Sepsis-associated Encephalopathy In ICU Admissions: Prevalence, Early Risk of Death, and its Early Prevent and Control

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Abstract

**Background:** Sepsis-associated encephalopathy (SAE) is a common encephalopathy in ICU. We are to define whether SAE present an high prevalence rate and early risk factors for death in ICU 48 hours, while to cognize its important of early prevention/ control.

**Methods:** We retrospectively enrolled patients with acute critically ill from ICU (January, 2015 to January, 2017). All patients were selected from onset to ICU ≤3 hours. The prevalence and some early risk factors of death in SAE was estimated by using a continuous head and thorax /abdominal cavity CT scans.

**Results:** 748 critically ill adults were analyzed. The prevalence of sepsis within initial 48 hours was 40.4% (302/748). The median time from infection to sepsis was 9 hours ( range, 1-48 ). The SAE (93.4%, 282/302) was diagnosed in sepsis patients, and most of them (96.8%) presented multiple organ dysfunction syndromes (MODS). While the fatality of SAE was in 32.0% at initial 48 hours and 69.1% at initial 14 days. Cox regression analysis, unused antibiotic within initial 3 hours (OR, 0.39; 95% CI, 0.22-0.89), severe inflammatory storm (OR, 0.70; 95% CI, 0.58- 0.94), lower GCS (OR, 2.7; 95% CI, 1.5-3.6), and MODS (OR, 0.37; 95% CI, 0.26-0.96) were early risk factors for death in SAE. Early risk factors for predicting SAE were related to severe inflammatory storm (OR, 3.10; 95% CI, 2.28-4.33), MODS (OR, 3.57; 95% CI, 2.73- 4.67), and unused antibiotics within initial 3 hours (OR, 0.25; 95% CI, 0.11-0.56).

**Conclusions:** SAE in ICU is an high prevalent acute brain dysfunction and most with MODS. The early bad prognosis in SAE was related to the failure of early prevention and control.

Introduction

Sepsis as an most frequent complication in critically ill adults has been become the leading cause of morbidity and mortality worldwide [1-4]. Moreover, a new sepsis-3 is defined sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection [5]. To the best of our knowledge, the human brain is very vulnerable to inflammatory storm. The brain may be the first organ to show a signs of life-threatening organ dysfunction caused by infection if control infection is uncompleted at initial. This brain dysfunction which is closely related to inflammatory storm caused by sepsis, is known as "sepsis- associated encephalopathy (SAE)". Although previous study shown that the prevalence and mortality of SAE was almost up to 70.0% of sepsis in ICU [6], whether SAE in ICU initial 48 hours would present an high rate of prevalence and early risk of death, which was still unknown. Our hypothesis was that the critical ill adults in ICU within initial 48 hours would be having an high rate of prevalence from community-acquired infection and early high risk of death in SAE. The aim of this study was to clear whether SAE present an high prevalence and early risk factors for death in ICU 48 hours, while to cognize its important of prevention/control for early infection.

Methods
Study setting and population

This study was retrospectively recruited critically ill adults who were consecutively admitted or transferred between January 2015 and January 2017, with the time $\leq$ 3 hours from onset to the ICU and a length of stay more than 24 hours in affiliated Shuyang Hospital of Xuzhou Medical University in China. The study was approved by the ethical committee on clinical research of the Affiliated Shuyang Hospital of Xuzhou Medical University. Because the study involved only a review of records obtained as a part of routine medical care, did not require all patients to write the information consent.

Patient identification

We examined the electronic medical records of these patients who were verified as having a critically ill event with an available record. In order to study these patients with community-acquired bacterial infection, we selected the patients with time $\leq$ 3 hours from critically ill event onset to the ICU. The patients who were more than 3 hours from onset to the ICU were excluded. We also excluded those possible critically ill due to the sudden infectious events caused by viral.

Definitions of SAE and inclusion criteria for sepsis/SAE

Sepsis-associated encephalopathy (SAE) is defined as a life-threatening acute brain dysfunction with or without extracranial multiple organ dysfunction due to infection, which is mainly driven by inflammatory storm (Fig. 1), SAE can range from delirium or confusion, and seizure or focal neurological sign, as well as diffuse or multifocal neurological deficits, to stupor or coma.

We included adult critically ill patients with sepsis on the criteria of sepsis-3 (infection plus one or more life-threatening organ dysfunction).[5] As SAE is a complex syndrome that involves the spread of infection, the driving of inflammatory storm and related mechanisms, and the participation of primary critically ill. Its complexity can cause a difficulty of identification. Thus, we consider that the diagnostic criteria of SAE have to at least meet any two items of the following 4 items: (1) a sepsis patient with SAE has to present a score on the GCS of $<15$, or there's a diffuse abnormal EEG/brain topographic map; (2) a SAE has to present a clinical manifestation/images of inflammatory storm and one or more organ dysfunction; (3) if a brain dysfunction with extracranial organ failure (especially multiple organ), this is almost meet the diagnosis of SAE even if not testing the cytokine in CSF; and (4) only when a pure brain dysfunction (without extracranial organ failure) is presented, the CSF analysis has to perform for rule out a direct primary meningitis/encephalitis.

Identification of infection and organ dysfunction events

In the present study, we used a continuous head and thorax/abdominal cavity CT scans for almost all critically ill patients on initial admission, this continuous CT scans is selected as a tool for screening early infections and organ dysfunction events at initial or repeat CT within 48 hours. Thereafter, also following the body fluid culture (including blood, sputum fluid, urine fluid, and cerebrospinal fluid).
Inflammatory storm (ie., cytokine storm) is clinically manifested as a systemic inflammatory response syndrome (SIRS).[7] The SIRS levels (1–4), i.e., the severity-stratifying levels for patients with inflammatory storm include 4 items as follow: (1) temperature > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) tachypnea > 20 respirations per minute or Pco2 < 32 mmHg; (4) white blood cell count > 12.0 × 10⁹/L or < 4.0 × 10⁹/L, or > 10% band forms. The severity of inflammatory storm was assessed (SIRS any1 item = mild; ≥ any 2 items = severe).

The SOFA scores were calculated for one or more organ dysfunction after critically ill event, which was measured within 48 hours on the ICU admissions. The acute organ dysfunction is defined as equivalent to a SOFA score ≥ 2 for a particular organ (on a scale from 0 to 4, with higher scores indicating with multiple organ failure) [8].

We used the SOFA criteria (including the GCS scores or GCS motor [GCSm] score if the patients intubated) for the brain to assess acute brain dysfunction: the GCS score = 10–14 scores indicate a mild brain dysfunction, GCS = 6–9 scores(GCSm < 6) indicate a moderate-severe brain dysfunction (e.g., stupor or coma), and GCS < 6 scores (GCSm < 3) with no autonomous breathing is identified to be an almost irreversible brain dysfunction (e.g., deep coma or brain death).

Continuous CT scan of the head and chest/abdominal cavity is the most convenient method to monitor the site of infection and acute organ dysfunction. It can detect an early infection of chest cavity (pneumonia) and abdominal cavity (gallbladder/cholangitis, peritonitis, pancreatitis). Especially the head CT scan, it is very helpful for the diagnosis of acute brain dysfunction. On the one hand, it can detect vasogenic brain edema and cytotoxic brain edema. It can also detect focal/multifocal or diffuse brain injury. On the other hand, it can reveal the diagnosis of primary causes (stroke, traumatic brain injury, encephalitis and brain abscess). In addition, an head CT scan can also determine whether the patient has life-threatening brain displacement or brain herniation.

Data collected

In addition to collect the cranial and thorax/abdominal cavity CT scans (at first 24 hours) findings, the collected clinical profile for this study in ICU included the patient demographics, time from critically ill event to infection, inflammatory storm (SIRS ≥ 2), initial GCS score ( or GCS motor score if the patients intubated ), vital sign data, experimental/laboratorial data, SOFA score, using of antibiotics in initial 3 hours, mechanical ventilation, traditional treatment, length of stay (LOS) in the ICU, and outcomes.

The early outcome measures was mortality at the first 48 hours and at the initial 14 days. Death from critically ill event with sepsis included cardiac respiratory arrest, irreversible brain failure, fatal septic shock, fatal respiratory failure, severe MODS, and unexpected death. The outcome events were reviewed by two of the investigators (the first and second author). To investigate the outcomes of patients at the first 48 hours and at the initial 14 days, survival results were determined from the hospital records.

Statistical methods
The results in each group were expressed as mean ± standard deviation (SD) or medians (IQR), and n (%) for qualitative values. Fisher’s exact test and the Mann-Whitney $U$ test were used to examine the relationship between baseline patient variables. Continuous variables were compared using Student’s $t$ test. Multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CIs) were estimated using a logistic-regression model if they were significant in the univariate analysis, or Cox proportional hazards model to examine sepsis baseline status and determine whether the variables played a role in the risk of death events. Survival analysis was performed using the Kaplan–Meier curve method. Differences between patients was considered significant if the p-value was < 0.05. Statistical calculations were performed using a proprietary, computerized statistics package (SPSS 17.0).

**Results**

Among 748 acute critically ill adult patients, 302 (40.4%) sepsis events were identified within initial 48 hours. The median time from onset to infection was 1 hour (range, 0.5–24). The median time from early infection to sepsis was 9.0 hours (range, 1–48). 282 SAE (93.4%) were diagnosed in sepsis. Among the 282 SAE patients, the median age was 59.9 years (range, 18–91 years), 63.2% were male, and the initial median GCS score was 7(3–15) (in the Supplementary Table 1). At initial admission, a score on the GCS of 15 had 9 (3.2%) cases, but then 8 patients rapidly progressed to a score on the GCS of 13 to 6 and the remaining case was also identified as SAE due to an abnormal EEG with a score on the GCS of 15 (Fig. 2). Thus, within initial 48 hours, the most common presenting symptom of SAE was consciousness dysfunction (99.6%, range from delirium to coma), followed by severe inflammatory storm (97.5%) and MODS (96.8%). A pure or isolated brain dysfunction was rare in ICU (3.2%).

Patients data for acute critically ill with and without SAE are described in Table 1. We found that SAE patients were more likely to present with a less median time from onset to ICU, lower GCS score, lower MAP, higher SOFA score, severe inflammatory storm (SIRS ≥ 2), higher qSOFS score, acute lung injury (ALI)/adult respiratory distress syndrome (ARDS), MODS, rapid heart rate, rapid respiratory, elevated WBC, elevated blood glucose, elevated lactic acid, elevated C-reactive protein, acute pneumonia, central herniation, and unused antibiotics treatment within initial 3 hours than those without sepsis (all p < 0.05). Of note, by logistic regression analysis, early risk factors for critically ill patients with SAE are related to severe inflammatory storm (OR, 3.10; 95% CI, 2.28–4.33), higher SOFA score (OR, 1.26; 95% CI, 1.11–1.42), lower initial GCS (OR, 0.89; 95% CI, 0.83–0.96), MODS (OR, 3.57; 95% CI, 2.93–4.66), and unused antibiotic treatment within initial 3 hours (OR, 0.25; 95% CI, 0.12–0.56). (Table 2)
Table 1
Univariable analysis of patients with SAE and without SAE in initial 48 hours in ICU (n = 748)

| Variable                                                                 | with SAE in initial 48 h (n = 282) | without SAE in initial 48 h (n = 466) | P Value |
|--------------------------------------------------------------------------|-----------------------------------|-------------------------------------|---------|
| Male gender, n (%)                                                       | 167(59.2)                         | 306(65.7)                           | 0.085   |
| Age (years, mean ± SD)                                                   | 60.5 ± 15.2                       | 59.6 ± 16.0                         | 0.493   |
| Median time from onset to ICU (h, range)                                 | 1.1(2.7)                          | 1.2(2.5)                            | < 0.001 |
| Initial GCS score (mean ± SD)                                            | 6.5 ± 3.0                         | 7.4 ± 3.1                           | < 0.001 |
| MAP (mmHg, mean ± SD)                                                    | 109.3 ± 31.9                      | 119.5 ± 27.6                        | 0.001   |
| Respiratory rate (breaths/min, mean ± SD)                                | 19.9 ± 7.6                        | 19.8 ± 5.3                          | < 0.001 |
| Body temperature (°C, mean ± SD)                                         | 97.8 ± 24.1                       | 83.6 ± 21.9                         | 0.022   |
| Heart rate (beats/min, mean ± SD)                                       | 14.3 ± 5.9                        | 11.7 ± 4.6                          | < 0.005 |
| Leukocyte count (x10^9/l, mean ± SD)                                     | 275(97.5)                         | 258(55.4)                           | 0.001   |
| Severe inflammatory storm, n (%)                                        | 9.9 ± 6.9                         | 8.8 ± 3.3                           | < 0.001 |
| Blood glucose (mmol/l, mean ± SD)                                       | 39.3(0.1–207)                     | 12.3(0.3128)                        | < 0.001 |
| Blood lactic acid (mmol/l, mean ± SD)                                   | 4.6 ± 1.8                         | 3.4 ± 1.5                           | 0.002   |
| C-reactive protein (mg/L, range)                                        | 1.4 ± 0.6                         | 1.1 ± 0.4                           | < 0.001 |
| Initial SOFA score (mean ± SD)                                          | 2.4 ± 0.9                         | 0.4 ± 1.0                           | < 0.005 |
| qSOFA score (mean ± SD)                                                  | 221(78.4)                         | 326(70.0)                           | < 0.001 |
| ALI/ARDS (needing intubated), n (%)                                     | 195(69.1)                         | 288(61.8)                           | 0.001   |
| MODS (mean ± SD)                                                        | 68 (24.1)                         | 87 (18.7)                           | < 0.001 |
| Community-acquired acute pneumonia, n (%)                               | 264(93.6)                         | 391(83.9)                           | 0.001   |
| Central herniation, n (%)                                               | 90 (32.0)                         | 98 (21.0)                           | < 0.001 |
| Uncal herniation, n (%)                                                 |                                   |                                     | 0.013   |

Abbreviation: ICU, intensive care unit; qSOFA, quick sequential organ failure assessment; sequential [sepsis-related] organ failure. GCS, Glasgow Coma Scale; ALI: acute lung injury; ARDS: adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome. MAP, mean arterial blood pressure;
| Variable                                      | with SAE in initial 48 h (n = 282) | without SAE in initial 48 h (n = 466) | P Value |
|-----------------------------------------------|------------------------------------|---------------------------------------|---------|
|                                               |                                    |                                       | 0.049   |
|                                               |                                    |                                       | 0.078   |
|                                               |                                    |                                       | < 0.001 |
|                                               |                                    |                                       | < 0.005 |

Abbreviation: ICU, intensive care unit; qSOFA, quick sequential organ failure assessment; sequential [sepsis-related] organ failure. GCS, Glasgow Coma Scale; ALI: acute lung injury; ARDS: adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome. MAP, mean arterial blood pressure;

Table 2
Logistic regression analysis to identify the early risk factors of SAE patients in initial 48 hours in ICU (n = 748)

| Variable                                      | OR       | 95% CI for OR | P Value |
|-----------------------------------------------|----------|---------------|---------|
| Severe inflammatory storm                     | 3.101    | 2.282–4.333   | < 0.001 |
| Lower GCS scores                              | 0.891    | 0.825–0.961   | 0.003   |
| MODS                                          | 3.568    | 2.730–4.663   | < 0.001 |
| Early SOFA score                              | 1.256    | 1.110–1.422   | < 0.001 |
| Unused antibiotics treatment in initial 3 hours| 0.249    | 0.112–0.555   | < 0.001 |

Abbreviations: GCS, Glasgow Coma Scale; ICU, intensive care unit MODS, multiple organ dysfunction syndrome; SOFA, sequential [sepsis-related] organ failure assessment.

In 282 SAE, the risk of death was in 32.0% (90/282) at initial 48 hours and in 69.1% (195/282) at initial 14 days in ICU. Our data shown that no-survival SAE patients were significantly associated with the community-acquired pneumonia, severe inflammatory storm, a lower GCS score, lower MAP, higher SOFA score, higher qSOFA score, higher temperature, rapid respiratory, elevated heart rate, elevated lactic acid, ALI/ARDS (requiring ventilation), central herniation, and unused antibiotic within initial 3 hours than those survival SAE patients(all p < 0.05). (Table 3). However, Cox regression risk analysis demonstrated that an adjusting and controlling factor for early survival in SAE was more likely to be related to unused antibiotic treatment within initial 3 hours (OR, 0.39; 95% CI, 0.22–0.89; p = 0.021), severe inflammatory storm (OR, 0.70; 95% CI, 0.58–0.94), lower GCS (OR, 2.7; 95% CI, 1.5–3.6), and MODS (OR, 0.37; 95% CI, 0.26–0.96). (Table 4).
| Variable                                                                 | Non-survival (n = 90) | Surviva (n = 192) | P Value |
|------------------------------------------------------------------------|-----------------------|-------------------|---------|
| Male gender, n (%)                                                     | 62(68.9)              | 124(64.6)         | 0.503   |
| Age (years, mean ± SD)                                                 | 60.0 ± 16.4           | 55.5 ± 16.0       | 0.044   |
| Initial GCS score (mean ± SD)                                          | 5.6 ± 2.8             | 6.7 ± 3.0         | < 0.005 |
| MAP (mmHg, mean ± SD)                                                  | 105.0 ± 40.9          | 111 ± 27.9        | 0.140   |
| Respiratory rate (breaths/min, mean ± SD)                              | 16.4 ± 8.7            | 20.8 ± 6.7        | < 0.001 |
| Body temperature (°C, mean ± SD)                                       | 37.3 ± 4.4            | 38.3 ± 1.2        | 0.004   |
| Heart rate (beats/min, mean ± SD)                                      | 95.7 ± 24.9           | 98.1 ± 23.2       | 0.432   |
| Leukocyte count (x10⁹/l, mean ± SD)                                    | 14.1 ± 0.7            | 14.1 ± 0.5        | 0.932   |
| Blood glucose (mmol/l, mean ± SD)                                     | 8.9 ± 3.9             | 9.9 ± 8.1         | 0.977   |
| Blood lactic acid (mmol/l, mean ± SD)                                  | 3.6 ± 2.7             | 3.2 ± 2.0         | 0.152   |
| C-reactive protein (mg/L, range)                                       | 97(63-169.3)          | 83.4(34.6-110.2)  | 0.073   |
| Initial SOFA score (mean ± SD)                                         | 5.0 ± 2.1             | 4.3 ± 1.7         | 0.005   |
| qSOFA score (mean ± SD)                                                | 1.4 ± 0.6             | 1.4 ± 0.6         | 0.940   |
| Severe inflammatory storm (mean ± SD)                                  | 2.7 ± 1.1             | 2.6 ± 1.0         | 0.028   |
| ALI/ARDS (intubated), n (%)                                            | 80(88.9)              | 151(78.6)         | 0.040   |
| MODS (mean ± SD)                                                       | 3.4 ± 1.0             | 2.3 ± 1.1         | 0.000   |
| Central herniation, n (%)                                              | 65(72.2)              | 113(58.9)         | 0.032   |
| Uncal herniation, n (%)                                                | 17(18.9)              | 52(27.1)          | 0.181   |
| Unused antibiotic in initial 3 hours, n (%)                             | 89(98.9)              | 175(91.1)         | 0.016   |

Abbreviation: ICU, intensive care unit; SOFA, sequential [sepsis-related] organ failure assessment; qSOFA, quick sequential organ failure assessment; GCS, Glasgow Coma Scale; MAP, mean arterial blood pressure; ALI: acute lung injury; ARDS: adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.
Table 4
Cox regression analysis in acute critically ill patients with SAE and without SAE initial 48 hrs in ICU (n = 282).

| Variable                              | OR    | 95% CI for OR | p value |
|---------------------------------------|-------|---------------|---------|
| Lower GCS score                       | 2.675 | 1.526–3.557   | 0.000   |
| Severe inflammatory storm             | 0.703 | 0.577–0.939   | 0.008   |
| MODS                                  | 0.371 | 0.257–0.959   | 0.000   |
| Unused antibiotic within initial 3 h  | 0.393 | 0.223–0.887   | 0.021   |

Abbreviations: ICU, intensive care unit.; GCS, Glasgow Coma Scale; MODS, multiple organ dysfunction syndrome.

Kaplan-Meier survival curves showed that early risk of bad survival in SAE at the initial 48 hours was significantly associated with infection patients who unused antibiotics treatment within the first 3 hours when compared with those used antibiotic treatment within first 3 hours (Log Rank, 6.7; p = 0.010). (Fig. 3)

By Kaplan-Meier survival curves analysis, the early risk of bad outcome in SAE at the initial 14 days was also significantly associated with infection patients who unused antibiotic treatment within first 3 hours when compared with those used antibiotic treatment within first 3 hours (Log Rank, 15.0; p = 0.000).

Discussion

In this study, we found that the prevalence rate of SAE within initial 48 hours accounted for 93.4 % of sepsis, and the main feature of SAE patients were presented with MODS (96.8%) driven by severe inflammatory storm. Previous studies shown that the prevalence of SAE was 53.0% to 87.0% of sepsis [9,10], and with 63% to 70% of hospital mortality [6,11]. However, our this study is clear: high prevalent SAE is almost near the epidemic rate of sepsis, which indicated the SAE was a leading life-threatening acute organ dysfunction and with 32.0% of fatality at initial 48 hours and 69.1% of fatality at initial 14 days.

Importantly, our study confirmed that the early risk factors for SAE were associated with a severe inflammatory storm, early elevated SOFA score, lower GCS, MODS, and unused antibiotic within initial 3 hours in ICU. We found that severe inflammatory storm is a independent risk factor for SAE. Moreover, above several risk factors had been recognized by previous studies [12-14]. However, by Cox regression analysis, the above factors were related to bad survival in critically ill patients with SAE in addition to the early elevated SOFA score.

Several possible interpretations for the SAE becoming an early with bad survival organ dysfunction are as following. The first, the brain itself is a leading organ of host response to infection, which is believed to be the blood-brain barrier (BBB) leakage due to an overwhelming in the pro-inflammatory cytokines and anti-
inflammation factors released and resulted in severe inflammatory storm [15]. The severe inflammatory storm is further responsible for these inflammation factors/toxins leak into the brain, and leading to the brain edema and cerebral ischemic injure as well as cell death [15-19]. The second, our data shown that 78.0%-81.0 of SAE had acute pneumonia/ALI/ARDS within initial 2 days. Moreover, the acute pneumonia/ALI play pivotal roles in the development of severe inflammatory storm in sepsis [10,21]. Like the current outbreak COVID-19 pneumonia, the mechanisms of bacterial pneumonia is also related to the angiotensin conversion enzyme 2 (ACE2) involved inflammatory response, leading to BBB leakage and inflammatory storm [20,22]. The third, a life-threatening brain failure is almost involved to MODS, and MODS (especially the brain) is the most vulnerable to hypoxia/ ischemia and oxidative stress caused by severe inflammatory storm[19,21]. The previous studies indicated that sepsis with MODS was more likely to exhibit a SAE [9,21,23,24].

By regression analysis, unused antibiotics treatment within initial 3 hours was estimated as an early risk factor of high morbidity and mortality for SAE. Moreover, Kaplan-Meier survival curves analysis at initial 48 hours and at initial 14 days also indicated a risk of over 6 foldon-15foldon death for SAE due to unused antibiotics treatment within initial 3 hours.

Although there is consensus which states that rapid antibiotics treatment for sepsis is need [25], the time in rapid antibiotics treatment for sepsis is within initial 3 hours after infection onset [26]. In the present study, we found that the median time from infection to sepsis was 9.0 hours, while the median time of early infection events in patients with sepsis were in 1.0 hour after critically ill onset. Moreover, our most sepsis patients within initial 1-3 hours after critically ill were rarely used a rapid antibiotic treatment, leading to an high morbidity and high risk of death in sepsis. Thus, we believe that within initial 1 hour after infection onset as the “golden hour” of rapid antibiotics treatment is optimal for survival sepsis, rather than waited recognition sepsis because this “golden hour” of early prevent and control would be delayed several hours and more.

The main strengths of our this study that early identification of SAE driven by inflammatory storm from community-acquired infection (pneumonia) and for its an early rapid antibiotic treatment within initial 1.0 hour in ICU is established the importance of the topic as a problem to prevent and control the early infection and to reduce the morbidity and mortality of SAE.

Some limitations of our study have to be addressed. Despite we use a strict diagnostic criteria for SAE, it is not possible to fully meet these criteria due to retrospective analysis. First, about 7% of septic patients in our series did not be meet the diagnosis of SAE. However, one of them has performed EEG examination and be conformed the diagnosis of brain dysfunction. Moreover, a diffuse abnormal EEG in septic patient with normal GCS has also been reported [27]. Therefore, those sepsis patients without by EEG examination may be missed the diagnosis of SAE. Second, some SAE patients with severe persistent inflammatory storms may have undetermined infection sites other than in lungs. In fact, It is not uncommon to have two sites infection in SAE patients who were with uncontrollable inflammatory storm or undergone an emergency craniotomy and extenal drainage. Moreover, we rarely do further examination
for the cytokines in blood or in CSF. Thus, some laboratorial data of inflammatory storm was absented, and a diagnosis of secondary CNS infection may be missed and lost the opportunity for intensive treatment. Third, we focused our analysis in sepsis patients within initial 48 hours in ICU, but some deceased cases (or abandoning treatment) missed the data of microbiologic proof due to less 48 hours during ICU stay, which may be a cause of the positive microbiologic culture underestimated; and for the same reason, we did not collected the data of delayed brain injure because an opportunity of repeat CT scan has been lost. In addition, although the prognosis for sepsis was related to the early use of antibiotics, we did not velify its link to organ failure. Therefore, further prospective studies are needed for its some of the links.

Conclusions

SAE in ICU is an high prevalent and early life-threatening brain dysfunction. Severe inflammatory storm, Lower GCS score, MODS, and unused antibiotic treatment within initial 3 hours in ICU was related to bad outcome for SAE. It may be reduced the morbidity and mortality of SAE to use a rapid antibiotics treatment in “golden hour” after the recognition of infection event.

Abbreviations

ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment; SOFA, sequential [sepsis-related] organ failure assessment; GCS, Glasgow Coma Scale; ALI: acute lung injure; ARDS: adult respiratory distress syndrome; MODS, multiple organ dysfuunction syndrome. MAP, mean arterial blood pressure;

Declarations

Contributions

TDM conceptualised and designed the study, did the initial analyses, drafted the initial Article, and reviewed and revised the Article. TDM and WSD conceptualised and designed the study, drafted the initial Article, and reviewed and revised the Article. All authors approved the final Article as submitted and agree to be accountable for all aspects of the work.

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NA

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics declarations**

Ethics approval and consent to participate

This study was approved by the institutional review boards of affiliated Shuyang Hospital of Xuzhou Medical University (No.2015006). Written informed consent was obtained from patient's family on admission.

**Disclosures of interest**

All authors declare that no conflicts of interest exist.

**Consent for publication**

NA

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**References**

1. Park DW, Chun BC, Kim JM, Sohn JW, Peck KR, Kim YS, et al. Epidemiological and Clinical Characteristics of Community- Acquired Severe Sepsis and Septic Shock: A Prospective Observational Study in 12 University Hospitals in Korea. J Korean Med Sci. 2012;27:1308–14.

2. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated cost of care. Crit Care Med. 2001;29(7):1303 – 1310.

3. Konrad Reinhart, Daniels N, Kissoon, et al. Recognizing sepsis as a global health priority—A WHO resolution. N Engl. J Med. 2017;377:414–7.

4. Coopersmith CM, De Backer D, Deutschman CS, et al. Surviving sepsis campaign: research priorities for sepsis and septic shock. Intensive Care Med. 2018;44:1400–26.

5. SingerM, DuetschmenCS, SeymourCW, et al. The Third. International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10.
6. Gofton TE, Young GB. Sepsis-associated encephalopathy. Nat Rev Neurol. 2012, 8:557–66. 10.1038/nrneurol.2012.183.

7. Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. Crit Care Med. 1996;24:163–72.

8. 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 medicine. 1996;22(7):707–10.

9. Sonnevile R, de Montmollin E, Poujade J, Garrouste-Orgeas M, Souweine B, Darmon M, et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med. 2017;43:1075–84.

10. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, et al. Sepsis: Multiple abnormalities, heterogeneous responses, and evolving understanding. Physiol Rev. 2013;93:1247–88.

11. Leonid A, Eidelman D, Puttermann C, Puttermann CL, Sprung. The spectrum of septic encephalopathy definitions, etiologies, and mortalities. JAMA. 1996;275:470–3.

12. Donnelly JP, Safford MM, Shapiro NI, Baddley JW, Wang HE. Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classification: A retrospective population-based cohort study. Lancet Infect Dis. 2017;17:661–70.

13. Kaukonen KM, Bailey M, Pilcher DC, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372:1629–38.

14. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992; 101:1644-55.

15. Shulyatnikova T, Verkhratsky A. Astroglia in sepsis associated encephalopathy. Neurochem Res. 2019 Feb 18.

16. Garofalo AM, Lorente-Ros M, Goncalvez G, et al. Histopathological changes of organ dysfunction in sepsis. Intensive Care Med Exp. 2019;25(Suppl 1):45. 7.

17. Sharshar T, Carlier R, Bernard F, et al. Brain lesions in septic shock: a magnetic resonance imaging study. Intensive Care Med. 2007;33:798–806.

18. Dal-Pizzol F, Tomasi CD, Ritter C. Septic encephalopathy: does inflammation drive the brain crazy? 2014, Rev Bras Psiquiatr 36:251–258.

19. Molnar L, Fulest B, Nemeth N, et al. Sepsis-Associated Encephalopathy: A review of literature. Neurol Indian. 2018;66:352–61.

20. Gaddam RR, Chambers S, Bhatia MACE. and ACE2 in Inflammation: A Tale of Two Enzymes. Inflamm Allergy Drug Targets. 2014;13(4):224–34.

21. Bral AL, Cerra FB. Multiple organ failure syndrome in 1990, systemic inflammatory response and organ dysfunction. JAMA. 1994;27:226–33.
22. Sodhi CP, Nguyen J, Yamaguchi Y, et al. A Dynamic Variation of Pulmonary ACE2 Is Required to Modulate Neutrophilic Inflammation in Response to Pseudomonas aeruginosa Lung Infection in Mice. J Immunol. 2019;203(11):3000–3012.

23. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy definitions, etiologies, and mortalities. JAMA. 1996;275:470–3.

24. Mihaylova S, Killian A. Mayer K at el. Effects of antiinflammatory vagus nerve stimulation on the cerebral microcirculation in endotoxinemic rats. J Neuroinflammation. 2012;9:183.

25. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock, 2016. Crit Care Med. 2017;45:486–552.

26. Seymour CW, Gesten F, Prescott HC, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376:2235–44.

27. Ma YJ, Ouyang B, Guan XD. Use of quantitative electroencephalogram in patients with septic shock. Natl Med J China. 2016;96:195–8.

**Figures**

![Diagram of SAE (sepsis-associated encephalopathy)]
The pathophysiology of SAE. Lungs (pneumonia) /abdominal infection cause an inflammatory storm and BBB leakage, leading to a life-threatening SAE and MODS.

Figure 2
EEG showing a generalized theta waveforms from a 81-year-old male with septic shock with a GCS scores=15. The images of patient showed bilateral acute pneumonia (A), a gallstone and cholecystitis (B), ischemic lesions on brain CT (C), and increased energy of theta band in both hemispheres on brain topographic map (D), His blood culture was positive for klebsiella and he had to be diagnosed as SAE.
Kaplan-Meier survival curves showed that early bad survival events in the initial 48 hours for SAE was significantly related to early infection patients with or without antibiotic treatment within the first 3 hours (Log Rank, 6.7; p=0.010).

**Supplementary Files**

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- 0.1.0.SAEsupplement.doc