

The effect of conscious disorder on the 30-day mortality of sepsis

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Research

Keywords: sepsis, conscious disorder, hypertension, hypernatremia, cephalosporin, urinary infection

Posted Date: August 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-52103/v1>

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Abstract

Background

Conscious impairment is related to worse prognosis in patients with sepsis. we aimed to evaluate the impact of conscious disorder on the 30-day mortality of patients with sepsis and identify the remediable risk factors for it.

Methods

Data were retrospectively retrieved from a prospective intensive care database. Conscious disorder was assessed by the Glasgow Coma Score (GCS). The impact of conscious dysfunction on the 30-day mortality of sepsis and its potentially modifiable risk factors were evaluated using Cox proportional hazard regression and logistic regression, respectively.

Results

A total of 4446 patients with sepsis were included in the study and conscious disorder ($GCS < 15$) was observed in 2126 (47.8%) patients. The results of Cox regression and Kaplan-Meier analysis demonstrated that $GCS \leq 12$ contributed to the increased 30-day mortality of patients with sepsis and was an independent risk factor for it. Considering the clinical risks and benefits, the results of logistic regression showed that hypertension (systolic pressure ≥ 140 mmHg), hypernatremia (serum sodium ≥ 145 K/uL), the utility of cephalosporin and urinary infection are the potentially remediable risk factors for patients with sepsis characterized by $GCS \leq 12$.

Conclusion

Moderate impairment of consciousness ($GCS 9-12$) and coma ($GCS 3-8$) were independently related to the 30-day mortality of sepsis. Potentially remediable risk factors for patients with sepsis characterized by $GCS \leq 12$ at ICU admission were hypertension, hypernatremia, cephalosporin adoption and urinary infection. Further studies are needed to investigate the causal relationship between medical interventions towards these risk factors and the incidence of moderate impairment of consciousness and coma in patients with sepsis.

Introduction

Sepsis-associated encephalopathy (SAE) is defined as diffused brain dysfunction occurring during the process of sepsis without evidence of an intracranial infection [1]. Patients with sepsis complicated by encephalopathy often suffer from increased short-term mortality [2], and long-term symptoms, such as memory deficits, learning disabilities, and depressive-like symptoms, which can then seriously lower patients' quality of daily life [3–5]. Thus, exploring the rectifiable risk factors contributing to the development of brain dysfunction during sepsis, and then eliminating them is of great significance under the condition of treatment absence. Two landmark studies focused on this field are from Eidelman LA et al [6], and Sonnevile R et al [7]. In the study of Eidelman LA et al, they demonstrated that hepatic and renal dysfunction as well as bacteremia were associated with an increased incidence of SAE. Sonnevile R et al found that acute renal failure, staphylococcus aureus infection, and common metabolic disturbances are potentially modifiable factors contributing to SAE. However, these two studies had limitations. In the study of Eidelman LA et al, they contained only 50 patients with sepsis diagnosed by Sepsis 1.0 [8], and among them, only 31 patients were

diagnosed as SAE. The relatively old definition of sepsis and low sample size may not well represents the characteristics of patients with sepsis and SAE. In the study of Sonnevile R et al, they defined SAE as GCS < 15 and/or delirium during sepsis, but fail to exclude etiological factors other than sepsis that may cause impaired consciousness [9], which may lead to higher numbers of SAE cases and then bias the analysis of risk factors.

Although several factors are considered to potentially contribute to the process of SAE [10–17], the definite pathogenesis is still unclear, making the diagnosis of SAE an excluding process by recognizing brain dysfunction first and then excluding the most common etiological factors causing it [18–20]. However, as brain dysfunction in the diagnosis of SAE contains several pathological changes (mainly include disorder of consciousness, delirium, and the changes of ultrastructure or electrical activity without clinical manifestations), it is impossible for one retrospective study to include the whole SAE cohort due to the limitation of databases (none of the available intensive care databases collect patients' data on all of these pathological changes). Consequently, except for designing prospective study containing all of these pathological changes, another viable solution based on the existing clinical databases may be to conduct retrospective studies focusing on different aspects of these pathological changes, and then to integrate the results of them.

Therefore, in this retrospective study by a large clinical database, we evaluate the effect of conscious disorder, one aspect of SAE, on the 30-day mortality of patients with sepsis and identify the remediable risk factors for it by using the newest definition of sepsis and implementing a strict exclusion criteria. The results of the study may facilitate clinicians to make timely treatment decision and reduce the incidence of SAE.

Methods

Data source

We conducted an observational study by retrieving data from the Medical Information Mart for Intensive Care (MIMIC III) open source clinical database, which contains de-identified health-related data of over forty thousand patients who received treatment in critical care units of the Beth Israel Deaconess Medical Center between 2001.06 and 2012.10 [21, 22]. The database is continuously updated and the newest version (MIMIC-III v1.4) was released on 2 September 2016, which enhanced data quality and provided a large amount of additional data. We use the MIMIC-III v1.4 in our study and all data in it was classified into 26 tables recording various individual information, such as demographics characteristics, treatment measures, nursing notes and laboratory tests. Besides, it contains survival outcome data obtained from the hospital and laboratory health record systems reporting the in-hospital mortality, or from the Social Security Administration Death Master File recording the out-of-hospital survival data. The MIMIC III database can be freely utilized after successful application and ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). Since all data are de-identified in this database to remove patient information, the requirement for individual patient consent is not indispensable.

Study population and data extraction

PgAdmin (version 4.1, Bedford, USA) was used to run structure query language (SQL) and then to extract data from the MIMIC III database. Seven tables were occupied in our study, including diagnoses_icd, icustays, chartevents, patients, labevents, microbiologyevents and prescriptions. We included adult patients (> 17 years of age) with a diagnosis of sepsis defined by Third International Consensus Definitions for Sepsis (Sepsis 3.0): (1) Patients with infection confirmed by the positive results of microbial cultivation, and (2) the Sequential Organ Failure Assessment (SOFA) score ≥ 2 [23]. Excluded were patients (1) with primary brain injury (traumatic brain injury, ischemic stroke,

hemorrhagic stroke, epilepsy or intracranial infection); (2) with pre-existing liver or kidney failure affecting consciousness; (3) with severe burn and trauma; (4) receiving cardiac resuscitation recently; (5) with chronic alcohol or drug abuse; (6) with hypertensive encephalopathy; (7) with severe electrolyte imbalances or blood glucose disturbances, including hyponatremia (< 120 mmol/l), hyperglycemia (> 180 mg/dl) or hypoglycemia (< 54 mg/dl); (8) dying or leaving within 24 hours since ICU admission; (9) without an evaluation of GCS. Eligible patients were included in the final cohort for investigation (Additional file 1: Figure S1). For the final cohort, we retrospectively collected the following data from the database: (1) demographic data including age, gender and ethnicity; (2) 30-day outcome; (3) comorbidity conditions as coded and defined by the International Classification of Diseases, Ninth Revision (ICD-9) code; (4) mean value of vital signs during the first 24 hours of ICU stay; (5) the first laboratory data since ICU admission; (6) site of infection and type of micro-organism; (6) Medical intervention, including vasopressor adoption, mechanical ventilation and the use of antibiotic, sedative and analgesic agents. The severity of illness and organ failure was assessed by modified forms of the simplified acute physiology score (SAPS II) and the sepsis-related organ failure assessment (SOFA) on the first day of ICU stay, respectively [24, 25]. The modified forms are SAPS II and SOFA score excluding the component of central nervous system. Besides, each component of the SOFA score was extracted to assess the function of each organ and a score > 2 was defined as acute organ failure [18].

Sepsis-associated impairment of consciousness

We defined sepsis-associated impairment of consciousness in the study as sepsis accompanied by the Glasgow Coma Score (GCS) < 15 on the first day of ICU admission. GCS was confirmed as an excellent tool for the assessment of conscious dysfunction [26], and for neurological evaluation of critically ill patients [27]. For sedated or postoperative patients, we adopted GCS measured before sedation or surgery.

Statistical analysis

The distribution of variables was assessed by Shapiro-Wilk tests. Normally distributed variables, non-normal variables and categorical data were expressed as mean \pm standard deviation (SD), median [interquartile ranges] and number (percentages), respectively.

The study population was divided into two groups (survivors and victims) based on the 30-day outcome since ICU admission. Normally distributed variables were compared between survivors and victims by unpaired Student's t test and non-normal variables by Mann-Whitney U test. The Chi-Squared test was adopted to assess the differences in categorical variables between the two groups.

Cox proportional hazard regression was used to screen risk factors independently associated with the 30-day mortality of sepsis. Specifically, univariate analysis was firstly conducted and variables with a p value < 0.1 were then entered into the multivariable analysis, where variables with p < 0.05 were picked out to calculate the change of hazard ratio (HR) from the univariate regression (uHR) to multivariate regression (mHR) [HR-change=(uHR-mHR)/uHR \times 100%]. Then, variables with HR-change < 10% were considered as the independent risk factors for the 30-day mortality of sepsis. Besides, the rank-hazard plot was used to visualize the relative importance of the independent risk factors in the Cox proportional hazard model [28].

As GCS was considered as an independent risk factor in the Cox regression, we divided the study cohort into four groups based on the GCS score, that is group with (1) normal consciousness (GCS = 15), (2) mild impairment of consciousness (GCS 13–14), (3) moderate impairment of consciousness (GCS 9–12), and (4) coma (GCS 3–8). Then, the probability of survival in the four groups were visualized by Kaplan-Meier analysis and compared by log-rank test, where patients with GCS 9–12 and GCS 3–8 had significantly lower survival rate than patients with GCS \geq 12. Then, the risk factors independently associated with GCS \leq 12 were recognized by logistic regression by a process similar to

Cox regression. Specifically, univariate analysis was firstly conducted and variables with a p value < 0.1 were entered into the multivariable analysis, where variables with p < 0.05 were picked out to calculate the change of odds ratio (OR) from the univariate regression (uOR) to multivariate regression (mOR) [OR-change=(uOR-mOR)/uOR × 100%]. Then, variables with OR-change < 10% were considered as independent risk factors. Sensitivity analyses were conducted in the same cohorts after exclusion of patients with a history of neurological diseases (mainly those with neurodegenerative diseases and cognitive impairment).

Statistical analyses were performed using R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Missing values were addressed with multiple imputation in the process of regression analysis and survival analysis. The imputation technique involves creating multiple copies of the data and replacing missing values with imputed values through a suitable random sample from their predicted distribution. We used the “mice” package of R to obtain 5 imputation datasets. A two-tailed p value < 0.05 was considered statistically significant.

Results

Characteristics of participants

There were a total of 16602 patients with infection in the database according to the results of microbial cultivation, and 7918 patients with a SOFA score ≥ 2 were diagnosed as sepsis. After screening by the exclusion criteria, a total of 4446 patients were included into the final cohort and conscious dysfunction (GCS < 15) was observed in 2126 (47.8%) patients.

The baseline characteristics and the characteristics at ICU admission of all participants were exhibited in **Table 1** and **Table 2**. Patients who died (victims) within 30-day since ICU admission were older than those who survived (survivors), with a median age of 78 [67, 86] in victims and 68 [55, 78] in survivors. Patients were predominantly male in both victims and survivors. Comorbidities showed that victims had higher proportion of cardiovascular diseases, chronic liver disease and coagulopathy. Organ failure and the state of illnesses were more severe in victims, with higher modified SOFA and SAPSII score, and higher frequency of coagulation, brain, cardiovascular and renal dysfunctions in victims than that in survivors. Victims had higher proportion of pulmonary and/or fungal infection than survivors. Besides, several vital signs and laboratory indexes were different between victims and survivors, with higher level of respiratory rate, lactate, AST, bilirubin, potassium, RDW and WBC, and lower level of arterial blood pressure, temperature, PO₂ and hemoglobin in victims, respectively.

Medical interventions are described in **Additional file 2 Table S1**. Victims had longer ICU stay time and shorter hospital stay time than survivors. The proportion of vasopressor adoption and mechanical ventilation were higher in victims than that in survivors. Moreover, victims had higher frequency use of carbapenems, vancomycin, benzodiazepines and analgesic drugs than survivors.

Table 1. Patients' baseline characteristics ^a

Variable	All patients n=4446	Survival n=3685	Death n=761	P value
Age, years	70 [56, 81]	68 [54, 80]	78 [67, 86]	<0.001
Gender, male	2397 (53.91)	1996 (54.17)	401 (52.69)	0.483
Ethnicity, n (%)				<0.001
White	3299 (74.20)	2749 (74.60)	550 (72.27)	
Black	333 (7.49)	296 (8.03)	37 (4.86)	
Hispanic or Latino	132 (2.97)	117 (3.18)	15 (1.97)	
Asian	88 (1.98)	72 (1.95)	16 (2.10)	
Others	594 (13.36)	451 (12.24)	143 (18.79)	
Comorbidity, n (%)				
Cardiovascular diseases	2512 (56.50)	2000 (54.27)	512 (67.28)	<0.001
Peripheral vascular disease	526 (11.83)	426 (11.56)	100 (13.14)	0.243
Other neurological Diseases	631 (14.19)	524 (14.22)	107 (14.06)	0.954
Hypertension	2226 (50.07)	1859 (50.45)	367 (48.23)	0.282
Chronic Pulmonary Disease	1039 (23.37)	830 (22.52)	209 (27.46)	0.004
Diabetes	839 (18.87)	693 (18.81)	146 (19.19)	0.847
Hypothyroidism	519 (11.67)	419 (11.37)	100 (13.14)	0.186
Liver Disease	395 (8.89)	295 (8.01)	100 (13.14)	<0.001
Coagulopathy	742 (16.69)	559 (15.17)	183 (24.05)	<0.001
Anemias	1158 (26.05)	966 (26.21)	192 (25.23)	0.605

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

Table 2. Patients' characteristics at ICU admission ^a

Variable	All patients n=4446	Survival n=3685	Death n=761	P value
First care unit n (%)				<0.001
CCU	538 (12.10)	433 (11.75)	105 (13.80)	
CSRU	555 (12.48)	510 (13.84)	45 (5.91)	
MICU	2107 (47.39)	1654 (44.88)	453 (59.53)	
SICU	675 (15.18)	584 (15.85)	91 (11.96)	
TSICU	571 (12.84)	504 (13.68)	67 (8.80)	
Severe Score ^b				
Modified SOFA	4.58±2.88	4.32±2.63	5.90±3.60	<0.001
Modified SAPSII	37.42±10.79	35.79±10.79	45.34±11.95	<0.001
GCS score	15 [13,15]	15 [13,15]	14 [12,15]	<0.001
Organ dysfunction (SOFA>2), n(%)				
Respiration	3719 (83.65)	3067 (83.23)	652 (85.68)	0.108
Coagulation	674 (15.16)	511 (13.87)	163 (21.42)	<0.001
Liver	2492 (56.05)	2064 (56.06)	428 (56.24)	0.934
CNS	526 (11.83)	404 (10.96)	211 (16.03)	<0.001
Cardiovascular	981 (22.06)	749 (20.33)	232 (30.49)	<0.001
Renal	742 (16.71)	506 (13.73)	237 (31.14)	<0.001
Vital signs ^c				
Mean heart rate (min ⁻¹)	88.69±16.18	88.52±15.92	89.48±17.41	0.163
Systolic pressure (mmHg)	113.39±14.41	113.98±14.11	110.51±15.44	<0.001
Diastolic pressure (mmHg)	57.82±9.68	58.37±9.55	55.18±9.90	<0.001
Mean respiratory rate (min ⁻¹)	20.00±4.15	19.76±3.99	21.17±4.66	<0.001
Mean temperature (°C)	36.93±0.68	36.98±0.66	36.69±0.72	<0.001
Mean SpO ₂ (%)	97.3 [96.0, 98.5]	97.4 [96.0, 98.5]	97.0 [95.5, 98.3]	<0.001
Laboratory tests ^d				
Lactate (mmol/L)	1.6 [1.1, 2.4]	1.5 [1.1, 2.3]	1.8 [1.3, 2.7]	<0.001
PCO ₂ (mmHg)	40 [35, 47]	40 [35,47]	39 [33,47]	0.006
PO ₂ (mmHg)	112 [75,199]	115 [76, 210]	98 [69,172]	<0.001
PH	7.368±0.096	7.371±0.092	7.358±0.110	0.003
Creatinine (K/uL)	1.1 [0.8, 1.7]	1.1 [0.8, 1.6]	1.4 [0.9, 2.4]	<0.001

BUN (K/uL)	23 [15, 37]	22 [15, 34]	31 [21, 50]	<0.001
ALT ^e	1.4 [1.2, 1.7]	1.4 [1.2, 1.7]	1.4 [1.1, 1.7]	0.755
AST ^f	1.5 [1.3, 1.8]	1.5 [1.3, 1.8]	1.6 [1.3, 1.9]	<0.001
Bilirubin (EU/dL)	0.6 [0.4, 1.1]	0.6 [0.4, 1.1]	0.7 [0.4, 1.6]	<0.001
Hemoglobin (g/dL)	11.59±2.23	11.71±2.24	11.03±2.11	<0.001
Platelet (K/uL)	226 [162, 302]	227 [167, 300]	220 [142, 314]	0.030
Potassium (K/uL)	4.2 [3.8, 4.6]	4.1 [3.7, 4.6]	4.3 [3.8, 4.8]	<0.001
Sodium (K/uL)	138 [135, 141]	138 [135, 141]	138 [134, 141]	0.087
PT (sec)	14 [12.9,16.3]	13.8 [12.9,15.9]	14.7 [13.2,18.5]	<0.001
RDW (%)	14.7 [13.7, 16.2]	14.5 [13.6, 16.0]	15.7 [14.3, 17.6]	<0.001
WBC (K/uL)	10.8 [7.5, 15.4]	10.6 [7.4, 15.1]	11.6 [8.2, 16.6]	<0.001
Lymphocyte (%)	9.5 [5.7, 16.0]	9.8 [6.0, 16.1]	8.0 [4.8, 13.9]	<0.001
Neutrophil (%)	81.3 [72.4, 87.8]	81.0 [72.0, 87.4]	83.4 [74.9, 89.6]	<0.001
MCV (fL)	90 [86,95]	90 [86,94]	92 [87,97]	<0.001
Infection site, n(%)				
Urine	1994 (44.85)	1650 (44.78)	344 (45.20)	0.860
Blood	1151 (25.89)	936 (25.40)	215 (28.25)	0.112
Lung	1708 (38.40)	1331 (36.12)	377 (49.54)	<0.001
Catheter	239 (5.38)	213 (5.78)	26 (3.42)	0.011
Gastrointestinal tract	268 (6.03)	216 (5.86)	52 (6.83)	0.346
Abdominal cavity	108 (2.43)	87 (2.36)	21 (2.76)	0.602
Skin/Soft tissue	758 (17.05)	627 (17.01)	131 (17.21)	0.936
Others	142 (3.19)	126 (3.42)	16 (2.10)	0.077
Microorganisms, n(%)				
Gram-positive	2269 (51.03)	1872 (50.80)	397 (52.17)	0.517
Gram-negative	1770 (39.81)	1483 (40.24)	287 (37.71)	0.209
Fungus	1338 (30.09)	989 (26.84)	349 (45.86)	<0.001

^a Normally distributed variables are presented as mean ± standard deviation (SD), non-normal variables are presented as median (interquartile ranges), whereas categorical data are presented as frequency (percentage)

^b Severe score is calculated on the first day of each ICU patients' stay

^c Vital signs is calculated on the first 24 hours of each ICU patients' stay

^d Laboratory tests recorded the first result of each patients' ICU stay

^e ALT in the table is the value after logarithmic transformation

^f ALT in the table is the value after logarithmic transformation

CCU, coronary care unit; CSRU, cardiac surgical intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; SOFA, sequential organ failure assessment; SAPS II: the simplified acute physiology score; RDW, red blood cell distribution widths; MCV, mean corpuscular volume;

Risk factors for the 30-day mortality of sepsis

The HR (95%CI) of variables with p value<0.05 in multivariate Cox regression were exhibited in **Table 3**. One variable with a HR-change<10% demonstrated that the impact of it on the 30-day mortality of patients with sepsis was not significantly influenced by the other variables in the multivariate Cox regression, and can be considered as the independent risk factor for the 30-day mortality of sepsis (**Additional file 3: Figure S2**). Then, the relative importance of independent risk factors were visualized by the rank-hazard plot (**Figure 1**). Results revealed that among the risk factors which were negatively associated with the 30-day mortality of sepsis, GCS score was the most important one with the highest relative hazard at a range of 3-13 except for that of Mean SpO₂ at the lower limit.

Table 3. Cox proportional hazard regression to identify variables independently associated with 30-day mortality of patients with sepsis.

Variables	Univariate Cox Regression				Multivariate Cox Regression				HR change(%)
	HR	95%CI		P value	HR	95%CI		P value	
Age, years	1.03	1.03	1.04	<0.001	1.04	1.03	1.04	<0.001	1.0
GCS score	0.95	0.93	0.97	<0.001	0.93	0.90	0.95	<0.001	2.1
Liver diseases	1.65	1.34	2.04	<0.001	1.62	1.25	2.09	<0.001	1.8
Solid tumor	1.57	1.23	2.01	<0.001	1.38	1.08	1.78	0.011	12.1
Lactate (mmol/L)	1.19	1.15	1.23	<0.001	1.08	1.04	1.12	<0.001	9.2
BUN (K/uL)	1.01	1.01	1.02	<0.001	1.00	1.00	1.01	0.018	1.0
AST ^a	1.45	1.26	1.68	<0.001	1.44	1.03	2.03	0.034	0.7
Bilirubin (EU/dL)	1.05	1.04	1.06	<0.001	1.02	1.01	1.04	0.005	2.9
RDW (%)	1.18	1.15	1.21	<0.001	1.13	1.09	1.17	<0.001	4.2
MCV (fL)	1.03	1.03	1.04	<0.001	1.02	1.01	1.03	<0.001	1.0
Heartrate (min ⁻¹)	1.00	1.00	1.01	0.074	1.01	1.00	1.01	0.005	1.0
Diastolic pressure (mmHg)	0.97	0.96	0.97	<0.001	0.99	0.98	1.00	0.017	2.1
Respiratory rate (min ⁻¹)	1.07	1.06	1.09	<0.001	1.06	1.04	1.08	<0.001	0.9
Temperature (°C)	0.56	0.51	0.62	<0.001	0.70	0.62	0.79	<0.001	25.0
Mean SpO ₂ (%)	0.92	0.90	0.95	<0.001	0.97	0.94	1.00	0.033	5.4
Mechanical ventilation	1.38	1.11	1.72	0.004	1.43	1.13	1.80	0.002	3.6
Vasopressor	2.17	1.88	2.50	<0.001	1.60	1.36	1.87	<0.001	26.3
Lung infection	1.62	1.40	1.86	<0.001	1.41	1.18	1.67	<0.001	13.0
Catheter-related infection	0.59	0.40	0.87	0.008	0.50	0.33	0.75	<0.001	15.3
Other infections	0.62	0.38	1.01	0.056	0.51	0.31	0.84	0.009	17.7
Fungal infection	2.06	1.79	2.38	<0.001	1.19	1.00	1.41	0.047	42.2

^a AST in the table is the value after logarithmic transformation.

GCS, Glasgow coma score; RDW, red blood cell distribution width; MCV, mean corpuscular volume.

C-index = 0.76

Survival analysis of patients with sepsis according to the GCS score

As GCS has been demonstrated to be an independent risk factor for the 30-day mortality of sepsis, Kaplan-Meier's survival analysis was then conducted to visualize the 30-day survival according to different GCS score of participants (**Figure 2**). Results showed that the 30-day survival had no difference between septic patients with normal consciousness (GCS=15) and those with mild impairment of consciousness (GCS 13-14) (log-rank $p=0.28$), whereas septic patients with moderate impairment of consciousness (GCS 9-12) or coma (GCS 3-8) had higher 30-day mortality than both of them (log-rank $p<0.0001$). Besides, the 30-day survival had no difference between septic patients with moderate impairment of consciousness and those with coma (log-rank $p=0.48$). These results indicated that it was GCS 3-12 that contribute to the increased 30-day mortality of patients with sepsis and was the independent risk factor for it.

Risk factors for sepsis-associated moderate impairment of consciousness and coma

The OR (95%CI) of variables with p value <0.05 in multivariate logistic regression were exhibited in **Table 4**. One variable with a OR-change $<10\%$ demonstrated that its effect on the incidence of $GCS\leq 12$ in patients with sepsis was not significantly influenced by the other variables in the multivariate logistic regression, and can be considered as the independent risk factor contributing to the moderate impairment of consciousness and coma in sepsis (**Figure 3**). Sensitivity analysis was conducted in patients without a history of neurological diseases and the results were exhibited in **Additional file 4: Figure S3**. Then, we divided the continuous variables of the independent risk factors into three groups based on their reference range and the proportion of patients with $GCS\leq 12$ in each group were calculated and visualized in **Figure 4**.

Table 4. Logistic regression to identify variables independently associated with sepsis-associated moderate impairment of consciousness and coma

Variables	Univariate Logistic Regression			Multivariate Logistic Regression			OR change(%)		
	OR	95%CI	P value	OR	95%CI	P value			
Respiration(SOFA>2)	0.59	0.50	0.71	<0.001	0.70	0.57	0.85	<0.001	18.6
Cardiovascular diseases	0.73	0.64	0.84	<0.001	0.81	0.69	0.95	0.009	23.3
Neurodegenerative disorders	3.56	2.98	4.25	<0.001	2.94	2.44	3.54	<0.001	16.3
Hemoglobin (g/dL)	1.06	1.03	1.10	<0.001	1.05	1.01	1.09	0.019	0.9
Sodium (K/uL)	1.04	1.02	1.05	<0.001	1.02	1.00	1.03	0.018	1.9
Neutrophil (%)	1.01	1.00	1.01	0.004	1.01	1.00	1.02	0.004	0.0
Systolic pressure (mmHg)	1.04	1.03	1.04	<0.001	1.03	1.02	1.04	<0.001	1.0
Urinary infection	1.20	1.04	1.38	0.011	1.17	1.00	1.37	0.045	1.7
Cephalosporin	1.31	1.13	1.52	<0.001	1.36	1.16	1.60	<0.001	3.1

SOFA, sequential organ failure assessment;

AUC = 0.67; Hosmer and Lemeshow test: $P=0.12$.

Discussion

In this retrospective analysis by MIMIC III database, we found that mild disturbance of consciousness (GCS 13–14) was not an independent risk factor for the 30-day mortality of sepsis, while moderate disorder of consciousness (GCS 9–12) and coma (GCS 3–8) was independently associated with it. Then, the mean value of systolic pressure on the first day of ICU admission, utility of cephalosporin, urinary infection, and the level of hemoglobin, neutrophil and serum sodium were identified to be the independent risk factors leading to the moderate impairment of consciousness and coma in patients with sepsis. After divided systolic pressure, hemoglobin, neutrophil and serum sodium into three groups based on their reference range, systolic pressure and/or serum sodium higher than the normal reference range (systolic pressure ≥ 140 mmHg, serum sodium ≥ 145 K/uL) was associated with increased incidence of moderate impairment of consciousness and coma, while the level of hemoglobin and neutrophil lower than the normal reference range (hemoglobin < 11 g/dL and neutrophil $< 50\%$) was related to decreased incidence of them. As reducing hemoglobin and neutrophil to a level lower than their normal reference range may bring adverse effect on patients, it is inappropriate to give intervention on both of them. Therefore, the risk factors that can be rectified to reduce the incidence of moderate conscious impairment and coma include hypertension (systolic pressure ≥ 140), hyponatremia (serum sodium ≥ 145 K/uL), the utility of cephalosporin and urinary infection. To the best of our knowledge, this is the first study to evaluate the effect of conscious impairment on the 30-day mortality of sepsis and explore the modifiable risk factors contributing to sepsis-associated disorder of consciousness.

Hypertensive encephalopathy is a hypertensive emergency defined by acute neurological dysfunction associated with an acute and severe increase in blood pressure (systolic pressure > 220 mmHg or diastolic pressure > 120 mmHg). Patients suffering from hypertensive encephalopathy often have alterations in mental status, or accompanied by seizures, visual disturbance, or headache [29]. However, in our study, patients with hypertensive encephalopathy according to the ICD-9 code has been excluded from the study cohort, and the highest systolic pressure in the study cohort was 180 mmHg, less than the typically lower limit of systolic pressure (220 mmHg) that may cause hypertensive encephalopathy. All of these ruled out the possibility of hypertensive encephalopathy as the cause of conscious dysfunction in patients with sepsis accompanied by high systolic pressure. Indeed, studies have revealed that hypertension is an independent risk factor for delirium in ICU patients [30–32], in patients after cardiac or abdominal operation [33, 34], and in patients at a general hospital [35]. As delirium is reported in 11–80% of patients with critically ill, and patients with delirium may clinically present as conscious disorder, we infer that the potential overlap of cohort between our study and the above ones may make hypertension an independent risk factor for the moderate impairment of consciousness and coma. Moreover, studies have demonstrated that hypertension is directly linked to memory impairment [36], diminished psychomotor speed [37] and inattention [38]. Therefore, if patients subject to intense physical or psychological stress (such as sepsis) in ICU, they may be more vulnerable to develop conscious impairment, but the exact mechanisms for the impairment of consciousness caused by hypertension is still unclear and need to be further studied.

The results from Sonnevile R et al suggested that hypernatremia might play a role in the pathophysiology of SAE [7]. They included patients with either hypernatremia or hyponatremia in their study, but only hypernatremia was finally identified as an independent risk factor for SAE in the logistic regression analysis. Interestingly, in our study, although patients with hyponatremia were excluded from the study cohort, hypernatremia is still independently related to GCS ≤ 12 in the logistic regression analysis, further confirmed that hypernatremia might have negative effects on the consciousness of patients with sepsis and need to be avoided.

Previous studies have suggested that antibiotics may play a role in the pathophysiology of SAE [39], which was consistent with our conclusion that cephalosporin was connected with the moderate impairment of consciousness and coma. Cephalosporin has been widely regarded as a neurotoxic antibiotic [39]. Therefore, dose monitoring should be conducted during the systematic use of cephalosporin as the neurotoxic effect are related to the overdose of antibiotics [40]. However, the causal relationship between cephalosporin use and sepsis-associated conscious dysfunction remains to be demonstrated.

Urinary tract infection is widely regarded as a common medical comorbidity in patients with disorders of consciousness [41–43], however, its impact on sepsis-associated impairment of consciousness was rarely reported. In the study of Sonnevile R et al [7], they found that it was staphylococcus aureus, rather than infection source, that was associated with SAE, while Zhang et al draw inconsistent conclusions that except for staphylococcus aureus, patients with biliary tract infections and intestinal infections were more prone to SAE [18]. In our study, we found that urinary infection was independently linked to moderate impairment of consciousness and coma in septic patients. Considering the similar exclusion criterion between the study of Zhang et al and ours, we tend to believe that infection site is a risk factor contributing to conscious dysfunction during sepsis. Therefore, clinical prevention of hospital-acquired urinary infection and active treatment towards urinary infection of various origins with appropriate antibiotics according to drug susceptibility results may be helpful to protect septic patients from the deterioration of consciousness and improve short-term prognosis□

Several strengths could be found in the present study. First, we use Sepsis 3.0 to define sepsis, which was rare in previous retrospective clinical studies. Second, the exclusion criteria of this study are relatively strict and comprehensive, which to the maximum extent ensure that conscious impairment is caused by sepsis instead of other pathogenic factors. Third, MIMIC III is a high-quality database including a large number of patients with sepsis of various origins. In this regard, our study may be the largest retrospective study focusing on the outcomes and risk factors of sepsis-associated disorder of consciousness. The large sample size of the study avoid overfitting in Cox and logistic regression, and ensure the accuracy and reliability of the results.

This study has certain limitations: First, the retrospective nature of this observational study determined that unidentified confounding factors may affect the results of regression analysis. Second, we focused on sepsis-associated disorder of consciousness in this study, while the other components of SAE, including sepsis-associated delirium, sepsis-associated ultrastructure changes of brain and sepsis-associated electrical activity changes were not involved, further studies are essential to evaluate their effect on the prognosis of sepsis and explore their remediable risk factors if needed. Third, we did not assess the impact of conscious impairment on the long-term mortality of patients with sepsis. Fourth, the causal relationship between the identified risk factors and sepsis-associated disorder of consciousness can not be determined from this observational study.

Conclusions

In this retrospective analysis by MIMIC III database, we found that moderate impairment of consciousness (GCS 9–12) and coma (GCS 3–8) were independently related to the 30-day mortality of sepsis. Potentially remediable risk factors for patients with sepsis characterized by $GCS \leq 12$ at ICU admission were hypertension (systolic pressure ≥ 140 mmHg), hypernatremia (serum sodium ≥ 145 K/uL), the utility of cephalosporin and urinary infection. Although these factors are likely to play a role in the pathophysiology of sepsis-associated disorder of consciousness, we can not draw the conclusion that medical interventions towards these remediable risk factors can surely reduce the incidence of moderate impairment of consciousness and coma. Further studies are needed to investigate the causal relationship between them.

Abbreviations

MIMIC III: Medical Information Mart for Intensive Care

Sepsis 3.0: The Third International Consensus Definitions for Sepsis

GCS Glasgow Coma Score

SAE Sepsis-associated encephalopathy

ICD-9: International Classification of Diseases, Ninth Revision

SQL: Structure Query Language

SOFA Sequential Organ Failure Assessment

SAPS Simplified Acute Physiology Score

OR: Odds Ratios

HR: Hazard Ratio

RDW Red blood cell distribution width

MCV, mean corpuscular volume

CCU: Coronary Care Unit

CSRU: Cardiac Surgical Intensive Care Unit

MICU: Medical Intensive Care Unit

SICU: Surgical Intensive Care Unit

TSICU: Trauma/Surgical Intensive Care Unit

Declarations

Ethics approval and consent to participate

The MIMIC III database has received ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). All data are de-identified in this database to remove patients' information, the requirement for individual patient consent is not indispensable.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding/Support

None.

Authors' contributions

YY, SL and QW analyzed the data and wrote the paper. KG and HW collected the data. EK and RL checked the integrity of the data and the accuracy of the data analysis. LL and YZ designed the study and revised the paper. All authors read and approved the final manuscript.

Acknowledgments

None

References

1. Wilson JX, Young GB. Sepsis-associated encephalopathy: evolving concepts. *Can J Neurol Sci.* 2003;30:98–105.
2. Sprung CL, Peduzzi PN, Shatney CH, et al. Impact of encephalopathy on mortality in the sepsis syndrome. *Crit Care Med.* 1990;18:801–6.
3. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA.* 2010;304(16):1787–94.
4. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc.* 2012;60(6):1070–7.
5. Gofton TE, Young GB. Sepsis-associated encephalopathy. *Nat Rev Neurol.* 2012;8(10):557–66.
6. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. *JAMA.* 1996;275:470–3.
7. Sonnevile R, de Montmollin E, Poujade J, et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. *Intensive Care Med.* 2017;43:1075–84.
8. Bone RC, Sprung CL, Sibbald WJ. Definitions for sepsis and organ failure. *Crit Care Med.* 1992;20:724–6.
9. Iacobone E, Bailly-Salin J, Polito A, Friedman D, Stevens RD, Sharshar T. Sepsis-associated encephalopathy and its differential diagnosis. *Crit Care Med.* 2009;37:331–6.
10. Ebersoldt M, Sharshar T, Annane D. Sepsis-associated delirium. *Intensive Care Med.* 2007;33:941–50.
11. Siami S, Annane D, Sharshar T. The encephalopathy in sepsis. *Crit Care Clin.* 2008;24:67–82.
12. Kadoi Y, Saito S. An alteration in the gamma aminobutyric acid receptor system in experimentally induced septic shock in rats. *Crit Care Med.* 1996;24:298–305.

13. Kadoi Y, Saito S, Kunimoto F, et al. Impairment of the brain beta-adrenergic system during experimental endotoxemia. *J Surg Res.* 1996;61:496–502.
14. Hellstrom IC, Danik M, Luheshi GN, et al. Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained IL-beta-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. *Hippocampus.* 2005;15:656–64.
15. Barichello T, Fortunato JJ, Vitali AM, et al. Oxidative variables in the rat brain after sepsis induced by cecal ligation and perforation. *Crit Care Med.* 2006;34:886–9.
16. Messaris E, Memos N, Chatzigianni E, et al. Time-dependent mitochondrial-mediated programmed neuronal cell death survival in sepsis. *Crit Care Med.* 2004;32:1764 – 1770.
17. Handa O, Stephen J, Cepinskas G. Role of eNOS-derived nitric oxide (NO) in activation and dysfunction of cerebrovascular endothelial cells during early onsets of sepsis. *Am J Physiol Heart Circ Physiol.* 2008;295(4):1712–9.
18. Zhang LN, Wang XT, Ai YH, Guo QL, Huang L, Liu ZY, Yao B. Epidemiological Features and Risk Factors of Sepsis-Associated Encephalopathy in Intensive Care Unit Patients: 2008–2011. *Chin Med J (Engl).* 2012;125(5):828–31.
19. Iacobone E, Salin JB, Polito A, Friedman D, Stevens RD, Sharshar T. Sepsis-associated Encephalopathy and Its Differential Diagnosis. *Crit Care Med.* 2009;37(10 Suppl):331-6.
20. Gofton TE, Young GB. Sepsis-associated Encephalopathy. *Nat Rev Neurol.* 2012;8(10):557–66.
21. Johnson A, Pollard T, Mark R. MIMIC-III Clinical Database (version 1.4). *PhysioNet.* 2016; <https://doi.org/10.13026/C2XW26>.
22. Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Scientific Data.* 2016;3:160035.
23. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016; 23;315 (8).
24. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;70:2957–63.
25. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22:707–10.
26. Teasdale G, Jennett B. Assessment of Coma and Impaired Consciousness. A Practical Scale. *Lancet.* 1974;2(7872):81–4.
27. Sharshar T, Citerio G, Andrews PJ, et al. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. *Intensive Care Med.* 2014;40(4):484–95.
28. Karvanen J, Harrell FE. Visualizing covariates in proportional hazards model. *Stat Med.* 2009;28:1957–66.
29. Miller JB, Suchdev K, Jayaprakash N, et al. New Developments in Hypertensive Encephalopathy. *Curr Hypertens Rep.* 2018;20(2):13.
30. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med.* 2007;33(1):66–73.
31. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an Intensive Care Unit: A Study of Risk Factors. *Intensive Care Med.* 2001;27(8):1297–304.
32. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A Systematic Review of Risk Factors for Delirium in the ICU. *Crit Care Med.* 2015;43(1):40–7.

33. Kumar AK, Jayant A, Arya VK, Magoon R, Sharma R. Delirium After Cardiac Surgery: A Pilot Study From a Single Tertiary Referral Center. *Ann Card Anaesth.* 2017;20(1):76–82.
34. Miyagawa Y, Yokoyama Y, Fukuzawa S, et al. Risk Factors for Postoperative Delirium in Abdominal Surgery: A Proposal of a Postoperative Delirium Risk Score in Abdominal Surgery. *Dig Surg.* 2017;34(2):95–102.
35. Kim H, Chung S, Joo YH, Lee JS. The Major Risk Factors for Delirium in a Clinical Setting. *Neuropsychiatr Dis Treat.* 2016;12:1787–93.
36. Madden DJ, Blumenthal JA. Slowing of Memory-Search Performance in Men With Mild Hypertension. *Health Psychol.* 1989;8(2):131–42.
37. King HE, Miller RE. Hypertension. Cognitive and Behavioral Considerations. *Neuropsychol Rev.* 1990;1(1):31–73.
38. Waldstein SR, Manuck SB, Ryan CM, Muldoon MF. Neuropsychological Correlates of Hypertension: Review and Methodologic Considerations. *Psychol Bull.* 1991;110(3):451–68.
39. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. *Neurology.* 2016;86:963–71.
40. De Waele JJ, Lipman J, Akova M, et al. Risk factors for target non-attainment during empirical treatment with beta-lactam antibiotics in critically ill patients. *Intensive Care Med.* 2014;40:1340–51.
41. Ganesh S, Guernon A, Chalcraft L, Harton B, Smith B, Louise-Bender Pape T. Medical Comorbidities in Disorders of Consciousness Patients and Their Association With Functional Outcomes. *Arch Phys Med Rehabil.* 2013;94(10):1899–907.
42. Ng YS, Chua KS. States of Severely Altered Consciousness: Clinical Characteristics, Medical Complications and Functional Outcome After Rehabilitation. *NeuroRehabilitation.* 2005;20(2):97–105.
43. Whyte J, Nordenbo AM, Kalmar K, et al. Medical Complications During Inpatient Rehabilitation Among Patients With Traumatic Disorders of Consciousness. *Arch Phys Med Rehabil.* 2013;94(10):1877–83.

Figures

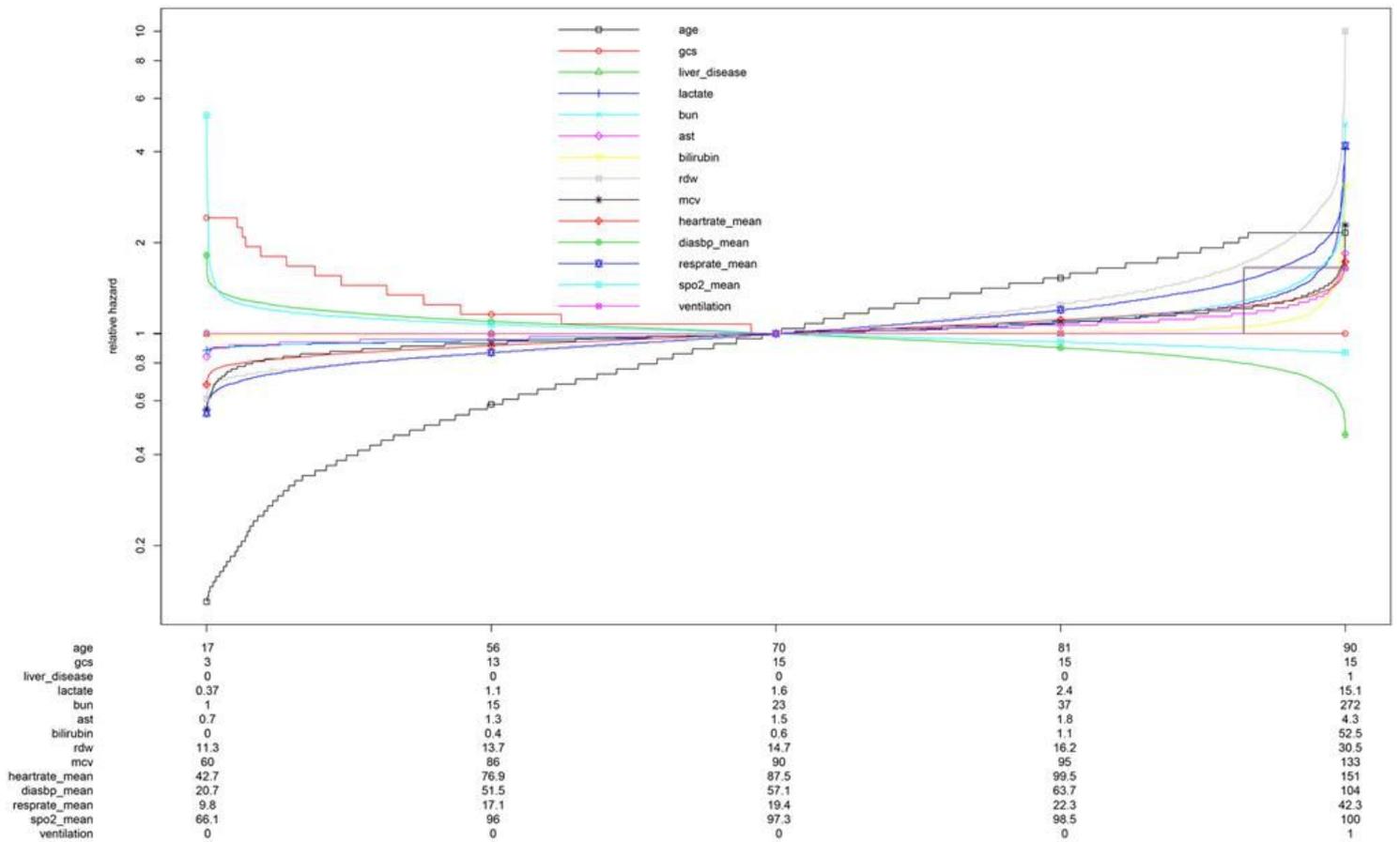


Figure 1

The rank-hazard plot to visualize the relative importance of independent risk factors for the 30-day mortality of patients with sepsis.

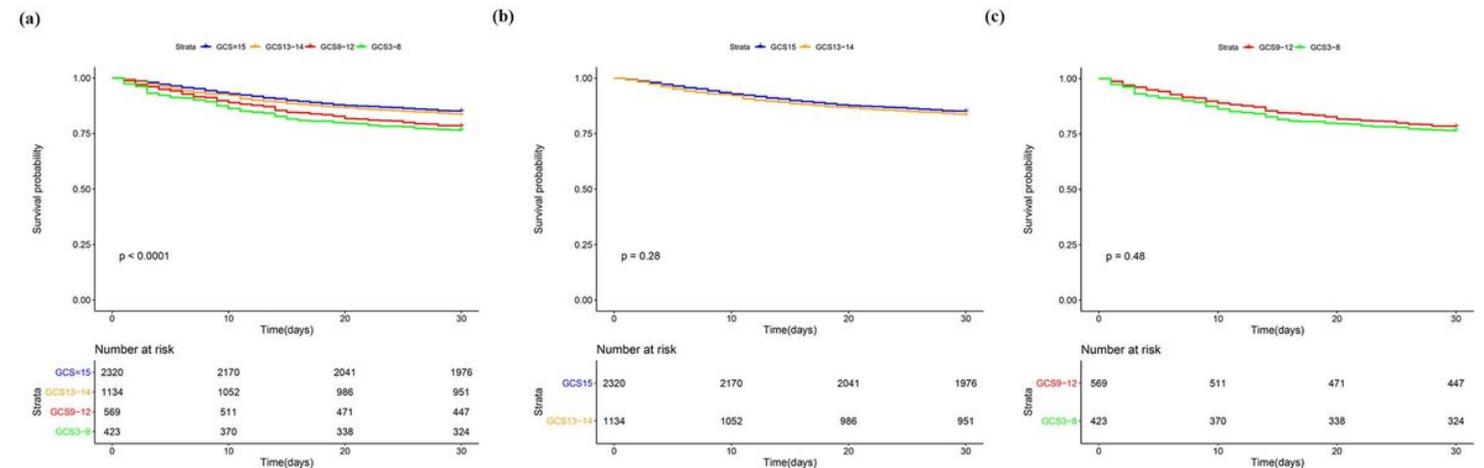


Figure 2

The Kaplan-Meier's survival estimated of the 30-day survival probability of patients with sepsis. Patients were divided into 4 groups according to the GCS score, namely GCS=15 (normal consciousness), GCS 13-14 (mild impairment of consciousness), GCS 9-12 (moderate impairment of consciousness) and GCS 3-8 (coma). (a) The curve showed that

septic patients with moderate impairment of consciousness or coma had higher 30-day mortality than those with normal consciousness or mild impairment of consciousness (log-rank $p < 0.0001$). (b) the 30-day survival had no difference between septic patients with normal consciousness and those with mild impairment of consciousness (log-rank $p = 0.28$). (c) The 30-day survival had no difference between septic patients with moderate impairment of consciousness and those with coma (log-rank $p = 0.48$).

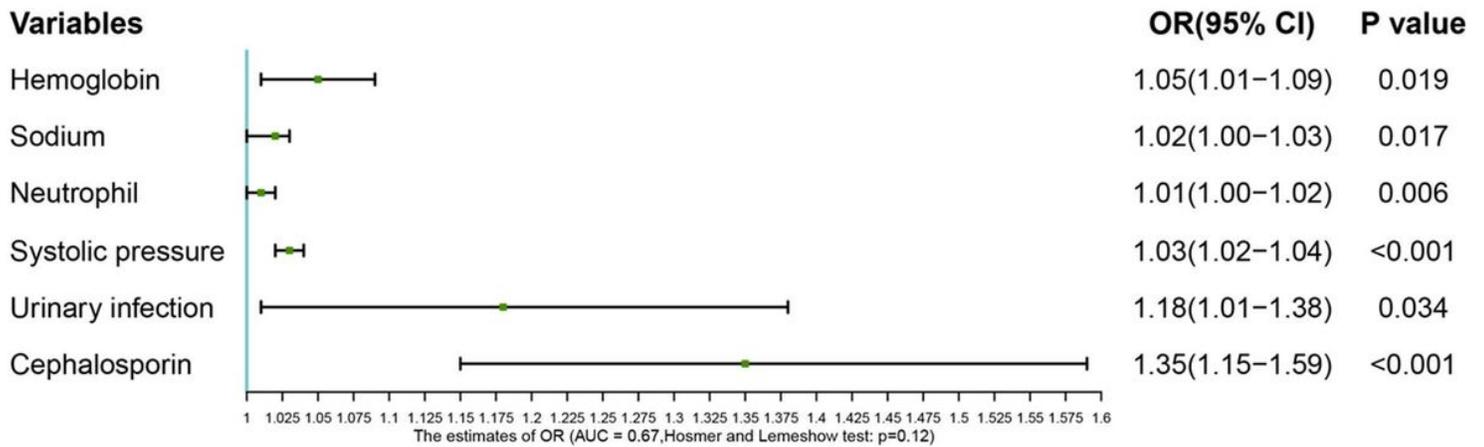


Figure 3

The forest plot of the risk factors independently associated with sepsis-associated moderate impairment of consciousness and coma in the logistic regression.

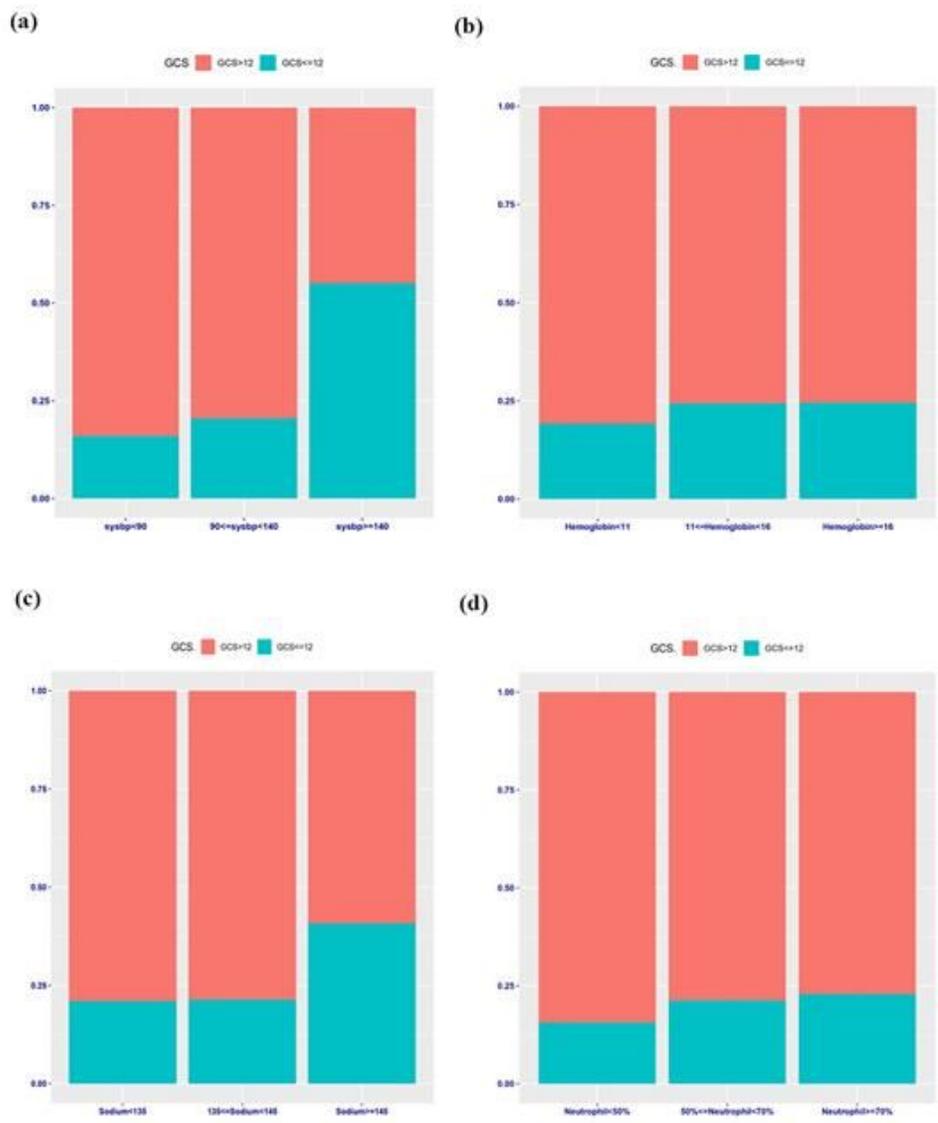


Figure 4

The stacked bar plot to show the proportion of patients with $GCS \leq 12$ in the three groups divided by the reference range of (a) systolic pressure, (b) hemoglobin, (c) serum sodium, and (d) neutrophil.

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