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Optimal Oxygen Saturation Targets in Patients with Sepsis-Associated Encephalopathy: A Cohort Study from the MIMIC-IV Database

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Research

Keywords: Sepsis, Sepsis- associated encephalopathy, Oxygen saturation, Incidence, Mortality

Posted Date: May 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-478223/v1

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Abstract

Objectives: Patients with sepsis-associated encephalopathy (SAE) in the intensive care unit (ICU) are treated with supplemental oxygen. However, few studies have investigated the impact of oxygenation status on the patient with SAE, and the optimal oxygenation status target remains unclear. We aimed to investigate the relationship between optimal oxygenation status and patients with SAE.

Methods: This study is a retrospective cohort study. Patients were diagnosed with sepsis3.0 at the first ICU admission between 2008 and 2019 from Medical Information Mart for Intensive Care IV (MIMIC IV). We use generalized additive models to estimate the optimal oxygen saturation targets in patients with SAE. Multivariate logistic analysis to further confirm it.

Measurements and Main Results: A total of 6714 patients with SAE were included. The incidence of patients with SAE was 66.8%, and hospital mortality was 7.9%. SpO$_2$ ≤ 92% was the independent risk factor of incidence in patients with SAE. The optimal range of SpO$_2$ was 93%–97%, which can reduce the incidence of patients with SAE. The optimal range of SpO$_2$ was 92%–96%, reducing the hospital mortality of patients with SAE.

Conclusions: The optimal range of SpO$_2$ was 93%–96% reduce the hospital mortality and incidence of patients with SAE. SAE patients need conservative oxygen therapy.

Introduction

Sepsis-associated encephalopathy (SAE) was defined as a cognitive dysfunction caused by the systemic inflammatory response in the absence of direct infection of the central nervous system [1]. The incidence of SAE was up to more than 70% of patients admitted to the ICU[2]. SAE is associated with higher mortality (50.3%), longer hospital stays, and poorer long-term outcomes[3].

Patients admitted to the intensive care unit (ICU) often receive supplemental oxygen administration. The low partial pressure of arterial oxygen (PaO$_2$) is detrimental. However, a high PaO$_2$ is associated with increased mortality, which has been confirmed by studies[4, 5]. In a medical-surgical population of adult critically ill patients, arterial oxygen saturation (SpO$_2$) supplementation titrated to 94%-98% was associated with favorable outcomes[6]. Oxygen frequently exposure above the protocol goal (PaO$_2$ > 80 mmHg and FiO$_2$ > 0.5) was associated with worse clinical outcomes in patients with acute respiratory distress syndrome[7]. The PaO$_2$ range of 77 to 220mmHg and PaO$_2$/FiO$_2$ ratio between 314 and 788 were associated with favorable neurologic outcomes[8]. Lower or higher oxygenation targets were associated with patient's favorable outcomes in ICU.

Potentially modifiable factors contributing to SAE including: acute renal failure, hyperglycemia > 10mmol/l, hypercapnia > 45mmHg, hypernatremia > 145mmol/l, et al[3]. The relationship between lower or higher oxygenation targets and the incidence, survival of patients with SAE remains unclear.

We aimed to evaluate the association of SpO$_2$ with SAE in ICU and elucidate the optimal oxygen saturation target in patients with SAE.

Materials And Methods

Setting
We collected patients admitted to an ICU between 2008–2019 from MIMIC-IV 0.4, including 69619 patients [9]. MIMIC-IV is grouped into three modules: core, hosp, and icu, provide demographics, laboratory measurements, microbiology cultures diagnoses, and so on for the patients. The MIMIC IV database (version 0.4) is publically available from https://physionet.org/content/mimiciv/0.4/. The raw data were extracted using structure query language (SQL) with navicat and further processed with R software.

**Patient**

Sepsis was diagnosed with an acute change in total sequential organ failure assessment (SOFA) score ≥ 2 and documented or suspected infection according to the sepsis-3.0[10]. The patient has an infection site or prescriptions of antibiotics and sampling of bodily fluids for microbiological culture were considered to have suspected infection. In line with previous research, when the antibiotic was given first, the microbiological sample must have been collected within 24 h; when the microbiological sampling occurred first, the antibiotic must have been administered within 72 h[11]. The SOFA score is the first 24h of the patient's admission to the ICU.

SAE in the study was defined Glasgow Coma Scale (GCS) < 15, diagnosed delirium, or use of haloperidol in sepsis patients[3, 12, 13]. Consciousness disorder with clear causes were excluded. GCS has been established as a clinically effective tool for characterizing SAE and distinguishing it from sepsis[3, 14]. For sedated or postoperative patients, GCS measured before sedation or surgery was extracted.

Inclusion criteria were as follows: 1) patients more than 18; 2) ICU stays with more than 24 hours of oxygen therapy; 3) patients who met the diagnostic criteria of sepsis 3.0.

Excluded were patients[3, 12]: 1) with brain injury (traumatic brain injury, meningitis, encephalitis intracerebral hemorrhage, cerebral embolism, ischemic stroke, epilepsy, or intracranial infection and another cerebrovascular disease) (Supplementary materials1- Supplementary materials5); 2) mental disorders and neurological disease (Supplementary materials6); 3) chronic alcohol or drug abuse (Supplementary materials7); 4) metabolic encephalopathy, hepatic encephalopathy, hypertensive encephalopathy, hypoglycemic coma, and other liver disease or kidney disease is affecting consciousness (Supplementary materials8); 5) severe electrolyte imbalances or glycemic disturbances, including hyponatremia (< 120 mmol/l), hyperglycemia (> 180 mg/dl), or hypoglycemia (< 54 mg/dl); 6) partial pressure of carbon dioxide (PaCO₂) ≥ 80mmHg; 7) without an evaluation of GCS. 8) Missing value of SpO₂, FiO₂, PaO₂ or with no signs of supplemental oxygen. Hyponatremia, hyperglycemia, hypoglycemia can cause metabolic encephalopathy, PaCO₂ ≥ 80mmHg can cause pulmonary encephalopathy, they are all excluded.

**Data Collection**

Demographic data (age, gender, ethnicity, type of admission, length of hospital stay, hospital mortality), laboratory values, coexisting illness, site of infection, microbiology type, advanced cardiac life support (mechanical ventilation, renal replacement therapy, vasopressors) were extracted demographic data by R statistical software (R foundation for statistical computing, Vienna, Austria). We collected laboratory mean values of the patients from the first 24 h of ICU stay, including arterial oxygen saturation (SpO₂), partial pressure of carbon dioxide (PaCO₂), partial pressure of oxygen (PaO₂), the fraction of inspired oxygen (FiO₂). Coexisting illnesses were collected based on the recorded International Classification of Diseases (ICD)-9 and ICD-10 codes, including hypertension, diabetes, pulmonary disease, cardiovascular disease, kidney disease. (Supplementary materials9-13). Disease severity score: SOFA score, the Simplified Acute Physiology Score II (SAPS II), GCS. The data profiling report for the entire data overview of the queue (Supplementary materials14). Only the data of each patient's first ICU admission were used in this study.

**Statistical Analysis**
Data were analyzed using R software. Data distribution was analyzed using the Shapiro-Wilk test. The data in this study are all skewed distributions. Continuous data (Age, PaCO$_2$, FiO$_2$, PaO$_2$, length of hospital stay, SAPS II, SOFA, GCS) were expressed as the median (interquartile range, IQR). Other categorical data are expressed as counts and proportions. Continuous variables were examined using the Mann-Whitney U test; categorical variables were compared using Fisher exact test.

PaO$_2$, S$_p$O$_2$ have a nonlinearity relationship with the incidence and mortality of SAE patients. We used generalized additive models[15] to estimate the association between median PaO$_2$, S$_p$O$_2$ and sepsis with SAE, and elucidate the optimal PaO$_2$, S$_p$O$_2$ target in reducing the incidence of SAE patients and hospital mortality.

We used the multivariate logistic regression to examine the associations between independent variables and SAE. A P value of less than 0.05 was in Table 1, and optimal PaO$_2$, S$_p$O$_2$ target in reducing the incidence of SAE patients according to generalized additive models were included in the multivariate logistic regression model to further verify the above optimal value. Univariate and multivariate logistic analysis was used to examine the associations between independent variables and survival of SAE.

**Results**

**Baseline characteristics**

A total of 19658 patients were included, meeting sepsis 3.0 from the 69619 patients in ICU. 9660 were excluded from the analysis because of brain injury, mental disorders, drug abuse, alcoholism, metabolic diseases, no FiO$_2$ above 21% or no records of oxygen index, etc. 10055 patients for the final analysis. 6714 were assigned to the SAE group and 3341 were assigned to the non-SAE group (Figure 1).

Table1 describe the characteristics of sepsis patients. The incidence of patients with SAE was 66.8%. Compared with the non-SAE group, patients in the SAE group are more likely to be infected by Gram-negative bacteria(18.3% vs 13.7%, P<0.001), including: Klebsiella(6.8% vs 4.8%, P<0.001), Escherichia coli(12.6% vs 10.2%, P<0.001), (16.7% vs 9.0%, P<0.001). The PaCO$_2$[46(40-52) vs 47(42-52), p<0.001], FiO$_2$[50(40-61) vs 50(40-64), p = 0.009], PaO$_2$[93.5(74-125) vs. 98(79-128), p<0.001], SpO$_2$≤99% (98.9% vs 99.7%, P<0.001), SpO$_2$≤98%(96.5% vs 97.4%, P=0.012), SpO$_2$≤97%(92.9% vs 93.8%, P=0.068) in SAE group were lower than non-SAE group. The SAE group had more patients with SpO$_2$≤93% (57.6% vs 53.6%, P<0.001), SpO$_2$≤92% (45.1% vs 39.2%, P<0.001), SpO$_2$≤91% (33.3% vs 26.3%, P<0.001) than the non-SAE group. Patients in the SAE group had higher SAPS II [35(28-46) vs 30(25-35), p<0.001], SOFA [5(3-7) vs 3(2-5), p<0.001], hospital mortality (7.9% vs 7.5%, P=0.476).

**Generalized additive models to estimate the optimal oxygen saturation targets in patients with SAE.**

Figure 2 shows an association between the incidence, mortality of SAE, and median SpO$_2$, PaO$_2$. SpO$_2$>97%, PaO$_2$>96mmHg were associated with increased incidence of SAE, and SpO$_2$≥91%, PaO$_2$≥96mmHg were associated with increased hospital mortality of SAE. Table 2 and Table 3 confirms them. The generalized additive models demonstrated a nonlinear association between them.

**Multivariate logistic analysis of risk factors to incidence in patients with SAE**

S$_p$O$_2$(93%-97%) [odds ratio (OR): 0.661, 95% confidence Interval (CI): 0.545-0.803, p<0.001], use of vasopressors (OR:0.705 95%CI:0.642-0.775, p<0.001), renal replacement therapy (OR:0.514, 95%CI:0.389-0.680, p<0.001) were protective factors in the incidence of SAE. S$_p$O$_2$≤92% (OR: 1.647, 95%CI:1.260-2.153, p=0.006), S$_p$O$_2$≤91% (OR:1.218,
The microbiology type of fungus (OR: 1.441, 95% CI: 1.243-1.671, p<0.001), SAPS II (OR: 1.032, 95% CI: 1.027-1.037, p<0.001), SOFA (OR: 1.275, 95% CI: 1.247-1.304, p<0.001) were risk factors in the occurrence of SAE, after adjusted of microbiology type (Klebslella, Escherichia Coli, Gram-negative bacteria), PaCO\textsubscript{2}, FiO\textsubscript{2}, SAPS II, and SOFA.

Univariate and multivariate logistic analysis of risk factors to hospital mortality.

SpO\textsubscript{2}(92%-96%) (OR: 0.572, 95% CI: 0.468-0.699, p<0.001) was a protective factor in the occurrence of SAE. Age (OR: 1.012, 95% CI: 1.005-1.019, p<0.001), sex (OR: 1.213, 95% CI: 1.011-1.455, p=0.038), site of infection (intestinal, urinary, catheter, skin and soft tissue, abdominal cavity), microbiology type (Klebslella, Escherichia Coli, Pseudomonas aeruginosa, Staphylococcus aureus, Gram-negative bacteria, Fungus), PaCO\textsubscript{2}, FiO\textsubscript{2}, use of vasopressors, renal replacement therapy, mechanical ventilation, SAPS II, SOFA, and GCS.

Discussion

Our cohort study’s primary outcome demonstrated that oxygen therapy is associated with incidence and survival in patients with SAE. The optimal range for the SpO\textsubscript{2} between 93% and 97% will not increase incidence of SAE, and SpO\textsubscript{2} between 92% and 96% will not increase hospital mortality of SAE. Therefore, the optimal SpO\textsubscript{2} target in patients with SAE was 93%-96%. They were indicating SpO\textsubscript{2} should be closely monitored during the SAE patients and give conservative oxygen therapy.

Previous studies have shown that SAE’s incidence is up to 70% [2], which supports our study results(66.8%), indicating that SAE still has high incidence. The study found that SAE’s hospital mortality is up to 50.9%, different from our study results (7.9%). It may be attributed to the difference in the population and the improvement of medical standards [3]. 45% of patients with SAE show long-term cognitive dysfunction after hospital discharge[16]. There is no specific treatment for SAE, early identification of potentially modifiable factors with the best chance of avoiding incidence, long-term cognitive dysfunction, and reducing mortality of SAE.

In this large cohort study, we found that targeting SpO\textsubscript{2} < 93% or SpO\textsubscript{2} > 97% can lead to the SAE by generalized additive models (Fig. 2). The optimal SpO\textsubscript{2} reduction in the incidence of SAE was 93%-97%. Table 2 confirms it. The results of the study show that lower or higher oxygenation can cause SAE.

Hyperoxemia is associated with neurological injury in patients with traumatic brain injury and aneurysmal subarachnoid hemorrhage [17, 18]. Hyperoxemia leads to the production of reactive oxygen species, which destroys cells and further promotes the inflammatory response[18]. Besides, active oxygen causes an increase in the production of oxygen free radicals. The excess free radicals further stimulate the hypersensitive arterial system to cause vasospasm[19]. Inflammatory response, oxygen free radicals, vasospasm are an important mechanism of SAE [20, 21].

Except for patients with brain injury and cerebral hemorrhage, we found that hyperoxemia (SpO\textsubscript{2} > 97%) is associated with SAE. The neurological injury in sepsis patients caused by hyperoxia may be attributed to the above reasons. We need further study to explore its pathophysiological mechanism in the future. [22]

Neurological injury caused by hypoxemia is confirmed by many studies[23, 24]. Hypoxia can increase the lactate/pyruvate and decreased the glutathione/oxidized glutathione ratios, upregulate inflammatory cytokine cascades, activation in apoptosis pathway to damage the cerebral cortex and neurons[22, 25]. Our study results further support it, demonstrating that SpO\textsubscript{2} < 93% can cause changes in consciousness in patients with sepsis. To reduce the
neurological injury by hypoxia or hyperoxia and incidence of SAE, we recommend that SpO\textsubscript{2} should be controlled between 93%-97\% in patients with SAE based on the results in Fig. 2 and Table 2.

Low oxygen saturations are regarded as detrimental. A liberal oxygen strategy is associated with mortality, especially in ICU patients, because oxygen is widely used in the ICU, and patients are often exposed to high oxygenation[26]. The relationship between exposure to hyperoxia and mortality has been reported in ICU by many studies [27, 28]. Especially in patients with critically ill patients, or ventilator-assisted breathing, to reduce the mortality of patients, the evaluation of optimal oxygen saturation is particularly important in recent years. Willem van den Boom et al. found that the optimal range of SpO\textsubscript{2} was 94–98\% was associated with decreased hospital mortality in critically ill patients[29]. The proportion of time spent in oxygen saturation 95–99\% is associated with reduced mortality in critically ill patients with mechanical ventilation was reported by Dawei Zhou et al.[30]. Derek K Chu et al. found that in acutely ill adults, liberal oxygen therapy increases mortality, oxygen saturation exceeding 94%-96\% will adversely affect the patient. We analyzed SAE patients through generalized linear model and logistic regression demonstrated that the optimal oxygen saturation of 92–96\% is associated with reduced hospital mortality in patients with SAE (Fig. 2 and Table 3)[31]. Consider both the mortality and incidence of SAE patients, targeting SpO\textsubscript{2} between 93–96\% reduces mortality and incidence for SAE patients. Our study support SAE patients should be treated with conservative oxygen therapy. The optimal oxygen saturation range for SAE may be narrower than acutely ill adults.

Oxygen saturation is different from PaO\textsubscript{2}. PaO\textsubscript{2} requires intermittent measurement of invasive blood gas analysis to obtain results. Oxygen saturation is non-invasive, cheap, convenient, and easy to be monitored at all times in clinical treatment, and the 93–96\% target is easily regulated and feasible. Although our study provides optimal oxygen saturation is 93–96\%, targets are not applicable to some patients. Such as SAE patients with acute respiratory distress syndrome, with mechanical ventilation, to reduce lung damage and must give restrictive ventilation[32], SpO\textsubscript{2} may be difficult to achieve 93%-96\%. SAE patients, after prolonged cardiopulmonary resuscitation, may need higher SpO\textsubscript{2} to reduce neurological injury caused by hypoxia[33]. In this study, we also analyzed the optimal PaO\textsubscript{2} for SAE patients. Unfortunately, we did not get the best range, may need a further detailed design to complete in the future.

Limitations:

First, the definition of SAE is based on the GCS < 15 score, using haloperidol drugs, and patients were diagnosed with delirium by ICD9 and ICD10, although brain hemorrhage, brain trauma and other diseases were excluded by us, absence of brain computed tomography, magnetic resonance imaging, electroencephalogram and other examinations to assess the nervous system, possible information bias in SAE cohort. Second, the study was an observational study, and we cannot prove the causal association with oxygen saturation and the incidence and mortality of SAE. However, we demonstrated the correlation between oxygen saturation and SAE through our large cohort study. It will still provide certain clinical reference value. Third, because of the interrelationship between diseases, some confounding factors still cannot be ruled out, cover up or exaggerate the connection between study factors and SAE.

Conclusions

High or low oxygen saturation is associated with incidence and mortality of SAE. We identified an optimal oxygen saturation 93%-96\% in SAE patients. Provide a reference target for clinicians to prevent the occurrence of SAE and reduce the hospital mortality of SAE patients. Besides, oxygen saturation 93%-96\% provides a reference target for future random experiments.

Abbreviations
SAE: sepsis associated encephalopathy;
PaCO$_2$: partial pressure of carbon dioxide;
FiO$_2$: the fraction of inspired oxygen;
PaO$_2$: partial pressure of oxygen;
SAPS II: patients’ simplified acute physiology score;
SOFA: sequential organ failure assessment;
GCS: Glasgow coma scale;
ICU: intensive care unit;
MIMIC-IV: Medical Information Mart for Intensive Care IV;

**Declarations**

**Ethical approval and consent to participate**

MIMIC IV was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

**Consent for publication**

Requirement for individual patient consent was waived because the project did not impact clinical care and all protected health information was deidentified.

**Availability of supporting data**

The MIMIC IV database (version 0.4) is publically available from https://mimic-iv.mit.edu/. Any researcher who adheres to the data use requirements is permitted access to the database.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS, serial number 2020-I2M-C&T-B-014）.

**Author contributions**

Dr. Lina Zhao and Dr. Yi Li developed this paper’s central ideas. Dr. Yunying Wang, Dr. Huadong Zhu, Zengzheng Ge collected the data regarding the paper. Dr. Lina Zhao wrote the first draft of the manuscript, Dr. Yi Li revised the paper, worked on the English, and made the final version of the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**
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Tables
| Baseline variables | SAE patients n=6714 | Non-SAE patients n=3341 | p |
|--------------------|---------------------|--------------------------|---|
| **Baseline variables** |                     |                          |   |
| Age                | 68(59-77)           | 69(59.5-77)              | 0.540 |
| Sex, (n (%))       |                     |                          |   |
| Female             | 2462(36.7)          | 1238(37.1)               | 0.709 |
| Male               | 4252(63.3)          | 2103(62.9)               |    |
| Coexisting illness, (n (%)) |           |                          |   |
| Charlson           | 5(4-7)              | 5(3-6)                   | <0.001 |
| Hypertension       | 1129(16.8)          | 553(16.6)                | 0.754 |
| Diabetes           | 1100(16.4)          | 558(16.7)                | 0.690 |
| Respiration        | 2015(30.0)          | 1065(31.9)               | 0.057 |
| Cardiovascular     | 6300(93.8)          | 3151(94.3)               | 0.350 |
| Renal              | 2754(41.0)          | 1362(40.8)               | 0.813 |
| Type of admission, (n (%)) |       |                          | 0.338 |
| Emergency          | 2331(34.7)          | 1095(32.8)               |    |
| Surgical           | 1424(21.2)          | 734(22.0)                |    |
| Urgent             | 1290(19.2)          | 657(19.7)                |    |
| Elective           | 530(7.9)            | 286(8.6)                 |    |
| Other              | 1139(17.0)          | 569(17.0)                |    |
| Ethnicity, (n (%)) |                     |                          | 0.940 |
| Black              | 419(6.2)            | 219(6.6)                 |    |
| White              | 4756(70.8)          | 2376(71.1)               |    |
| Asian              | 173(2.6)            | 88(2.6)                  |    |
| Other              | 1336(19.9)          | 658(19.7)                |    |
| Site of infection, (n (%)) |           |                          | 0.336 |
| Intestinal         | 44(0.66)            | 16(0.48)                 |    |
| Urinary            | 360(5.4)            | 200(6.0)                 | 0.212 |
| Lung               | 370(5.5)            | 185(5.5)                 | 0.965 |
| Catheter           | 96(1.4)             | 65(1.9)                  | 0.062 |
| Skin and soft tissue | 205(3.1)          | 103(3.1)                 | 0.954 |
| Abdomi and soft tissue | 134(2.0)         | 79(2.4)                  | 0.239 |
| Microbiology type, n (%) |               |                          | <0.001 |
| Klebslella         | 454(6.8)           | 161(4.8)                 |    |
| Acinetobacter baumanni | 20(0.3)          | 6(0.18)                  | 0.306 |
| Escherichia Coli   | 845(12.6)          | 340(10.2)                | <0.001 |
| Pseudomonas aeruginosa | 308(4.6)          | 133(4.0)                 | 0.164 |
| Staphylococcus aureus | 63(0.9)          | 38(1.1)                  | 0.342 |
| Gram-negative bacteria | 1231(18.3)      | 459(13.7)                | <0.001 |
| Gram-positive bacteria | 362(5.4)         | 170(5.1)                 | 0.538 |
| Virus              | 8(0.08)             | 1(0.03)                  | 0.288 |
| Fungus             | 1118(16.7)          | 300(9.0)                 | <0.001 |
| PaCO₂, mmHg        | 46(40-52)           | 47(42-52)                | <0.001 |
| FiO₂, %            | 50(40-61)           | 50(40-64)                | 0.009 |
| PaO₂, mmHg         | 93.5(74-125)        | 98(79-128)               | <0.001 |
| SpO₂, % (n (%))    | ≤99                 | 6639(98.9)               | <0.001 |
|                  | ≤98                 | 6478(96.5)               | 0.012 |
| ≤97 | 6234(92.9) | 3133(93.8) | 0.086 |
| ≤96 | 5898(87.8) | 2931(87.7) | 0.873 |
| ≤95 | 5410(80.6) | 2647(79.2) | 0.111 |
| ≤94 | 4698(70.0) | 2281(68.3) | 0.085 |
| ≤93 | 3870(57.6) | 1790(53.6) | <0.001 |
| ≤92 | 3031(45.1) | 1310(39.2) | <0.001 |
| ≤91 | 2233(33.3) | 879(26.3) | <0.001 |

Mechanical ventilation, (n (%))

Renal replacement therapy, (n (%))

Score system

|   | SAPS II | SOFA | GCS |
|---|---------|------|-----|
|   | 35(28-46) | 5(3-7) | 13(8-14) |
| 30(25-35) | 3(2-5) | 15(15-15) |
<0.001 | <0.001 | <0.001 |

Use of vasopressors, (n (%))

Length of hospital stay, days

Hospital mortality

PaCO₂: partial pressure of carbon dioxide; SpO₂: arterial oxygen saturation; PaO₂: partial pressure of oxygen; GCS: Glasgow coma scale; FiO₂: the fraction of inspired oxygen; SAPSII: simplified acute physiology score; SOFA: sequential organ failure assessment.

**Table 2** Multivariate logistic analysis of risk factors to morbidity in patients with SAE

|                          | P     | OR   | 95.0% CI Lower | 95.0% CI Upper |
|--------------------------|-------|------|----------------|---------------|
| Charlson                 | <0.001| 0.952| 0.935          | 0.969         |
| Microbiology type, (n (%))|       |      |                |               |
| Klebslella               | 0.106 | 0.783| 0.582          | 1.054         |
| Escherichia Coli         | 0.141 | 0.787| 0.573          | 1.082         |
| Gram-negative Bacteria   | 0.080 | 1.343| 0.966          | 1.869         |
| Fungus                   | <0.001| 1.441| 1.243          | 1.671         |
| PaCO₂, mmHg              | 0.508 | 0.999| 0.995          | 1.003         |
| PaO₂, mmHg               | 0.873 | 1.014| 0.858          | 1.197         |
| SpO₂, % (n (%))          |       |      |                |               |
| ≤91                      | 0.010 | 1.218| 1.048          | 1.416         |
| ≤92                      | <0.001| 1.647| 1.260          | 2.153         |
| 93-97                    | <0.001| 0.661| 0.545          | 0.803         |
| FiO₂, %                  | 0.001 | 0.996| 0.994          | 0.999         |
| Use of vasopressors, (n (%))|       |      |                |               |
| Renal replacement therapy, (n (%))| <0.001| 0.705| 0.642          | 0.775         |
| Score system             | <0.001| 0.514| 0.389          | 0.680         |

PaCO₂: partial pressure of carbon dioxide; SpO₂: arterial oxygen saturation; PaO₂: partial pressure of oxygen; FiO₂: the fraction of inspired oxygen; SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score.
Table 3: Univariate and multivariate logistic analysis of risk factors to hospital mortality.

|                        | Univariate analysis |                          | Multivariate analysis |                          |
|------------------------|---------------------|--------------------------|-----------------------|--------------------------|
|                        | P       | OR     | 95.0% CI | P       | OR     | 95.0% CI |
|                        | Lower   | Upper  |          | Lower   | Upper  |          |
| Age                    | <0.001  | 1.014  | 1.007 1.021 | <0.001  | 1.012  | 1.005 1.019 |
| Sex, (n (%))           | 0.006   | 1.289  | 1.077 1.543 | 0.038   | 1.213  | 1.011 1.455 |
| Charlson               | 0.481   | 0.989  | 0.958 1.020 |          |        |          |
| Site of infection, (n (%)) |        |        |          |          |        |          |
| Intestinal             | 0.196   | 0.049  | 0.001 4.731 |          |        |          |
| Urinary                | 0.903   | 1.025  | 0.693 1.514 |          |        |          |
| Lung                   | <0.001  | 2.363  | 1.758 3.177 | <0.001  | 1.932  | 1.399 2.668 |
| Catheter               | 0.009   | 2.147  | 1.207 3.822 | 0.493   | 1.246  | 0.664 2.338 |
| Skin and soft tissue   | 0.312   | 0.737  | 0.409 1.331 |          |        |          |
| Abdomial cavity        | 0.016   | 1.828  | 1.118 2.989 | 0.152   | 1.452  | 0.872 2.418 |
| Microbiology type, (n (%)) |        |        |          |          |        |          |
| Klebsella              | 0.273   | 1.203  | 0.864 1.674 |          |        |          |
| Acinetobacter          | 0.729   | 1.295  | 0.300 5.596 |          |        |          |
| baumannii              | 1.141   | 0.806  | 0.605 1.074 |          |        |          |
| Escherichia coli       | 0.031   | 1.648  | 1.046 2.598 |          |        |          |
| Pseudomonas aeruginosa | 0.838   | 0.909  | 0.364 2.268 |          |        |          |
| Staphylococcus aureus  | 0.611   | 0.941  | 0.746 1.188 |          |        |          |
| Gram-negative bacteria | 0.468   | 0.857  | 0.565 1.300 |          |        |          |
| Gram-positive bacteria | 0.634   | 1.665  | 0.204 13.556 |          |        |          |
| Virus                  | 0.511   | 0.922  | 0.722 1.176 |          |        |          |
| Fungus                 | 0.684   | 1.001  | 0.995 1.008 |          |        |          |
| PaCO₂, mmHg            | 0.398   | 1.002  | 0.998 1.006 |          |        |          |
| PaO₂, mmHg             | 0.057   | 0.821  | 0.670 1.006 |          |        |          |
| SPO₂, %                | <0.001  | 0.495  | 0.413 0.594 | <0.001  | 0.572  | 0.468 0.699 |
| Mechanical ventilation, (n (%)) | 0.001 | 0.714 | 0.587 0.869 |          |        |          |
| Renal replacement therapy, (n (%)) | 0.643 | 0.888 | 0.538 1.466 |          |        |          |
| Use of vasopressors, (n (%)) | 0.016 | 0.803 | 0.671 0.959 |          |        |          |
| Score system           |        |        |          |          |        |          |
| SAPS II                | 0.324   | 0.997  | 0.990 1.003 |          |        |          |
| SOFA                   | 0.317   | 1.015  | 0.986 1.045 |          |        |          |
| GCS                    | 0.260   | 1.013  | 0.991 1.035 |          |        |          |
PaCO$_2$: partial pressure of carbon dioxide; SpO$_2$: arterial oxygen saturation; PaO$_2$: partial pressure of oxygen; GCS: Glasgow coma scale; FiO$_2$: the fraction of inspired oxygen; SAPS II: simplified acute physiology score; SOFA: sequential organ failure assessment.

**Figures**

A total of 69619 patients from ICU

The patients were diagnosed as a sepsis3.0 who were admitted to the ICU for the first time

Less than 18 years old (n=3)

Excluded the following patients (n=9600)
- Intracerebral hemorrhage, cerebral embolism and ischemic stroke (n=989)
- Traumatic brain injury (n=135)
- Meningitis and encephalitis (n=261)
- Epilepsy (n=237)
- Other cerebrovascular disease (n=229)
- Mental disorders and neurological disease (n=342)
- Chronic alcohol or drug abuse (n=399)
- Metabolic encephalopathy (n=59)
- Hypertensive encephalopathy (n=2)
- Hepatic encephalopathy (n=64)
- Other liver disease or kidney disease affecting consciousness (n=36)
- Hyponatremia (< 120 mmol/l) (n=38)
- Hyperglycemia (> 180 mg/dl) (n=560)
- Hypoglycemia (< 54 mg/dl) (n=346)
- PCO$_2$ > 80 mmHg (n=43)
- No FiO$_2$ above 21% or no records of oxygen index (n=5860)

19655 patients were included in the study

10055 patients for the final analysis

Patients with sepsis-associated encephalopathy (n=6714)

Patients without sepsis-associated encephalopathy (n=3341)

**Figure 1**

Flow chart of patient selection. ICU: intensive care unit; PaCO$_2$: partial pressure of carbon dioxide; FiO$_2$: the fraction of inspired oxygen.
Figure 2

Generalized additive model plot for the median of SPO2 and PaO2 on the logit of probability for incidence and hospital mortality in patients with sepsis associated encephalopathy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.1.docx
- Supplementarymaterials.2.docx
- Supplementarymaterials.3.docx
