Prevalence of and risk factors for infections in patients with spontaneous intracerebral hemorrhage at the intensive care unit

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Intracerebral hemorrhage (ICH) is a severe neurological disease with high morbidity and mortality.[1,2] Infection rates of 26% to 58% have been reported in patients with ICH.[3] Infections not only increase the length of hospital stay and healthcare costs but also increase mortality, worsen functional outcomes, and increase hospital readmission rates. The current study sought to determine the prevalence of and risk factors associated with infections in patients with ICH and to investigate their impact on patient outcome upon discharge from the hospital.

The discharge records of the patients who were diagnosed with ICH in the intensive care unit (ICU) of our hospital between January 2015 and January 2019 were analyzed retrospectively. Exclusion criteria were hospitalized for <72 h; age ≤18 years; or ICH due to trauma, tumor, arteriovenous malformation, or infarction. Patients were also excluded if key data (computed tomography results, Glasgow Coma Scale [GCS], modified Rankin Scale [mRS]) were not recorded. Prophylactic antibiotics were used for no more than 2 days to prevent surgery-related infections or for an increase in white blood cell (WBC) count. The routine clinical treatments for all patients were hemostasis, decreasing intracranial pressure, anti-infection, and rehabilitation.

The patient data were divided into two groups based on whether any infection occurred during the hospital stay. The baseline demographics, risk factors, imaging findings, initial GCS, Acute Physiology and Chronic Health Evaluation (APACHE) II score, history of aspiration, the incidence of invasive procedures (such as mechanical ventilation, central venous, and urinary catheters), nasogastric feeding, surgical hematoma evacuation, external ventricular drainage, intubation, temperature, WBC count and C-reactive protein (CRP) upon admission, complications (length of stay [LOS] in the ICU and mortality), and outcomes were compared between groups. The survival and functional outcomes of all patients were assessed at the time of discharge from the hospital. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. Poor outcome was defined as an mRS score of 3 to 5.

Descriptive data are presented as the means ± standard deviations (SDs) or medians with upper and lower quartiles. Students' t-tests, χ^2 tests, or Mann-Whitney U tests were used for between-group comparisons according to the distribution of the data. Univariate and multivariate regression analyses were performed to identify factors for infections. All statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA). $P < 0.050$ was considered statistically significant, and all confidence intervals (CIs) were 95%.

Data from 400 charts were reviewed [Supplementary Figure 1, http://links.lww.com/CM9/A728]. Seventy-seven cases were excluded because of incomplete data. Therefore, 323 ICH patients were included in the primary analysis. A total of 183 patients (56.7%, 95% CI: 0.522–0.630) were clinically diagnosed with at least one type of infection. Patients with infections had longer days in hospital (17.40 ± 11.00 days $vs.$ 10.70 ± 7.20 days, $P < 0.050$), higher admission APACHE II score (14 ± 6 $vs.$ 10 ± 5, $P < 0.050$), and poorer outcome (discharge mRS score ≥3, 80 [24.8%] $vs.$ 28 [8.6%], $P < 0.050$). The most common infections were pneumonia (79.8%, 95%

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CI: 0.754–0.842), urinary tract infections (UTIs) (22.9%, 95% CI: 0.206–0252), bloodstream infections (18%, 95% CI: 0.138–0.222), and meningitis or ventriculitis (4.9%, 95% CI: 0.026–0.073). The ICU mortality rate was 16.1%. Gram-negative bacteria were the leading causative organisms. The top three species were *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. There were 230 strains of bacteria altogether; among them, 54 strains were *A. baumannii*, 46 strains were *K. pneumoniae*, and 27 strains were *S. aureus* [Supplementary Table 2, http://links.lww.com/CM9/A728]. The highest prevalence of pneumonia-causing microorganisms was pandrug-resistant *K. pneumoniae*, followed by pandrug-resistant *A. baumannii* and pandrug-resistant *Pseudomonas aeruginosa*. The three most common UTI-causing microorganisms were pandrug-resistant *A. baumannii*, *Candida albicans* (which was sensitive to fluconazole), and pandrug-resistant feces *Enterococcus*. Additionally, the microorganism with the highest prevalence that caused bloodstream infections was multidrug-resistant *S. aureus*, followed by *Staphylococcus epidermidis* and *A. baumannii*. Multidrug-resistant *S. aureus* and pandrug-resistant *A. baumannii* were the main microorganisms that caused meningitis or ventriculitis.

Univariate analysis of infections showed that 13 factors were significantly (*P* < 0.050) associated with infections, as shown in Table 1. The outcomes of the multivariate regression model are also shown in Table 1. After adjusting for all the significant factors identified in the univariate analysis, the odds ratio (OR) of diabetes mellitus for developing infections was 7.08 (95% CI: 2.310–21.740; *P* = 0.001). The OR of developing infections for subjects who required the prophylactic use of antibiotics was 1091.08 (95% CI: 165.06–7212.27; *P* = 0.001). A greater number of days in the hospital significantly increased the risk of infections (OR, 3.39; 95% CI: 1.060–10.830; *P* = 0.039). Patients with infections were more likely than those without infections to have a lower GCS at admission (OR, 6.45; 95% CI: 1.130–36.710, *P* = 0.036).

Patients with infections had a higher in-hospital mortality rate than those without infections (10.5% *vs.* 5.6%, respectively; *P* = 0.220), but the difference was not statistically significant. The presence of infections had a significant impact on the outcome at discharge (43.2% *vs.* 20.3%, *P* < 0.001). Patients with respiratory infections alone had worse outcomes than those with urinary infections alone (46.0% *vs.* 36.8%; *P* = 0.001). Next, the LOS of subjects discharged alive was compared with that of those who died in the hospital because of infections. The mean LOS ± SD for patients with and without infections who were discharged alive was 18.54 ± 11.11 days and 11.25 ± 7.33 days, respectively (*P* < 0.001). For the subjects who died in the hospital, the mean LOS for patients with and without infections was significantly different (12.41 *vs.* 7.50 days, *P* = 0.042).

In this study, we investigated the rate of infections and the risk factors associated with infections in patients with ICH in the ICU. Approximately 56.7% of the patients with ICH developed infections which underline the susceptibility of ICH patients to infections. Specifically, the development of infections in patients with ICH increases the risk of adverse outcomes, including the LOS in the ICU and the likelihood of poor outcomes, which is consistent with previous studies [Supplementary Table 1, http://links.lww.com/CM9/A728].[4] The infection-related indicators can be assessed using clinical markers like fever, APACHE II score, and biomarkers like WBC, CRP, and neutrophil-to-lymphocyte ratio (NLR). NLR has also been proposed as a valuable outcome predictor in different neurological disorders, such as stroke and traumatic brain injury. For instance, a higher level of NLR in patients with ICH is independently related to poor mortality and 90-day outcome after ICH. High neutrophils promote the neuro-inflammatory cascade worsen edema and hematoma growth, increase the mass effect and intracranial pressure, and result in neurological deterioration. There are several potential mechanisms by which infections may worsen outcomes after ICH, including inflammation,

Table 1: Univariate and multivariate analyses of nosocomial infection.

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Smoking	2.82	1.760–4.530	<0.001	/	/	/
Diabetes mellitus	4.05	2.460–6.690	<0.001	7.08	2.31–21.74	0.001
Prophylactic use of antibiotics	478.96	110.920–2068.100	<0.001	1091.08	165.06–7212.27	0.001
Days in hospital	4.58	2.850–7.360	<0.001	3.39	1.06–10.83	0.039
Admission GCS	1.22	1.150–1.300	<0.001	6.45	1.13–36.71	0.036
Admission APACHE II score	0.89	0.850–0.930	<0.001	/	/	/
Operation	4.32	2.690–9.940	0.001	/	/	/
Invasive procedure	1.76	1.070–2.880	0.026	/	/	/
Hematoma volume	4.12	2.570–6.610	<0.001	/	/	/
Location of ICH	5.32	1.900–14.960	0.002	/	/	/
External ventricular drain	2.65	1.360–5.180	0.004	/	/	/
Admission temperature	0.63	0.470–0.850	0.003	/	/	/
Admission white blood count	0.88	0.830–0.930	<0.001	/	/	/
Admission CRP	0.98	0.970–0.990	<0.001	/	/	/

APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: Confidence intervals; CRP: C-reactive protein; GCS: Glasgow Coma Scale; ICH: Intracerebral hemorrhage; OR: Odds ratio; /: No data.

promotion of secondary neuronal injury, and cardiopulmonary deconditioning. Brain-immune interactions after stroke may have adverse effects because injury to the central nervous system causes significant immune depression, which places patients at a higher risk for infections.[5] Infections might also lead to secondary neuronal injury and worsened functional outcomes after ICH by enhancing proinflammatory cascades and causing general lymphocyte activation. Several known risk factors are strongly associated with post-stroke infection, including poor GCS, dysphagia, intubation, pulmonary edema, vein thromboses, and invasive procedures. The current analysis showed that the development of infections was associated with the earlier use of prophylactic antibiotics in acute stroke. However, current national guidelines do not recommend the use of prophylactic antibiotics in patients with acute stroke, and the current findings support further evaluation. Another interesting observation was that the volume and location of the ICH, tracheostomy operation, invasive procedure (central venous catheters and nasogastric tubes) were significant variables in the univariate analysis. It is possible that patients with more severe ICH often require life-saving surgical procedures, exhibit an excess stress response in the acute phase, require feeding via a nasogastric tube due to dysphagia, and are more likely to have infectious complications that lead to the placement of a central catheter.

The following limitations to the current study must be acknowledged. First, the study was retrospective in design, which may introduce bias. Second, the sample size was relatively small, this was a single-site study, and no longterm outcome data were available. Outcomes, such as long-term functional neurological outcomes, would be more useful for elucidating the effects of infections on longterm disability in ICH patients; however, the retrospective design prevented this analysis. Finally, the cause-effect relationship between infection and prolonged hospitalization is unclear.

The current study revealed a high frequency of infections in patients with ICH. The impact of infections on morbidity and LOS in the ICU highlights the importance of implementing major preventive measures to reduce the rate of hospital-acquired infections. Strategies to reduce infection rates in these patients may eventually lead to reductions in the morbidity and mortality associated with ICH.

Conflicts of interest

None.

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