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Research Article

High Prevalence and High Risk of Death for Sepsis Associated Brain Dysfunction in ICU: A Cohort Study from Quick Diagnostic Tests

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Abstract

Purpose Whether sepsis associated brain dysfunction (SABD) would present an high prevalence and high risk of death in ICU, while is still unknown. **Methods:** We retrospectively enrolled patients with acute critically ill with sepsis from a single ICU in a medical University of China (January 1, 2018 to November 30, 2019). All patients were selected from onset to ICU stay>24 hours. We used a continuous head and thorax/abdominal cavity CT scans to screen infection before on admission. We also measured the dynamic profile of laboratory findings. The risk factors of death in SABD was estimated by using a logistic- regression analysis. **Results:** A total of 214 critically ill patients with sepsis from onset to initial 24 hours in ICU was diagnosed by Sequential [sepsis-related] Organ Failure Assessment (SOFA) criteria. Of them, 202 SABD (94.4%, 202/214) was identified according to SOFA criteria for the brain. 135 was male (66.8 %) with mean age 66.7 ± 16.1 years. The most common SABD was delirium (50.0 %) followed by a stupor or coma (35.1%). Among the 202 sepsis patients with SABD, the most common infection was pneumonia/ lungs infection (86.6%, 175/202). The fatality of SABD was 60.4% at initial 60 days. By multifactors regression analysis, severe inflammatory storm (OR, 7.2; 95% CI, 2.58- 24.94), higher SOFA scores (OR, 1.8; 95% CI, 1.5-3.6), and elevated CRP level (OR, 1.0; 95% CI, 1.26-1.96) were the independent risk factors for death in SABD. **Conclusions**: SABD in ICU is an high prevalent life-threatening acute organ dysfunction. The bad prognosis in SABD was related to the severe inflammatory storm, higher SOFA score, and elevated CPR level.

Keywords: Sepsis; Acute brain dysfunction; Infection; Inflammatory storm; Prevalence; Outcome.

Introduction

Sepsis as an most frequent complication in critically ill adults has been become the leading cause of morbidity and mortality worldwide [1-3]. Moreover, in 2016, the Third International Consensus (sepsis-3) has defined sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection [4]. To the best of our knowledge, the brain dysfunction if is closely related to sepsis is defined as equivalent to a Sequential Organ Failure Assessment (SOFA) score ≥1 (on a scale from 0 to 4) [5]. The value of This SOFA criteria for diagnosis sepsis associated brain dysfunction (SABD) have reported by documents [3-6],

especially it has been accepted by sepsis-3 [4]. However, whether a SABD in ICU would present an high prevalence and high risk of death, which is still understanding incomplete. Our hypothesis was that the critical ill adults in ICU would be having an high rate of prevalence from community-acquired infection and high risk of death in SABD. The aim of this study was to clear whether these SABD present an high prevalence and high risk of death in ICU, so to cognize its important of prevention/control SABD.

Methods

Procedures and population

We conducted a retrospective cohort study from adult patients with sepsis who were admitted to The Affiliated Shuyang Hospital of Xuzhou Medical University, a 21-bed tertiary care hospital, from Jan 1, 2018, to Nov 30, 2019 with a length of stay of more than 24 hours. We examined the electronic medical records of patients who were verified as having a brain-chest-abdomen CT scan before on admission. We excluded possible critically ill patients who did not have CT data before on the ICU, or no medical records due to either death or transport out of the ICU within the first 24 hours. The study was approved by the ethical committee on clinical research of the Affiliated Shuyang Hospital of Xuzhou Medical University, and written informed consent was obtained from **parents or legal guardian**.

Patients identification, inclusion criteria, related definitions, and mainly measurement for SABD

SABD is defined as equivalent to a SOFA score ≥ 1 for the brain organ (on a scale from 0 to 4) [5]. We used this SOFA criteria for the brain to assess acute brain dysfunction/brain failure during the initial 24 hrs in ICU .

In this study, diagnosis of sepsis is based on one or more life-threatening organ dysfunction (a total SOFA scores ≥ 2 points) caused by infection. The identification of infection event is meant a suspected or confirmed infection (e.g., a cold, SIRS ≥ 2, confirmed pneumonia or other infection). In the present study, the time of onset infection is limited to before organ failure. If there is only an isolated brain failure, the time of onset infection had to be before (or simultaneously) brain dysfunction rather than behind it. Thus, these critically ill patients who were performed a continuous head and chest /abdominal CT scans before on admission were enrolled in this study. It is more likely to detect the ultra-early infection of chest (pneumonia) and abdominal (gallbladder/ cholangitis, peritonitis, pancreatitis).

Systemic inflammatory response syndrome (SIRS) has been recognized as a clinical manifestations host response to infection. A systemic inflammatory response mainly involves to a massive inflammatory cytokine release [7]. More recently, it's called a cytokine storm, which is a life-threatening systemic inflammatory storm [8]. Moreover, this inflammatory syndrome also involves other inflammatory mediators in the blood (e.g; D-dimer, C-reactive protein, and procalcitonin). The clinical manifestations of SIRS include follow 4 points: (1) temperature> 38˚**C** or < 36˚C; (2) heart rate >90 beats per minute; (3) tachypnea> 20 respirations per minute or or PCo_2 less than 32mmHg ; (4) white blood cell count > 12.0×10^9/L or < 4.0×10^9/L, or > 10% band forms. The identified criteria for SIRS must be at least ≥ 2 points/scores (≥3 points/scores= severe). We also measured the dynamic profile of laboratory findings, SIRS sores, SOFA scores, and so forth, which can effect on outcomes.

Our primary outcome was the prevalence of SABD. Our secondary outcomes were the in–hospital mortality at 60 days in ICU on the SABD nonsurvivors or survivors. The outcome events were reviewed by two of the investigators (the first and second author).In order to assessment the outcomes of patients in-hospital 60 days, survival state was confirmed by the medical records. If the patient died after discharge, the information was followed-up to 60 days.

Data collected

All clinical data were gathered from the electronic medical records written by residents or attending physicians of the emergency and ICU. In addition to collect the cranial and thorax/ abdominal cavity CT scans findings, the collected clinical profile for this study in ICU included the patient demographics, time from critically ill event to infection, initial SIRS level, initial SOFA score, initial GCS score (or GCS motor score if the patients were in intubation), vital sign data, experimental/ laboratorial data, mechanical ventilation, traditional treatment, length of stay (LOS) in the ICU, and outcomes.

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. 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 214 critically ill adult patients with sepsis were admitted to ICU, which was met the inclusion criteria for sepsis-3. Finally, 202 patients with SABD (94.4%,202/214) were diagnosed and included in this study. Of them, there was 149 (73.8%)

community-acquired SABD and 53 (26.2%) hospital-acquired SABD. Based on SOFA for brain criteria, the distribution of SABD within initial 72 hours in the ICU was showed in the Table 1. Of these patients, the most common initial presenting SABD were delirium [101 (50..0%)], followed by acute stupor/coma [71 (35.1%)]. The Study population included 132 males and 70 females, with the average age of 67 years. The clinical characteristics of the 202 SABD are shown in Table 2. The median time from onset to ICU admission was 3.2 hours (range, 0.5-240 h).

SOFA for the brain	**SABD**	**N,%**
	N = 202	
SOFA score 1 (GCS=13-14)= delirium	101	50
SOFA score 2 (GCS=10-12)= drowsiness	20	10
SOFA score 3 (GCS=6-9)= stupor/ coma	71	35
SOFA score 4 (GCS<6)= deep coma	10	5
All of SABD	202	100

Table 1: SOFA score for the brain to diagnosis SABD within first 72 h in ICU (n = 202); Abbreviation-ICU: Intensive Care Unit; GCS: Glasgow Coma Scale; SOFA: Sequential [sepsis-related] Organ Function Assessment; SABD: Sepsis Associated Brain Dysfunction.

	Total (n = 202)	**Non-survivors (n = 115)**	**Survivors (n = 87)**	**p Value**
Age (years, mean ± SD)	66.7 ± 16.1	68.1 ± 16.1	65.0 ± 16.1	0.181
Male gender (n,%)	135(66.8)	77(67.0)	58(66.7)	1
Initial GCS score, (mean±SD)	10.5 ± 3.3	10.3 ± 3.1	10.7 ± 3.5	0.522
Comorbidities				
Hypertension (n,%)	98(48.5)	54(47.0)	44(50.6)	0.67
Cardiac-cerebral vesculardisease (n,%)	72(35.6)	39(33.9)	33(37.9)	0.557
Diabetes (n,%)	35(17.3)	22(19.1)	13(14.9)	0.46
Clonical lung disease (n,%)	30(14.9)	11(9.6)	19(21.8)	0.017
Cancer (n,%)	19(9.4)	10 (8.7)	9(10.3)	0.809
Initial presenting symptoms				
Fever, (n,%)	91(45.0)	59(41.3)	32(36.8)	0.046
Alterd mental status/deliriun, (n,%)	88(43.6)	57(50.0)	31(35.6)	0.062
Acute stopor/coma, (n,%)	73(36.1)	49(42.6)	24(27.6)	0.038
Cough/dyspnea, (n,%)	64(31.7)	44(38.3)	20(23.0)	0.023
Chest/abdominal pain, (n,%)	12(6.0)	6(5.0)	6(6.9)	0.766
Dizziness/headache,(n,%)	11(5.4)	5(4.3)	6(7.0)	0.536
Other, (n,%)	5(2.5)	3(2.6)	2(2.3)	1
Acute pneumonia/lung infection, n (%)	174(86.1)	98(85.0)	76(87.4)	0.236
Abdomen infection, n. (%)	18 (10.0)	13(10.9)	5(5.3)	0.138
Other infection. n (%)	12 (5.9)	8(7.0)	4(4.6)	0.497

Community-acquired sepsis, n (%)	158(78.2)	88(76.5)	70(80.5)	0.006
Median(IQR) time from onset to ICU(hours)	3.2(0.5-240)	2.7(0.5-144)	5.5(0.5-240)	0.012
Median (IQR) temperature (°C)n (%)	37.5(35.3-40.0)	37.8(36-40.0)	36.9(35.3-39.7)	0.075
Median(IQR)arterial pressure(mmHg)	93(40-160)	93(40-160)	98.7(90-130)	0.266
Median(IQR)Heart rate(beats/min)	102(58-107)	102(70-107)	102(58-148)	0.354
Median(IQR)Respiratory rate(breaths/mim)	27(0-45)	27(5-35)	27(0-45)	0.818
MODS, n (%)	188(93.!)	115(100.0)	73(83.9)	0
Intubation and IMV, n (%)	198(98.0)	115(100.0)	83(95.4)	0
Antibiotic therapy during initial 6 hours, n (%)	202(100.0)	115(100.0)	87(100.0)	NA
Antibiotic therapy within initial 1 hours, n (%)	94(46.5)	43(37.4)	51(58.6)	0.003
LOS (days,IQR)	9.8(1-127)	7.7(1-90)	12(2-127)	0.305
Mortality at 60 days, n (%)	122(60.4)	NA	NA	NA

Table 2: Clinical characteristics in patients with SABD (n=202); Abbreviations-ICU: Intensive Care Unit; GCS: Glasgow Coma Scale; SOFA: Sequential [sepsis-related] Organ Function Assessment; IMV: Invasive Mechanical Ventilation; LOS: Length of Stay; IQR: Interquartile Range MODS: Multiple Organ Dysfunction Syndrome.

Among the 202 sepsis patients with SABD, the most common infection was pneumonia/lungs infection (84.6%, 171/202) and early onset of pneumonia is more likely to relate to rapid brain edema/SABD (Figures 1 and 2). The secondary causes was abdominal infection (10.0%) , followed by other infection(5.4%). The outcome of using antibiotics treatment within initial 1.0 hours in ICU was better in the survivors with SABD than in those nonsurvivors with SABD (58.6% *VS*, 37.4%; $p<0.005$). The subsequent confirmed that patients with positive blood culture were 15.3% of SABD and patients with abnormal CSF analysis were 14.4% of SABD. In all SABD patients, the risk of death was 35.4% at the initial 72 hours and 60.4 % (122/202) at the initial 60 days.

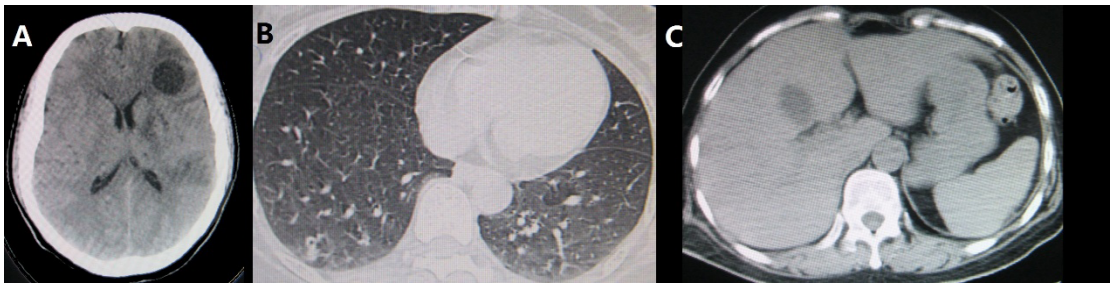

Figure 1: The features of brain / chest/abdominal computed tomographic (CT) images; Figure 1 A-C is from a 57 year-old female patient with fever 2 days and drowsiness 1 day was admitted. On day 1, brain CT showed the focus of infection and diffuse edema (A), chest CT showed bilateral pneumonia(B), and abdominal CT showed the focus of infection (C), On days 3, fever up to 39.0°C, On days 3 blood pressure drop to 81/54mmHg, and deep coma, On days 4, she died and was discharged.

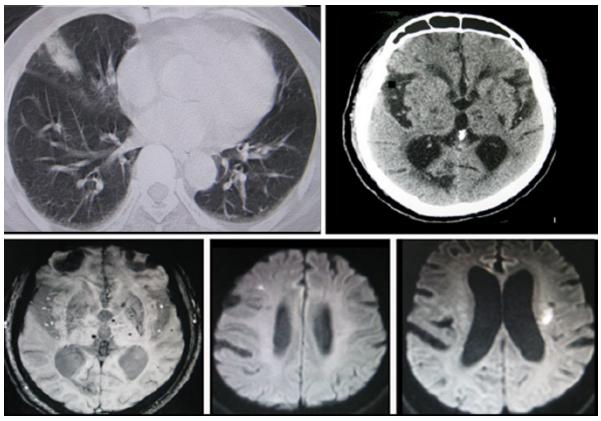

Figure 2: (A-E) is from a 70 year-old male with delirium and cough for 2 days admitted, On admission, chest CT showed pneumonia in the right lung, brain CT showed lacunar infarction in the bilateral basal ganglia. Day 3 of admission, MRI-DWI of brain demonstrated the microbleeding (C) and acute ischemic lesions (D,E) in the bilateral subcortical white matter. After using antibiotics IV, he was discharged from hospital.

Risk factors for the SABD survivors or nonsurvivors are described in Table 3. The main dynamic profile for sepsis/SABD included 6 parameters, which were from within the initial 1 day to 24 days after ICU admission at 3-day intervals. We found that a high risk of dynamic profile of risk factors for SABD was significant higher in the nonsurvivors than in survivors(p<0.05). (Figure 3).

Variable	Non-survivors (n = 115)	Survivors (n = 87)	P Value
Male gender, n (%)	81(70.4)	54(62.1)	0.23
Age (years, mean ± SD	67.7 ± 15.6	66.1 ± 16.5	0.486
MAP(mmHg, mean ± SD)	90.3.0 ± 24.0	93.3 ± 21.9	0.496
Respiratory rate(breaths/mim, mean ± SD)	25.1 ± 6.6	24.6 ± 7.1	0.599
Body temperature (°C, mean ± SD)	37.7 ± 1.1	37.3 ± 1.1	0.091
Heart rate(beats/min, mean ± SD)	107 ± 21.0	103 ± 29.0	0.289
Sequential median (IQR)WBC (x10^9/l)	13.3(2.3-34.6)	13.0(0.87-34.6)	0.847
Sequential median(IQR)Platelet count, x10^9/L	177(23-887)	168(3.0-493)	0.265
Sequential median(IQR)Blood glucose (mmol/l)	8.6(3.6-44.5)	8.1(4.0-41.0)	0.323
Sequential median(IQR) lactic acid (mmol/l)	3.2(1.2-12.2)	3.0(1.2-15.9)	0.384
Sequential median(IQR) creatinine (umol/L)	99.6(38.99-739)	72(10.4-494)	0.019
Sequential median(IQR) total blirubin (mmol/l)	19.2(6.2-1245)	19.1(4.7-181)	0.783
Sequential median(IQR)CRP,(mg/L)	133(40-230)	95(30--300)	0.005
Sequential median(IQR)Procalcitonin(ng/mL)	2.7(0.03-500)	1.2(0.3-35.4)	0.006
Sequential median(IQR)D-dimer(mg/mL)	2.3(0.3-29.7)	0.9(0.2-6.4)	0.038
Sequential median(IQR)Interleukin-6(pg/mL)	68(6.5-200)	10.0(5.5-56)	0
Sequential median(IQR PaO_2/Fi O_2, mmHg	99.8(80-220)	305.8(300-360)	0
Sequential median(IQR)GCS score	11(5-14)	13(5-14)	0.034
Sequential median(IQR)SOFA score	11.2(6-18)	7.4(2-13)	0
Sequential median(IQR)qSOFA score	2.0(0-3)	1.7(0-3)	0,042

Sequential SIRS criteria	3.5(3-4)	2.5(2-4)	0
LOS (days, mean ± SD)	15.5 ± 19.1	17.6 ± 21.9	0.63

Table 3: Comparison of clinical features of SABD patients with survivors and non-survivors in ICU (n=202); Abbreviation-SABD: Sepsis Associated Brain Dysfanction; ICU: Intensive Care Unit; SISS: Systemic Inflammatory Storm Syndrome; SOFA: Sequential [sepsis-related] Organ Failure Assessment; Qsofa: Quick Sequential Organ Failure Assessment; GCS: Glasgow Coma Scale; MAP: Mean Arterial Lood Pressure; SpO_2: Saturation of Arterial Oxygen; ARDS: Adult Respiratory Distress Syndrome; MODS: Multiple Organ Dysfunction Syndrome; LOS: Length of Stay.

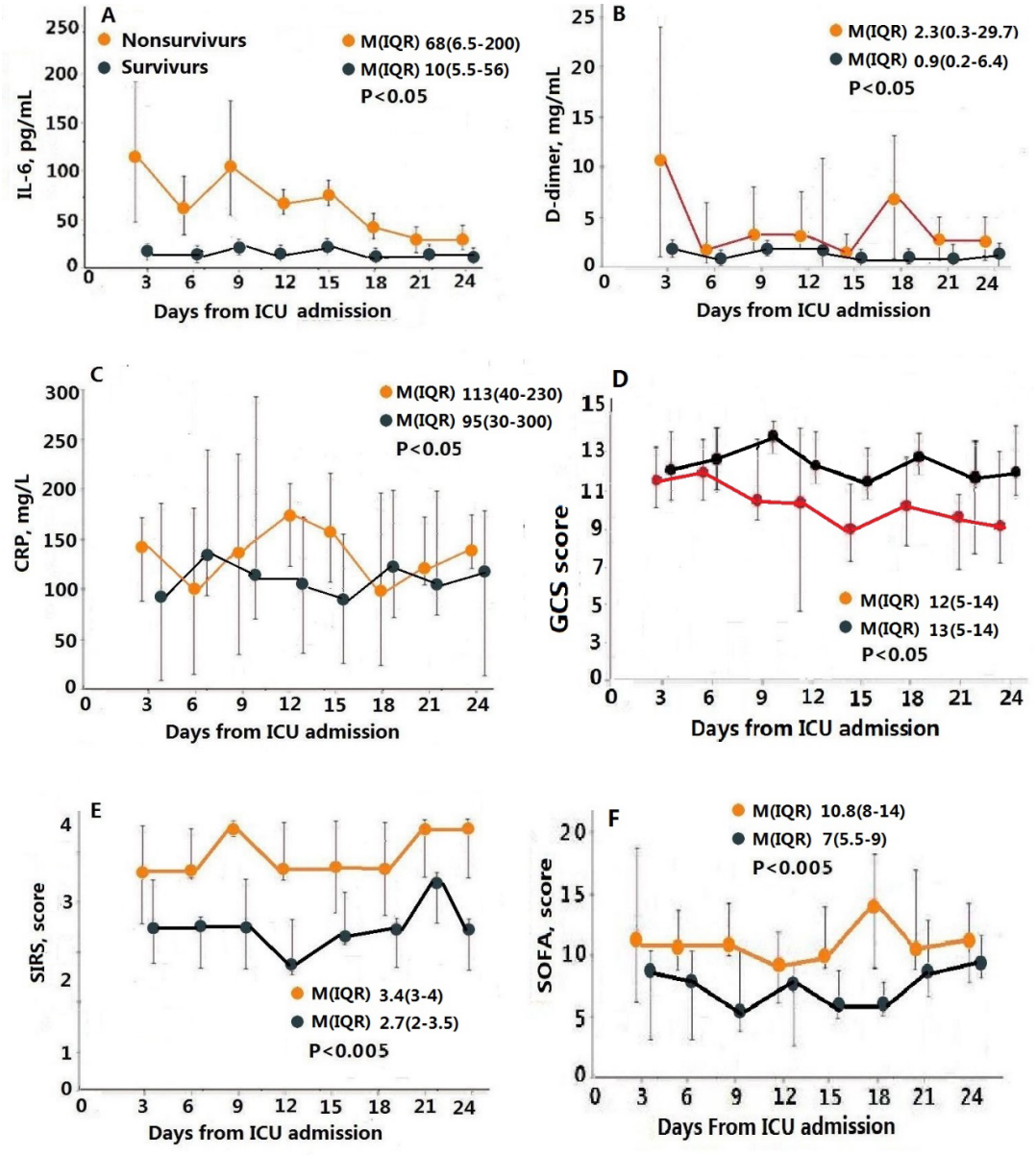

Figure 3: Changes in laboratory parameters from sepsis in the ICU. lL-6 (A), D-dimer (B), CRP (C), GCS score (D), the SIRS score (E), and SOFA score (F) were higher in nonsurvivors than in survivors (all *P*<0.05); IL-6, Interleukin-6; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome; GCS, Glasgow Coma Scale; SOFA, sequential [sepsis-related] organ function assessment.

In addition, our data also found that SABD nonsurvivors were more likely to present with a lower PaO_2/FiO_2 ratio, higher qSOFA scores, elevated procalcitonin, and elevated creatinine level than survivors (all $p<0.05$). But, the white blood cell counts, platelet count, blood glucose, lactic acid level、total bilirubin level, and the rate of pneumonia/lungs infection were similarly high between the nonsurvivors and survivors (Table 3). The sequential median(IQR) SIRS level, SOFA scores, qSOFA scores, GCS scores, Interleukin-6 level, CRP level, procalcitonin level, D-dimer level, creatinine level, and PaO_2/FiO_2 ratio were significant in the univariate analysis; therefore, we selected these veriables for multivariate regression analysis.

By multivariate regression analysis, risk factors associated with worse outcomes for SABD in the ICU are showed in the Table 4. Risk factors for SABD with worse outcomes between groups were a severe inflammatory storm (SIRS) score (OR, 7.2; 95% CI, 2.64-26.38), a higher SOFA score (OR, 1.8; 95% CI, 1.18- 2.04) which showed existing MODS, and an elevated CRP level (OR, 1.0; 95% CI, 1.93-1.66).

Variable	OR	95% CI for OR	P Value
Severe inflammatory storm (SIRS≥3)	7.2	2.337-19.59	0
SOFA score	1.8	1.317-2.535	0
CRP	1	1.002-1.029	0.02

Table 4: Logistic regression analysis to identify the high risk factors of SABD patients in ICU (n = 202); Abbreviations-SIRS: Systemic Inflammatory Storm Syndrome; ICU: Intensive Care Unit; SOFA: Sequential [Sepsis-related] Organ Failure Assessment; CRP: C-Reactive Protein; SABD: Sepsis Associated Brain Dysfunction

On current SIRS criteria, 100.0% sepsis patients presented a SIRS criteria of ≥ 2, of them, 64.0% patients were met SIRS criteria of ≥ 3. Moreover、MODS were significantly higher in nonsurvivors (100.0%) than in survivors (83.9%),. The risk of morbidity and mortality of 202 SABD in the ICU is shown in Figure 4. Bain failure was associated with up to up to 94.4% morbidity and 56.9% mortality at 28 days.

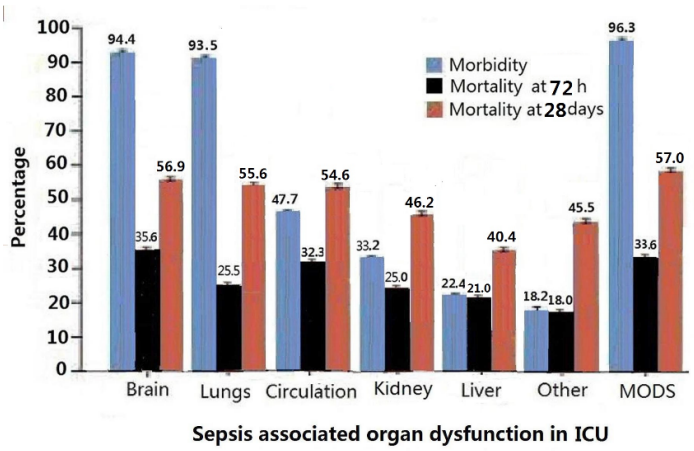

Figure 4: Risk of morbidity and mortality of 202 SABD with acute organ dysfunctions in the ICU, according to the sepsis-sequential organ function assessment (SOFA).

Discussion

Previous studies had shown the prevalence and risk factors of sepsis-associated encephalopathy SAE) [6,9]; however, the prevalence and clinical features of SABD from sepsis-3 criteria remain to be elucidated. The current study is the first largest study that revealed the prevalence, clinical feature, risk factors, and outcome of SABD. In the present study, we found that the prevalence rate of SABD from onset to initial 72 hours in ICU accounted for 94.4% of sepsis, and the main feature of SABD patients were presented with MODS (93.6%). However, our this study is clear, high prevalent SABD is almost near the epidemic rate of sepsis, which indicated the SABD was a leading life-threatening acute organ dysfunction.

Importantly, our study found that the risk factors for SABD were associated with a severe inflammatory storm (SIRS), elevated SOFA scores, and elevated CRP level in ICU. Previous studies showed that severe inflammatory storm, higher SOFA scores, and elevated CRP level had been recognized as a marker of infection、and related to the severity of the disease [10-12]. Severe inflammatory storm, elevated SOFA score, and elevated CRP level were higher in SABD nonsurvivors than in those SABD survivors,

suggesting that the inflammation was stronger and more severe in nonsurvivors with SABD than in those survivors with SABD.

Several possible interpretations for the SABD 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 [13]. 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 [11-15]. The second, our data shown that 78.0%-81.0 of SABD had acute pneumonia/ARDS within initial 2 days. Moreover, the acute pneumonia/ARDS play pivotal roles in the development of severe inflammatory storm in sepsis [8,16]. 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 [17,18].

In addition, massive cytokines (including interleukin-6 and tumor necrosis factor alpha (TNFα) lead inflammation-derived injurious storm (i.e;cytokine storm) [15,19]. Cytokine storm can cause devastating inflammatory conditions, which include MODS and death of the patient [20]. MODS is the most vulnerable to hypoxia/ischemia and oxidative stress caused by severe inflammatory storm. The previous studies indicated that sepsis with MODS was more likely to exhibit a SABD [15,17].

To the best of our knowledge, this is the first largest study that revealed the prevalence of SABD. The main strengths of our this study that early identification of SABD driven by inflammatory storm from community-acquired infection (pneumonia). For its an early rapid antibiotic treatment within initial 1.0 hour in ICU is recommend the importance of the topic as a problem to reduce the morbidity and mortality of SABD [3,21].

Some limitations of our study have to be addressed due to retrospective analysis. First, we use a strict diagnostic criteria for SABD, but the current sample of SABD was from a single center and may have selection bias. However, this hospital ICU is a unique regional ICU (open 21-bed) with an emergency center (with 10 ambulances) that is responsible for all critically ill referrals in this area. Thus, we believe that this sample does not have a large bias. Second, some SABD patients with severe persistent inflammatory storms may have undetermined infection sites other than in lungs. It is not uncommon to have two sites infection in SABD patients, especially were those who undergone an emergency craniotomy and external drainage. Despite we do further CSF examination, but the proportion is very low (only 14%). Thus, a diagnosis of secondary CNS infection may be missed. Third, we focused our analysis in sepsis patients within initial 24 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 had been underestimated (seen in appendix). In addition, although the prognosis for sepsis was related to the early use of antibiotics, we did not verlify its link to organ failure. Therefore, further prospective studies are needed for its some of the links.

Conclusion

SABD in ICU is an high prevalent and early life-threatening brain dysfunction. Severe inflammatory storm, higher SOFA scores, and elevated CRP level in ICU was related to bad outcome for SABD. It may be reduced the morbidity and mortality of SABD to use a rapid antibiotics treatment at initial 1 h after the recognition of infection event.

Disclosures of interest

All authors declare that no conflicts of interest exist.

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