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ORIGINAL RESEARCH

Systemic Inflammatory Response Syndrome on Admission and Clinical Outcomes After Intracerebral Hemorrhage

Lijun Liu[1,2], Anxin Wang[1,2], Dandan Wang[1,2], Jiahuan Guo[1,2], Xiaoli Zhang[2], Xingquan Zhao[1–3,*], Wenjuan Wang[1,2,*]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, People's Republic of China; [2]China National Clinical Research Center for Neurological Diseases, Beijing, People's Republic of China; [3]Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xingquan Zhao; Wenjuan Wang, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, 119 West Road, South4th Ring, Fengtai District, Beijing, 100070, People's Republic of China, Tel +86-010-59978330; Tel +86-010-59978891, Fax +86-010-67013383, Email zxq@vip.163.com; tong_ttyy@163.com

Background: Since studies on systemic inflammatory response syndrome (SIRS) in patients with acute intracerebral hemorrhage (ICH) are insufficient. This study investigated the associations between SIRS on admission and clinical outcomes after acute ICH.

Patients and Methods: The study included 1159 patients with acute spontaneous ICH from January 2014 to September 2016. In accordance with standard criteria, SIRS was defined as two or more of the following: (1) body temperature >38°C or <36°C, (2) respiratory rate >20 per minute, (3) heart rate >90 per minute, and (4) white blood cell count >12,000/μL or <4000/μL. The clinical outcomes of interest were death and major disability (defined as a modified Rankin Scale of 6 and 3–5), combined and separate at 1 month, 3 months and 1 year follow-up.

Results: SIRS was observed in 13.5% (157/1159) of patients and independently increased the risk of death at 1 month, 3 months, or 1 year: hazard ratio (HR) 2.532 (95% confidence interval [CI] 1.487–4.311), HR 2.436 (95% CI 1.499–3.958), HR 2.030 (95% CI 1.343–3.068), respectively ($P<0.05$ for all). The relationship between SIRS and ICH mortality was more pronounced in older patients or patients with larger hematoma volumes. Patients with in-hospital infections were at greater risk of major disability. The risk was enhanced when SIRS was incorporated.

Conclusion: The presence of SIRS at the time of admission was associated with mortality in patients with acute ICH, particularly in older patients and those with large hematomas. SIRS may exacerbate the disability caused by in-hospital infections in patients with ICH.

Keywords: systemic inflammatory response syndrome, intracerebral hemorrhage, in-hospital infections, death, disability

Introduction

Among all stroke types, intracerebral hemorrhage (ICH) is the most catastrophic, resulting in high morbidity and mortality. However, studies have not found any strong evidence of any medical treatment to date. In addition to global brain inflammation,[1] there are also peripheral inflammatory changes following intracerebral hemorrhage.[2–4] It is generally accepted that inflammation is triggered by ICH[1] with extra-central nervous system damage, including immune abnormalities,[3,5] cardiac dysfunction,[5,6] and lung injury.[7] The interactions of the brain-inflammation system may provide novel therapeutic options for ICH.

Systemic inflammatory response syndrome (SIRS), a marker of systemic inflammation, is usually triggered by an infectious disease, but can also be triggered by a non-infectious disease. Prior study has identified that SIRS following stroke correlates with elevated NIH Stroke Scale (NIHSS), worsening Glasgow Coma Scale (GCS), hematoma volume of ICH, and infarction size.[8] Presentation with SIRS increases the risk of death, as well as reduces the odds of favorable

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outcomes for ischemic stroke patients with endovascular treatment.[9,10] In patients treated with intravenous thrombolysis, SIRS remains an independent risk factor for adverse outcomes.[11] Besides ischemic stroke, SIRS has independently predicted subsequent complications after subarachnoid hemorrhage, such as vasospasm, normal pressure hydrocephalus, and systemic complications.[12]

SIRS occurs in approximately 21.3–23.8% of ICH patients during their hospital stay.[13,14] The presence of SIRS diminishes with time,[8] and the use of antibiotics during hospitalization could influence the detection. SIRS on admission, the most stable and accessible index, varies greatly depending on different definitions, ranging from 14% to 53%. It has been suggested to be associated with hematoma enlargement[15] and infectious complications during hospitalization.[16] However, the prediction of SIRS on the functional outcome of cerebral hemorrhage remains controversial.[14,16] Moreover, most previous studies have been characterized by small sample sizes, based on single center, or focused on single timepoint. In addition, these studies on SIRS of ICH patients did not further stratify and refine. Therefore, we sought to determine the associations between SIRS on admission and clinical outcomes of ICH patients throughout both short-term and long-term follow-up in a multicenter, large sample size study.

Subjects and Methods

Study Design and Participants

Study participants were recruited from 13 hospitals in Beijing, China, in a prospective, hospital-based, multicenter observational cohort study. From January 2014 to September 2016, a total of 1964 spontaneous intracerebral hemorrhage patients within 72 hours of onset were recruited consecutively. Written informed consent was obtained directly from each patient or from a legal surrogate in situations where the patient was incapable of providing the consent.

We performed a retrospective analysis of the prospectively collected database. The inclusion criteria were as follows: (1) ICH was diagnosed by the WHO standard and confirmed by a computerized tomography (CT) scan; (2) arriving at the hospital within 72 hours of the onset of ICH symptoms (defined by the "last see normal" principle); (3) aged 18 years or older; (4) acute-onset ICH for the first time; and (5) informed consent was obtained in writing. The exclusion criteria were as follows: (1) history of ICH; (2) congenital or acquired disorder of coagulation; and (3) complications with severe concomitant medical conditions or late-stage diseases. Among all the recruited patients, we screened 1833 patients with acute initial ICH. Fifty-nine individuals were excluded due to premorbidity (scores on the modified Rankin Scale, mRS $\geq$ 3), 574 individuals without follow-up records and 41 individuals with primary intraventricular hemorrhage (IVH). Eventually, a total of 1159 patients were included in the final analyses (Figure 1).

The presence of SIRS was defined according to standard criteria: (1) body temperature greater than 38°C or less than 36°C, (2) respiratory rate greater than 20 breaths per minute, (3) heart rate greater than 90 beats per minute, and (4) white blood cell count greater than 12,000/μL or less than 4000/μL. SIRS was defined based on vital signs and laboratory tests at the admission, with at least two or more of the above criteria being met.

Data Collection

At the time of enrollment, baseline demographic information and clinical characteristics were collected by our trained investigators, including age, sex, medical history (hypertension, diabetes, antihypertensive medication use, smoking and alcohol use), and time from symptom onset to admission. The vital signs were recorded on admission, including systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, respiratory rate, and heart rate. For descriptive purposes, the time from onset to admission was divided into 3 groups: <6 h, 6–24 h, and 24–72 h. At baseline, stroke severity was assessed using the GCS and NIHSS score (ranging from 0 to 42, with higher scores denoting more severe neurologic deficits). The routine laboratory examinations (including white blood cell count) and CT scans of the brain were performed in accordance with standardized procedures on admission. In-hospital infection was defined as diagnosis of a clinical infection during the hospital stay that was documented in the electronic medical record with classified as pneumonia, urinary tract infection, bloodstream infection, and central nervous system infection. Additionally, we recorded whether the patients underwent any brain surgery during their hospitalizations, including decompressive craniectomy, aspiration of hematoma, craniotomy evacuation of hematoma, and lateral ventriculopuncture drainage.

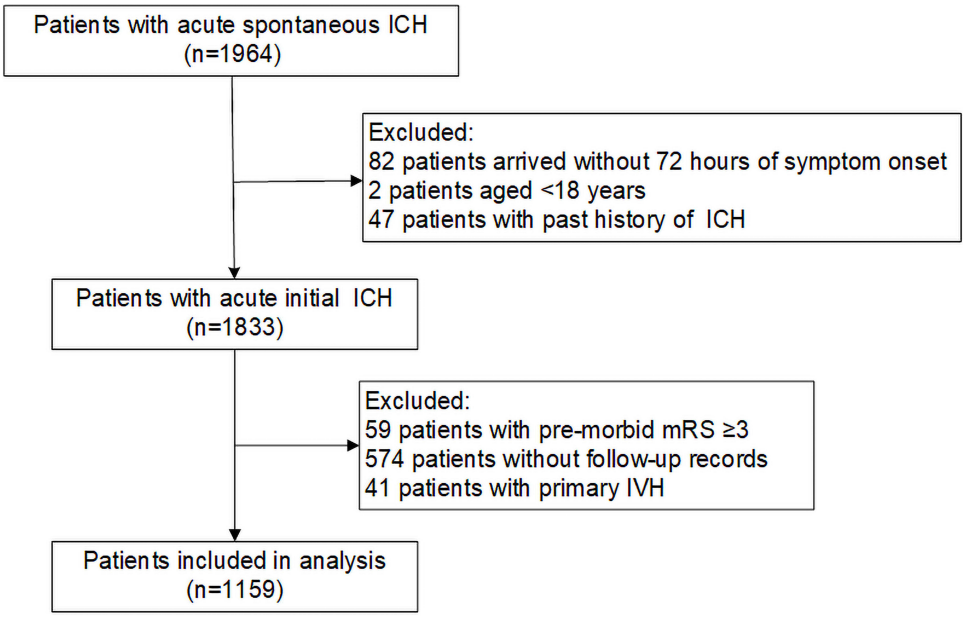

Figure 1 Flow chart for selection of study patients.
Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; IVH, intraventricular hemorrhage.

Neuroradiological Information Assessment

The central analysis was conducted on digital computed tomographic images. The location of the hematoma was evaluated and classified as lobar, basal ganglia, thalamus, brainstem, and cerebellum. Any intraventricular extension and presence of bleeding into the subarachnoid space were assessed after reviewing all plain CT images by visual inspection on the axial slice. Meanwhile, the hematoma volumes were calculated manually by using the ABC/2 formula[17] based on the initial CT scans. In the subgroup analyses, the baseline hematoma volumes were divided into 3 groups labeled <10 mL, 10–30 mL, and >30 mL.

Follow-Up and Clinical Outcomes

The study participants were followed up via telephone structured interviews at 1 month, 3 months, and 1 year separately after ICH onset. The information was obtained directly from the patients or their legal representatives in case the patients were unable to provide information themselves. These assessments were carried out by trained staff who were blinded to the patients' baseline characteristics. Functional outcome was evaluated using the modified Rankin Scale (mRS), a stroke outcome scale with score range of 0 (no symptoms) to 6 (dead). Unfavorable outcomes of interest in these analyses were death or major disability, death, and major disability (defined as an mRS of 3–6, 6, and 3–5, respectively).

Statistical Analysis

Statistical analysis was performed using Statistical Analysis Software Studio Version 9.4 (SAS Institute, Cary, North Carolina, USA). All the continuous variables in clinical characteristics were abnormally distributed, summarized by medians (interquartile ranges, IQRs), and analyzed using the Wilcoxon rank-sum tests. When categorical variables were analyzed, the Pearson or Fisher exact tests were used as appropriate, which were expressed as frequencies (percentages, %). Multivariable logistic regression models were used to assess the associations between SIRS, death or major disability and major disability. Multivariable Cox proportional hazard models were used to evaluate the effects of SIRS on death alone. Adjusted variables in the multivariable analyses were determined according to univariable analyses (P <0.1000), literature review, and medical knowledge. The correlation and collinearity between adjusted variables were also examined. For these analyses, we included odds ratios or hazard ratios with two-sided 95% confidence intervals (ORs/HRs, 95% CIs) for crude and adjusted regression models. Further analyses were performed to examine the relation

between SIRS only, infection only, SIRS plus infection, and the clinical outcomes of ICH. All tests were 2-tailed, and statistical significance was determined by a *P*-value <0.05.

Results

Baseline Characteristics

In total, 1159 patients with ICH were included in our study. There were 787 (67.9%) males and 372 (32.1%) females. There were 735 patients (63.4%) who arrived at hospitals within 6 hours of the onset of symptoms, and 1014 patients (87.5%) arrived within 24 hours. At the time of admission, SIRS was detected in 13.5% (157/1159) of the participants. Table 1 shows the clinical characteristics of patients with or without SIRS. The former were significantly younger (52 years, IQR [42–62] versus 57 years, IQR [49–66]), had higher SBP and DBP, lower GCS scores (8, IQR [6–14] versus 14, IQR [12–15]), higher NIHSS scores (18, IQR [12–28] versus 8, IQR [3–15]), an increased frequency of in-hospital infection (56.1% versus 23.4%) and brain surgery (39.5% versus 17.4%) compared to the patients without SIRS (*P* <0.05 for all). Both groups had similar distributions of gender, history of hypertension, prior mRS, smoking, and time from ICH to admission. In the study, noncontrast computed tomography was obtained in only 1150 patients, including 154 patients with SIRS and 996 patients without SIRS. The baseline hematoma volumes were larger in patients who presented with

Table 1 Clinical Characteristics Between SIRS and No SIRS Group

	SIRS (n=157)	No SIRS (n=1002)	*P*-value
Age, years, median (IQR)	52 (42–62)	57 (49–66)	<0.0001
Male, n (%)	115 (73.3)	672 (67.1)	0.1412
History of hypertension, n (%)	106 (67.5)	685 (68.4)	0.8539
History of diabetes, n (%)	22 (14.0)	143 (14.3)	1.0000
Prior mRS	0 (0, 0)	0 (0, 0)	0.1406
Antihypertensive use, n (%)	45 (28.7)	336 (33.5)	0.2364
Smoking, n (%)	77 (49.0)	426 (42.5)	0.1409
Alcohol, n (%)	70 (44.6)	372 (37.1)	0.0776
Time from ICH to admission, n (%)			0.1230
<6 h	99 (63.1)	636 (63.5)	
6–24 h	45 (28.7)	234 (23.4)	
24–72 h	13 (8.3)	132 (13.2)	
SBP, mmHg, median (IQR)	173 (150–193.5)	160 (144–182)	0.0004
DBP, mmHg, median (IQR)	100 (86–114)	94.5 (81–107)	0.0006
GCS score, median (IQR)	8 (6–14)	14 (12–15)	<0.0001
NIHSS score, median (IQR)	18 (12–28)	8 (3–15)	<0.0001
In-hospital infection, n (%)	88 (56.1)	234 (23.4)	<0.0001
Surgery during hospitalization, n (%)	62 (39.5)	174 (17.4)	<0.0001
Hematoma location, n (%)[a]			
Lobar	52 (33.8)	252 (25.3)	0.0266
Basal ganglia	68 (44.2)	492 (49.4)	0.2258
Thalamus	17 (11.0)	140 (14.1)	0.3101
Brainstem	11 (7.1)	56 (5.6)	0.4535
Cerebellum	6 (3.9)	56 (5.6)	0.3773
Intraventricular extension, n (%)[a]	91 (59.1)	333 (33.4)	<0.0001
Subarachnoid extension, n (%)[a]	53 (34.4)	137 (13.8)	<0.0001
Hematoma volume, mL, median (IQR)[a]	34.3 (11.3–62.8)	13.0 (5.0–30.0)	<0.0001

Note: [a]Admission non-contrast computed tomography was obtained in only 1150 patients, including 154 patients in the SIRS group and 996 patients in the No SIRS group.

Abbreviations: SIRS, systemic inflammatory response syndrome; IQR, interquartile range; ICH, intracerebral hemorrhage; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

SIRS (34.3 mL, IQR [11.3–62.8] versus 13.0 mL, IQR [5.0–30.0]). In addition, those with SIRS were more likely to suffer from lobar hemorrhage, intraventricular extension, and subarachnoid extension (P <0.05 for all).

Association Between SIRS and Clinical Outcomes

Multivariate analyses were conducted to determine whether SIRS was associated with clinical outcomes (shown in Table 2). Based on multivariate logistic regression, age, sex, alcohol use, systolic and diastolic blood pressures, GCS, NIHSS, in-hospital infection, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume were adjusted. Patients with SIRS were likely to have increased mortality at 1 month, 3 months, and 1 year: HR 2.532 (95% CI 1.487–4.311), HR 2.436 (95% CI 1.499–3.958), HR 2.030 (95% CI 1.343–3.068), respectively. As the follow-up period progressed, there was a trend toward a decreasing risk of mortality. SIRS at admission was also an independent risk factor for death or major disability and major disability at 1 year: OR 1.943 (95% CI 1.144–3.301) and OR 1.904 (95% CI 1.056–3.430), respectively.

Subgroup Analysis of SIRS and Mortality

ICH patients had a mortality of 12.9% (149/1159) during the follow-up period of the study. We further conducted a stratified analysis, as shown in Figure 2. The relationship between SIRS and high mortality of ICH patients remained significant even after adjustment for relevant risk factors, especially in the older patient group (60 years or older) or larger baseline hematoma volume group (more than 30 mL). Similar results are presented at 1 month, 3 months, and 1-year follow-ups.

Effects of SIRS on Admission and In-Hospital Infection on Clinical Outcomes

There were 322 patients (27.8%) who developed infections during hospitalizations. ICH patients with SIRS on admission were more likely to develop infections during their hospital stay (56.1% versus 23.4%, P <0.0001). We further divided the patients into categories of no infection or SIRS, SIRS only, infection only, and SIRS plus infection to explore whether these categories were associated with poor clinical outcomes in ICH patients (shown in Table 3). After adjusting for confounding factors, including age, sex, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume, patients with SIRS in the absence of infection had an increased risk of death at 1 month, 3 months, and 1 year: HR 2.484 (95% CI 1.158–5.330), HR 2.201 (95% CI 1.057–4.582), HR 2.314 (95% CI

Table 2 Effects of SIRS on Death and Major Disability

Outcomes	No. of Events (%)		Crude		Multivariable Analysis	
	SIRS (n=157)	No SIRS (n=1002)	OR/HR (95% CI)	*P*-value	OR/HR (95% CI)	*P*-value
Death/major disability[a]						
1-month	128 (81.5)	519 (51.8)	4.107 (2.694–6.262)	<0.0001	1.489 (0.841–2.639)	0.1723
3-month	120 (76.4)	438 (43.7)	4.176 (2.830–6.163)	<0.0001	1.717 (0.997–2.959)	0.0514
1-year	109 (69.4)	360 (35.9)	4.050 (2.816–5.823)	<0.0001	1.943 (1.144–3.301)	0.0140
Death[b]						
1-month	39 (24.8)	44 (4.4)	6.493 (4.212–10.010)	<0.0001	2.532 (1.487–4.311)	0.0006
3-month	43 (27.4)	58 (5.8)	5.581 (3.753–8.301)	<0.0001	2.436 (1.499–3.958)	0.0003
1-year	49 (31.2)	100 (10.0)	3.866 (2.739–5.457)	<0.0001	2.030 (1.343–3.068)	0.0008
Major disability[a]						
1-month	89 (56.7)	474 (47.3)	3.127 (2.018–4.845)	<0.0001	1.393 (0.774–2.509)	0.2693
3-month	77 (49.0)	380 (37.9)	3.089 (2.043–4.668)	<0.0001	1.608 (0.913–2.833)	0.1000
1-year	60 (38.2)	260 (25.9)	3.087 (2.057–4.632)	<0.0001	1.904 (1.056–3.430)	0.0321

Notes: Adjustment for age, sex, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, in-hospital infection, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume. [a]Analyzed by multivariable logistic regression models; [b]analyzed by multivariable Cox proportional hazard models.

Abbreviations: SIRS, systemic inflammatory response syndrome; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

A

Subgroup	No. of patients	No. of events (%) SIRS	No. of events (%) Non-SIRS	Forest Plot	HR (95% CI)	*P*-value
Age, years[a]						
<60	684	27 (24.3)	23 (4.0)		1.954 (0.909-4.201)	0.0861
⩾60	475	12 (26.1)	21 (4.9)		3.533 (1.591-7.845)	0.0019
Sex[b]						
Male	787	27 (23.5)	29 (4.3)		2.282 (1.171-4.445)	0.0153
Female	372	12 (28.6)	15 (4.6)		2.708 (1.047-7.005)	0.0399
Hematoma volume, mL[c]						
<10	444	2 (5.9)	6 (1.5)		0.569 (0.063-5.144)	0.6156
10-30	383	9 (25.0)	14 (4.0)		2.263 (0.722-7.093)	0.1613
>30	323	22 (27.2)	23 (9.5)		3.266 (1.601-6.662)	0.0011

B

Subgroup	No. of patients	No. of events (%) SIRS	No. of events (%) Non-SIRS	Forest Plot	HR (95% CI)	*P*-value
Age, years[a]						
<60	684	29 (26.1)	27 (4.7)		1.700 (0.842-3.432)	0.1386
⩾60	475	14 (30.4)	31 (7.2)		3.179 (1.552-6.512)	0.0016
Sex[b]						
Male	787	30 (26.1)	37 (5.5)		2.346 (1.283-4.289)	0.0056
Female	372	13 (31.0)	21 (6.4)		2.615 (1.076-6.354)	0.0338
Hematoma volume, mL[c]						
<10	444	2 (5.9)	10 (2.4)		0.851 (0.116-6.212)	0.8733
10-30	383	11 (30.6)	16 (4.6)		2.823 (1.041-7.655)	0.0415
>30	323	24 (29.6)	30 (12.4)		2.825 (1.486-5.371)	0.0015

C

Subgroup	No. of patients	No. of events (%) SIRS	No. of events (%) Non-SIRS	Forest Plot	HR (95% CI)	*P*-value
Age, years[a]						
<60	684	29 (26.1)	33 (5.8)		1.491 (0.771-2.884)	0.2357
⩾60	475	20 (43.5)	67 (15.6)		2.423 (1.392-4.216)	0.0017
Sex[b]						
Male	787	31 (27.0)	65 (9.7)		1.801 (1.056-3.070)	0.0307
Female	372	18 (42.9)	35 (10.6)		2.384 (1.169-4.861)	0.0169
Hematoma volume, mL[c]						
<10	444	4 (11.8)	20 (4.9)		1.769 (0.436-7.174)	0.4246
10-30	383	13 (36.1)	35 (10.1)		1.992 (0.903-4.391)	0.0876
>30	323	26 (32.1)	43 (17.8)		2.326 (1.300-4.162)	0.0045

Figure 2 Subgroup analysis to evaluate the relationship of SIRS on admission and death in cerebral hemorrhage patients of different age (< 60 years or ≥ 60 years), gender, and baseline hematoma volume (<10 mL, 10–30 mL, or >30 mL). (**A**–**C**) Show the relationship at 1-month, 3-month and 1-year follow-ups.

Notes: [a]Adjustment for sex, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, in-hospital infection, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume; [b]Adjustment for age, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, in-hospital infection, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume; [c]Adjustment for age, sex, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, in-hospital infection, surgery, lobar hemorrhage, intraventricular extension, and subarachnoid extension.

Abbreviations: SIRS, systemic inflammatory response syndrome; HR, hazard ratio; CI, confidence interval.

Table 3 Effects of SIRS and In-Hospital Infection on Poor Clinical Outcomes After Cerebral Hemorrhage

	No Infection or SIRS (n=768)	SIRS Only (n=69)		Infection Only (n=234)		SIRS Plus Infection (n=88)	
		OR/HR (95% CI)	*P*-value	OR/HR (95% CI)	*P*-value	OR/HR (95% CI)	*P*-value
1-month follow-up							
Death/major disability[a]							
Crude	Ref.	2.943 (1.739–4.981)	<0.0001	7.106 (4.880–10.347)	<0.0001	15.941 (7.269–34.960)	<0.0001
Adjusted	Ref.	1.341 (0.666–2.699)	0.4106	2.625 (1.699–4.129)	<0.0001	4.764 (1.927–11.778)	0.0007
Disabled[a]							
Crude	Ref.	1.975 (1.113–3.504)	0.0200	6.979 (4.773–10.205)	<0.0001	12.843 (5.791–28.481)	<0.0001
Adjusted	Ref.	1.273 (0.617–2.629)	0.5140	2.601 (1.645–4.112)	<0.0001	4.273 (1.698–10.754)	0.0020
Death[b]							
Crude	Ref.	9.186 (5.030–16.777)	<0.0001	2.279 (1.249–4.157)	0.0072	7.863 (4.420–13.989)	<0.0001
Adjusted	Ref.	2.484 (1.158–5.330)	0.0195	0.757 (0.376–1.524)	0.4357	1.948 (0.996–3.931)	0.0625
3-month follow-up							
Death/major disability[a]							
Crude	Ref.	3.600 (2.146–6.040)	<0.0001	5.696 (4.092–7.927)	<0.0001	11.073 (6.033–20.325)	<0.0001
Adjusted	Ref.	1.705 (0.843–3.450)	0.1377	1.905 (1.242–2.921)	0.0031	3.301 (1.552–7.022)	0.0019
Disabled[a]							
Crude	Ref.	2.481 (1.401–4.394)	0.0018	5.644 (4.021–7.922)	<0.0001	8.482 (4.518–15.923)	<0.0001
Adjusted	Ref.	1.639 (0.785–3.424)	0.1886	1.872 (1.209–2.897)	0.0049	2.935 (1.337–6.447)	0.0073
Death[b]							
Crude	Ref.	7.335 (4.128–13.035)	<0.0001	2.444 (1.445–4.136)	0.0009	7.497 (4.454–12.617)	<0.0001
Adjusted	Ref.	2.201 (1.057–4.582)	0.0350	0.808 (0.432–1.511)	0.5050	2.114 (1.114–4.013)	0.0221
1-year follow-up							
Death/major disability[a]							
Crude	Ref.	3.553 (2.152–5.865)	<0.0001	6.654 (4.821–9.185)	<0.0001	12.105 (6.960–21.054)	<0.0001
Adjusted	Ref.	1.757 (0.865–3.568)	0.1190	2.542 (1.678–3.852)	<0.0001	5.546 (2.705–11.372)	<0.0001
Disabled[a]							
Crude	Ref.	2.190 (1.179–4.067)	0.0131	6.580 (4.650–9.311)	<0.0001	10.100 (5.595–18.232)	<0.0001
Adjusted	Ref.	1.629 (0.718–3.696)	0.2434	2.643 (1.691–4.130)	<0.0001	5.880 (2.705–12.779)	<0.0001
Death[b]							
Crude	Ref.	5.605 (3.375–9.306)	<0.0001	2.941 (1.968–4.396)	<0.0001	5.512 (3.478–8.737)	<0.0001
Adjusted	Ref.	2.314 (1.239–4.322)	0.0085	1.117 (0.689–1.810)	0.6532	2.084 (1.186–3.662)	0.0107

Notes: Adjustment for age, sex, alcohol use, systolic blood pressure, diastolic blood pressure, Glasgow Coma Scale, National Institutes of Health Stroke Scale, surgery, lobar hemorrhage, intraventricular extension, subarachnoid extension, and baseline hematoma volume. [a]Analyzed by multivariable logistic regression models; [b]analyzed by multivariable Cox proportional hazard models.

Abbreviations: SIRS, systemic inflammatory response syndrome; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

1.239–4.322), respectively. The effect of SIRS on death was most pronounced at 1 month of onset, consistent with the results of the overall patient regression analysis above. In addition, in-hospital infections increased the risk of death/major disability, and major disability alone at 1 month: OR 2.625 (95% CI 1.699–4.129) and OR 2.601 (95% CI 1.645–4.112), respectively. SIRS enhanced the effect sizes when it was incorporated. Similar results are presented at 3-month and 1-year follow-ups.

Discussion

This multicenter cohort study demonstrated a strong association of SIRS on admission with higher mortality in ICH patients. SIRS on admission was significantly associated with higher risk for death within 1 year of ICH onset, especially in older patients and patients with large hematomas. Furthermore, infectious complications during hospitalization were associated with both combined death and disability, and disability alone. These data indicate that SIRS may be particularly fatal, while in-hospital infections may be more likely to be disabling.

Our study found a prevalence of SIRS of 13.5% on admission, similar to the incidence of 14% in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) cohort.[16] Consistent with a previous study,[8] we found that patients with more severe strokes, as measured by a higher NIHSS score, lower GCS score or larger hematoma, were more likely to develop SIRS. A possible mechanism by which intracerebral hemorrhage influences systemic inflammation may be the

brain-immune system. Brain-immune system interactions are mediated by two major pathways: the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Primary and secondary lymphoid organs are highly innervated by sympathetic/norepinephrinergic nerves, which release norepinephrine that regulates lymphocytes' transport, circulation and proliferation, and cytokine production.[18] Moreover, larger hematomas and more severe ICH lead to severe brain damage and augmented neuronal necrosis. Damaged neurons and white matter trigger inflammation by releasing damage-related molecules, activating microglia and astrocytes, and upregulating pro-inflammatory cytokines, all of which result in recruitment of peripheral immune cells. In addition, the broken blood-brain barrier promotes the systemic inflammatory response.[1,2] Therefore, the systemic inflammation involved will be more aggressive through the aforementioned pathways of brain-immune system and the broken blood-brain barrier in patients with severe ICH. In addition, previous studies have found that SIRS is also likely to occur in patients with subarachnoid hemorrhage, the incidence ranged from 54% to 86%.[12,19] Our study found that ICH patients with SIRS were more likely to have subarachnoid extension in their baseline CT scans (34.4% versus 13.8%). Patients with cerebral hemorrhage ruptured into the subarachnoid space should be more concerned about the combination of SIRS.

Even though SIRS is associated with stroke severity, there have been conflicting reports on the relationships between SIRS and clinical outcomes in ICH patients. A previous analysis of 249 patients with cerebral hemorrhage found that SIRS was not significantly associated with mortality.[13] However, an analysis of 518 patients showed the opposite conclusion that in-hospital SIRS was an independent risk factor for in-hospital mortality or poor discharge outcome,[20] which was also confirmed in the 3-month functional outcome.[14] The ERICH cohort evaluated SIRS on hospital admission and did not confirm the association between SIRS and poorer outcomes at discharge or 3 months.[16] These widely divergent findings emphasize the importance of prognostic indicators, follow-up periods, and evaluation periods of SIRS. We provided more comprehensive evidence that SIRS on admission was independently associated with mortality at 1 month, 3 months, and even 1 year following ICH. ICH triggers a robust immune response within minutes and persists for weeks in the injured brain tissues, and extends throughout the global brain.[1] The ICH-related systemic inflammatory response and immune dysregulation have emerged as important elements in stroke progression, recovery, and outcome.[2] Growing evidence now suggests that the existing global brain inflammation and systemic inflammation might contribute to lasting neurodegeneration and affect brain function after stroke.[1,21,22] Thus, the fatality and disability of SIRS may persist over the long term in patients with ICH. The severe ICH patients typically die within short time follow-up, which may account for the decreasing hazard ratio over time.

It may be possible to identify which ICH patients with SIRS were at the highest risk of dying from the stratification analysis. Our study demonstrated that SIRS was an independent risk factor for ICH mortality among older adults (60 years or older) or patients with larger hematoma volumes (>30 mL). ICH patients with SIRS are younger,[16] suggesting that systemic inflammation is less intense in older patients. Once elderly patients have developed SIRS, their worse physiologic conditions may not be able to withstand the shock of intense inflammation. Moreover, for immunocompetence influenced by estrogen levels, men show weaker cell-mediated and humoral immune responses than women.[23,24] SIRS may cause a more robust inflammatory response in women, which may explain the higher odds of mortality.

The presence of SIRS at the time of admission increased infectious complications. The ERICH study indicated that patients with ICH who had either SIRS and in-hospital infection or only infection had poorer functional outcomes at discharge and three months.[16] In our study, combined SIRS increased the impact of infection on poor prognosis. SIRS is a systemic inflammatory index that combines heart rate, leukocyte, respiration and body temperature. Previous studies have shown that the white blood cell count was associated with hematoma expansion and outcomes in ICH patients.[25,26] A post hoc analysis of ATACH-2 (Antihypertensive Treatment in Intracerebral Hemorrhage 2) showed that every 10-bpm increase in heart rate increased the probability of unfavorable outcome by 4.3%.[27] In a retrospective study on a prospective ICH database, antihyperthermic treatment for 48 hours resulted in good outcome in 31.8% of the patients.[28] Our findings may encourage future researchers to explore the modulation of the acute inflammatory response to improve prognosis. It is now widely recognized that inflammation plays an important role in ICH, which has led to a number of clinical trials aimed at reducing inflammation and counteracting secondary brain injury during the acute and subacute stages. In fact, ICH therapeutic strategies to date have focused on novel intervention targets in systemic complications as their entity,[29,30] such as treatment with celecoxib,[31] minocycline,[32,33] and fingolimod for reducing

perihematomal edema, attenuating neurologic deficits, and promoting recovery.[34] The SIRS criteria may assist in selecting patients for immunomodulation or anti-inflammatory therapies.

Our study does have some limitations. First, there was a single time point to evaluate SIRS at the time of admission and lack of a strict 24-hour definition. The incidence may be affected by other factors, such as arrhythmia, comorbidity, and endotracheal intubation in pre-hospital care. Second, in-hospital infections in this study were defined by clinical diagnosis, and antibiotic use during hospital stays may underestimate the incidence of infections. However, this study provided estimates in a multicenter, prospective, observational cohort from a real-world perspective to determine the generalizability. Furthermore, the analyses were not prespecified, and the cohort did not have a complete set of inflammatory biomarkers. Inflammatory biomarkers need further studies to investigate the prognostic influences.

Conclusions

In conclusion, this study showed that SIRS on admission was associated with mortality and disability in ICH patients. The association between SIRS and death could last for one year, especially in older patients and patients with large hematomas. Early identification and subsequent management of ICH patients with SIRS may prevent death and disability and is of great clinical importance.

Ethics Statement

In accordance with ethical guidelines of the 1975 Declaration of Helsinki, this study was approved by the Institutional Review Board (IRB No. KY2014-023-02) of Beijing Tiantan Hospital, Capital Medical University. All participating hospitals were approved by their respective ethics committees or IRB prior to the initiation of the study.

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Disclosure

The authors report no conflicts of interest in this work.

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