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Conservative oxygen therapy in critically ill and perioperative period of patients with sepsis-associated encephalopathy

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Objectives: Sepsis-associated encephalopathy (SAE) patients in the intensive care unit (ICU) and perioperative period are administered supplemental oxygen. However, the correlation between oxygenation status with SAE and the target for oxygen therapy remains unclear. This study aimed to examine the relationship between oxygen therapy and SAE patients.

Methods: Patients diagnosed with sepsis 3.0 in the intensive care unit (ICU) were enrolled. The data were collected from the Medical Information Mart for Intensive Care IV (MIMIC IV) database and the eICU Collaborative Research Database (eICU-CRD) database. The generalized additive models were adopted to estimate the oxygen therapy targets in SAE patients. The results were confirmed by multivariate Logistic, propensity score analysis, inversion probability-weighting, doubly robust model, and multivariate COX analyses. Survival was analyzed by the Kaplan-Meier method.

Results: A total of 10055 patients from eICU-CRD and 1685 from MIMIC IV were included. The incidence of SAE patients was 58.43%. The range of PaO₂ (97-339) mmHg, PaO₂/FiO₂ (189-619), and S_pO₂ ≥ 93% may reduce the incidence of SAE, which were verified by multivariable Logistic regression, propensity score analysis, inversion probability-weighting, and doubly robust model estimation in MIMIC IV database and eICU database. The range of PaO₂/FiO₂ (189-619) and S_pO₂ ≥ 93% may reduce the hospital mortality of SAE were verified by multivariable COX regression.

Conclusions: SAE patients in ICU, including perioperative period, require conservative oxygen therapy. We should maintain S_pO₂ ≥ 93%, PaO₂ (97-339) mmHg and PaO₂/FiO₂ (189-619) in SAE patients.

KEYWORDS

sepsis, sepsis-associated encephalopathy, oxygen saturation, incidence, mortality

Introduction

Sepsis-associated encephalopathy (SAE) refers to cognitive dysfunction that can be attributed to systemic inflammatory responses in the absence of direct infection of the central nervous system (1). The incidence of SAE is over 70% of patients admitted to the intensive care unit (ICU) (2). SAE correlates with higher mortality (50.3%), longer hospital stays, and poorer long-term outcomes (3).

Patients admitted to the ICU and perioperative period are administered supplemental oxygen as low partial pressure of arterial oxygen (PaO_2) is detrimental. However, a high PaO_2 correlates with increased mortality, as confirmed in previous studies (4, 5). In a medical-surgical population of adult critically ill patients, arterial oxygen saturation (SpO_2) supplementation titrated to 94%-98% correlates with favorable outcomes (6). The frequent oxygen exposure above the protocol goal ($\text{PaO}_2 > 80$ mmHg and $\text{FiO}_2 > 0.5$) correlates with worse clinical outcomes in patients who develop acute respiratory distress syndrome (7). PaO_2 between (77-220) mmHg and the $\text{PaO}_2/\text{FiO}_2$ ratio in the range of 314-788 also correlates with favorable neurologic outcomes (8). Lower or higher oxygenation targets correlate with worse patient outcomes in ICU and perioperative period.

Potentially adjusted factors contributing to SAE include acute renal failure, hyperglycemia > 10 mmol/l, hypercapnia > 45 mmHg, and hyponatremia > 145 mmol/l (3). The relationships between lower or higher oxygen therapy targets and the incidence and survival in SAE patients remain unclear. This study aimed to assess the correlation of SpO_2 , PaO_2 , and $\text{PaO}_2/\text{FiO}_2$ with SAE in ICU and perioperative period, and elucidate the optimal oxygen therapy targets in SAE patients.

Materials and methods

Study settings

We collected information on patients admitted to the ICU between 2008-2019 from the MIMIC-IV 0.4 and between 2014-2015 from the eICU-CRD v2.0 (NO. 336903880) database. MIMIC IV comprises 69619 and eICU-CRD of 200859 ICU admissions. The eICU database is a multi-center dataset. These were approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (9). The requirement for individual

patient consent was waived because the project does not impact clinical care and all patient confidential information was anonymized. MIMIC-IV and eICU included the demographics, laboratory measurements, microbiology cultures diagnoses, and other patient data. The MIMIC IV database (version 1.0) is publicly available on <https://physionet.org/content/mimiciv/1.0/> and the eICU is publicly available on <https://eICU-crd.mit.edu/about/eICU/>. The raw data were extracted by employing structure query language (SQL) with Navicat and further processed using the R software.

Patients

Sepsis was diagnosed with an acute change in the total sequential organ failure assessment (SOFA) score ≥ 2 and documented or suspected infection complied with the sepsis-3.0 criteria (10). The patients with infection sites or prescriptions of antibiotics and samples of bodily fluids for microbiological culture had suspected infection. In line with the existing literature, the microbiological sample must have been collected within 24 h when the antibiotic was first administered, and at the first occurrence of microbiological sampling, the antibiotic administration would be within 72 h (11). The SOFA score was defined in the first 24 h of the admission of the patient to the ICU.

SAE in this study was defined as the Glasgow Coma Scale (GCS) < 15 or diagnosed delirium (3, 12, 13). Consciousness disorder with clear causes was excluded. GCS has been established as a clinically effective tool to characterize SAE and distinguish it from sepsis (3, 14). Specifically for the sedated or postoperative patients, GCS that was evaluated before sedation or surgery was extracted.

Inclusion criteria were as follows: 1) patients aged over 18 years; 2) ICU stays with more than 24 h of oxygen therapy, and 3) patients complying with the diagnostic criteria as in sepsis 3.0.

Following were the exclusion criteria (3, 12): 1) patients with brain injury (e.g., traumatic brain injury, meningitis, encephalitis intracerebral hemorrhage, cerebral embolism, ischemic stroke, epilepsy, brain tumor or intracranial infection, and any other cerebrovascular disease); 2) mental disorders and neurological disease; 3) chronic alcohol or drug abuse; 4) metabolic encephalopathy, hepatic encephalopathy, hypertensive encephalopathy, hypoglycemic coma, and other liver disease or kidney disease that affected consciousness; 5) severe electrolyte imbalances or glycemic disturbances, including hyponatremia (< 120 mmol/l), hyperglycemia (> 180 mg/dl), or hypoglycemia (< 54 mg/dl); 6) those without GCS assessment; 7) missing values of SpO_2 , FiO_2 , PaO_2 or no signs of administration of supplemental oxygen. Hyponatremia, hyperglycemia, and hypoglycemia can cause metabolic encephalopathy. Patients with any of the above-mentioned conditions were excluded.

Abbreviations: SAE, sepsis-associated encephalopathy; PaCO_2 , partial pressure of carbon dioxide; FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen; SpO_2 pulse oxygen saturation; arterial oxygen saturation; SOFA, sequential organ failure assessment; GCS, Glasgow coma scale; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV.

Data collection

Patient information (e.g., age, gender, length of hospital stay, and hospital mortality), laboratory indicators, co-existing illnesses, sites of infection, microbiology types, and advanced cardiac life support (e.g., mechanical ventilation and vasopressors) were extracted as the demographic data using SQL. The laboratory indicators of the patients were collected within the first 24 h of their ICU stay, including pulse oxygen saturation (S_pO_2), partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), and a fraction of inspired oxygen (FiO_2). The coexisting illnesses were determined following the recorded International Classification of Diseases (ICD)-9 and ICD-10 codes (e.g., hypertension, diabetes, pulmonary disease, and kidney disease). Disease severity scores included the SOFA score and GCS. Only the data of the first ICU admission of the corresponding patients have been included.

Statistical analysis

The data were analyzed using the R software. Data distributions were analyzed by the Shapiro-Wilk test. Herein, all the data exhibited skewed distributions. Continuous data (age, $PaCO_2$, FiO_2 , PaO_2 , S_pO_2 , length of hospital stay, SOFA, and GCS) were expressed as median and interquartile ranges (IQR). Other categorical data were expressed in counts and proportions. Continuous variables were examined using the non-parametric Mann-Whitney U-test. Furthermore, categorical variables were compared using the Fisher exact test.

PaO_2 and PaO_2/FiO_2 show a nonlinear correlation with the incidence in SAE patients. The generalized additive models (15) were adopted to estimate the association between median PaO_2 , PaO_2/FiO_2 , and SAE, and the range of PaO_2 , PaO_2/FiO_2 target was determined for reducing the incidence and hospital mortality among SAE patients.

The range of PaO_2 , S_pO_2 , PaO_2/FiO_2 targets for incidence and hospital mortality of SAE patients as determined using multivariate Logistic, COX regression models, propensity score analysis, inversion probability-weighting, and doubly robust model for further validation of the oxygen values. An independent association between blood oxygen index levels and patients' SAE was inferred through the doubly robust estimation method. Multivariate Logistic regression and Extreme Gradient Boosting (XGBoost) were used to create propensity score models for the 7 covariables (Figure 3) in sepsis patients with SAE. A cohort of inverse probability of treatment weighting (IPTW) was generated from the estimated propensity scores. Afterward, we performed a Logistic Regression on the weighted cohort to adjust for remaining unbalanced variables in the propensity score model between SAE groups and non-SAE groups, resulting in a double robust analysis. To determine whether IPTW reduced the imbalance of covariate distribution, the standardized mean

difference (SMD) of the original cohort was compared with the SMD of the IPTW cohort. The Kaplan-Meier curves were analyzed using Log-rank tests.

Results

Baseline characteristics

A total of 51395 patients met the sepsis 3.0 criteria in the MIMIC IV database and the eICU database; among them, 39655 patients were excluded from the analysis due to intracerebral hemorrhage, encephalitis, brain tumor, brain injury, mental disorders, drug abuse, alcoholism, Alzheimer's disease, metabolic encephalopathy, hepatic encephalopathy, the absence of FiO_2 over 21%, missing records of the oxygen index, or no records of GCS scores; three patients were younger than 18 years and other conditions. A total of 11740 patients were included in the final analysis (Figure 1).

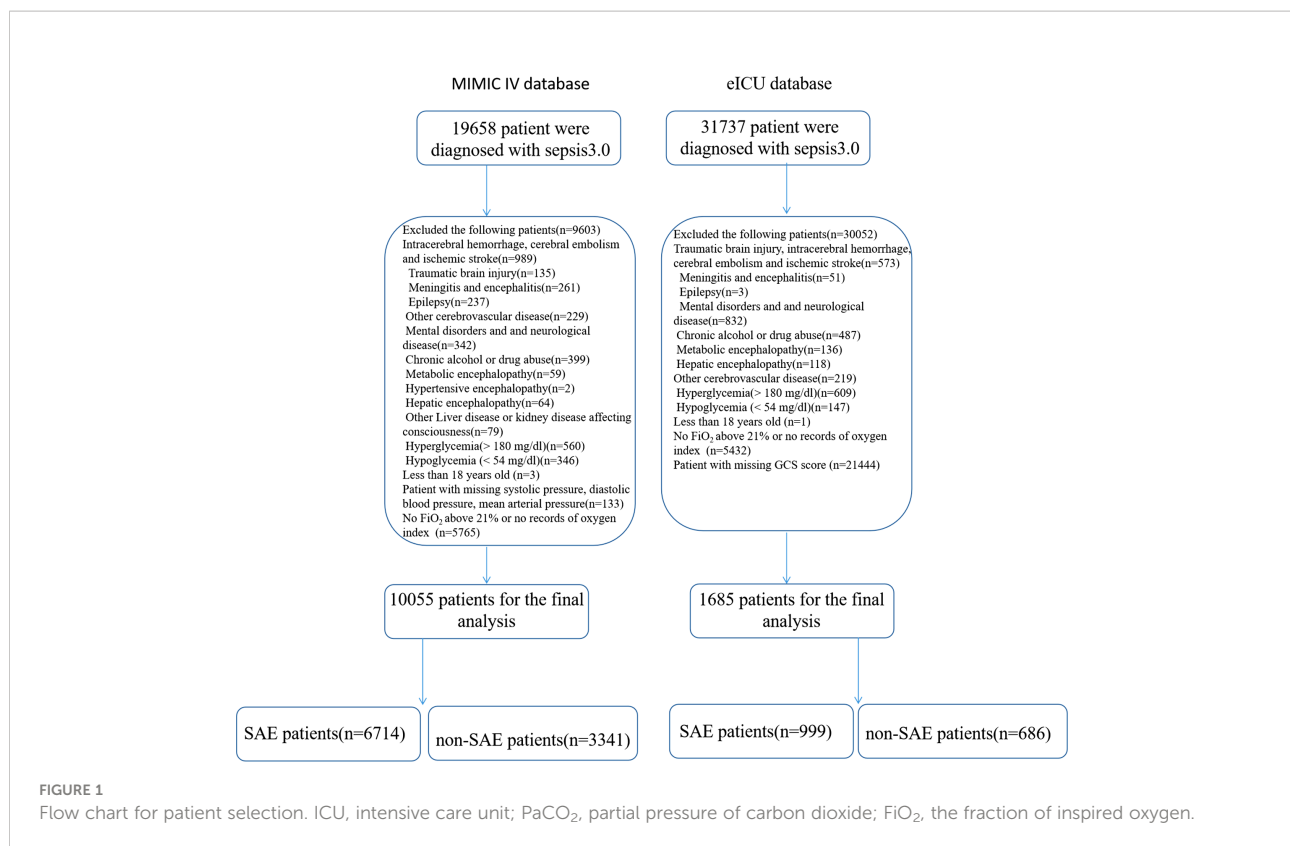
Table 1 summarized the characteristics and outcomes of sepsis in the MIMIC IV database. Relative to the non-SAE group in the original cohort, patients in the SAE group were more likely to suffer from Klebsiella, Escherichia coli, or fungus infection. The SAE group showed higher respiratory rates, FiO_2 , and lower PaO_2 , S_pO_2 , and PaO_2/FiO_2 , relative to the non-SAE group. Patients in the SAE group exhibited higher SOFA and hospital mortality with a longer length of hospital stay.

Generalized additive models to estimate the optimal oxygen therapy targets for incidence of SAE

Figure 2 illustrated the correlation between the incidence of SAE and the median S_pO_2 , PaO_2 , and PaO_2/FiO_2 determined using the generalized additive models in MIMIC IV database. The generalized additive models demonstrated a nonlinear correlation between PaO_2 and PaO_2/FiO_2 with SAE incidence. $S_pO_2 < 93\%$, $PaO_2 < 97$ mmHg and > 339 mmHg, and $PaO_2/FiO_2 < 189$ and > 619 were associated with increased incidence of SAE, as shown in Table 2.

Multivariate logistic analysis for risk factors of SAE incidence

According to the results of the generalized additive model, as shown in Figure 2, PaO_2 (97-339) mmHg, PaO_2/FiO_2 (189-619), and $S_pO_2 \geq 93\%$ may reduce the incidence of SAE. After adjusting for confounders, PaO_2 (97-339) mmHg [odds ratio (OR): 0.566, 95% confidence interval (CI): 0.471-0.681, $p < 0.001$], PaO_2/FiO_2 (189-619) [OR: 0.513, 95% CI: 0.452-0.582, $p < 0.001$], and $S_pO_2 \geq 93\%$ [OR: 0.324, 95% CI: 0.272-0.387, $p < 0.001$] were



identified as protective factors against SAE conduct internal assessment in the MIMIC IV database ([Supplementary Material 1](#)). Besides, using the eICU database for external evaluation ([Supplementary Material 2](#)), after adjusting for confounders, PaO₂ (97-339) mmHg [OR: 0.703, 95% CI: 0.547-0.903, p=0.006], PaO₂/FiO₂ (189-619) [OR:0.750, 95% CI: 0.555-0.982, p=0.048], and S_pO₂≥93% [OR:0.779, 95% CI: 0.631-0.961, p=0.020] were identified as protective factors ([Supplementary Materials 1, 2](#)).

Propensity match analysis

To further confirm the reliability of the results, the data in the MIMIC IV database is used for internal verification and the data in the eICU database is used for external verification by propensity score analysis, inversion probability-weighting, and doubly robust model. A propensity matching scoring model was constructed using 7 covariates with statistically significant differences in [Table 1](#) of the original cohort in the MIMIC IV database ([Figure 3](#)). For standardizing the differences between the SAE group and the non-SAE group, the estimated propensity scores were used. Covariates were well balanced between classes after IPTW (<0.1) ([Figure 3](#)). After matching the difference covariates, PaO₂, S_pO₂, and PaO₂/FiO₂ were significantly different between the SAE group and the non-SAE group

([Table 1](#)). To evaluate the relationship between the PaO₂, S_pO₂, and PaO₂/FiO₂ levels (estimated as per generalized additive model) and SAE incidence, we used propensity-matching score, proportion score IPTW and a doubly robust model with two databases to statistical analysis. The estimation models led to the same conclusion in the MIMIC IV and eICU database that S_pO₂≥93%, PaO₂/FiO₂ (189-619), and PaO₂(97-339) mmHg were protective factors for patients with SAE ([Table 2](#)).

Prognostic analyses of patients with SAE

To further examine the effect of SAE on the prognoses of patients with sepsis, their survival was analyzed by the Kaplan-Meier method. Patients in the non-SAE group showed better survival rates than the SAE group (p<0.001) ([Figure 4](#)).

Demographic and clinical characteristics of SAE

[Table 1](#) and [Figure 4](#) illustrated that SAE patients had poor prognoses. To further examine the effect of oxygen therapy on the prognoses of patients with SAE, we divided the SAE patients into the survival and non-survival groups in the MIMIC IV and eICU database. The results as listed in [Supplementary Material 3](#)

TABLE 1 Baseline characteristics and outcomes of sepsis patients.

| | Original cohort | | | Match cohort | | |
|--|------------------------------|--------------------------|--------|------------------------------|--------------------------|--------|
| | Non-SAE patients (n=3341) | SAE patients (n=6714) | P | Non-SAE patients (n=3327) | SAE patients (n=3327) | P |
| Baseline variables | | | | | | |
| Age(years) (median [IQR]) | 69.00 [60.00, 77.00] | 68.00[59.00, 77.00] | 0.540 | 69.00[59.00, 77.00] | 68.00[59.00, 77.00] | 0.036 |
| Gender,M (%) | 2103 (62.9) | 4252 (63.3) | 0.722 | 2099 (63.1) | 2105 (63.3) | 0.899 |
| Coexisting illness, (n(%)) | | | | | | |
| Hypertension | 553 (16.6) | 1129 (16.8) | 0.760 | 548 (16.5) | 532 (16.0) | 0.618 |
| Diabetes | 558 (16.7) | 1100 (16.4) | 0.707 | 558 (16.8) | 484 (14.5) | 0.014 |
| Respiration | 1065 (31.9) | 2015 (30.0) | 0.059 | 1059 (31.8) | 713 (21.4) | <0.001 |
| Renal | 1362 (40.8) | 2754 (41.0) | 0.807 | 1357 (40.8) | 1222 (36.7) | 0.001 |
| Site of infection, (n (%)) | | | | | | |
| Urinary | 200 (6.0) | 360 (5.4) | 0.215 | 195 (5.9) | 167 (5.0) | 0.144 |
| Lung | 185 (5.5) | 370 (5.5) | 0.993 | 182 (5.5) | 122 (3.7) | 0.001 |
| Catheter | 65 (1.9) | 96 (1.4) | 0.063 | 64 (1.9) | 39 (1.2) | 0.017 |
| Skin and soft tissue | 103 (3.1) | 205 (3.1) | 0.984 | 56 (1.7) | 102 (3.1) | <0.001 |
| Abdominal cavity | 89 (2.7) | 166 (2.5) | 0.612 | 88 (2.6) | 64 (1.9) | 0.059 |
| Microbiology type, (n (%)) | | | | | | |
| Acinetobacter baumannii | 6 (0.2) | 20 (0.3) | 0.373 | 5 (0.2) | 12 (0.4) | 0.145 |
| Klebsiella | 161 (4.8) | 454 (6.8) | <0.001 | 160 (4.8) | 177 (5.3) | 0.371 |
| Escherichia Coli | 340 (10.2) | 845 (12.6) | <0.001 | 338 (10.2) | 352 (10.6) | 0.601 |
| Pseudomonas aeruginosa | 133 (4.0) | 175 (2.6) | <0.001 | 120 (3.6) | 117 (3.5) | 0.895 |
| Staphylococcus aureus | 38 (1.1) | 63 (0.9) | 0.403 | 36 (1.1) | 32 (1.0) | 0.715 |
| Fungus | 300 (9.0) | 1118 (16.7) | <0.001 | 299 (9.0) | 302 (9.1) | 0.932 |
| Vital signs, (median [IQR]) | | | | | | |
| Respiratory rate (bpm) | 26.00 [23.00, 31.00] | 27.00[24.00, 31.00] | <0.001 | 26.00[23.00, 31.00] | 26.00[23.00, 30.00] | 0.001 |
| S _p O ₂ , % | 94.00 [92.00, 95.00] | 93.00[90.00, 95.00] | <0.001 | 95.00[93.00, 96.00] | 94.00[92.00, 95.00] | <0.001 |
| FiO ₂ , % | 50.00 [40.00, 55.00] | 50.00[40.00, 66.00] | <0.001 | 43.00[40.00, 50.00] | 50.00[40.00, 55.00] | <0.001 |
| PaO ₂ , mmHg | 99.00 [80.00, 129.00] | 93.00[74.00, 123.00] | <0.001 | 118.00[95.00, 152.00] | 99.00[80.00, 129.00] | <0.001 |
| PaCO ₂ , mmHg | 47.00 [42.00, 52.00] | 47.00[41.00, 52.00] | 0.171 | 47.00[42.00, 52.00] | 44.00[39.00, 49.00] | <0.001 |
| PaO ₂ /FiO ₂ | 219.00 [150.00, 264.00] | 216.00 [136.70, 248.00] | <0.001 | 248.60 [219.00, 316.00] | 219.00 [150.00, 264.00] | <0.001 |
| Laboratory parameters (median [IQR]) | | | | | | |
| White blood cell (×10 ⁹ /L) | 14.10 [10.70, 18.70] | 14.10[10.50, 18.60] | 0.58 | 14.10[10.70, 18.70] | 13.90[10.40, 18.10] | 0.078 |
| Hemoglobin(g/dL) | 9.30 [8.10, 10.70] | 9.30 [8.10, 10.70] | 0.278 | 9.30 [8.00, 10.70] | 9.20 [8.00, 10.50] | 0.025 |
| Platelet (×10 ⁹ /L) | 141.00[107.00, 201.00] | 144.00[108.75, 206.00] | 0.022 | 141.00[107.00, 201.00] | 136.00[104.00, 191.00] | <0.001 |
| Creatinine(mg/dL) | 1.00 [0.80, 1.40] | 1.00 [0.80, 1.40] | 0.255 | 1.00 [0.80, 1.40] | 1.00 [0.80, 1.40] | 0.233 |
| Blood urea nitrogen (mg/dL) | 19.00 [14.00, 28.00] | 19.00[14.00, 29.00] | 0.209 | 19.00[14.00, 27.00] | 18.00[14.00, 27.00] | 0.036 |
| Glucose(mg/dL) | 133.00[113.00, 164.00] | 134.00[113.00, 165.00] | 0.407 | 133.00[112.50, 164.00] | 132.00[111.00, 161.00] | 0.164 |
| Sodium (mmol/l) | 140.00[137.00, 142.00] | 140.00[137.00, 142.00] | 0.629 | 140.00[137.00, 142.00] | 140.00[138.00, 142.00] | 0.342 |
| Lactates (mmol/L) | 1.70 [1.20, 2.40] | 1.70 [1.20, 2.30] | 0.003 | 1.70 [1.20, 2.40] | 1.60 [1.20, 2.30] | 0.004 |
| The score system, (median [IQR]) | | | | | | |
| SOFA | 3.00 [2.00, 5.00] | 5.00 [3.00, 7.00] | <0.001 | 3.00 [2.00, 5.00] | 5.00 [3.00, 7.00] | <0.001 |
| GCS | 15.00 [15.00, 15.00] | 13.00[8.00, 14.00] | <0.001 | 15.00[15.00, 15.00] | 13.00[8.00, 14.00] | <0.001 |
| Mechanical ventilation, (n(%)) | 2575 (77.1) | 5153 (76.8) | 0.737 | 2563 (77.0) | 2500 (75.1) | 0.075 |
| Use of vasopressors, (n(%)) | 2080 (62.3) | 4036 (60.1) | 0.040 | 2070 (62.2) | 1966 (59.1) | 0.010 |
| Length of hospital stays, days (median [IQR]) | 2.30 [1.30, 4.90] | 2.40 [1.30, 5.10] | 0.142 | 2.30 [1.30, 4.90] | 2.30 [1.30, 4.80] | 0.876 |
| Hospital mortality, (n(%)) | 250 (7.5) | 914 (13.6) | <0.001 | 248 (7.5) | 222 (6.7) | 0.232 |

GCS, Glasgow coma scale; SOFA, sequential organ failure assessment; PaCO₂, partial pressure of carbon dioxide; S_pO₂, arterial oxygen saturation; PaO₂, partial pressure of oxygen.

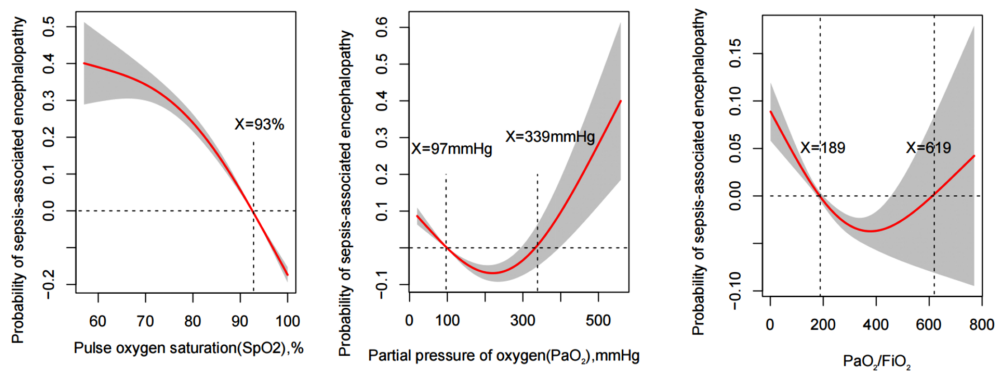


FIGURE 2

Generalized additive model plots for the median of S_pO_2 , PaO_2 , and PaO_2/FiO_2 indicating the probability of sepsis-associated encephalopathy incidence.

showed that non-surviving patients had higher PaO_2 and PaO_2/FiO_2 .

Multivariate COX analysis for risk factors of hospital mortality in SAE

According to the results of the generalized additive model, as shown in Figure 2, after adjusting for confounders, $S_pO_2 \geq 93\%$ and PaO_2/FiO_2 (189–619) were independent protective factors for SAE prognoses in the MIMIC IV and eICU database (Table 3; Supplementary Materials 4, 5).

Discussion

As demonstrated from the primary outcome of this cohort study, oxygen therapy may be correlated with SAE incidence. The PaO_2 range of 97 to 339 mmHg, the PaO_2/FiO_2 ratio between 189 and 619, and $S_pO_2 \geq 93\%$ may be correlated with reducing SAE incidence. The PaO_2 range of 97 to 339 mmHg and the PaO_2/FiO_2 ratio between 189 and 619 may be correlated with reduce SAE hospital mortality. Conservative oxygen therapy should be performed for SAE patients.

As reported in existing studies, the SAE incidence can reach up to 70% (2), in line with the results of this study (58.43%), which suggested a high SAE incidence. The results of the cohort study showed that hospital mortality was 13.6% in SAE patients, the hospital mortality of SAE group was significantly higher than that of non-SAE group, and that SAE patient with a higher SOFA score and longer hospital stay. These results with consistent with the findings of a previous study (3). It has been reported that 45% of SAE patients show long-term cognitive dysfunction after hospital discharge (16). Taken together, SAE shows a high incidence and poor prognosis. However, specific treatment for SAE is rare, and early identification of potentially modifiable

factors with the optimal chance of avoiding incidence, long-term cognitive dysfunction, and reducing mortality are needed. In this large cohort study, the PaO_2 range of 97 to 339 mmHg and the PaO_2/FiO_2 ratio between 189 and 619 were associated with reduced incidence and hospitalization mortality of SAE. Thus, lower or higher oxygenation could induce SAE.

Hyperoxemia is correlated with neurological injury in patients with traumatic brain injury and aneurysmal subarachnoid hemorrhage (17, 18). Hyperoxemia leads to the production of reactive oxygen species, thereby destroying cells and further promoting inflammatory responses (18). Moreover, active oxygen can cause an increase in the production of free radicals of oxygen, whereby excess free radicals can stimulate the hypersensitive arterial system, resulting in vasospasm (19). Inflammatory responses, oxygen-free radicals, and vasospasm are vital mechanisms underlying SAE (20, 21). Nguyen Mai et al. propose a conceptual model of lung-brain coupling, the use of supplemental oxygen can induce cardiac arrest, neuronal injury, neuroinflammation, and memory deficits (22). The results of this study demonstrated that $PaO_2 > 339$ mmHg and $PaO_2/FiO_2 > 619$ may increase the incidence of encephalopathy in patients with sepsis. Hyperoxemia has been proven to be correlated with SAE. The neurological injury in sepsis patients attributed to hyperoxia may be due to the above-mentioned reasons. A subsequent study is thus required to evaluate the underlying pathophysiological mechanism in the future (23).

Neurological injury attributed to hypoxemia has been extensively confirmed (24, 25). Kim I Chisholm et al. report that sepsis leads to increased sensitivity of cortical mitochondria to hypoxemia, and such increased sensitivity is mirrored by a decrease in cortical tissue oxygen tension in mice (26). Transcription-dependent mechanisms triggered by hypoxia and reticulum stress could activate AMP-activated protein kinase, thereby stimulating the inflammatory activities. AMP protein is vital and is stimulated by immune factors in the brain, and consequently, the MAP signaling pathway is inhibited, decreased meta apoptosis and

TABLE 2 Multiple models analysis of blood oxygen index to incidence in sepsis with encephalopathy.

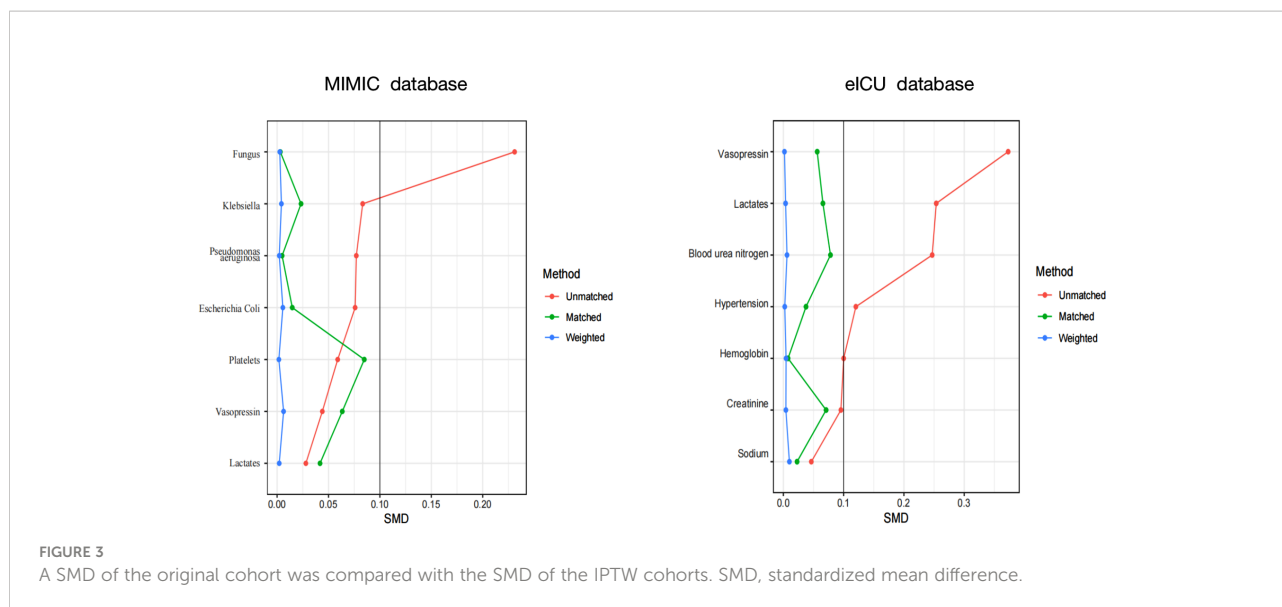
| Models | OR | CI | | P |
|---|------|------|-------|--------|
| | | 2.5% | 97.5% | |
| Internal cohort study(MIMIC database cohort study) | | | | |
| Multivariate Logistic analysis (Original cohort) | | | | |
| S _p O ₂ ≥93% | 0.32 | 0.27 | 0.39 | <0.001 |
| PaO ₂ /FiO ₂ (189-619) | 0.51 | 0.45 | 0.58 | <0.001 |
| PaO ₂ (97-339)mmHg | 0.57 | 0.47 | 0.68 | <0.001 |
| Propensity score matching | | | | |
| S _p O ₂ ≥93% | 0.59 | 0.55 | 0.65 | <0.001 |
| PaO ₂ /FiO ₂ (189-619) | 0.87 | 0.80 | 0.95 | 0.002 |
| PaO ₂ (97-339)mmHg | 0.76 | 0.70 | 0.82 | <0.001 |
| Propensity score IPW | | | | |
| S _p O ₂ ≥93% | 0.61 | 0.56 | 0.67 | <0.001 |
| PaO ₂ /FiO ₂ (189-619) | 0.88 | 0.81 | 0.96 | 0.003 |
| PaO ₂ (97-339)mmHg | 0.79 | 0.72 | 0.86 | <0.001 |
| Doubly robust with all covariates | | | | |
| S _p O ₂ ≥93% | 0.85 | 0.82 | 0.87 | <0.001 |
| PaO ₂ /FiO ₂ (189-619) | 0.96 | 0.93 | 0.98 | 0.002 |
| PaO ₂ (97-339)mmHg | 0.92 | 0.90 | 0.95 | <0.001 |
| External validation cohort study(eICU database cohort study) | | | | |
| Multivariate Logistic analysis | | | | |
| S _p O ₂ ≥93% | 0.78 | 0.63 | 0.96 | 0.020 |
| PaO ₂ /FiO ₂ (189-619) | 0.75 | 0.56 | 0.98 | 0.048 |
| PaO ₂ (97-339)mmHg | 0.70 | 0.55 | 0.90 | 0.006 |
| Propensity score matching | | | | |
| S _p O ₂ ≥93% | 0.79 | 0.65 | 0.96 | 0.018 |
| PaO ₂ /FiO ₂ (189-619) | 0.73 | 0.60 | 0.90 | 0.002 |
| PaO ₂ (97-339)mmHg | 0.32 | 0.24 | 0.41 | <0.001 |
| Propensity score IPW | | | | |
| S _p O ₂ ≥93% | 0.78 | 0.64 | 0.96 | 0.020 |
| PaO ₂ /FiO ₂ (189-619) | 0.76 | 0.62 | 0.94 | 0.011 |
| PaO ₂ (97-339)mmHg | 0.69 | 0.57 | 0.85 | 0.001 |
| Doubly robust with all covariates | | | | |
| S _p O ₂ ≥93% | 0.91 | 0.84 | 0.98 | 0.012 |
| PaO ₂ /FiO ₂ (189-619) | 0.90 | 0.83 | 0.97 | 0.006 |
| PaO ₂ (97-339)mmHg | 0.87 | 0.81 | 0.94 | <0.001 |

PaCO₂, partial pressure of carbon dioxide; S_pO₂, arterial oxygen saturation; PaO₂, partial pressure of oxygen.

autophagy (22, 27). Hypoxia increases the levels of lactate/pyruvate, decreases the glutathione/oxidized glutathione ratio, upregulates inflammatory cytokine cascades, activates the apoptosis pathway, all leading to the damage of the cerebral cortex and neurons (23, 28). The results of this study further demonstrated that PaO₂ <97mmHg, PaO₂/FiO₂<189, and SPO₂<93% may cause changes in consciousness among sepsis patients. To mitigate the neurological injury by hypoxia or hyperoxia and incidence of SAE, PaO₂ with 97-339 mmHg, PaO₂/FiO₂ in the range of 189-619, and SPO₂≥93% should be taken in SAE patients.

Low oxygen saturations are considered detrimental. A liberal oxygen strategy is correlated with mortality, especially in ICU

patients, as oxygen is extensively used in the ICU, and patients are commonly exposed to high oxygenation (29). The correlation between exposure to hyperoxia and mortality has been reported in ICU in previous studies (30, 31). Specifically for critically ill patients or those on ventilator-assisted breathing, to reduce mortality, the assessment of optimal oxygen saturation is particularly important. Willem van den Boom et al. report that the optimal range of S_pO₂ is 94%–98% which is correlated with decreased hospital mortality among critically ill patients (32). The proportion of time of oxygen saturation of 95%–99% correlates with reduced mortality in critically ill patients on mechanical ventilation, as reported by Dawei Zhou et al. (33).



According to Derek K Chu et al., in acutely ill adults, liberal oxygen therapy increases mortality, and oxygen saturation of 94%-96% adversely affects the patients (34). In this study, the $S_pO_2 < 93\%$ was significantly associated with hospital mortality among SAE patients. The range of PaO_2 (97-339) mmHg and PaO_2/FiO_2 (189-619) are associated with lower hospital mortality in SAE patients. The findings support that SAE patients should be administrated with conservative oxygen therapy for reducing the incidence and hospital mortality.

Limitation

First, the definition of SAE is compliance with $GCS < 15$ score, and patients diagnosed with delirium according to ICD9 and ICD10. Though brain hemorrhage, brain trauma, and other diseases were excluded, the absence of brain computed tomography scans, magnetic resonance imaging,

electroencephalogram, and other examinations to assess the nervous system, the result information bias maybe in the SAE cohort. Second, this was an observational study, and the causal correlation between oxygen therapy and the incidence and mortality of SAE could not be proved. However, the correlation between oxygen therapy and SAE was demonstrated in this large cohort study by multiple databases and Multiple statistical methods. The findings provide certain clinical reference values. Finally, due to the interrelationship between diseases, some confounding factors remained, thereby covering up or exaggerating the relationship between study factors and SAE.

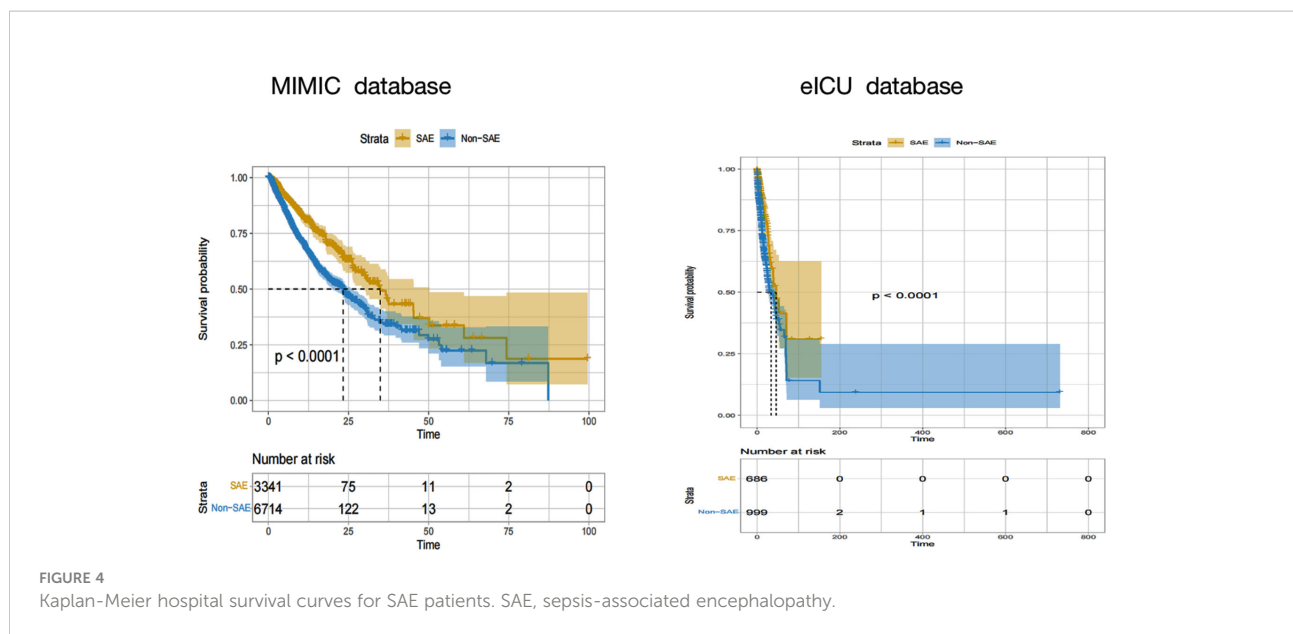
Conclusions

In conclusion, high or low PaO_2 , PaO_2/FiO_2 and S_pO_2 were correlated with the incidence of SAE. The range of PaO_2 (97-339) mmHg, PaO_2/FiO_2 (189-619) and $S_pO_2 \geq 93\%$ were identified in

TABLE 3 Multiple COX regression model analysis of blood oxygen index to hospital mortality in sepsis with encephalopathy.

| Models | OR | CI | | P |
|---|------|------|-------|--------|
| | | 2.5% | 97.5% | |
| Internal cohort study(MIMIC IV database cohort study) | | | | |
| $S_pO_2 \geq 93\%$ | 0.68 | 0.49 | 0.93 | 0.017 |
| $PaO_2/FiO_2(189-619)$ | 0.38 | 0.32 | 0.45 | <0.001 |
| $PaO_2(97-339)$ mmHg | 0.93 | 0.69 | 1.25 | 0.63 |
| External validation cohort study(eICU database cohort study) | | | | |
| $S_pO_2 \geq 93\%$ | 0.78 | 0.63 | 0.96 | 0.020 |
| $PaO_2/FiO_2(189-619)$ | 0.75 | 0.56 | 0.98 | 0.048 |
| $PaO_2(97-339)$ mmHg | 0.70 | 0.55 | 0.90 | 0.006 |

$PaCO_2$, partial pressure of carbon dioxide; S_pO_2 , arterial oxygen saturation; PaO_2 , partial pressure of oxygen.



SAE patients in ICU and perioperative period. A reference target was provided which is expected to aid clinicians in preventing the occurrence and reducing the incidence and hospital mortality of SAE. PaO_2 (97-339) mmHg, $\text{PaO}_2/\text{FiO}_2$ (189-619) and $\text{SpO}_2 \geq 93\%$ as reference targets for subsequent experiments.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The MIMIC IV database (version 1.0) is publicly available at <https://mimic-iv.mit.edu/> and the eICU database is publicly available at <https://eicu-crd.mit.edu/about/eicu/>. Any researcher who adheres to the data use requirements is permitted access to these databases. The codes are available at <https://github.com/MIT-LCP/mimic-iv>.

Author contributions

YL, LZ, KX, and YHY conceived the central ideas of the study. YY, KZ, YJ, and ZW collected the data. YL and LZ wrote the first draft of the manuscript. KX and YHY revised the paper, worked on the English, and drafted the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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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/fimmu.2022.1035298/full#supplementary-material>

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