

# Epidemiological and clinical characteristics of sepsis-associated encephalopathy in the ICU: a retrospective observational study

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## Research article

**Keywords:** sepsis, sepsis-associated encephalopathy, incidence, mortality, epidemiology

**Posted Date:** September 16th, 2019

**DOI:** <https://doi.org/10.21203/rs.2.14475/v1>

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# Abstract

Background Sepsis has an annual incidence of 30 million new cases around worldwide. However, the epidemiological and clinical characteristics in patients with sepsis-associated encephalopathy (SAE) remain understudy. Methods We prospectively enrolled patients with acute critically ill from ICU during 2 years period (2014-2015). The epidemiological and clinical characteristics for critically ill adults with SAE in ICU were analyzed by related statistics. Results Of the 1349 ICU patients with acute critically ill, 748 were enrolled. Among these, the prevalence of sepsis was 48.4% (362/748), with fatality at initial 30 days was 62.4%. The prevalence of SAE accounted for 97.2% of sepsis (352/362), with fatality at initial 30 days was 65.1%. We found that the two strong clinical predictors for SAE were systemic inflammatory response syndrome (SIRS)  $\geq 2$  (OR, 3.2; 95% CI, 0.304- 0.673) and sequential (sepsis-related) organ function assessment (SOFA) score  $\geq 6$  (GCS $<13$ )(OR, 3.0; 95% CI, 0.304-0.673); the sensitivity was 67.3% and specificity was 55.3% for SIRS $\geq 2$ , while the sensitivity was 99.1% and specificity was 99.0% for SOFA score $\geq 6$ . Cox logistic adjusted analysis revealed that lower mean arterial pressure (OR, 1.504; 95% CI, 1.001-1.707), higher SOFA score (OR, 1.783; 95% CI, 1.145- 1.923), and no using antibiotics treatment in initial 3 hours (OR, 0.683; 95% CI, 0.492-0.947) were the powerful predictors of the risk of death among ICU patients with SAE. Conclusion SAE is a best frequent epidemiological type of sepsis in ICU, with an high hospital fatality. No using antibiotics treatment within initial 3 hours was related to the worse survival SAE.

## Introduction

Back in 1990, the term “sepsis-associated encephalopathy (SAE)” has been introduced by Yonger et al [1], and with the fatality rate of 70%[2]. While sepsis as an most common complication in critically ill adults has been become the leading cause of morbidity and mortality in ICUs worldwide [3-5]. resulting in an economic burden in intensive care [5]. The current estimates of 30 million new cases of sepsis and more than 6 million deaths per year around the worldwide come from a systematic review [6]. A new sepsis-3 is defined sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection [7]. The Brain is an organ that is the easiest to be insulted by sepsis if infection was uncompleted at initial. As a result, SAE may be a high epidemic and high death disease similar to sepsis, which almost kills a critically ill patient every five seconds worldwide. However, whether the epidemiological of sepsis would be represented the epidemiological trend of SAE, which is still unknown. Our hypothesis was that SAE as a commonest organ failure of sepsis would present with a high epidemic and high death risk following critically ill adults in ICU. The aim of this study was to investigate the epidemiological and clinical characteristics of SAE following critically ill adults in a general ICU.

## Materials And Methods

### Study design and settings

This is a retrospective observational study to investigate the epidemiology and clinical characteristics of critically ill adult patients with sepsis/SAE during 2 years period (2014-2015) in a general ICU in affiliated Shuyang Hospital of Xuzhou Medical University in China. The study was approved by the local ethical committee on clinical research of the hospital. Because of the retrospective nature of this study, the need for informed consent was waived.

In this study population, the subjects included acute critically ill adult patients within 3 hours from onset to the ICU, while patients with sepsis were identified by the definition of sepsis-3 (infection plus one or more life-threatening organ dysfunction) [7], and the SAE was identified by following conditions: (1) present evidence of sepsis; (2) a primary SAE has to present a score on the GCS of <15 with sepsis but not evidence of other acute brain injury; and (3) a secondary SAE has to present a score on the GCS of <15 with sepsis following an acute primary brain injury. Moreover, patients with a score on the GCS of 15 and with infection plus extracranial organ failure were considered to have sepsis but not SAE.

Patients who were more than 3 hours from onset to the ICU were excluded. We also excluded the possible critically ill patients who did not have data in their medical records due to either death/morbidity or transport out of the ICU (due to giving up treatment) within initial 3-6 hours. We excluded those patients who were with a stay in ICU because of post-surgery/intervention and who were presented with evidence of direct meningitis/encephalitis and non-infection encephalopathy or effects of sedatives.

## **Definitions**

Previously, SAE is defined as a diffuse, possible also multifocal, disturbance of cerebral function as a consequence of the systemic inflammatory response syndrome (SIRS) triggered by the contact of the host with potent pathogenic microbes other than absence of direct CNS infection [1]. The severity of SAE can range from mild delirium to deep coma [2]. Based on the new definition of sepsis-3, the definition of SAE in the ICU has to be updated: SAE is defined as the sepsis associated a life-threatening diffuse cerebral dysfunction (ranging from delirium to coma) caused by dysregulated host response to infection/SIRS, and without evidence of direct meningitis/encephalitis or other non-infective encephalopathy.

Infection is defined as a phenomenon of systemic inflammatory reaction (or focal tissue injury) caused by the microorganisms invading, settle down, or migrate to one or more elsewhere in the host. According to the standard definitions of the Centers for Disease Control and Prevention [8], infection is classified into community-acquired and nosocomial-acquired infection.

## **Identification of infection and organ failure events**

Because SIRS is a dysregulated host response to infection, we identified infection events using a SIRS criteria  $\geq 2$  from initial test value at the ICU. Moreover, the SIRS criteria have been used to screen infection events by previous studies ( $\geq 2$  criteria for positive) [7,9,10]. The SIRS criteria as following: (1) temperature greater than 38°C or less than 36°C; (2) heart rate greater than 90 beats per minute; (3)

tachypnea >20 respirations per minute or Pco<sub>2</sub> <32mmHg; (4) white blood cell count greater than 12.0×10<sup>9</sup>/L or less than 4.0×10<sup>9</sup>/L, or more than 10% band forms.

The sites of infection were estimated by clinician seen in checking, CT scan found, surgical explored, intervene operation given, and specimen culture from special site in the body. The sources of infection were defined by surgical confirmed an abscesses exist or by positive body fluid culture (including blood, peritoneal or pleural fluid, cerebrospinal fluid, sputum fluid, and urine fluid).

The SOFA scores were calculated for one or more organ dysfunction after critically ill event, which was measured within 24 hours, 48 hours, and 72 hours or more later on the ICU admission. The acute organ dysfunction was defined as equivalent to a SOFA score  $\geq 2$  for a particular organ (on a scale from 0 to 4, with higher scores indicating multi-organ failure)[11].

The SOFA criteria used to assess acute brain failure as follow: the GCS score=10-12 scores (SOFA=2) were only a mild brain failure, and GCS <6 scores (SOFA=4) were identified to be a severe brain failure. The SOFA criteria for other organ failure were modified from previous criteria [11]: cardiovascular dysfunction/ septic shock (systolic blood pressure  $\leq 90$  mmHg or mean arterial pressure  $\leq 70$  mmHg, or requiring vasopressors to maintain systolic blood pressure > 90 mmHg or mean arterial pressure >70 mmHg), respiratory dysfunction (ratio of partial arterial oxygen tension to inspired fractional oxygen  $\leq 300$ , or labored breathing requiring intubated/tracheotomy for mechanical ventilation to maintain respiratory), hepatic dysfunction (bilirubin >33  $\mu\text{mol/L}$ , without evidence of viral hepatitis), renal dysfunction (serum creatinine  $\geq 171$   $\mu\text{mol/L}$  rather than chronic kidney failure), hematologic dysfunction (blood platelet <100  $\times 10^9/\text{L}$ , or INR (International Normalized Ratio) >1.5 in the absence of systemic anticoagulant agents), metabolic dysfunction (arterial pH  $\leq 7.30$ , serum glucose >10mmol/l, serum sodium >155 mmol/l or <125mmol/l in the absence of non-infective disease).

### **Data collected and group assignments**

Collected clinical profile for this study in ICU included the patient demographics, time from critically ill event to infection, cranial CT scans findings, initial GCS score ( or GCS motor score if the patients intubated ), vital sign data, laboratory data ( or critical value), SOFA score, using of antibiotics in initial 3 hours, mechanical ventilation, traditional treatment, length of stay(LOD) in ICU, and outcomes.

The main outcome measure was mortality at the first 30 days. Death from critically ill event with sepsis included fatal cardiac respiratory arrest, fatal brain failure, fatal septic shock, fatal respiratory failure, fatal multiple organ dysfunction syndrome (MODS), and unexpected death. The outcome events were reviewed by two of the investigators (the first and second authors). To investigate the outcomes of patients at the 30 days on hospital stay, survival results were initially determined from the hospital records. If the length of hospitalization was less than 30 days and patient died after discharge, followed-up information was obtained from the patient's closest living relative.

Based on the criteria for SAE after critically ill event, the study data was divided into critically ill event with SAE group and critically ill event without SAE group for statistic analysis.

## Statistical methods

The results in each group were expressed as mean $\pm$  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 risk ratios (OR) and 95% confidence intervals (CIs) were estimated using a logistic-regression model. If variables were significant in the multivariate analysis, its diagnostic values were confirmed by the receiver operating characteristic (ROC) curves analysis. 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

A total of 1349 acute critically ill patients over 18 years old were admitted during this period. We excluded the acute critically ill patients from onset to ICU over 3 hours (N=49), the patients without medical data due to death/morbidity (N=248) and transport out of the ICU due to abandoning treatment (N=87) within initial 3-6 hours, the patients with a stay in ICU because of post-surgery/intervention (N=214), and with direct meningitis/ encephalitis (N=3). Finally, 748 acute critically ill patients were included in our study.

Characteristics of the observational study for acute critically ill in ICU patients with SAE are described in Table 1. Most of the patients (473/748) were males, with mean age of 59.9 years (range, 18-91 years). Among 447 (59.8%) infection events, the median time from onset to infection was 1 hour (range, 0.5-24) and the median time from infection to sepsis was 9.2 hours (range, 1-168). The prevalence of sepsis was 48.4% (362/748), with fatality at initial 30 days was 62.4% (226/362). The prevalence of SAE was 47.1% (352/748), with fatality at initial 30 days was 65.1% (229/352). Epidemiological trend of SAE was similar to sepsis, with a peak in the initial first days on ICU and following weeks decreased over time (Figure 1).

An 79.0% of prevalence was observed in SAE from community- acquired infection during the initial 48 hours, while rest 21% of SAE was from nosocomial-acquired infection. Our data found that the SAE was the best frequent life-threatening organ dysfunction. While the most common comorbidity of SAE caused by extracranial organ failure was acute lung failure (243/352), followed by septic shock (124/352), acute liver failure (99/352), and acute renal failure (58/352). The MODS accounted for 97.4% (343/352) of SAE.

The clinical characteristics of acute critically ill patients with and without SAE are described in Table 2.

We found that there was significantly difference in age, MAP, body temperature, heart rate, respiratory rate, leukocyte count, qSOFA score, SIRS  $\geq 2$  criteria, lactic acid, LOS in ICU, and SOFA scores between the two groups. During 30 days follow-up, the mortality rate was also higher (65.1% vs. 45.9%, $p=0.005$ ) among acute critically ill patients with SAE than those without SAE.

However, by logistic regression analysis, only SIRS  $\geq 2$  (OR, 3.2; 95% CI, 0.304-0.673) and SOFA score  $\geq 6$  (OR, 3.0; 95% CI, 0.304- 0.673) were established as strong predicting factors for acute critically ill patients with SAE (Table 3).

The ROC curves analysis for SIRS $\geq 2$  and higher SOFA score in patients with SAE showed that the area under the ROC curve (AUC) was 0.560 ( $p<0.005$ ) and 0.602 ( $p<0.001$ ), respectively (Table 4). It was shown by ROC curves analysis that the sensitivity was 67.3% and specificity was 55.3% for SIRS, while the sensitivity was 99.1% and specificity was 99.0% for SOFA score (Figure 2),

When the significant factors were entered into a Cox regression model, this model has shown that independent factors that affected mortality in acute critically ill patient with SAE were only lower MAP (OR, 1.504; 95% CI, 1.001-1.707,  $p=0.004$ ) higher SOFA score (OR, 1.783; 95% CI, 1.145-1.923,  $p<0.001$ ), and without using antibiotics treatment in initial 3 hours (OR, 0.683; 95% CI, 0.492-0.947,  $p=0.022$ ) (Table 5).

Kaplan-Meier survival curves shown that acute critically ill patients with SAE at the first 30 days may not have better outcomes compared to those without SAE. The ORs for worse survival was significantly associated with acute critically ill patients with SAE at the first 30 days (Log Rank, 4.5;  $p=0.033$ ). (Figure 3)

Kaplan-Meier survival curves shown that acute critically ill patients who did not undergo antibiotic treatment within the first 3 hours may not have better outcomes compared to those who undergo antibiotic treatment within the first 3 hours. The ORs for worse survival was significantly associated with acute critically ill patients who did not undergo antibiotic treatment within the first 3 hours (Log Rank, 25.3;  $p<0.001$ ). (Figure 4)

## Discussion

This larger data observational study has mainly investigated the epidemiological and clinical characteristics of patients with SAE in a general ICU, although several studies have been reported on the epidemiological and prognostic features for SAE in ICU [1,12,13]. Our current study shown that the prevalence of SAE was similar to the epidemiological trend of sepsis, i.e., a peak of the prevalence of SAE was in the onset first day and following few weeks decreased over time. While the SAE patients in the peak of the prevalence were fully from community-acquired infection. The mortality was higher in patients with SAE than those without SAE at the 30 days followed-up, suggesting that the prevalence of SAE has represented the epidemiological characteristics of sepsis which almost Kills a critically ill patient every five seconds in the worldwide. However, critically ill patient with SAE remains a challenging

diagnosis because of not be recognized biomarkers for identify SAE. Recently, a WHO resolution for recognizing sepsis indicated that the progression from infection to sepsis may be insidious and is unpredictable[14]. But, our study is clear: the median time of sepsis onset is at 9 hours after early community-acquired infection events.

Importantly, our data shown that only SIRS  $\geq 2$  and higher SOFA scores were established as the powerful clinical predictors for acute critically ill patients with sepsis/SAE in ICU, this was similar to previous studies [2,10,11,15]. Moreover, we found that the only two strong clinical predictors for recognizing SAE were SIRS  $\geq 2$  and SOFA scores  $\geq 6$ , which was demonstrated by the ROC curves analysis. Thus, we believe that the SIRS  $\geq 2$  and higher SOFA scores could be considered as a clinical diagnostic criteria for SAE.

More importantly, Cox regression analysis shown that the predictors for worse survival in critically ill patients with SAE were related to the lower MAP, higher SOFA scores, and no using antibiotics treatment in initial 3 hours in ICU. Although the effect of the lower MAP and higher SOFA scores have been recognized [9,12,13], especially higher SOFA scores for sepsis/SAE indicated MODS exist[11-13], which was more likely to have a worse outcome or death [10,12,13,16]. However, this study shown that no using antibiotics treatment in initial 3 hours had more higher risk on death. Although there is report which states that rapid antibiotics treatment of sepsis is need, the optimal time in rapid antibiotics treatment for sepsis do not coincide in opinion[17,18]. In the present study, we found that the early infection events in critically ill patients with SAE mainly were within initial 0.5-1 hour after onset. Indeed, our patients within the first 3 hours following critically ill patients with SAE were rarely treated with antibiotics, which result in an high risk of death for SAE. Therefore, these findings indicate that a rapid antibiotics treatment for sepsis should be performed immediately within 0.5-1 h after infection onset rather than to wait recognition sepsis/SAE. More specifically, when the infection has been acquired in the community, using antibiotics has to be started immediately within initial 0.5-1 hour in the ICU or in the pre-hospital first aid.

Although our data is from a prospective registration and the data analysis is available, some limitations have to be considered because of retrospective analysis. First, the definition of SAE in current study may not meet Yonger et al. previously criteria for SAE because most of patients with SAE was in comatose patients in a general ICU, and the criteria for diagnostic SAE is from sepsis-3 identified SOFA criteria. Second, 97% of sepsis patients within initial 2 days had a SAE (including primary and secondary), which may be potentially overestimated. However, the previous studies indicated that sepsis patients with multi-organ failure were more likely to exhibit a SAE [13 16,19,20]. Moreover, the present study shown that the multi-organ dysfunction accounted for 97.4% of sepsis patients. Thus, the early risk of SAE among sepsis patients might not be overestimated. In addition, the patients with SAE were usually associated with a vasogenic brain edema or subcortical white matter ischemic lesions on imaging [21,22]. Although all of patients were performed brain CT scans, CT is more likely to be less sensitive than MRI for assessment of patients with septic brain lesions. However, MRI was less performed due to the limitation of objective reasons in the present study. Therefore, further prospective brain MR studies are needed.

# Conclusion

We found that 97% of patients with sepsis in ICU had a SAE, and with an high hospital mortality at initial 30 days. The two powerful clinical predictors for SAE were SIRS criteria  $\geq 2$  and SOFA score  $\geq 6$ . The predictors for worse survival in patients with SAE were related to the lower MAP, higher SOFA scores, and no using antibiotics treatment in initial 3 hours. The optimal time of using antibiotics IV for surviving SAE should be started immediately within initial 0.5-1 hour in the ICU or in the pre-hospital first aid.

# Abbreviations

**ICU**: intensive care unit;

**SAE**, sepsis associated encephalopathy;

**SIRS**, systemic inflammatory response syndrome;

**GCS**, Glasgow Coma Scale;

**SOFA**, Sequential [sepsis- related] Organ Function Assessment;

**qSOFA**, qick Sequential [sepsis-related] Organ Function Assessment;

**AUC**, the area under the receiver operating characteristic curve.

**MAP**, mean arterial pressure;

**LOS**, length of stay.

# Declarations

## *Acknowledgment*

We would like to thank everyone who contributed to the study, namely the staff of the ICU who facilitated the access to patient records and the nurses and physicians for reviewing medical records.

## *Funding*

From Clinical Key Specialty Construction Project (20160019), the Medical Research Council, affiliated Shuyang Hospital of Xuzhou Medical University, Jiangsu, China.

***Availability of data and materials.*** Please contact author for data requests

## *Competing interests*

All authors declare that no conflicts of interest exist.

### ***Authors' contributions***

Conceived and designed the experiments: TDM and ZYT.

Performed the experiments: TDM, ZYT.

Analyzed the data: TDM, ZYT and WSD.

Contributed reagents/materials/analysis tools: DMT ZYT, WSD, WGS, WYW, and WY.

Wrote the paper: TDM.

Agree with manuscript results and conclusions: TDM, ZYT, WSD, WGS, WYW, and WY.

### ***Ethics approval and consent to participate***

The study was approved by the ethical committee on clinical research of the Affiliated Shuyang Hospital of Xuzhou Medical University. Because of the retrospective nature of this study, the need for informed consent was waived.

### ***Consent for publication***

Not applicable.

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## Tables

Table 1 Epidemiological characteristics of SAE in 748 ICU admissions

Characteristics	Value
Male gender n, (%)	473(63.2)
Age (years, mean±SD)	59.9±15.7
Primary critically ill confirmed by CT in ICU	
Acute stroke, n, (%)	263(35.1)
Traumatic brain injury, n, (%)	207(27.7)
Other, n, (%)	278(37.2)
Median time from onset to ICU(h, range)	1(0.5-3.0)
Median time from onset to infection (h, range)	1(0.5-24)
Median time from infection to sepsis(h, range)	9.2(1-168)
Frequency of infection/n/SIRS ≥2,n (%)	447(59.8)
Community-acquired infection	348(46.5)
Nosocomial-acquired infection	99(13.2)
Site of infection	
Respiratory, n. (%)	287(38.4)
Wound/soft tissue, n. (%)	113(15.1)
Abdominal, n. (%)	28(4.0)
Other/unknown, n. (%)	19(2.5)
Positive body fluid culture,n(%)	367(49.1)
Initial GCS score (median,range)	7(3-15)
Score of 15	24(3.2)
Score of 9-14	95(12.7)
Score of 3-8	629(84.1)
Sepsis, n (%)	362(48.4)
SAE, n (%)	352(47.1)
Number of SAE-related extracranial organ failure	
Lung failure, n (%)	243(32.5)
Septic shock, n (%)	124(16.6)
Hepatic failure , n (%)	99(13.2)
Renal failure , n (%)	58(7.8)
Other , n (%)	11(1.5)

## Number of-organ failure in sepsis

1, n (%)	19(2.5)
2, n (%)	203(27.1)
3, n (%)	93(12.4)
≥ 4 , n (%)	47(6.3)
SAE from community-acquired infection, n. (%)	286(38.2)
SAE from nosocomial-acquired infection, n. (%)	76(10.2)
No using antibiotic within initial 3 h, n (%)	308(41.2)
Mechanical ventilation, n (%)	303(40.5)
Mortality of sepsis at 30 days, n (%)	226(30.2)
<u>Mortality of SAE at 30 days, n (%)</u>	<u>229(30.6)</u>

Abbreviations: ICU, intensive care unit; SAE, sepsis associated encephalopathy; SIRS, systemic inflammatory response syndrome; GCS, Glasgow Coma Scale; SOFA, Sequential [sepsis- related] Organ Function Assessment (scale ranges from 0 to 4, ≥2 indicates organ failure, and higher scores indicate more severe organ failure).

Table 2 Clinical characteristics of patients with SAE and without SAE in ICU (n=748)

variable	with SAE (n=352)	WithoutSAE (n=396)	p Value
Male gender (%)	211(59.9)	242(61.1)	0.224
Age (years, mean±SD)	58.4± 16.0	61.4±15.3	0.011
Median time from onset to ICU(h, range)	1.2(2.5)	1.1(2.8)	0.057
GCS score (mean±SD)	6.8±3.1	7.2±3.0	0.052
MAP (mean±SD)	100.3±31.8	112.0±27.4	0.000
Body temperature(°C, mean±SD)	37.8±3.8	36.7±5.1	0.000
Heart rate(beats/min, mean±SD)	107.2±23.3	85.9±23.1	0.000
Respiratory rate(breaths/min,mean±SD)	21.1±8.6	18.8±5.4	0.000
WBC count (x10 <sup>9</sup> /l, mean±SD)	13.8±5.7	11.9±4.8	0.000
Lactate acid (mmol/L, mean±SD)	3.2±2.3	2.7±2.1	0.001
Serum glucose (mmol/L,mean±SD)	9.5±6.4	8.9±3.5	0.118
qSOFA score (mean±SD)	8.4±1.9	3.7±1.9	0.000
SOFA score(mean±SD)	1.4±0.6	1.1±0.4	0.000
SIRS ≥2,n (%)	237(67.3)	219(55.3)	0.001
Not using antibiotic within initial 3 h, n (%)	284(80.7)	342(86.3)	0.038
On mechanical ventilation,n (%)	257(73.0)	290(73.2)	1.000
LOS in ICU (mean±SD)	6.6±7.0	3.0±3.4	0.000
Mortality at 30 days,n (%)	229(65.1)	184(46.5)	0.000

Abbreviations: ICU, intensive care unit; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; GCS, Glasgow Coma Scale; SOFA, Sequential [sepsis-related] Organ Function Assessment; LOS, length of stay;

Table 3 Logistic regression analysis to identify the early risk factors of SAE patients in ICU (n=748)

Variable	With SAE (n=352)	Without SAE (n=396)	OR (95% CI)	P Value
SIRS $\geq 2$ , n (%)	305(61.1)	142(28.7)	3.2(1.664-6.080)	<0.001
qSOFA score, mean $\pm$ SD	8.4 $\pm$ 1.9	3.7 $\pm$ 1.9	3.0(2.569-3.543)	<0.001
SOFA score, mean $\pm$ SD	1.4 $\pm$ 0.6	1.1 $\pm$ 0.4	0.3(0.164-0.583)	<0.001
Respiratory rate, mean $\pm$ SD	21 $\pm$ 8.6	18.8 $\pm$ 5.4	1.1(1.063-1.146)	<0.001
Lactate, mean $\pm$ SD	3.2 $\pm$ 2.3	2.7 $\pm$ 2.1	0.9(0.779-0.976)	0.017
LOS in ICU, mean $\pm$ SD	6.6 $\pm$ 6.9	3.0 $\pm$ 3.4	1.1(1.061-1.200)	<0.001

Abbreviations: SIRS, systemic inflammatory response syndrome; qSOFA, quick Sequential [sepsis-related] Organ Function Assessment; SOFA, Sequential [sepsis-related] Organ Function Assessment; LOS, length of stay; ICU, intensive care unit.

Table 4 ROC curve analysis for early risk factors of SAE patients in ICU .

Variable	AUC	95%CI	P value
qSOFA score	0.604	0.561-0.642	< 0.001
SIRS $\geq 2$	0.560	0.519-0.601	< 0.005
SOFA score	0.512	0.471-0.554	0.570
Respiratory rate	0.516	0.474-0.558	0.447
Lactate	0.520	0.478-0.561	0.355
LOS in ICU	0.544	0.503-0.585	0.034

Abbreviation: SIRS, systemic inflammatory response syndrome; qSOFA, quick Sequential [sepsis-related] Organ Function Assessment; SOFA, Sequential [sepsis-related] Organ Function Assessment; LOS, length of stay; ICU, intensive care unit; AUC, the area under the receiver operating characteristic curve.

Table 5 Cox regression analysis in acute critically ill patients with SAE and without SAE in ICU (n=748) .

Variable	OR	95% CI for OR	p value
Lower MAP	1.504	1.001-1.707	0.004
Higher SOFA score	1.783	1.145-1.923	0.000
No using antibiotic within initial 3h	0.683	0.492-0.947	0.022

Abbreviations: MAP, mean arterial pressure; SOFA, Sequential [sepsis-related] Organ Function Assessment; ICU, intensive care unit.

## Figures

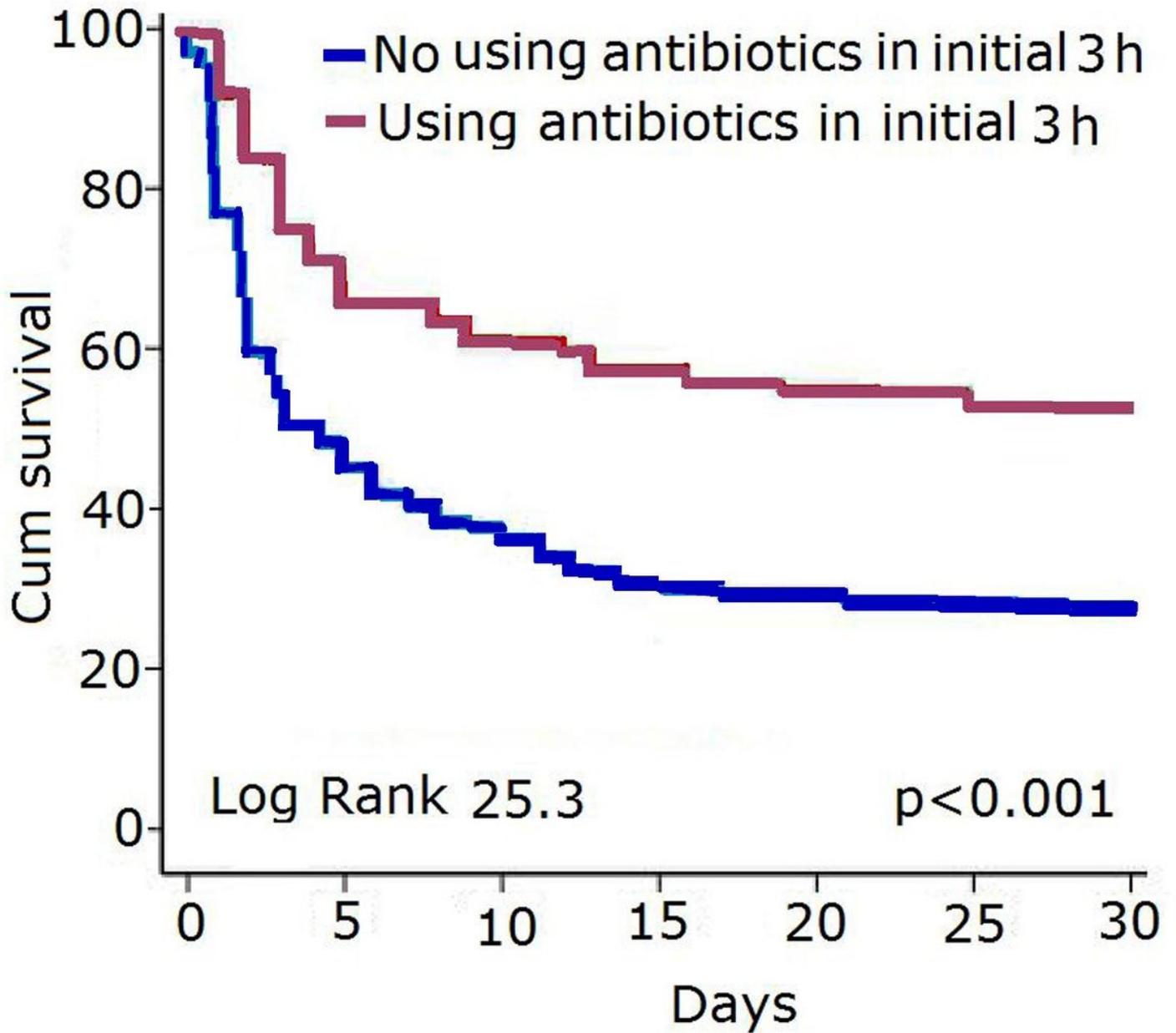


Figure 1

The ROC curves of SIRS and SOFA score for critically ill patients with SAE were significantly associated with clinical diagnostic value ( $p < 0.005$ ).

## ROC Curve

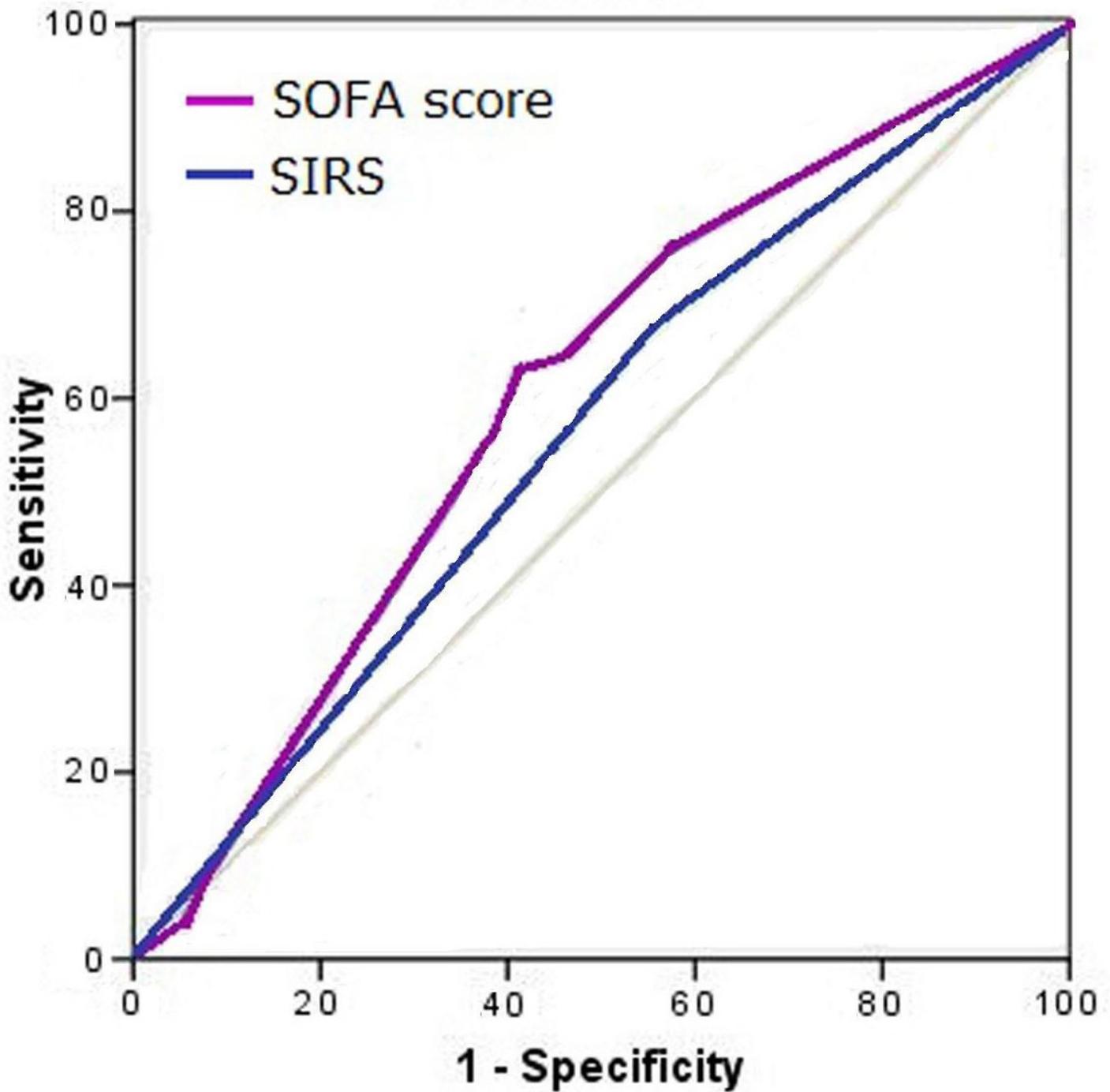


Figure 2

Epidemiological trend of SAE was similar to sepsis, with a peak in the initial first day on ICU and following weeks decreased over time.

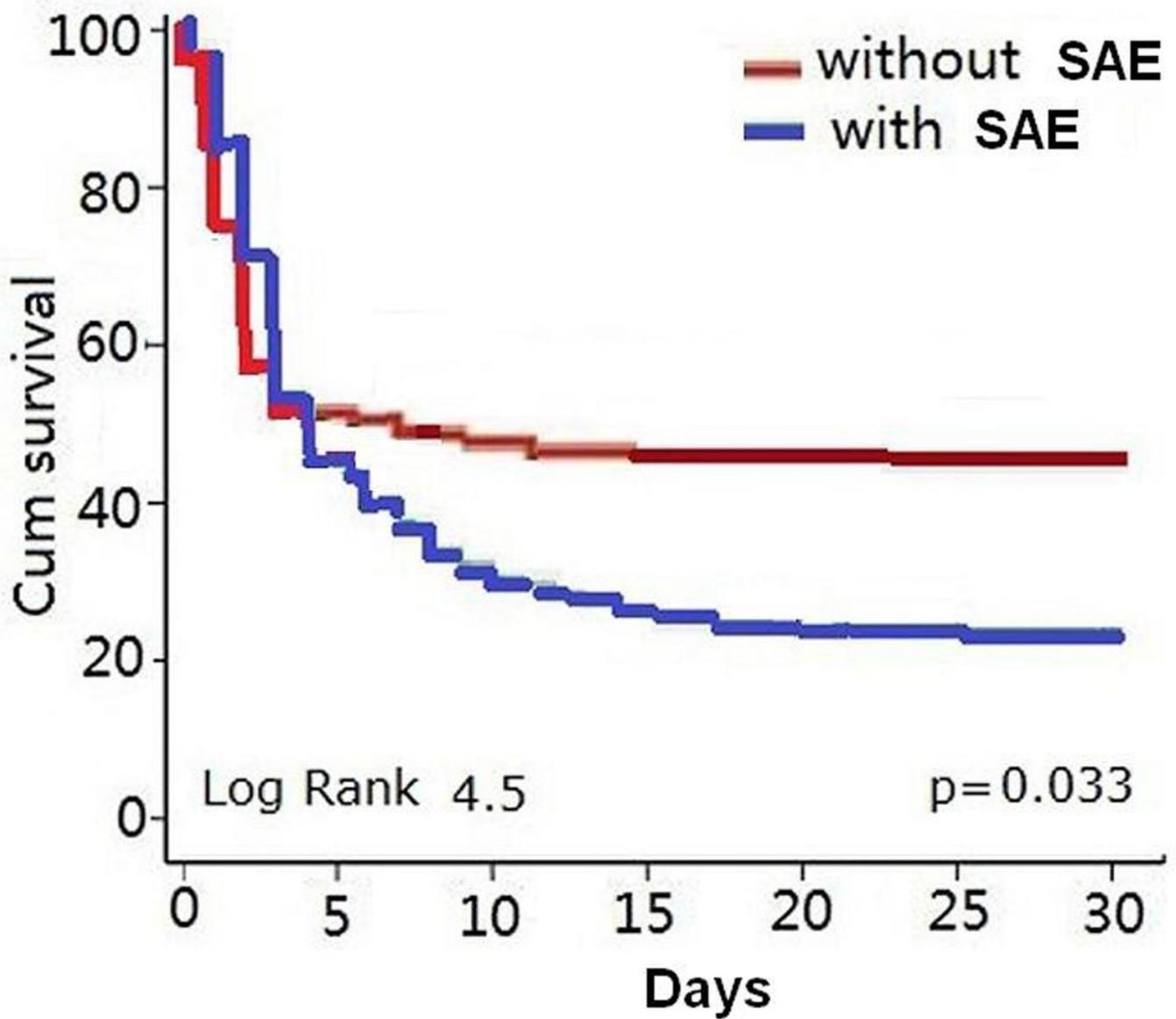


Figure 3

Kaplan-Meier survival curves that included critically ill patients with and without SAE events at the first 30 days, the worse survival was significantly associated with critically ill patients with SAE events (Log Rank, 4.5;  $p=0.033$ ).

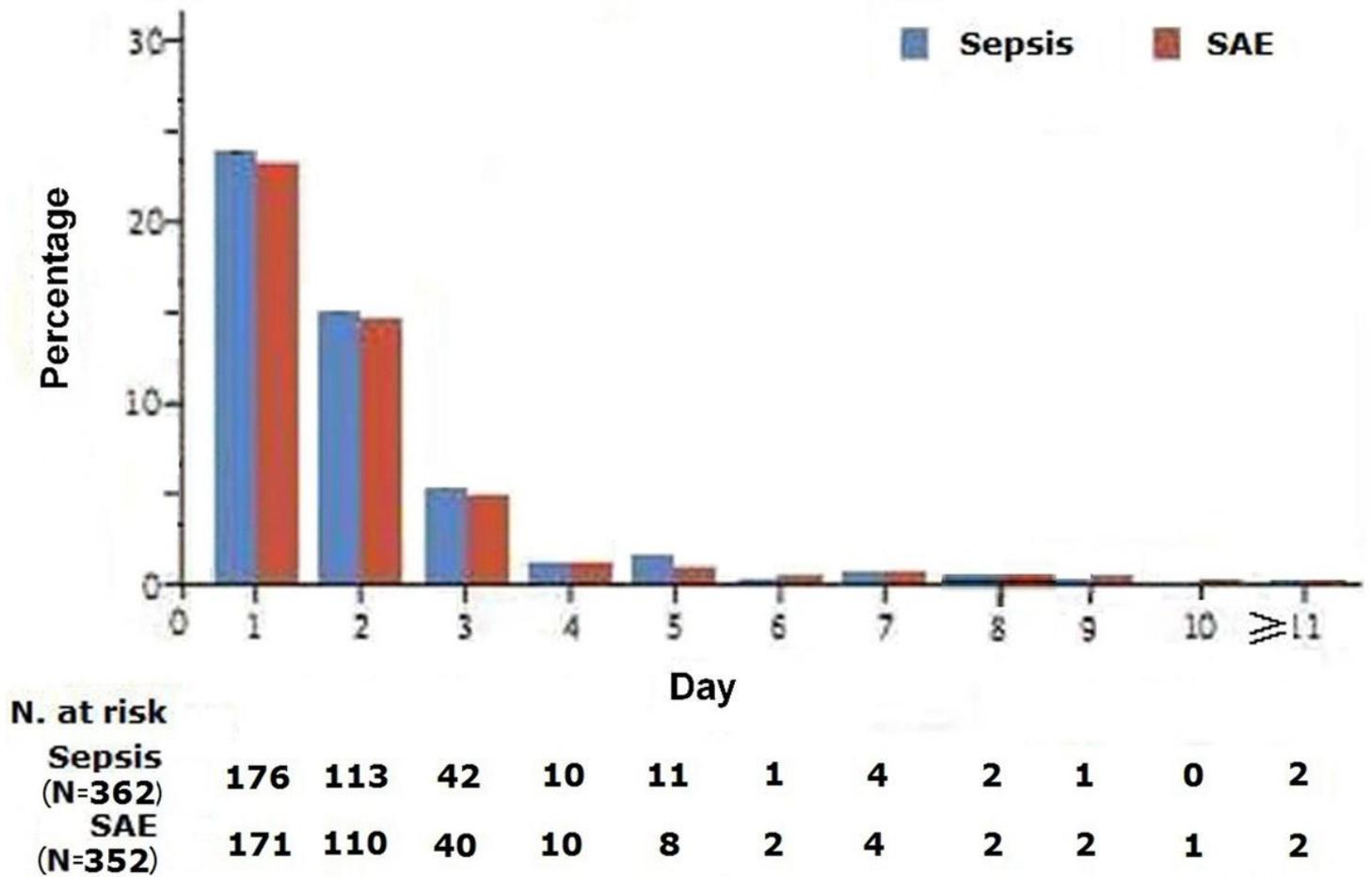


Figure 4

Kaplan-Meier survival curves showed that included critically ill patients with and without undergo antibiotic treatment within the first 3 hours following SAE. The worse survival was significantly associated with SAE patients who did not undergo antibiotic treatment within the first 3 hours (Log Rank, 25.3;  $p < 0.001$ ).