Impact and risk factors of sepsis on long-term outcomes after spontaneous intracerebral hemorrhage

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To the Editor: Spontaneous intracerebral hemorrhage (sICH) has a high incidence of acute cerebrovascular illness in elderly people in China, with high mortality and long-term functional impairment among survivors. However, there is still controversy over whether secondary infection during the course of hospitalization after ICH has a negative impact on long-term function. Ali et al[1] illustrated that infection has nothing to do with the functional prognosis of patients 90 days after ICH. In contrast, Lord et al[2] found a significant correlation between complicated infection after ICH and poor prognosis. Previous studies indicate that sepsis-associated encephalopathy is an independent risk factor for nosocomial coma after ICH,[3,4] but clinical studies on the proportion and impact of sepsis on long-term outcomes after sICH are still lacking.

We retrospectively collected data from all adult patients (≥18 years) with sICH admitted to the Neurosurgical Intensive Care Unit of Southwest Hospital between January 2018 and June 2020. The present study was approved by the Ethics Committee of Southwest Hospital (KY2021042) and registered in the Chinese Clinical Trial Registry (ChiCTR2100043517). Consent to participate was waived due to the retrospective and observational nature of this study. The diagnosis of sepsis was based on Sepsis-3 definitions and diagnostic criteria in 2016. Patients with the following were excluded: chronic organ dysfunction, ICH due to neoplastic or vascular malformation causes, no treatment until discharge, or history of stroke. The process of patient inclusion and exclusion is presented in Supplementary Figure 1, http://links.lww.com/CM9/A903.

Of the 239 patients identified, 68 (28.9%) met the Sepsis-3 criteria and had a higher mean age (59.6 ± 12.5 years) than patients without sepsis (P < 0.001). sICH patients experiencing sepsis had worse Glasgow Coma Scale (GCS) scores (P < 0.001) and a higher incidence of hematoma extending into the lateral ventricles (47.8%, P = 0.015), but no difference in diabetes mellitus, activated partial thromboplastin time (APTT), or thrombin time at admission was observed. We also found patients with sepsis who underwent more invasive operations, including craniotomy (59.4%, P = 0.010), continuous lumbar cistern drainage/lumbar puncture (LP) (47.8%, P < 0.001), deep vein catheterization (50.7%, P < 0.001), and endotracheal intubation/tracheotomy (73.9%, P < 0.001), whereas there was no significant difference regarding hematoma location (P = 0.222). In addition, an increased concentration of D-dimer was observed in the sepsis group at admission. The details are shown in Table 1.

Twenty-eight day mortality data were available for 204 patients, 60 of whom had sepsis. Forty-seven patients were lost to follow-up at 6 months (19.7%), and the poor outcome rate was 66.7% (128 of 192 patients). In all patients, there was a trend toward higher mortality in those patients with sepsis (15/60, 25.0%) than those without sepsis (3/144, 2.1%) at 28 days after ICH (P < 0.001). Worse modified Rankin Scale (4.40 ± 1.50) and Glasgow Outcome Scale (2.66 ± 1.53) scores as well as a higher rate of poor outcomes (67.2%) were observed in the sepsis group at 6 months after ictus. We compared the peak level of procalcitonin (PCT) between the two groups (11.13 ± 22.96 vs. 0.60 ± 0.85 ng/mL) and demonstrated that there was a significant difference (P < 0.001). The
The patients with sepsis were divided into the poor outcome group and good outcome group by outcomes at the 6-month follow-up. The Acute Physiology and Chronic Health Evaluation II score in the poor outcome group of sepsis patients was $18.31 \pm 6.04$, which was significantly higher than that in the good outcome group ($10.26 \pm 4.85$, $P < 0.001$). There were significant differences among the respiratory system ($P = 0.002$), urinary system ($P = 0.008$), hematological system ($P = 0.002$), and nervous system ($P = 0.001$) scores. However, in the comparison between the sepsis group and the non-sepsis group, we also found a significant difference in the circulatory system score ($P = 0.027$) in addition to the abovementioned systems.

The results revealed that compared to the nonsepsis group, the D-dimer level, and APTT increased, whereas the platelet and lymphocyte counts decreased, in the sepsis group ($P < 0.05$). The details are shown in Supplementary Table 2, http://links.lww.com/CM9/A903.

In univariate analysis, age, GCS at admission, hematoma extending into the side ventricles, continuous lumbar cistern drainage/LP, deep vein catheter, endotracheal intubation/tracheotomy, and PCT concentration at admission were associated with sepsis occurrence in sICH patients. In multivariate logistic regression analysis, we considered the abovementioned variables and found that age, continuous lumbar cistern drainage/LP, and endotracheal intubation/tracheotomy were independently associated with sepsis occurrence after sICH. The details are

**Table 1: Baseline characteristics and clinical features of sICH patients with or without sepsis.**

| Variables                              | Overall ($n = 239$) | Yes ($n = 69$) | No ($n = 170$) | $P$ value |
|----------------------------------------|---------------------|---------------|---------------|-----------|
| Demographics                           |                     |               |               |           |
| Age (years), mean (SD)                 | 54.88 (12.38)       | 59.55 (12.47) | 52.83 (11.82) | $< 0.001$ |
| Female, $n$ (%)                        | 76 (31.80)          | 23 (33.33)    | 53 (31.18)    | 0.745     |
| Smoking history, $n$ (%)               | 97 (40.59)          | 21 (30.43)    | 76 (44.71)    | 0.041     |
| Drinking history, $n$ (%)              | 105 (43.93)         | 24 (34.78)    | 81 (47.65)    | 0.069     |
| Hypertension, $n$ (%)                  |                     |               |               | 0.046     |
| None                                   | 29 (12.13)          | 4 (5.80)      | 25 (14.71)    |           |
| Class I                                | 17 (7.11)           | 2 (2.90)      | 15 (8.82)     |           |
| Class II                               | 35 (14.64)          | 9 (13.04)     | 26 (15.29)    |           |
| Class III                              | 158 (66.11)         | 54 (78.26)    | 104 (61.18)   |           |
| Diabetes mellitus, $n$ (%)             |                     |               |               | 0.046     |
| None                                   | 29 (12.13)          | 12 (17.39)    | 17 (10.00)    | 0.112     |
| GCS at admission, median (IQR)         | 12.00 (8.00–14.00)  | 8.50 (6.00–13.00) | 12.50 (9.00–14.00) | $< 0.001$ |
| Hematoma volume (mL), mean (SD)        | 39.00 (22.73)       | 43.62 (20.66) | 36.94 (23.38) | 0.063     |
| Hematoma location, $n$ (%)             |                     |               |               | 0.222     |
| Occipital lobe                         | 15 (6.28)           | 3 (4.5)       | 12 (7.06)     | 0.433     |
| Parietal lobe                          | 28 (11.72)          | 9 (13.04)     | 19 (11.18)    | 0.684     |
| Temporosphenoid lobe                   | 39 (16.32)          | 9 (13.04)     | 30 (17.65)    | 0.382     |
| Frontal lobe                           | 17 (7.11)           | 5 (7.25)      | 12 (7.06)     | 0.959     |
| Epencephal                             | 12 (5.02)           | 5 (7.25)      | 7 (4.12)      | 0.315     |
| Thalamus                               | 15 (6.28)           | 9 (13.04)     | 6 (3.53)      | 0.006     |
| Basal ganglia                          | 158 (66.11)         | 42 (60.87)    | 116 (68.24)   | 0.275     |
| Brainstem                              | 10 (4.18)           | 3 (4.35)      | 7 (4.12)      | 0.935     |
| Encephalocele                          | 2 (0.84)            | 0             | 2 (1.18)      | 0.365     |
| Hematoma extending into lateral ventricle, $n$ (%) | 86 (35.98) | 33 (47.33) | 53 (31.18) | 0.015 |
| Invasive operations, $n$ (%)           |                     |               |               |           |
| Craniotomy                             | 111 (43.02)         | 41 (59.42)    | 70 (41.18)    | 0.010     |
| Decompressive craniotomy               | 50 (20.92)          | 19 (27.54)    | 31 (18.24)    | 0.109     |
| EVD                                    | 39 (16.32)          | 15 (21.74)    | 24 (14.12)    | 0.149     |
| Continuous lumbar cistern drainage/LP  | 73 (30.54)          | 33 (47.83)    | 40 (23.53)    | $< 0.001$ |
| Deep vein catheter                     | 81 (33.89)          | 35 (50.72)    | 46 (27.06)    | $< 0.001$ |
| Endotracheal intubation/tracheotomy     | 93 (38.91)          | 51 (73.91)    | 42 (24.71)    | $< 0.001$ |
| PCT at admission (ng/mL), mean (SD)    | 0.19 (0.85)         | 0.42 (1.53)   | 0.09 (0.15)   | 0.105     |
| Coagulation indicators at admission, mean (SD) | 27.32 (4.07) | 26.87 (3.88) | 27.52 (4.15) | 0.317     |
| APTT (seconds)                         | 17.74 (2.48)        | 17.73 (2.32)  | 17.74 (2.56)  | 0.974     |
| TT (seconds)                           | 1.35 (2.36)         | 1.91 (3.14)   | 1.10 (1.86)   | 0.031     |

Independent-samples $t$ test was used to compare continuous variables presented as mean (SD), and $\chi^2$ test of independence compared all categorical variables presented as $n$ (%). Variables that not followed normal distribution and equal were presented as median (IQR) and compared by Mann-Whitney $U$ test. APTT: Activated partial thromboplastin time; EVD: External ventricular drainage; GCS: Glasgow Coma Scale; IQR: Interquartile range; LP: lumbar puncture; PCT: Procalcitonin; sICH: Spontaneous intracerebral hemorrhage; SD: standard deviation; TT: Thrombin time.

Details are presented in Supplementary Table 1, http://links.lww.com/CM9/A903.
presented in Supplementary Table 3, http://links.lww.com/CM9/A903.

The variables, including sepsis occurrence, age, GCS at admission, hematoma volume, hematoma extending into the side ventricles, craniotomy, decompressive craniotomy, external ventricular drain, continuous lumbar cistern drainage/LP, deep vein catheter, endotracheal intubation/tracheotomy, peak PCT value, APTT, D-dimer, lymphocytes, and red blood cells (RBCs) at peak PCT, were significantly associated with poor outcomes in univariate analysis. Above that, multivariate analysis presented that sepsis (odd ratio: 5.098, 95% confidence interval: 1.784–14.569, P = 0.002), age, drink history, hematoma volume, hematoma extending into the side ventricles, craniotomy, deep vein catheter, and endotracheal intubation/tracheotomy, were independently associated with poor outcomes at 6 months after ictus. The details are presented in Supplementary Table 4, http://links.lww.com/CM9/A903.

Significant association with poor outcome in sICH patients could be found on GCS at admission, hematoma volume, hematoma extending into the side ventricles, endotracheal intubation/tracheotomy, APTT, and RBC at peak PCT in univariate analysis. Multivariate analysis revealed that hematoma volume, GCS at admission, and APTT at peak PCT were independently associated with poor outcomes at 6 months after ictus. The details are presented in Supplementary Table 5, http://links.lww.com/CM9/A903.

Approximately, 53.6% (128/239) of sICH patients had infections, and more than half of them (69/128, 53.9%) were diagnosed with sepsis. Tracing the source of the infection, we found that the lower respiratory tract was the primary place for nosocomial infection (89/128, 69.5%). Meanwhile, clinical operation infections were not a small proportion (15/128, 11.7%) and comprised catheter-related infections, operative wound infections, and ventilator-related infections. More details are showed in Supplementary Figure 2, http://links.lww.com/CM9/A903.

Among 51 sepsis patients with germiculture positivity (73.9%), the main infectious bacteria were Klebsiella pneumoniae (25, 49.0%). In addition, 16 patients (31.4%) had fungal infections. Over the whole course, we observed that more than half of sepsis patients (55.1%) suffered from an infection peak at 3 to 5 days after sICH. The details are presented in Supplementary Figures 3 and 4, http://links.lww.com/CM9/A903.

In recent years, sepsis mortality has shown a decreasing trend in the general ICU population by virtue of early recognition and effective management.[5] But the influence of sepsis after sICH on long-term outcomes is controversial and lacks specific study. Our study investigated the higher frequency of sepsis after sICH than the common incidence in ICU patients in the previous reports (16.7%–18.9%).[5] and found that the occurrence of sepsis was associated with a 12-fold increase in mortality at 28 days after onset (25% for sepsis patients and 2.08% for nonsepsis patients, P < 0.05). The proportion of poor outcomes in patients with sepsis was approximately three times higher than that in patients without sepsis. Although the study has many limitations, such as a lack of multicenter research and the inaccuracy of retrospective diagnosis, it still provides data to improve early diagnosis and optimize treatment of infection and sepsis in sICH patients to have a major benefit on patient outcomes. We also found that older age, larger hematoma volume, and more invasive operations were independent risk factors for sepsis in sICH. The serum PCT concentration was elevated during the period of ICH combined with sepsis, mostly peaked at 3 to 5 days after ICH along with the peak period of brain edema and was tightly related to poor outcomes.

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Conflicts of interest

None.

Trial registration

Chinese Clinical Trial Registry, ChiCTR2100043517. Registered February 21, 2021.

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