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Research Article

Early Risk and Influence Factors on Death of Sepsis Following Acute Intracerebral Hemorrhage: A Retrospective Cohort Study

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Keywords

- Sepsis
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Abstract

Background: The early risk and influence factors on death of sepsis following acute intracerebral hemorrhage (ICH) was previously unclear.

Methods: We retrospectively enrolled patients with identified sepsis after acute ICH from an ICU in China. We used Systemic Inflammatory Response Syndrome (SIRS) criteria to screen infection, and used Sequential Organ Failure Assessment (SOFA) criteria to diagnosis sepsis after acute ICH. The odd ratios (OR) of risk and outcome for sepsis were estimated by logistic regression.

Results: Among 507 acute ICH patients, 189 (37.3%, 189/507) had sepsis events during their hospitalizations. The early risk of sepsis in ICH patients at initial 48 hours was in 21.9% (111/507). The mortality of sepsis at initial 48 hours was in 49.5%. The main factor of influence early death was related to no using antibiotics within initial 3 hours (OR, 0.3; 95% CI, 0.153- 0.506), higher SOFA score (OR, 1.5; 95% CI, 0.304- 0.673), and higher SIRS criteria (OR, 1.5; 95% CI, 1.209- 1.938). At 30 days, the mortality of sepsis after ICH was in 55.6%, and the influence on death was associated with elevated serum lactate levels (OR, 1.3; 95% CI, 1.190-1.402), elevated SOFA scores (OR, 1.1; 95% CI, 1.032-1.151), higher NIHSS scores (OR, 1.1; 95% CI, 1.074-1.141), less ICU days (OR, 0.8; 95% CI, 0.734-845), and decreased GCS scores (OR, 0.7; 95% CI, 0.641-0.834).

Conclusions: High risk sepsis is an early complication and with high mortality following acute ICH. The antibiotics treatment for sepsis after ICH must be performed early.

INTRODUCTION

The acute spontaneous intracerebral hemorrhage (ICH) is the most common causes (26.0%) of critical illness in the intensive care unit (ICU) [1], with a 30-day mortality rate is 43%-52% [2,3]. Moreover, nearly half of these deaths occur during the first 2 days [3]. Transient survivors might still suffer from a life-threatening event due to not only neurological complications (e.g., brain edema, cerebral ischemia, and seizures) but also non-neurological complications, including pneumonia, respiratory failure/distress, and sepsis [4,5]. Recently, the incidence of high-risk systemic infections in ICH patients occur about 31% to 58% [6,7]. Moreover, sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection [8]. However, few availability report was found the trends of risk and influence on outcome for sepsis following patients with acute ICH. Our hypothesis was that the highest risk of sepsis after acute ICH would is within anitial 48 hours and with high mortality. The aim of this study was to assess whether sepsis after acute ICH would be with an early high risk and increased mortality. This study could facilitate early identification and more timely using antibiotics treatment for ICH patients with sepsis.

METHODS

Study settings

This study was a retrospective study of one -centers registered patients who were in the ICU of the Affiliated Shuyang Hospital of Xuzhou Medical University in Northern China (January 1, 2013 through December 31, 2017). This hospitals are the national hospital of three teaching levels. 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.

Identification of patients

Using the guidelines for the diagnosis of spontaneous intracerebral hemorrhage from the American Heart Association/

American Stroke Association (2015) [9]. We identified patients who had acute spontaneous ICH within the study period based on the prospective registration of their primary diagnosis in the ICU. We also examined the electronic medical records of these patients who were verified as having an acute ICH according to their cranial CT scan in emergency or in the first 24 hours after admission. Patients with a subdural hematoma, secondary ICH resulting from an underlying neoplasm, ICH resulting from an annticoagulation, and ICH due to the hemorrhagic transformation of an ischemic infarct were not included. We excluded the ICH patients who did not have data in their medical records due to either death/moribundity within first 24 hours.

Inclusion criteria for sepsis after acute ICH

Based on the new definition of sepsis-3, sepsis is one/more acute life-threatening organ dysfunction caused by infection. In this study, most patients had a primary brain failure due to acute ICH at initial. Thus, the inclusion criteria for sepsis after acute ICH had to include the following criteria: (1) a total of sequential [sepsis- related] organ failure assessment (SOFA) score >4; or a SOFA score for brain ≥2; (2) a systemic inflammatory response syndrome (SIRS) criteria ≥ 2; or with confirmed infection. We excluded those patients who were presented with evidence of organ dysfunction due to the effects of sedatives/other medications or non-infection related organ failure.

Identification of infection events and organ failure events

We identified infection events using a SIRS criteria ≥ 2 within initial 24 hours on the ICUs, which were used to screen infection events by previous studies (≥ 2 criteria for positive) [10-12]. The SIRS criteria as follows: (1) temperature greater than 38 or less than 36; (2) heart rate greater than 90 beats per minute;(3) tachypnea >20 respirations per minute or Pco2 <32mmHg; (4) white blood cell count greater than 12.0×10^9/L or less than 4.0×10^9/L, or more than 10% band forms. We also used quick CT scans to confirm a thorax infection.

The SOFA scores were calculated for one or more organ dysfunction after acute ICH, 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 ≥ 2 for a particular organ (on a scale from 0 to 4, with higher scores indicating multi-organ failure) [13].

The SOFA criteria used to assess acute brain failure as follow: the GCS score=10-12 points were only a mild brain failure (SOFA=2), and GCS <6 points were identified to be a severe brain failure (SOFA=4). In this population, most patients at initial were suddenly in coma (a GCS score< 8 or a motor function score of GCS < 6) due to acute ICH. Therefore, we had to use that a SOFA score was >4 for brain; or a SOFA score ≥2 with brain imaging not be explained by factors other than a septic brain failure. The SOFA criteria for other organ failure are shown in The Supplement Table 1.

Clinical assessments

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 were measured using the standard ABC/2 formula (A is the longest diameter of the hematoma, B is the widest diameter of the hematoma, and C is the thickness of the hematoma) [14].

The hospital charts of all ICH patients with and without sepsis were reviewed by a senior author (TDM) to extract the detailed clinical information about infections, organ dysfunction, and other findings during the study period. To assess the relationship between in-ICU mortality of sepsis patients at 48 hours and antbiotics treatment in initial 3 hours, we focused on the time from admission to starti antibiotic treatment.

Significant intracerebral hemorrhage growth was defined by a hematoma expansion of greater than one-third on a repeat CT scan [15], or hematoma enlargement leading to a brain herniation. Brain herniation was divided into uncal and central types [16].

Patients outcomes

The neurological status at 30 days was assessed using the Glasgow Outcome Scale (GOS; ranging from 1=death to 5=good recovery) obtained from the medical records. If the patient was moribundity transferred out of ICU, the information was from the interviewed proxies to ascertain the circumstances of the participant's death.

Table 1: Characteristics of sepsis after acute ICH patients, N=189.

Characteristics	All cases (N=189)
Female, n (%)	75 (39.7)
Median age (years, range)	62.7(30-94)
Median time from onset to infection (h, range)	1.3 (0,5-120.0)
Site of infection	
Respiratory n (%)	140 (74.1)
Urinary tract, n (%)	23 (12.2)
Intestinal tract, n (%)	11(5.8)
Other, n (%)	15 (7.9)
Possitive body fluid culture, n (%)	90 (48.9) §
Sepsis-related organ failure	
Brain failure, n (%)	141(74.6)#
Septic shock, n (%)	23 (12.2)
Respiratory failure, n (%)	56 (29.6)
Renal failure, n (%)	31 (16.4)
Hepatic failure, n (%)	16 (8.5)
Multiple organ failure, n (%)	63 (33.3)
Mortality of sepsis at initial 48 hrs, n (%)	55 (49.5)
Mortality of sepsis at 30 days, n (%)	105 (55.6)

§, including blood culture, sputun culture, and urine culture., brain failure due to a nosocomial coma, or a diffuse brain lesion confirmed by imaging,Others includes skin, central nervous system, and unknown. ICH, intracerebral hemorrhage; SAE, sepsis associated encephalopathy; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; SOFA, Sequential [sepsis- related] Organ Failure Assessment (scale ranges from 0 to 4, ≥ 2 indicates organ failure, and higher scores indicate more severe organ failure);

Statistical methods

Discrete data are presented as numbers and percentages, means and standard deviations, medians and interquartile ranges, or proportions with 95% confidence intervals. Accordingly, chi-square tests were summarized as numbers with percentages. Independent *t* test were used to compare differences in continuous variables between the two groups. Chi-squared tests were used to explore the relationships between baseline variables. Multivariate-adjusted odd ratios (ORs) and 95% confidence intervals (CIs) were estimated using a logistic regression model. The Cox proportional hazards model was used to examine baseline sepsis status and to determine whether the variables played a role in the risk of death during the first 30days. Survival analysis was performed using the Kaplan-Meier curve method. Differences between groups were considered significant if the p-values were <0.05.The statistical calculations were performed using a commercial computerized statistics package (SPSS 10.0).

RESULTS

A total of 716 adult acute ICH patients were recruited from the general ICU of Shuyang People's Hospital. Of them, 209 ICH patients who were death or moribundity within first 24 hours were excluded due to missing data in their medical records. Ultimately, 507 acute ICH patients were included in the present investigation.

Of 507 acute ICH patients, 48.9% (248/507) of acute ICH cases were screened to infection events (SIRS criteria ≥ 2). The time of starting antibiotic treatment considered infection: about 20% was within initial 3 hrs. 65 % of the patients was in 4 hours later on ICU. Only 15% did not use any antibiotics. The diseases underlying of ICH and other baseline characteristics see in The Supplement Table II.

The characteristics of sepsis after acute ICH is shown in Table 1. A total of 189 sepsis after ICH were diagnosed by the inclusion criteria, which was in 37.3% (189/507) of acute ICH in ICU. The median time from onset to infection was 1.3 hours. The most common acute organ failure for sepsis after ICH was acute brain failure (74.6%). The mortality at initial 48 hours was in 49.5% and at 30 days in 55.6%.

Table 2 shows the results for variable on risk of ICH patients with and without sepsis within initial 48 hours. The early risk of sepsis after ICH patients at initial 48 hours was in 21.9% (111/507). We found that sepsis patients were significantly more likely to present with a lower GCS score (6.3 ± 1.5 vs 7.0 ± 2.3,), higher SOFA score (6.8 ± 1.9 vs. 3.8 ± 2.1), higher SIRS criteria (3.1 ± 1.1 vs. 1.4 ± 1.4), and no using antibiotic within initial 3 hours (89.2% vs. 78.5%) than those without sepsis(all p<0.05). The blood pressure of patients were significantly lower in the sepsis group than in the non-sepsis group (170.4 ± 43.4 vs.182.3 ± 37.9 and 96.5 ± 26.5 vs.102.3 ± 22.8, respectively). However, only higher SOFA score (OR, 1.5; 95% CI, 0.304- 0.673), higher SIRS criteria (OR, 1.5; 95% CI,1.209- 1.938), and no using antibiotics treatment within initial 3 hours (OR, 0.3; 95% CI, 0.153- 0.506) were established by logistic regression as independent risk factors for ICH patients with sepsis within initial 48 hours (Table 3).

The variables influencing outcome in ICH patients with and without sepsis at 30 days shows in the Table 4. Cox regression risk analysis demonstrated that only elevated lactate level (OR, 1.3; 95% CI,1.190-1.402; p=0.000) lower GCS score (OR, 0.7; 95% CI, 0.641-0.834; p=0.000) increased NIHSS score (OR, 1.1; 95% CI, 1.074-1.141; p=0.000)higher SOFA score (OR, 1.1; 95% CI, 1.032-1.151; p=0.009), and less ICU days (OR, 0.8; 95% CI, 0.734-845; p=0.000) were significantly related to survival in acute ICH patient (Table 5).

Based on Kaplan- Meier survival curves that included ICH patients with and without sepsis events during the 30-day follow-

Table 2: Variables the risk of in ICH patients with and without sepsis within first 48 hours (n=507).

Variable	ICH with sepsis at 48 hrs (n=111)	ICH without sepsis at 48 hrs (n=396)	p Value
Male gender (%)	69 (62.2)	231 (58.3)	0.513
Age (years, mean ± SD)	61.7 ± 13.0	63.2 ± 12.8	0.266
SBP (mmHg, mean ± SD)	170.4 ± 43.4	182.3 ± 37.9	0.015
DBP (mmHg, mean ± SD)	96.5 ± 26.5	102.3 ± 22.8	0.021
GCS score (mean ± SD)	6.3 ± 1.5	7.0 ± 2.3	0.002
INHSS score (mean ± SD)	27.5 ± 7.0	27.1 ± 6.9	0.614
Hematoma volume (mL, mean ± SD)	35.4 ± 28.9	38.7 ± 29.1	0.289
Lactic acid (mmol/L, mean ± SD)	2.4 ± 1.1	2.2 ± 1.2	0.143
Serum glucose (mean ± SD)	8.3 ± 3.0	8.2 ± 6.0	0.913
Sepsis-SOFA score (mean ± SD)	6.8 ± 1.9	3.8 ± 2.1	0
SIRS criteria,(mean ± SD)	3.1 ± 1.1	1.4 ± 1.4	0
No using antibiotic within initial 3 h, n (%)	99 (89.2)	311 (78.5)	0.013
Intubation breathing/mechanical ventilation, n (%)	82 (73.9)	276 (69.7)	0.412
Mortality at initial 2 days,n (%)	55 (49.5)	10 (2.5)	0

Abbreviations: ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; SIRS: systemic inflammatory response syndrome; GCS: Glasgow Coma Scale; SOFA: Sequential [sepsis-related] Organ Function Assessment.

Table 3: Logistic regression analysis to identify the early risk of ICH patients with sepsis within first 48 hours (n=507).

Variable	OR	95% CI for OR	p value
No using antibiotics within initial 3hrs	0.3	0.153-0.506	0
SIRS criteria≥2	1.5	1.209-1.938	0
SOFA score	1.5	1.304-1.718	0

Abbreviations: ICH: intracerebral hemorrhage; SIRS: systemic inflammatory response syndrome; SOFA: Sequential [sepsis-related] Organ Failure Assessment.

Table 4: Variables influencing outcome in ICH patients with and without sepsis at 30 days (n=507).

Variable	ICH with sepsis At 30 d (n=189)	ICH without sepsis at 30 d (n=318)	p Value
Male gender (%)	114 (60.3)	186 (58.5)	0.709
Age (years, mean ± SD)	62.2 ± 12.5	63.3 ± 13.1	0.365
SBP (mmHg, mean ± SD)	172.7 ± 46.5	183.6 ± 34.3	0.003
DBP (mmHg, mean ± SD)	97.5 ± 27.9	103.1 ± 20.9	0.011
GCS score (mean ± SD)	6.3 ± 1.5	7.2 ± 2.4	0
Lactic acid (mmol/L, mean ± SD)	2.4 ± 1.1	2.1 ± 1.2	0
Serum glucose (mean ± SD)	8.7 ± 8.2	8.0 ± 3.1	0.222
Sepsis-SOFA score (mean ± SD)	7.2 ± 1.7	2.9 ± 1.0	0
SIRS criteria,(mean ± SD)	3.3 ± 0.8	0.9 ± 1.0	0
INHSS score (mean ± SD)	28.2 ± 6.6	26.6 ± 7.0	0.012
Nosocomial-onset coma, n (%)	43 (22.8)	24 (7.5)	0
Hematoma volume (mL, mean ± SD)	35.5 ± 28.2	39.4 ± 29.5	0.147
Intraventricular extension (%)	98 (51.9)	161(51.2)	0.854
Intubation breathing/echanical ventilation, n (%)	137 (72.5)	221 (69.5)	0.483
Operation, n (%)	53 (28.0)	74 (23.3)	0.245
GOS score at 30 days (%)			
4-5 score (%)	13 (6.9)	96 (30.2)	0
2-3 score (%)	71 (37.6)	92 (28.9)	0.049
1 score (%)	105 (55.6)	130 (40.9)	0.002

Abbreviations: ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; SIRS: systemic inflammatory response syndrome; GCS: Glasgow Coma Scale; SOFA: Sequential [sepsis-related] Organ Failure Assessment; GOS: Glasgow Outcome Scale (range from 1=death to 5=good recovery).

Table 5: Cox regression analysis to identify the influence on outcome in ICH patients with sepsis at 30 days (n=507).

Variable	OR	95% CI for OR	p value
Serum lactate level	1.3	1.190-1.402	0
GCS score	0.7	0.641-0.834	0
NIHSS score	1.1	1.074-1.141	0
SOFA score	1.1	1.032-1.151	0.002
ICU days	0.8	0.734-0.845	0

Abbreviations: ICH: intracerebral hemorrhage; GCS: Glasgow Coma **Scale;** NIHSS: National institutes of Health stroke scale; SOFA: Sequential [sepsis-related] Organ Failure Assessment; ICU: intensive care unit.

up period, the ORs for worse survival was significantly associated with ICH patients with sepsis events (OR, 4.345; p=0.037) (Figure 1).

DISCUSSION

Although the prevalence of sepsis (1.7%-33.7%) among acute ICH patients have been estimated by previous studies [17,18], the accurate risk for sepsis is still unclear. In the present study, 37.3% of sepsis events in acute ICH patients in ICU were diagnosed by jointing SIRS and SOFA criteria. Moreover, our data shown that the mortality of sepsis in patients with acute ICH at initial 48 hours was in 49.5% and at initial 30 days in 55.6%.

In fact, several studies have demonstrated that the prevalence of infection among ICH patients is high [7,19-21], and that subsequent sepsis events in stroke patients are very common [22,23]. In the present study, we used the SIRS criteria

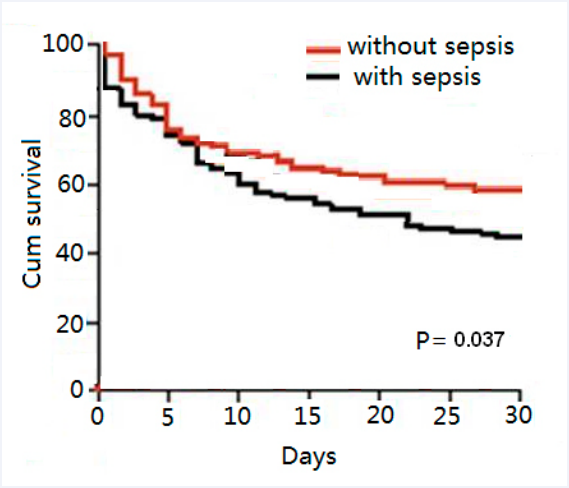

Figure 1 Kaplan-Meier survival curves showing that ICH patients with sepsis events had significantly worse survival than ICH patients without sepsis events during the 30-day follow-up (OR, 4.345; p=0.037).

to screen the early infection event, which was clearly shown that the prevalence of early infection among ICH patients was up to 48.9%.

Importantly, we found that the high risk sepsis after acute ICH mainly was within initial 48 hours on admission, not only indicated the early source of sepsis involved community acquired infection, but also suggested a time bundle for sepsis care and rapid treatment of antibiotics. And we also found that the most common acute organ failure for sepsis after ICH was acute brain failure. This is consistent with previous study [24].

Interestingly, we found that hematoma volumes did not differ between the groups within initial 48 hours, but an increase in the risk of death was observed in ICH patients with sepsis compared to those without sepsis. Therefore, our study indicated that sepsis after ICH contributed to an increased risk of death in patients with acute ICH.

More importantly, ICH patients with sepsis without using antibiotics treatment within initial 3 hours shown that a delay time given antibiotic treatment was associated with an high risk in-ICU mortality, which was confirmed by our study, supporting that rapid antibiotics treatment within the first 3 hours of sepsis can reduce hospital mortality [25].

Moreover, Cox regression analysis revealed that the risk factors for worse survival in sepsis after ICH at initial 30 days were related to the decreased GCS scores, less ICU days, higher NIHSS scores, higher SOFA scores, and elevated lactate level.

To the best of our knowledge, previous studies have found that a decreased GCS scores, increased ICH volume, and increased NIHSS scores was related to neurological deterioration and the high rate of poor outcomes in acute ICH patients [9,26,27], and our current study also found that the decreased GCS scores, increased ICH volume, and increased NIHSS scores were related to the worse outcomes. Although several large clinical studies also confirmed that an increased SOFA scores and elevated lactate levels is the main markers for sepsis in non-ICH population [8,11,13,28], we found that an elevated SOFA scores and elevated serum lactate levels were more likely to have a strong association with the risk of death in ICH population with sepsis at initial 30 days.

However, our data shown that a life-threatening risk of over 4-fold on death in ICH patients with sepsis was confirmed by a Kaplan–Meier curve analysis. Therefore, we considered that the optimal time of rapid antibiotics treatment for sepsis after ICH who had a median time from onset to infection only 1.3 hours has to perform within initial 1 hour on admission.

Some limitations of our study must be considered. First, based on SOFA clinical criteria, sepsis with a GCS<13 score is identified as a brain failure. In fact, this is also called sepsis associated encephalopathy (SAE), which is accounted for approximately 70% of the septic patients [24]. Patients with GCS scores of 12 or less potential a SAE and with higher mortality have been found by a previous study [29]. Moreover, patients with a low GCS score was more likely to exhibit multiple organ failure (including brain failure) which was also been confirmed by previous studies [5,24,29]. However, in this population, more than 70 % ICH patients within initial 2 days had an acute brain failure. In order to avoid the acute brain failure (a GCS score<13) was misdiagnosed as SAE, we mainly set the baseline SOFA score >4 as criteria of diagnosing sepsis events. Thus, the risk of septic events among acute ICH patients in the current study might be underestimated. Second, acute ICH with SAE is always a challenging diagnosis. The patients with SAE usually associated with a vasogenic brain edema or subcortical white matter ischemic lesions on imaging [30,31], which is more likely to be less sensitive on CT than on MRI. Thus, brain MRI scans for acute ICH patients with septic brain lesions are very important. However, MRI was less performed in the present study. Therefore, further prospective brain MR studies are needed.

CONCLUSIONS

Sepsis is a early frequent complication of acute ICH, and it greatly increases the risk of death among ICH patients in ICUs. Our findings demonstrate that the high risk sepsis after acute ICH mainly is within initial 48 hours on admission. The findings facilitate earlier identification and more timely antibiotics treatment for ICH patients with sepsis.

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