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

Lina Zhao
Peking Union Medical College Hospital
Yunying Wang
Peking Union Medical College Hospital
Zengzheng Ge
Peking Union Medical College Hospital
Huadong Zhu
Peking Union Medical College Hospital
Yi Li (billliyi@126.com)
Emergency Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
https://orcid.org/0000-0002-7158-3624

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

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%. $SpO_2 \leq 92\%$ 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 ($PaCO_2$) ≥ 80mmHg; 7) without an evaluation of GCS. 8) Missing value of SpO_2, FiO_2, PaO_2 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 (SpO_2), partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), the fraction of inspired oxygen (FiO_2). 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, S_PO_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_PO_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_PO_2 and sepsis with SAE, and elucidate the optimal PaO_2, S_PO_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_PO_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%, SpO_2<93%, PO_2>307mmHg, PaO_2<96mmHg were associated with increased incidence of SAE, and SpO_2>96%, SpO_2<92%, PaO_2>350mmHg, 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_PO_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_PO_2≤92% (OR: 1.647, 95%CI:1.260-2.153, p=0.006), S_PO_2≤91% (OR:1.218,

95%CI:1.048-1.416, p=0.010), 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), $PaCO_2$, FiO_2, SAPS II, and SOFA.

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

S_PO_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 of lung(OR:1.932, 95%CI:1.399-2.668, p<0.001) were risk factors in the occurrence of SAE, after adjusted of charlson, 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), $PaCO_2$, FiO_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_2 between 93% and 97% will not increase incidence of SAE, and SpO_2 between 92% and 96% will not increase hospital mortality of SAE. Therefore, the optimal SpO_2 target in patients with SAE was 93%-96%. They were indicating SpO_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_2 < 93% or SpO2 > 97% can lead to the SAE by generalized additive models (Fig. 2). The optimal SpO_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_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_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_2 should be controlled between 93%-97% in patients with SAE based on the results in Fig. 2and 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_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 logstic 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_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_2. PaO_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], S_PO_2 may be difficult to achieve 93%-96%. SAE patients, after prolonged cardiopulmonary resuscitation, may need higher S_PO_2 to reduce neurological injury caused by hypoxia[33]. In this study, we also analyzed the optimal PaO_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

Not applicable

References

1. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. efinitions, etiologies, and mortalities. JAMA. 1996;275(6):470–3.
2. Ely, Wesley E. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753.
3. Sonneville R, de Montmollin E, Poujade J, Garrouste-Orgeas M, Souweine B, Darmon M, Mariotte E, Argaud L, Barbier F, Goldgran-Toledano D, et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med. 2017;43(8):1075–84.
4. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788–800.
5. Schjrring OL, Jensen A, Nielsen CG, Ciubotariu A, Rasmussen BS. Arterial oxygen tensions in mechanically ventilated ICU patients and mortality: a retrospective, multicentre, observational cohort study. Br J Anaesth. 2020;124(4):420–9.
6. Rinaldi LMA, Morelli A, Antonelli M, Singer M. **Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial**. *JAMA*, 316(**15**):1583–1589.
7. Aggarwal NR, Brower RG, Hager DN, Thompson BT, Netzer G, Shanholtz C, Lagakos A, Checkley W. **Oxygen exposure resulting in arterial oxygen tensions above the protocol goal was associated with worse clinical outcomes in acute respiratory distress syndrome**. *Critical Care Medicine* 2017:517–524.
8. Chang WT, Wang CH, Lai CH, Yu HY, Chou NK, Wang CH, Huang SC, Tsai PR, Chou FJ, Tsai MS, et al. Optimal arterial blood oxygen tension in the early postresuscitation phase of extracorporeal cardiopulmonary resuscitation: a15-Year retrospective observational study. Crit Care Med. 2019;47(11):1549–56.
9. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R: **MIMIC-IV** (**version 0.4**). **PhysioNet**. 2020.
10. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al: **The third international consensus definitions for sepsis and septic shock** (**Sepsis-3**). *JAMA* 2016, **315**(8):801–810.
11. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, et al: **Assessment of clinical criteria for sepsis**: **for the third international consensus definitions for sepsis and septic shock** (**Sepsis-3**). *JAMA* 2016, **315**(8):762–774.
12. Yang Y, Liang S, Geng J, Wang Q, Wang P, Cao Y, Li R, Gao G, Li L. Development of a nomogram to predict 30-day mortality of patients with sepsis-associated encephalopathy: a retrospective cohort study. J Intensive Care. 2020;8(1):45.
13. Boogaard M, Schoonhoven L, Care TAJC. **Haloperidol prophylaxis in critically ill patients with a high risk for delirium**. 2013, 17(1):1–11.
14. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis[J]. JAMA. 2010;304(16):1787.
15. Wood SN: **Generalized Additive Models**: **an introduction with R**, **Second Edition**. 2017.
16. Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med. 2015;3(1):61–9.
17. Reynolds RA, Amin SN, Jonathan SV, Tang AR, Lan M, Wang C, Bastarache JA, Ware LB, Thompson RC. **Hyperoxemia and cerebral vasospasm in aneurysmal subarachnoid hemorrhage**. *Neurocrit Care* 2020.

18. Koivisto PA-PM, Djafarzadeh T, Bendel S. S.: A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress. Acta Anaesthesiol Scand. 2018;62(6):801–10.
19. Damiani E, Donati A, Girardis M. Oxygen in the critically ill: friend or foe? Curr Opin Anaesthesiol. 2018;31(2):129–35.
20. Ren C, Yao RQ, Zhang H, Feng YW, Yao YM. Sepsis-associated encephalopathy: a vicious cycle of immunosuppression. J Neuroinflammation. 2020;17(1):14.
21. Checinski A, Polito A, Friedman D, Siami S, Annane D, Sharshar T. Sepsis-associated encephalopathy and its differential diagnosis. Crit Care Med. 2010;5(6):901–9.
22. Guo R, Hou W, Dong Y, Yu Z, Stites J, Weiner CP. Brain injury caused by chronic fetal hypoxemia is mediated by inflammatory cascade activation. REPRODUCTIVE SCIENCES. 2010;17(6):540–8.
23. Aminah S, Meng X, Liu J, Alexandra M, Kao J, Mcquillen PS, Kanold PO. Neonatal hypoxia-ischemia causes functional circuit changes in subplate neurons[J]. Cereb Cortex. 2018;29(2):765–76.
24. Arjun R, Acharya S, Shender BS, Rorres C, Hrebien L, Kam M. Correlation of cognitive scores and the onset of hypoxia. Aerosp Med Hum Perform. 2019;90(5):429–39.
25. Overgaard M, Rasmussen P, Bohm AM, Seifert T, Secher NH. Hypoxia and exercise provoke both lactate release and lactate oxidation by the human brain. Faseb Journal Official Publication of the Federation of American Societies for Experimental Biology. 2012;26(7):3012.
26. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, van Westerloo DJ. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. Ann Intensive Care. 2014;4(23):23.
27. Helmerhorst H, Arts DL, Schultz MJ, Voort P, Westerloo D. Metrics of arterial hyperoxia and associated outcomes in critical care. Crit Care Med. 2016;45(2):187–95.
28. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, Beasley R. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med. 2012;38(1):91–8.
29. van den Boom W, Hoy M, Sankaran J, Liu M, Chahed H, Feng M, See KC. The search for optimal oxygen saturation targets in critically ill patients: observational data from large ICU databases. Chest. 2020;157(3):566–73.
30. Zhou DLZ, Shi G. Zhou **Time spent in oxygen saturation 95–99% is associated with reduced mortality in critically ill patients with mechanical ventilation**. Crit Care Med. 2005;9(2):24(21).
31. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schunemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391(10131):1693–705.
32. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319(7):698–710.
33. Ruiz E, Robinson DDB,EP, Tomlinson MJ, Lange J, Wieland MJ, Sherman R. Cerebral resuscitation after cardiac arrest using hetastarch hemodilution, hyperbaric oxygenation and magnesiumion. Resuscitation. 1986;14(4):213–23.

Tables

Table 1 Baseline characteristics and outcome of patient with SAE

		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 (%))				
	Intestinal	44(0.66)	16(0.48)	0.336
	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
	Abdomiol cavity	134(2.0)	79(2.4)	0.239
Microbiology type, n (%)				
	Klebslella	454(6.8)	161(4.8)	<0.001
	Acinetobacter baumannii	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
$PaCO_2$, mmHg		46(40-52)	47(42-52)	<0.001
FiO_2, %		50(40-61)	50(40-64)	0.009
PaO_2, mmHg		93.5(74-125)	98(79-128)	<0.001
S_PO_2, % (n (%))				
	≤99	6639(98.9)	3331(99.7)	<0.001
	≤98	6478(96.5)	3255(97.4)	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 (%))		5153(76.8)	2575(77.1)	0.725
Renal replacement therapy, (n (%))		239(3.6)	85(2.5)	0.007
Score system				
	SAPS II	35(28-46)	30(25-35)	<0.001
	SOFA	5(3-7)	3(2-5)	<0.001
	GCS	13(8-14)	15(15-15)	<0.001
Use of vasopressors, (n (%))		4036(60.1)	2080(62.3)	0.039
Length of hospital stay, days		2.4(1.3-5.1)	2.3(1.3-4.9)	0.149
Hospital mortality		531(7.9)	250(7.5)	0.476

$PaCO_2$: 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; SAPSII: simplified acute physiology score; SOFA: sequential organ failure assessment.

Table2 Multivariate logistic analysis of risk factors to morbidity in patients with SAE

		P	OR	95.0% CI	
				Lower	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
$PaCO_2$, mmHg		0.508	0.999	0.995	1.003
PaO_2, mmHg					
	96-307	0.873	1.014	0.858	1.197
S_PO_2, % (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
FiO_2, %		0.001	0.996	0.994	0.999
Use of vasopressors, (n (%))		<0.001	0.705	0.642	0.775
Renal replacement therapy, (n (%))		<0.001	0.514	0.389	0.680
Score system					
	SAPS II	<0.001	1.032	1.027	1.037
	SOFA	<0.001	1.275	1.247	1.304

$PaCO_2$: partial pressure of carbon dioxide; SpO_2: arterial oxygen saturation; PaO_2: partial pressure of oxygen; FiO_2: 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				
	Abdomiol cavity	0.016	1.828	1.118	2.989	0.152	1.452	0.872	2.418
Microbiology type, (n (%))									
	Klebslella	0.273	1.203	0.864	1.674				
	Acinetobacter	0.729	1.295	0.300	5.596				
	baumannii								
	Escherichia coli	0.141	0.806	0.605	1.074				
	Pseudomonas aeruginosa	0.031	1.648	1.046	2.598				
	Staphylococcus aureus	0.838	0.909	0.364	2.268				
	Gram-negative bacteria	0.611	0.941	0.746	1.188				
	Gram-positive bacteria	0.468	0.857	0.565	1.300				
	Virus	0.634	1.665	0.204	13.556				
	Fungus	0.511	0.922	0.722	1.176				
$PaCO_2$, mmHg		0.684	1.001	0.995	1.008				
FiO_2, %		0.398	1.002	0.998	1.006				
PaO_2, mmHg	96-350	<0.001	0.619	0.515	0.744	0.057	0.821	0.670	1.006
S_PO_2, % (n (%))	92-96	<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	0.050	0.801	0.641	1.000
Renal replacement therapy, (n (%))		0.643	0.888	0.538	1.466				
Use of vasopressors, (n (%))		0.016	0.803	0.671	0.959	0.344	0.907	0.741	1.110
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

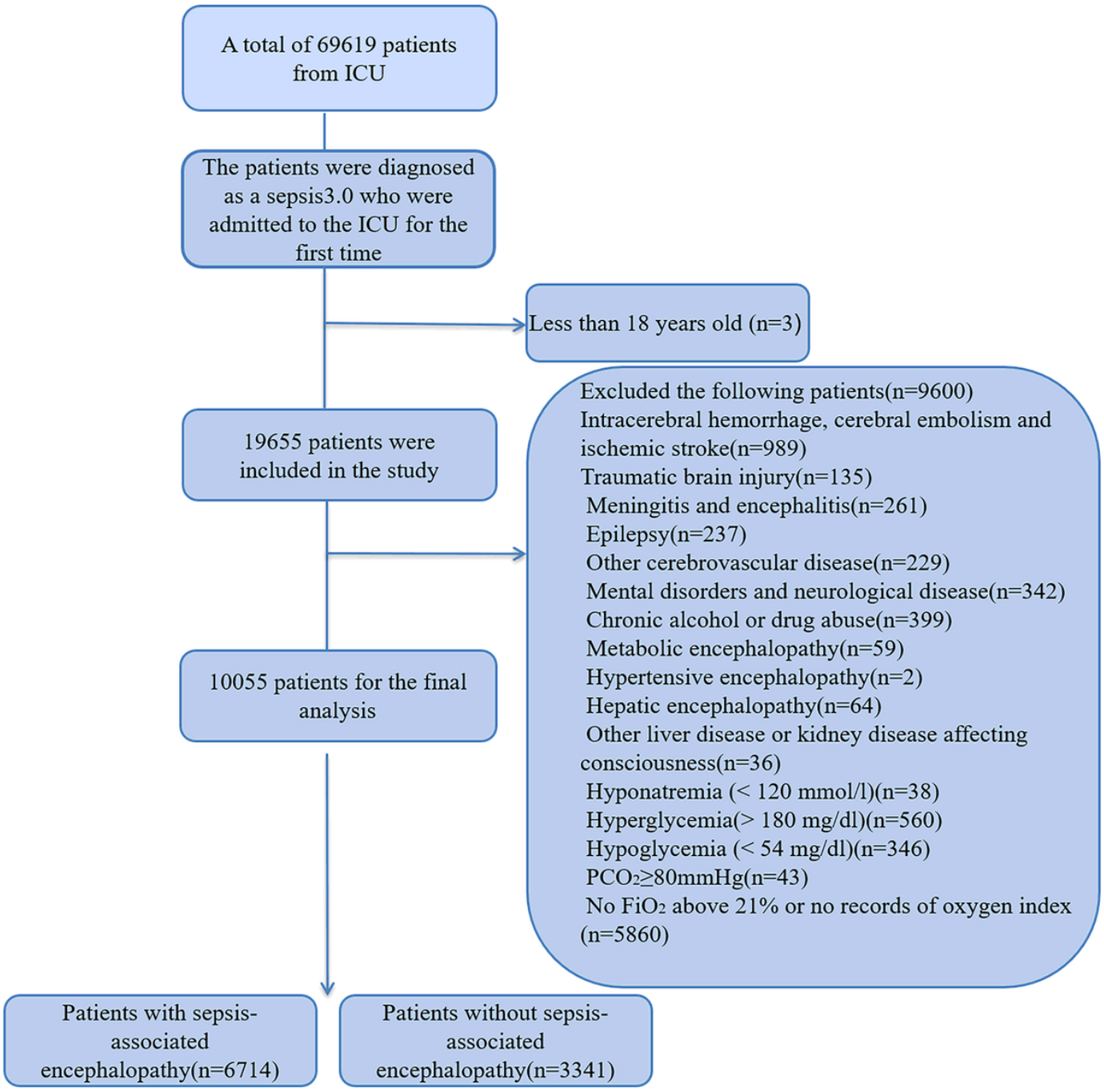

Figure 1

Flow chart of patient selection. ICU: intensive care unit; PaCO2: partial pressure of carbon dioxide; FiO2: the fraction of inspired oxygen.

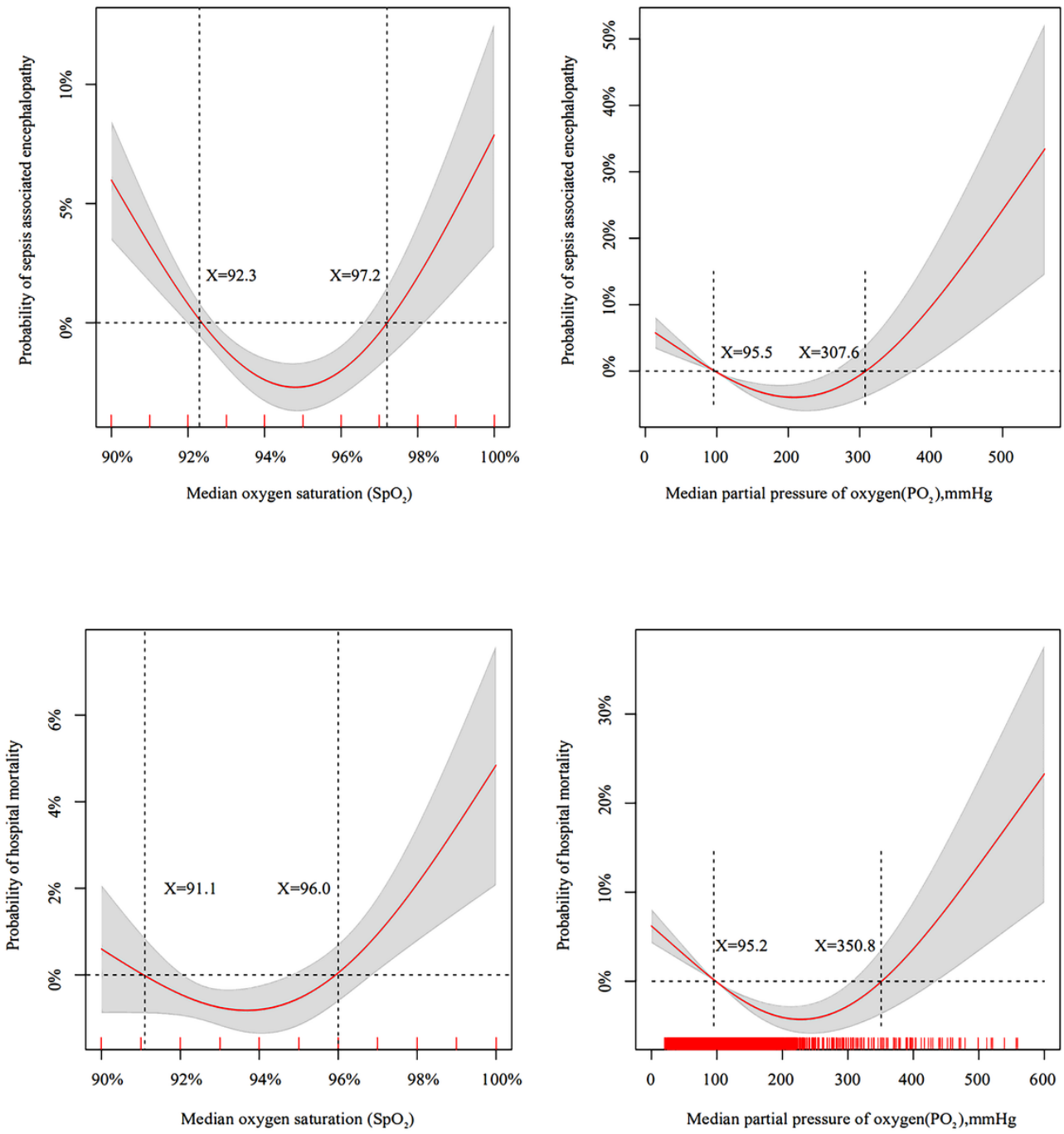

Figure 2

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

- Supplementarymaterials.4.docx
- Supplementarymaterials.5.docx
- Supplementarymaterials.6.docx
- Supplementarymaterials.7.docx
- Supplementarymaterials.8.docx
- Supplementarymaterials.9.docx
- Supplementarymaterials10.doc
- Supplementarymaterials.11.docx
- Supplementarymaterials.12.docx
- Supplementarymaterials.13.docx
- Supplementarymaterials14.pdf