HL conceived the study, participated in the design, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2023.1084868/full#supplementary-material>



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