

Sepsis Associated Encephalopathy Predicts Poor Outcome among Acute Supratentorial Intracerebral Hemorrhage with Coma

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How to cite this paper: Tong, D.-M., Zhou, Y.-T. and Wang, S.-D. (2018) Sepsis Associated Encephalopathy Predicts Poor Outcome among Acute Supratentorial Intracerebral Hemorrhage with Coma. *Neuroscience & Medicine*, 9, 123-134. <https://doi.org/10.4236/nm.2018.93013>

Received: July 13, 2018

Accepted: September 2, 2018

Published: September 5, 2018

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Abstract

Background: Both sepsis associated encephalopathy (SAE) and supratentorial intracerebral hemorrhage (SICH) are a significant cause of coma and death throughout the world. The aim of this study was to investigate whether the presence of SAE among acute SICH with coma would predict a poor outcome. **Methods:** A retrospective of consecutive patients was selected for study. All registered an adult intensive care unit (ICU) of university teaching hospital between June, 2013 and July, 2015. Brain computed tomography (CT) scans were analyzed on admission and at coma onset or after coma onset. Univariate and Cox regression analyses were performed. **Results:** A total of 379 SICH with coma was studied. Among these, 245 (64.6%) SICH patients with coma due to SAE and 134 (35.4%) SICH with coma no SAE was compared. Our data showed that the frequency of the SAE in SICH patients increased at about double the proportion over the four SIRS criteria. The SICH patients with SAE were more likely to present with infection (100% vs 35.8%) and multiple organ failure (1.2 ± 0.9 vs 0.1 ± 0.3), especially nosocomial brain failure (60.4%). The 30 days mortality was significantly higher in the SAE group than those who did not (60.8% vs 11.2%). In Cox multivariate logistic analysis, the SAE (RR, 4.4; 95% CI, 2.296 - 8.422; $P = 0.000$) was more likely to related to risk on death in SICH patient with coma. **Conclusions:** SAE is a frequent complication of SICH, which greatly increased risk of death among SICH patients with coma.

Keywords

Sepsis, Sepsis Associated Encephalopathy, Supratentorial Intracerebral Hemorrhage, Coma, Outcome

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection [1]. The consensus definition of sepsis requires proven infection, at least one organ failure, and signs that meet two or more criteria for the SIRS [2] [3] [4] [5]. Importantly, sepsis associated encephalopathy (SAE) is the most common type of sepsis that is seen in the ICUs. The incidence of SAE was about 70% of septic patients [6]. The mortality of sepsis patients with primary stroke was 56.5% [7], especially those who had SAE; its mortality is closer to 63.0% [8]. Therefore, SAE could be identified as a significant risk factor for increased mortality. Acute supratentorial intracerebral hemorrhage (SICH) is a common cause of coma, with a 28-day mortality rate of 43.0% [9] [10]. Recently, the incidence of ICH patients who are at high risk for systemic infection has increased [11] [12] [13] and thus comprehensive treatment strategies are required to treat infection diseases. In particular, the number of patients who are managing stroke and also suffer from SAE has been increasing, and the mortality rate was over half of patients [7] [8], suggesting that the prognosis of stroke with sepsis/SAE may be worse. However, there are few special reports discussing predictors that affect the neurological outcome of SICH in patients with SAE. We sought to determine whether the presence of SAE among acute SICH with coma would predict a poor outcome.

2. Methods

2.1. Study Settings

This was a retrospectively study of all registered an adult ICU of university teaching hospital in China between June, 2013 and July, 2015. The study was approved by the Ethical Committee on Clinical Research of Shuyang People's Hospital, because the study involved only a review of records obtained as a part of routine medical care, without patient consent was required.

2.2. Patients Identified

Based on the International Statistical Classification of Diseases 10th Revision (ICD-10) by WHO in 1994 discharged, we identified those patients who had acute spontaneous supratentorial ICH with coma (code I61.9, R40.2) in a consecutive 2-years period. A total of 447 consecutive patients with ICH with coma were recruited. We excluded infratentorial ICH ($n = 57$), intraventricular ($n = 5$), and ICH volume recorded unknown ($n = 6$). Finally, 379 SICH patients with coma were included in our study.

In this study, sepsis was diagnosed using clinical indicators of suspected infection and concurrent acute organ failure [1] [2] [3] [4] [5], adapting Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria [1]. For SAE, we used the following diagnostic criteria: 1) acute brain dysfunction is related to sepsis, including an inflammatory response processes and at least exhibiting a sepsis-related organ failure [1] [2] [3] [4] [5]; and 2) a lower

Glasgow Coma Scale (GCS) score [14] that could not be fully explained by isolated ICH. The exclusion criteria were used for SAE: 1) with evidence of meningitis/encephalitis; 2) with evidence of non-septic encephalopathies; and 3) with evidence of organ dysfunction due to the effects of sedatives or other medications.

2.3. Clinical Assessment

All clinical parameters was measured based on data recorded in the initial 24 h of admission to ICU and the sepsis-related Sequential Organ Failure Assessment (SOFA) score was assessed later 5 days.

All patients underwent an initial brain CT scan on admission and at least one repeat brain CT scan after coma onset. We analyzed the CT data that were collected at the closest in time following onset. The hematoma volumes on admission and closest in time of rebleeding were measured and using the standard ABC/2 formula (where A is the longest diameter of the hematoma, B is the widest diameter of the hematoma, and C is the layer thickness of the hematoma) [15].

Infection was assessed using clinical two or more systemic inflammatory response syndrome (SIRS) criteria: 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 Pco₂ < 32 mmHg; 4) white blood cell count greater than 12.0 × 10⁹/L or less than 4.0 × 10⁹/L, or more than 10% band forms [3].

Sepsis-related organ failure was diagnosed by a sepsis-related Sequential Organ Failure Assessment (SOFA) score (range 0 - 4, with higher scores indicating more severe organ failure) ≥ 2 for a particular organ after the onset of infection [16]. The following were considered to be organ failure: [16] brain—GCS < 13 score; respiratory—bilateral infiltrates on chest thorax radiograph and arterial oxygen pressure/fraction of inspired oxygen ratio (PaO₂/FiO₂) ≤ 300 or the need for supplemental oxygen to maintain oxygen saturation > 90% (excluding the prior need for oxygen); circulation—hypotension (systolic blood pressure < 90 mm Hg or mean arterial pressure < 65 mmHg or decrease > 40 mmHg in the systolic pressure); liver—total serum bilirubin > 33 uml/L; renal—creatinine > 171 uml/L; blood—platelet count ≤ 100 × 10⁹/L, glucose > 27.8 mmol/L or <2.8 mmol/L, or sodium > 160 mmol/L or <110 mmol/L.

The following data in SICH patient with coma were also collected to examine the relationships between clinical outcome, including age, sex, ICU days, underlying disease, hematoma location, hemorrhage growth, hematoma volume, accompanying intraventricular hemorrhage, acute physiology and chronic health evaluation II (APACHE II) score, initial National Institutes of Health Stroke Scale (NIHSS) score. We recorded the onset-to coma time, the length of ICU stay, and outcomes at 30 days of follow-up.

2.4. Related Definition

Significant intracerebral hemorrhage growth was defined as hematoma expan-

sion of greater than one-third on repeat CT [17] or hematoma enlargement lead a brain herniation. Midline shift was measured as described in the literature [18] [19]. Cisterns were recorded as normal, compressed, or absent, based on Marshall Scale criteria [20]. Brain herniation has been divided into uncal and central types [21]. Central herniation referred to the ascending reticular activating system (ARAS) compressed in the central diencephalon, radiologically with midline shift and perimesencephalic cisterns compressed, and clinically with stupor or coma. Uncal herniation was more likely to have the unilateral uncal gyrus downward displacement and was compressed the midbrain and ARAS than bilateral, radiologically with midline shift and the third nerve compressed, and clinically with coma, pupil asymmetry of >2 mm and loss of reactivity to light.

2.5. Statistical Methods

The results in each group were expressed as mean \pm standard deviation (SD) or medians (IQR), and *n* (%) for qualitative values. Continuous variables were compared using the *t* test. Chi-squared tests and Pearson's correlation coefficients were used to explore the relationships between baseline variables. Multivariate-adjusted risk ratios (RR) and 95% confidence intervals (CIs) were estimated with the use of the logistic-regression model if they were significant in the univariate analysis, or Cox proportional hazards model to examine severe 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. There was significant difference between the groups if the *P*-value was < 0.05. Statistical calculations were performed using a proprietary, computerized statistics package (SPSS 10.0).

3. Results

Of 379 patients included into the study, mean age was 61.5 ± 10.6 years, 62.0% were male, 231 (60.9%) had a prehospital coma (PC) events, and 148 (39.1%) had a nosocomial coma (NC) events. Of the SICH, 58.9% had a striato-capsula hemorrhage. For SICH underlying diseases and more baseline characteristics, see **Table 1**.

Among 379 SICH with coma, 245 (64.6%) had SAE events. The characteristics of SICH patients with SAE and no SAE are shown in **Table 2**. In patients with SAE, the most frequent SIRS criterion that was met was at a threshold of four SIRS criteria (51.0%), whereas at a threshold of two SIRS criteria only 23.1%. We found that there was significant difference in sepsis events (100.0% vs 5.2%, *p* = 0.000), temperature (38.1 ± 1.2 vs 37.1 ± 1.0 , *P* = 0.000), pulse rate (96.0 ± 15.8 vs 85.0 ± 15.5 , *P* = 0.000), elevated WBC (14.8 ± 5.5 vs 12.2 ± 6.2 , *P* = 0.000) in addition to respiratory rate (24.9 ± 5.8 vs 23.8 ± 6.4 , *P* = 0.096) between the two groups. Infection was higher in patients with SAE than in patients without SAE (100% vs 35.8%, *P* < 0.001). In patients with SAE, the commonest infection focal was mainly from respiratory infection (58.4%). While hospital-acquired infection was present in 48.2% and community-acquired infection was present in

Table 1. Baseline characteristics in supratentorial intracerebral hemorrhage patients with coma (n = 379).

Characteristics	Value
Male gender (%)	235 (62.0)
Age (years, mean \pm SD)	61.5 \pm 10.6
Time from onset to admission, median (h, range)	2 (1 - 240.0)
Location of hemorrhage	
Striato-capsula (%)	227 (58.9)
Lobar (%)	117 (30.9)
Thalamus (%)	35 (9.2)
Intraventricular extension (%)	101 (26.6)
Underlying diseases	
Hypertension (%)	341 (90.0)
Diabetes (%)	45 (11.9)
Atrial fibrillation (%)	14 (3.7)
Previous stroke (%)	70 (18.5)
Hospitalized conditions	
Prehospital coma (%)	231 (60.9)
Nosocomal coma (%)	148 (39.1)
SBP, mmHg	180 \pm 39.4
DBP, mmHg	104 \pm 21.4
Initial GCS score (mean \pm SD)	8.4 \pm 2.4
length of ICU (days)	5.9 \pm 6.7
Hematoma aspiration (%)	36 (9.5)
Mechanical ventilation (%)	196 (51.7)
Initial NIHSS score, mean \pm SD	26.1 \pm 8.6
CT characteristics at coma onset	
Midline shift (%)	206 (54.4)
Basal cisterns compressed (%)	341 (90.0)
Vasogenic edema (%)	137 (36.1)
Subcortical whiter matter lesion (%)	39 (10.3)
Central herniation (%)	259 (68.3)
Uncal herniation (%)	91 (24.0)
Hematoma growth (%)	87 (23.0)
Hematoma volume (mL, mean \pm SD)	34.9 \pm 23.4
Outcome	
Vegetative state (%)	83 (21.9)
Mortality in 30 days (%)	164 (43.3)

Abbreviation: NC, nosocomal coma; PC, prehospital coma; OCT, onset-to-coma time; GCS, Glasgow coma scale; SBP, systolic blood pressure; DBP, diastolic blood pressure.

51.8%. Most of the patients were performed bacteriological examination, and blood cultures were microbiologically confirmed in minority of the clinical sepsis (35.1%). In patients with SAE, the commonest subsequent organ failure was nosocomal brain failure (60.4%). The patients with SAE were significantly more likely to present with higher SOFA score (4.1 ± 1.4 vs 3.3 ± 0.7 , $P = 0.000$) and higher number of organ failure (1.2 ± 0.9 vs 0.1 ± 0.3 , $P = 0.000$) than those no SAE. In correlate analysis, the number of organ failure in SICH patients with SAE were positively correlated with the number of SIRS' criteria from 0 - 4 ($r = 0.671$, $P = 0.000$), and also was positively correlated with death ($r = 0.490$, $P = 0.000$).

On those univariate analyses of patients with SAE and no SAE after SICH are summarized in **Table 3**. We found that in addition to no difference in sex and

Table 2. The characteristics in SICH patients with SAE and no SAE (n = 379).

Characteristics	SAE (n = 245)	No SAE (n = 134)	P Value
Male gender (%)	145 (59.2)	90 (67.2)	0.126
Age (years, mean \pm SD)	61.9 \pm 11.5	60.8 \pm 8.6	0.352
Sepsis (%)	245 (100.0)	7 (5.2)	0.000
SIRS 0 criteria (%)	0 (0.0)	86 (64.2)	0.000
SIRS 1 criteria (%)	0 (0.0)	48 (35.8)	0.000
SIRS 2 criteria (%)	57 (23.3)	0 (0.0)	0.000
SIRS 3 criteria (%)	63 (25.7)	0 (0.0)	0.000
SIRS 4 criteria (%)	125 (51.0)	0 (0.0)	0.000
Body temperature ($^{\circ}$ C, mean \pm SD)	38.1 \pm 1.2	37.1 \pm 1.0	0.000
Heart rate (beats/min, mean \pm SD)	96 \pm 15.8	85 \pm 15.5	0.000
Respiratory rate (breaths/min, mean \pm SD)	24.9 \pm 5.8	23.8 \pm 6.4	0.096
leukocyte count ($\times 10^9$ /l, mean \pm SD)	14.8 \pm 5.5	12.2 \pm 6.2	0.000
Without infection (%)	0 (0.0)	86 (64.2)	0.000
With infection (%)	245 (100.0)	48 (35.8)	0.000
Infection conditions			
Pneumonia (%)	118 (48.2)	23 (17.2)	0.000
Tracheobronchial (%)	25 (10.2)	9 (6.7)	0.256
Bloodstream (%)	24 (9.8)	0 (0.0)	0.000
Intestinal tract (%)	8 (3.3)	0 (0.0)	0.034
Urinary tract (%)	8 (3.3)	0 (0.0)	0.034
Central nervous system (%)	0 (0.0)	2 (1.5)	0.055
Unknown (%)	62 (25.3)	14 (10.4)	0.001
Community-acquired (%)	127 (51.8)	48 (100.0)	0.003
Hospital-acquired (%)	118 (48.2)	0 (0)	0.000
Subsequent organ failure			
Acute respiratory failure (%)	66 (26.9)	2 (1.5)	0.000
Nosocomial brain failure (%)	148 (60.4)	0 (0.0)	0.000
Septic shock (%)	12 (49.0)	0 (0.0)	0.009
Acute renal failure (%)	41 (16.7)	5 (3.7)	0.000
Acute hepatic failure (%)	7 (2.9)	0 (0.0)	0.000
Hyperglycemia (%)	38 (15.5)	15 (11.2)	0.247
Hypernatremia (%)	13 (5.3)	0 (0.0)	0.007
Hyponatremia (%)	3 (2.0)	0 (0.0)	0.198
Acute seizures (%)	15 (6.1)	16 (11.9)	0.048
SOFA score (mean \pm SD)	4.1 \pm 1.4	3.3 \pm 0.7	0.000
No. of organ failure (mean \pm SD)	1.2 \pm 0.9	0.1 \pm 0.3	0.000

Abbreviation: SAE, sepsis associated encephalopathy; SICH, supratentorial intracerebral hemorrhage; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

age, APACHE II score, SOFA score, sepsis events, acute respiratory failure, nosocomial brain failure, septic shock, acute renal failure, hypernatremia, acute seizure, midline shift, basal cisterns compressed, vasogenic edema, white matter lesions, central herniation, uncal herniation, and hematoma volume was significantly associated with differences between the groups (all $P < 0.05$). However, in Cox multivariate logistic analysis, only the SAE (RR, 4.4; 95% CI, 2.296 - 8.422; $P = 0.000$) was significantly related to risk on death in SICH patient (**Table 4**).

During 30 days follow-up, survival data were available for our patients with SAE or no SAE. The survival rate was higher among SICH patients without SAE

Table 3. Univariate analyses of SICH patients with SAE and no SAE (n = 379).

Variable	SAE (n = 245)	No SAE (n = 134)	P Value
Male gender (%)	145 (59.2)	90 (67.2)	0.126
Age (years, mean ± SD)	61.9 ± 11.5	60.8 ± 8.6	0.352
APACHEII score (mean ± SD)	26.5 ± 6.2	17.2 ± 5.0	0.000
SOFA (mean ± SD)	4.1 ± 1.4	3.3 ± 0.7	0.000
Sepsis (%)	245 (100.0)	7 (5.2)	0.000
Acute respiratory failure (%)	66 (26.9)	2 (1.5)	0.000
Nosocomial brain failure (%)	148 (60.4)	0 (0.0)	0.000
Septic shock (%)	12 (4.9)	0 (0.0)	0.009
Acute renal failure (%)	41 (16.7)	5 (3.7)	0.000
Hyperglycemia (%)	39 (15.9)	13 (9.7)	0.247
Hypernatramia (%)	13 (5.3)	0 (0.0)	0.007
Acute seizure (%)	15 (6.1)	16 (11.9)	0.048
Midline shift (%)	147 (60.0)	59 (44.0)	0.003
Basal cisterns compressed (%)	212 (86.5)	129 (96.3)	0.003
Vasogenic edema (%)	110 (44.9)	27 (20.1)	0.000
Subcortical whiter matter lesion (%)	31 (12.6)	8 (6.0)	0.041
Central herniation (%)	147 (60.0)	112 (83.6)	0.000
Uncal herniation (%)	81 (33.1)	10 (7.5)	0.000
Hematoma growth (%)	53 (21.6)	34 (25.4)	0.408
Hematoma volume (mL, mean ± SD)	37.2 ± 26.2	30.6 ± 16.3	0.008
Vegetative state (%)	52 (21.2)	31 (23.1)	0.667
Mortality in 30 days (%)	149 (60.8)	15 (11.2)	0.000

Abbreviation: SAE, sepsis associated encephalopathy; SICH, supratentorial intracerebral hemorrhage; APACHEII, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Table 4. Cox multivariate analysis of the association of outcome for SICH patients with coma (n = 379).

Variable	RR	95% CI for RR	P Value
SAE	4.379	2.296 - 8.422	0.000
High SOFA score	1.457	1.251 - 1.698	0.000
Uncal herniation	2.125	1.405 - 3.231	0.000
Hematoma volume	1.018	1.011 - 1.025	0.000
Acute renal failure	0.513	0.292 - 0.902	0.021
Acute respiratory failure	0.483	0.267 - 0.791	0.001
Vesogenic edema	1.800	1.067 - 3.037	0.028

Abbreviation: SAE, sepsis associated encephalopathy; SICH, supratentorial intracerebral hemorrhage; SOFA, sequential organ failure assessment.

than among those with SAE. The respective mortality rates among SICH patients with SAE were significantly higher (60.8% vs 11.2%) at 30 days. Kaplan-Meier survival curves show that patients with SAE had significantly worse survival than patients without SAE (risk ratio = 6.8; 95% CI, 4.630 - 13.16; $P = 0.000$). (**Figure 1**)

4. Discussion

Both SAE and SICH are a significant cause of coma and death throughout the

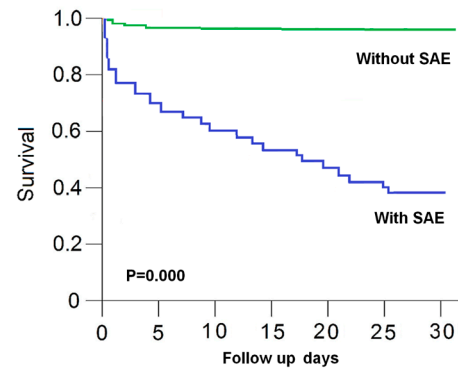


Figure 1. Kaplan-Meier survival curves for SICH patients with sepsis and no sepsis. Kaplan-Meier survival curves show that SICH patients with sepsis had significantly worse survival than patients no sepsis during the 30 days follow-up (risk ratio = 6.8; 95% CI, 4.630 - 13.16; $P = 0.000$).

world. Previous studies demonstrated that a decreased GCS, increased ICH volume, and presence of intraventricular hemorrhage were related to neurological deterioration and the high rate of poor outcomes in ICH patients [22] [23] [24] [25]. Current studies emphasized that neurological deterioration due to hematoma enlargement, including early hematoma growth, was poor outcome and increased mortality factors in SICH [16] [26] [27]. Our study showed that the mean volume of hematomas in the SAE group was significantly larger than those who did no. This suggests that hematoma volume or hematoma growth was related to poor outcome in SICH patient with coma. However, in our study, 245 (64.6%) SICH patients with SAE were diagnosed according to the criteria for SAE. Therefore, our data suggests that there was a high prevalence of SAE in patients with SICH with coma.

Several studies have demonstrated that the prevalence of infection among patients with ICH is high [11] [12] [13], and that the sepsis in stroke patients did not be infrequency [8] [28]. Our study showed that the patients who had infection and organ failure, a threshold meeting two or more SIRS criteria occurred in 64.6% (245/379) of SICH patients with coma, supporting these acute SICH patients with coma had SAE events.

On proportion analysis, mortality increased significantly with each additional SIRS criterion from 2 to 4, without any transitional increase in risk at a threshold of one SIRS criteria. Moreover, our study confirmed that the mortality of SAE among SICH patients who met four SIRS criteria was 20% higher than that those who met 2 - 3 SIRS criteria, and the number of SIRS criterion that SICH patients met were positively correlated with the number of organ failure. This showed that the higher grades of SIRS and the scores of SOFA, the more poor of the short-term outcome will be.

Brain herniation is a common form of acute brain failure. Our data showed that such organ failure due to sepsis was mostly focused on brain failure. The rates of uncal herniation events in SICH patients with SAE were significantly

higher than in those who did not. Brain herniation had usually resulted from supratentorial mass effect [18] [24], but current study demonstrated that vasogenic edema was significantly higher in SICH patients with SAE than those who did not. The development of vasogenic cerebral edema is related to the inflammatory mechanism [29] [30] [31]. Furthermore, there is evidence of blood-brain barrier dysfunction in both patient and rodent models of sepsis [32]. Our data showed that late brain failure were present in 60.4% sepsis after acute SICH. According to literature records, 70% of sepsis might develop brain dysfunction [6] [33], suggesting that our majority of SICH patients with sepsis may present with the component of SAE. Moreover, a Cox multivariate risk analysis is also confirmed that SAE and uncal herniation may be more likely to relate to worse outcome in SICH patient with coma.

The above findings confirmed that the SAE has impaired the outcome and mortality of SICH patients with coma. Our findings suggest that three aspects are possible interpretations. One hand, the mortality of SAE is high, which has been confirmed [7] [8]. Second hand, the SAE patients with a GCS score < 8 had a poor outcome and a high risk of death, which was also confirmed by the previous study [8]. In addition, other factors such as high SOFA score, acute renal failure, acute respiratory failure, vesogenicedeam, and greater hematoma volume may affect jointly the host response and increase the risk of the death, which is confirmed by current Cox multivariate risk analysis. However, this study's findings showed that high prevalence of SAE and its multiple organ failure was more likely to develop a poor outcome among SICH patients with coma. Moreover, previous studies suggested that a high mortality rate in sepsis is almost always due to multiple organ failure [34]. Therefore, knowing the above cases of sepsis after patients with SICH may help identify clinical therapeutic targets, and assist in decision making for SICH patients with sepsis who develop coma.

Limitations: some limitations have to be considered in our study. First, restriction to SICH patients with coma in this set may have to be created an overestimation of incidence for SAE. However, high rate of 70% in patients with SAE has been reported [6]. Second, some patients had not microbiologically examined or only confirmed by the sputum culture, this may be the reason for the low positive rate of microbiologic proof of infection, but the blood culture negative sepsis was not uncommon [35] [36]. Furthermore, the consensus has been formed that sepsis diagnostic criteria requires proven infection and organ failure, and signs that meet two or more criteria for the SIRS [2] [3] [4] [5] [36]. Therefore, we believe, high prevalence of SAE events in SICH patients with coma in current study should not be overestimated. In addition, about 70% of septic patients were associated with an encephalopathy [6], while subcortical white matter ischemic lesions and microinfarctions have been confirmed [4]. Thus, a brain MRI for SICH patients with sepsis and with brain lesions is very important, however, the scan of MR imaging in this study was absent.

Conclusion: SAE is a frequent complication of SICH, which greatly increased

risk of death in SICH patients with coma. It is research novelty that SAE may be pivotal in the pathogenesis of SICH patients with coma, which should be received attention in the field of SICH Care.

Acknowledgements

This work is supported by a grant from the Medical Research Council, Shuyang Hospital, Xuzhou Medical University, China.

Potential Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

- [1] Shankar-Hari, M., Phillips, G.S., Levy, M.L., *et al.* (2016) Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **315**, 775-787. <https://doi.org/10.1001/jama.2016.0289>
- [2] (1992) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *Critical Care Medicine*, **20**, 864-874. <https://doi.org/10.1097/00003246-199206000-00025>
- [3] Bone, R.C., Sibbald, W.J. and Sprung, C.L. (1992) The ACCP-SCCM Consensus Conference on Sepsis and Organ Failure. *Chest*, **101**, 1481-1483. <https://doi.org/10.1378/chest.101.6.1481>
- [4] Levy, M.M., Fink, M.P., Marshall, J.C., *et al.* (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine*, **31**, 1250-1256. <https://doi.org/10.1097/01.CCM.0000050454.01978.3B>
- [5] Kaukonen, K.M., Bailey, M., Pilcher, D., Cooper, D.J. and Bellomo, R. (2015) Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. *The New England Journal of Medicine*, **372**, 1629-1638. <https://doi.org/10.1056/nejmoa1415236>
- [6] Bolton, C.F., Young, G.B. and Zochodne, D.W. (1993) The Neurological Complications of Sepsis. *Annals of Neurology*, **33**, 94-100. <https://doi.org/10.1002/ana.410330115>
- [7] Berger, B., Gumbinger, C., Steiner, T. and Sykora, M. (2014) Epidemiologic Features, Risk Factors, and Outcome of Sepsis in stroke Patients Treated on a Neurologic Intensive Care Unit. *Journal of Critical Care*, **29**, 241-248. <https://doi.org/10.1016/j.jcrc.2013.11.001>
- [8] Eidelman, L.A., Putterman, D., Putterman, C. and Sprung, C.L. (1996) The Spectrum of Septic Encephalopathy: Definitions, Etiologies, and Mortalities. *JAMA*, **275**, 470-473. <https://doi.org/10.1001/jama.1996.03530300054040>
- [9] Fogelholm, R., Avikainen, S. and Murros, K. (1997) Prognostic Value and Determinants of First-Day Mean Arterial Pressure in Spontaneous Supratentorial Intracerebral Hemorrhage. *Stroke*, **28**, 1396-1400. <https://doi.org/10.1161/01.STR.28.7.1396>
- [10] Rabinstein, A.A., Atkinson, J.L. and Wijdicks, E.F. (2002) Emergency Craniotomy in Patients Worsening Due to Expanded Cerebral Hematoma: To What Purpose? *Neurology*, **58**, 1367-1372. <https://doi.org/10.1212/WNL.58.9.1367>

- [11] Yilmaz, G.R., Cevik, M.A., Erdinc, F.S., Ucler, S. and Tulek, N. (2007) The Risk Factors for Infections Acquired by Cerebral Hemorrhage and Cerebral Infarct Patients in a Neurology Intensive Care Unit in Turkey. *Japanese Journal of Infectious Diseases*, **60**, 87-91.
- [12] Mascia, L., Sakr, Y., Pasero, D., Payen, D., Reinhart, K. and Vincent, J.L. (2008) Extracranial Complications in Patients with Acute Brain Injury: A Post-Hoc Analysis of the SOAP Study. *Intensive Care Medicine*, **34**, 720-727. <https://doi.org/10.1007/s00134-007-0974-7>
- [13] Sykora, M., Diedler, J., Poli, S., *et al.* (2011) Autonomic Shift and Increased Susceptibility to Infections after Acute Intracerebral Hemorrhage. *Stroke*, **42**, 1218-1223. <https://doi.org/10.1161/STROKEAHA.110.604637>
- [14] Teasdale, G. and Jennett, B. (1974) Assessment of Coma and Impaired Consciousness. A Practical Scale. *The Lancet*, **304**, 81-84. [https://doi.org/10.1016/S0140-6736\(74\)91639-0](https://doi.org/10.1016/S0140-6736(74)91639-0)
- [15] Kwak, R., Kadoya, S. and Suzuki, T. (1983) Factors Affecting the Prognosis in Thalamic Hemorrhage. *Stroke*, **14**, 493-500. <https://doi.org/10.1161/01.STR.14.4.493>
- [16] Vincent, J.L., Moreno, R., Takala, J., *et al.* (1996) The SOFA (Sepsis-Related Organ Failure Assessment) Score to Describe Organ Dysfunction/Failure. *Intensive Care Medicine*, **22**, 707-710. <https://doi.org/10.1007/BF01709751>
- [17] Brott, T., Broderick, J., Kothari, R., *et al.* (1997) Early Hemorrhage Growth in Patients with Intracerebral Hemorrhage. *Stroke*, **28**, 1-5. <https://doi.org/10.1161/01.STR.28.1.1>
- [18] Ropper, A.H. (1986) Lateral Displacement of the Brain and Level of Consciousness in Patients with an Acute Hemispherical Mass. *The New England Journal of Medicine*, **314**, 953-958. <https://doi.org/10.1056/NEJM198604103141504>
- [19] Quattrocchi, K.B., Prasad, P., Willits, N.H. and Wagner, F.C. (1991) Quantification of Midline Shift as a Predictor of Poor Outcome Following Head Injury. *Surgical Neurology*, **35**, 183-188. [https://doi.org/10.1016/0090-3019\(91\)90069-L](https://doi.org/10.1016/0090-3019(91)90069-L)
- [20] Marshall, L.F., Marshall, S.B., Klauber, M.R., *et al.* (1991) A New Classification of Head Injury Based on Computerized Tomography. *Journal of Neurosurgery*, **75**, S14-S20.
- [21] Plum, F. and Posner, J.B. (1980) Supratentorial Lesions Causing Coma. In: *The Diagnosis of Stupor and Coma*, 3rd Edition, FA Davis, Philadelphia, 87-151.
- [22] Broderick, J.P., Brott, T.G., Duldner, J.E., Tomsick, T. and Huster, G. (1993) Volume of Intracerebral Hemorrhage: A Powerful and Easy-to-Use Predictor of 30-Day Mortality. *Stroke*, **24**, 987-993. <https://doi.org/10.1161/01.STR.24.7.987>
- [23] Cho, D.Y., Chen, C.C., Lee, H.C., Lee, W.Y. and Lin, H.L. (2008) Glasgow Coma Scale and Hematoma Volume as Criteria for Treatment of Putaminal and Thalamic Intracerebral Hemorrhage. *Surgical Neurology*, **70**, 628-633. <https://doi.org/10.1016/j.surneu.2007.08.006>
- [24] Morgenstern, L.B., Hemphill, J.C., Anderson, C., Becker, K., Broderick, J.P., Connolly, E.S., *et al.* (2010) Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*, **41**, 2108-2129. <https://doi.org/10.1161/STR.0b013e3181ec611b>
- [25] Broderick, J.P., Diringer, M.N., Hill, M.D., *et al.* (2007) Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators Determinants of Intracerebral Hemorrhage Growth: An Exploratory Analysis. *Stroke*, **38**, 1072-1075.

- <https://doi.org/10.1161/01.STR.0000258078.35316.30>
- [26] Zazulia, A.R., Diringer, M.N., Derdeyn, C.P. and Powers, W.J. (1999) Progression of Mass Effect after Intracerebral Hemorrhage. *Stroke*, **30**, 1167-1173.
<https://doi.org/10.1161/01.STR.30.6.1167>
- [27] Rodriguez-Luna, D., Rubiera, M., Ribo, M., Coscojuela, P., Piñeiro, S., Pagola, J., *et al.* (2011) Ultrawearly Hematoma Growth Predicts Poor Outcome after Acute Intracerebral Hemorrhage. *Neurology*, **77**, 1599-1604.
<https://doi.org/10.1212/WNL.0b013e3182343387>
- [28] Park, D.W., Chun, B.C., Kim, J.M., Sohn, J.W., Peck, K.R., Kim, Y.S., *et al.* (2012) Epidemiological and Clinical Characteristics of Community-Acquired Severe Sepsis and Septic Shock: A Prospective Observational Study in 12 University Hospitals in Korea. *Journal of Korean Medical Science*, **27**, 1308-1314.
<https://doi.org/10.3346/jkms.2012.27.11.1308>
- [29] del Zoppo, G., Ginis, I., Hallenbeck, J.M., *et al.* (2000) Inflammation and Stroke: Putative Role for Cytokines, Adhesion Molecules and iNOS in Brain Response to Ischemia. *Brain Pathology*, **10**, 95-112.
<https://doi.org/10.1111/j.1750-3639.2000.tb00247.x>
- [30] Wang, J. (2010) Preclinical and Clinical Research on Inflammation after Intracerebral Hemorrhage. *Progress in Neurobiology*, **92**, 463-477.
<https://doi.org/10.1016/j.pneurobio.2010.08.001>
- [31] Bone, R.C. (1996) Toward a Theory Regarding the Pathogenesis of the Systemic Inflammatory Response Syndrome: What We Do and Do Not Know about Cytokine Regulation. *Critical Care Medicine*, **24**, 163-172.
<https://doi.org/10.1097/00003246-199601000-00026>
- [32] Nishioku, T., Dohgu, S., Takata, F., *et al.* (2009) Detachment of Brain Pericytes from the Basal Lamina Is Involved in Disruption of the Blood-Brain Barrier Caused by Lipopolysaccharide-Induced Sepsis in Mice. *Cellular and Molecular Neurobiology*, **29**, 309-316. <https://doi.org/10.1007/s10571-008-9322-x>
- [33] Young, G.B., Bolton, C.F., Austin, T.W., *et al.* (1990) The Encephalopathy Associated with Septic Illness. *Clinical & Investigative Medicine*, **13**, 297-304.
- [34] Bone, R.C., Grodzin, C.J. and Balk, R.A. (1997) Sepsis: A New Hypothesis for Pathogenesis of the Disease Process. *Chest*, **112**, 235-243.
<https://doi.org/10.1378/chest.112.1.235>
- [35] Reinhart, K., Brunkhorst, F.M., Bone, H.G., *et al.* (2010) Prevention, Diagnosis, Therapy and Follow-Up Care of Sepsis: 1st Revision of S-2k Guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv-und Notfallmedizin (DIVI)). *German Medical Science*, **8**, Doc14.
- [36] Gumbinger, C., Hug, A., Mürle, B., *et al.* (2013) Early Blood-Based Microbiological Testing Is Ineffective in Severe Stroke Patients. *Journal of the Neurological Sciences*, **325**, 46-50. <https://doi.org/10.1016/j.jns.2012.11.014>