# Association between systemic inflammatory response syndrome and hematoma expansion in intracerebral hemorrhage

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None declared

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## Abstract

**Background.** Hematoma expansion (HE) is a relatively common complication after intracerebral hemorrhage.

**Objectives.** To explore the association between systemic inflammatory response syndrome (SIRS) and HE in patients with intracerebral hemorrhage (ICH).

**Materials and methods.** From June 2013 to October 2020, the sociodemographic data and clinical data of 780 ICH patients were collected. The logistic regression analysis with odd ratios (ORs) and 95% confidence intervals (95% CIs) was performed to analyze the risk factors for HE in patients with ICH.

**Results.** Hematoma expansion occurred in 151 (19.36%) patients with ICH. Significant differences were presented between SIRS and HE (OR = 2.549, 95% CI: [1.497; 4.342], p = 0.0006). After adjusting the covariates, a further analysis showed that the respiratory rate >20 beats/min (OR = 3.436, 95% CI: [1.981; 5.960], $p < 0.0001$), white blood cell (WBC) $> 12\times10^9$/L or WBC $\leq 4\times10^9$/L (OR = 2.489, 95% CI: [1.494; 4.149], p = 0.0005) increased the risk for HE in ICH patients. Our study also found that the significant differences between HE and non-HE patients in proportion of patients with history of diabetes mellitus, basal ganglia hemorrhage, hypothalamus hemorrhage and fasting blood glucose (all $p < 0.05$) (OR = 2.076, 95% CI: [1.274; 3.381], p = 0.0034), basal ganglia hemorrhage (OR = 2.512, 95% CI: [1.496; 4.218], p = 0.0005), hypothalamus hemorrhage (OR = 2.121, 95% CI: [1.007; 4.466], p = 0.0479), high C-reactive protein (CRP) (OR = 1.013, 95% CI: [1.002; 1.024], p = 0.0184), and hyperglycemia (OR = 1.099, 95% CI: [1.026; 1.178], p = 0.0074) were associated with an increased risk of HE in ICH patients.

**Conclusions.** The SIRS is closely associated with the risk of HE. Respiratory rate >20 beats/min and WBC count >12($10^9$/L) or ≤4($10^9$/L) increased the risk for HE in ICH patients. These findings can help to achieve the early prevention of HE and improve the prognosis of ICH patients.

**Key words:** risk factors, C-reactive protein, SIRS, intracerebral hemorrhage, hematoma expansion

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# Background

Hematoma expansion (HE), which is defined as an increase in hematoma volume by >33% or an absolute increase in hematoma volume by >12.5 mL, is a relatively common complication after intracerebral hemorrhage (ICH).[1] Several studies demonstrated that HE was closely related to the neurologic deterioration,[2] poor neurologic functional outcome and ICH mortality.[3] Acute HE is an important factor leading to the deterioration of the clinical condition of stroke patients. Research has shown that HE occurred in ICH patients and was a major influence factor for early deterioration and poor clinical prognosis.[3,4]

A prior study found that the mortality rate of ICH patients in the HE group was 53.6%, while in the non-HE group the mortality rate was 6.3%.[5] The HE has been proven to be an independent predictive factor of 30-day mortality and poor prognosis.[6] Numerous studies focused on the risk factors for HE in ICH.[7] Several laboratory indicators have been identified as risk factors for HE, such as basal ganglia hemorrhage was associated with HE,[7] early peripheral blood neutrophilia was an imaging marker of secondary damage to cerebral hematoma and a risk factor for poor prognosis of ICH,[2,7] the increase in the level of pro-inflammatory cytokine C-reactive protein (CRP) was a general risk factor for HE,[8] and so on. To our knowledge, there were rare reports on the association between systemic inflammatory response syndrome (SIRS) and HE. The SIRS was defined by the presence of 2 or more of the following factors: body temperature <36°C or >38°C, respiratory rate >20 breaths per min, heart rate >90 beats per min, or white blood cell (WBC) count $<4 \times 10^9$/L or $>12 \times 10^9$/L in the absence of infection.[9] Furthermore, SIRS is an immune-related aseptic inflammatory response, which is common in various critically ill patients.[10] The SIRS is common in patients with vascular disease.[11] It was also found that SIRS was observed in 14% of ICH patients on admission and was related to the severity of stroke, infection and prognosis.[12] However, the association between SIRS and HE in ICH patients remains undetermined.

# Objectives

To recognize the risk factors for HE in ICH patients is of great importance for the early prevention of HE. In this study, we assessed and retrospectively analyzed the general data, imaging data and laboratory indicators of patients with ICH, with the aim of identifying the association between SIRS and HE.

# Materials and methods

## Patients

This was a retrospective study. The sociodemographic and clinical data of 780 patients with ICH, who were diagnosed using baseline computed tomography (CT) scan within 6 h after the symptoms onset at The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, between June 2013 and October 2020, were collected. Patients aged ≥18 years were included in this study. Exclusion criteria: 1) patients with a secondary cause of their ICH such as potential aneurysm, vascular malformations, neoplasms, head injury, venous infarction, and hemorrhagic transformation of an ischemic stroke; 2) patients with the history of acute infection or fever 1 month before ICH; 3) patients with cardiovascular and cerebrovascular diseases or surgical trauma within 3 months before ICH; 4) patients with severe hepatic and renal dysfunction, and coagulation impediment; 5) patients with incomplete or missing information. All patients voluntarily participated in the study and an informed consent was obtained from every patient or their next of kin prior to the collection of data. The study was approved by the Institutional Review Board of The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China (approval No. 201310-3).

## Data collection

We collected sociodemographic and clinical data for patients with ICH on admission, including age, gender, smoking history (patients who smoked more than 100 cigarettes in their whole life), drinking history (patients who had at least 12 drinks (12 ounces of beer, a 5 ounce glass of wine or 1.5 ounces of liquor) of any type of alcoholic beverage in any given year of their life), underlying diseases conditions and SIRS data (body temperature, heart rate, respiratory rate, and WBC count). The underlying diseases included hypertension, diabetes, hemorrhagic stroke, and ischemic stroke.

All patients underwent Glasgow Coma Scale (GCS) and Graeb score[13] assessment and blood pressure measurement. The Graeb score is based on the left, the right, the 3rd and the 4th lateral ventricle score, and the possible total score is 12 points.[13] The score of 0 points indicates no intraventricular hemorrhage, from 1 to 4 points indicates mild intraventricular hemorrhage, from 5 to 8 points indicates moderate intraventricular hemorrhage, and from 9 to 12 points indicates severe intraventricular hemorrhage. Also, all patients underwent head CT examination for midline shift within 3 h of symptoms onset. After that, we collected 5 mL of venous blood from patients for blood routine, liver and kidney function, coagulation function and myocardial enzyme spectrum examination, and performed fasting blood glucose (FBG) test the next day.

All patients underwent cranial CT scan again 24 h from the symptoms onset to identify hematoma features: hematoma volume (ABC/2 method), midline shift and ICH location. The ICH volumes of the CT scans were calculated using the ABC/2 formula. The HE was defined as an increase in hematoma volume by >33% or an absolute increase in hematoma volume by >12.5 mL. The GCS and Graeb score were used to measure the severity of ICH.

The laboratory indicators were as follows: international normalized ratio (INR), platelet (PLT), hemoglobin (Hb), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), body temperature, heart rate, WBC, neutrophils and lymphocytes (LC) count, and CRP.

## Statistical analyses

The statistical analysis was conducted using IBM SPSS v. 20.0 statistical software (IBM Corp., Armonk, USA). All statistical tests were two-tailed. The data were tested using Kolmogorov–Smirnov test for normality (Table 1). The non-normal data were described using median and quartiles (M (Q1, Q3)) and the comparison between groups was performed with the Mann–Whitney U test. The numeric data were compared using $\chi^2$ test and presented as n (%). The value of $p < 0.05$ was considered statistically significant. The logistic regression was used to analyze the possible risk factors of HE in ICH patients. The variables with significant differences in univariate analysis were included in the multivariable logistic regression for adjustment, and stepwise logistic regression was performed with significance level for entry (SLENTRY) = 0.05, and significance level for entry (SLSTAY) = 0.05 for entering and removing risk factors, respectively. The presence of collinearity (having less than 2 variance inflation factors in Table 2,3), goodness-of-fit and $R^2$ measure on the influencing factors of the multivariable logistic model were calculated.

# Results

## Baseline characteristics of patients

Seven hundred and eighty ICH patients were involved in the study (498 males and 282 females), with the median age of 63 years. There were 240 cases (30.77%) of smoking, 209 cases (26.79%) of drinking, 42 cases (5.38%) with history of hemorrhagic stroke, 57 cases (7.31%) with history of ischemic stroke, 552 cases (70.77%) with the history of hypertension, and 104 cases (13.33%) with the history of diabetes mellitus. Among 780 ICH patients, 151 patients (19.36%) experienced HE (HE group) and 629 patients (80.64%) did not experience HE (non-HE group).

## Univariate analysis for HE in ICH patients

The results of univariate analysis for HE in ICH patients were listed in Table 4, and the distribution of studied variables is demonstrated in Fig. 1A and Fig. 1B. The values in the HE group were significantly higher than those in the non-HE group in proportion of patients with history of diabetes mellitus ($\chi^2 = 6.919$, $p = 0.0085$), midline shift >0.5 cm ($\chi^2 = 8.708$, $p = 0.0032$), basal ganglia hemorrhage ($\chi^2 = 9.000$, $p = 0.0111$), body temperature >38 or <36°C ($\chi^2 = 6.249$, $p = 0.0124$), WBC count >12 or $<4\times10^9$/L ($\chi^2 = 7.039$, $p = 0.0080$), and fasting blood

**Table 1.** Test of normal distribution within compared groups

| Variables | Non-HE group | | HE group | |
|---|---|---|---|---|
| | Statistics | p-value | Statistics | p-value |
| Age [years] | 0.038 | 0.0300 | 0.106 | <0.0100 |
| Hematoma volume [mL] | 0.182 | <0.0100 | 0.199 | <0.0100 |
| SBP [mm Hg] | 0.049 | <0.0100 | 0.087 | <0.0100 |
| DBP [mm Hg] | 0.055 | <0.0100 | 0.060 | >0.1500 |
| GCS score | 0.199 | <0.0100 | 0.198 | <0.0100 |
| INR | 0.459 | <0.0100 | 0.425 | <0.0100 |
| PLT [$10^9$/L] | 0.060 | <0.0100 | 0.067 | 0.0910 |
| Hb [mg/L] | 0.091 | <0.0100 | 0.092 | <0.0100 |
| Neutrophils count [$10^9$/L] | 0.078 | <0.0100 | 0.164 | <0.0100 |
| LC count [$10^9$/L] | 0.122 | <0.0100 | 0.137 | <0.0100 |
| NLR [%] | 0.146 | <0.0100 | 0.251 | <0.0100 |
| PLR [%] | 0.130 | <0.0100 | 0.220 | <0.0100 |
| CRP [mg/L] | 0.372 | <0.0100 | 0.319 | <0.0100 |
| FBG [mmol/L] | 0.136 | <0.0100 | 0.142 | <0.0100 |

HE – hematoma expansion; SBP – systolic blood pressure; DBP – diastolic blood pressure; GCS – Glasgow Coma Score; INR – international normalized ratio; PLT – platelet; Hb – hemoglobin; LC – lymphocytes; NLR – neutrophil/lymphocyte ratio; PLR – platelet/lymphocyte ratio; CRP – C-reactive protein; FBG – fasting blood glucose.

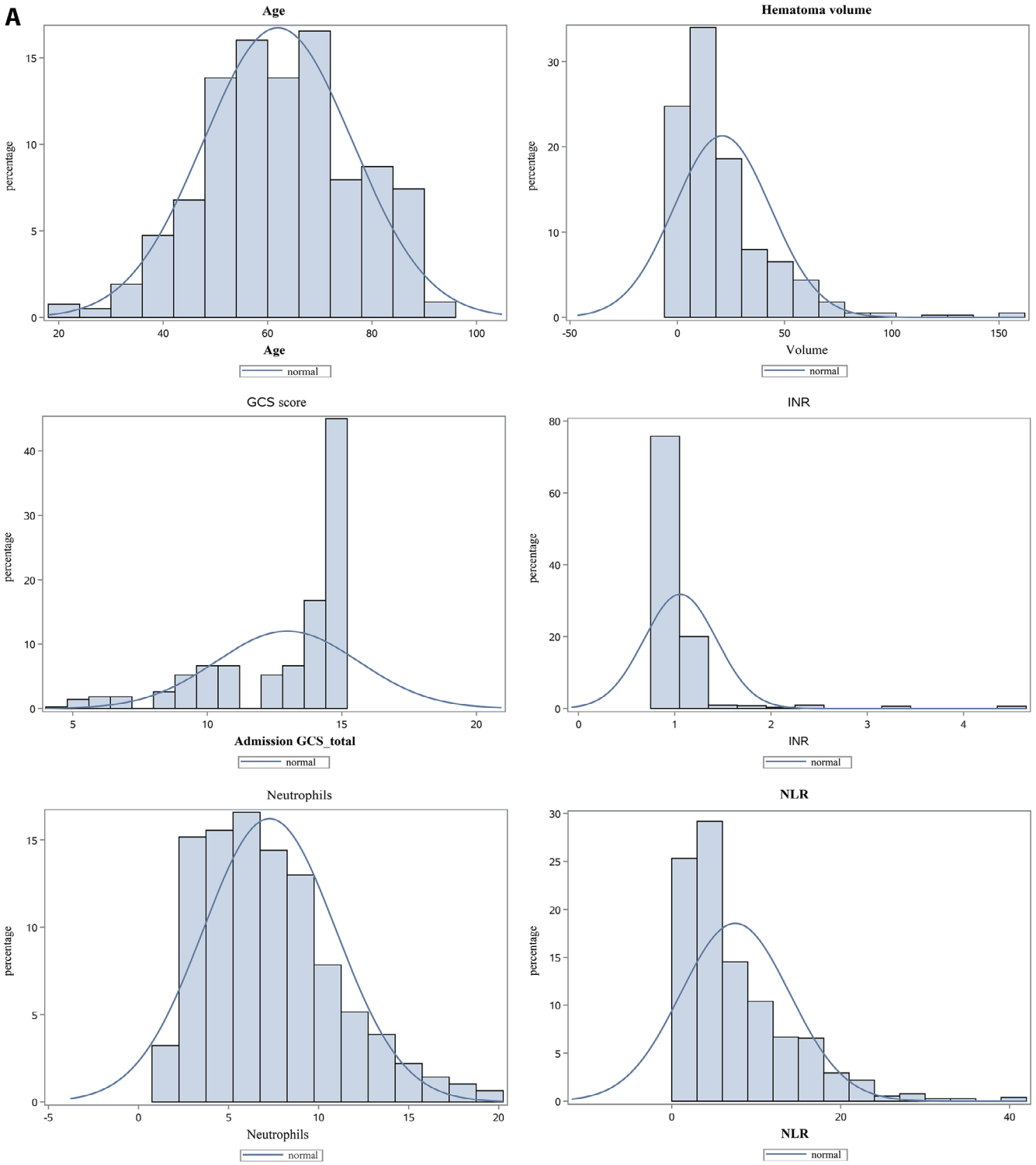


Fig. 1A. Distribution of the studied variables

GCS – Glasgow Coma Score; INR – international normalized ratio; NLR – neutrophil/lymphocyte ratio.

glucose (Z = 2.831, p = 0.0046). Meanwhile, the values in the HE group were significantly lower than those in the non-HE group in proportion of patients smoking ($\chi^2$ = 5.065, p = 0.0244), neutrophils count (Z = –4.403, p < 0.0001), respiratory rate >20 breaths/min ($\chi^2$ = 39.959, p < 0.0001), PLT (Z = –1.930, p = 0.0536), NLR (Z = –3.377, p = 0.0007), and PLR (Z = –2.488, p = 0.0128).

## Multivariate logistic regression analysis for HE in ICH patients

According to the results of univariate analysis, the history of diabetes, smoking history, midline shift, ICH location, SIRS (body temperature, heart rate, respiratory rate, WBC count), INR, PLT, neutrophils count, NLR,

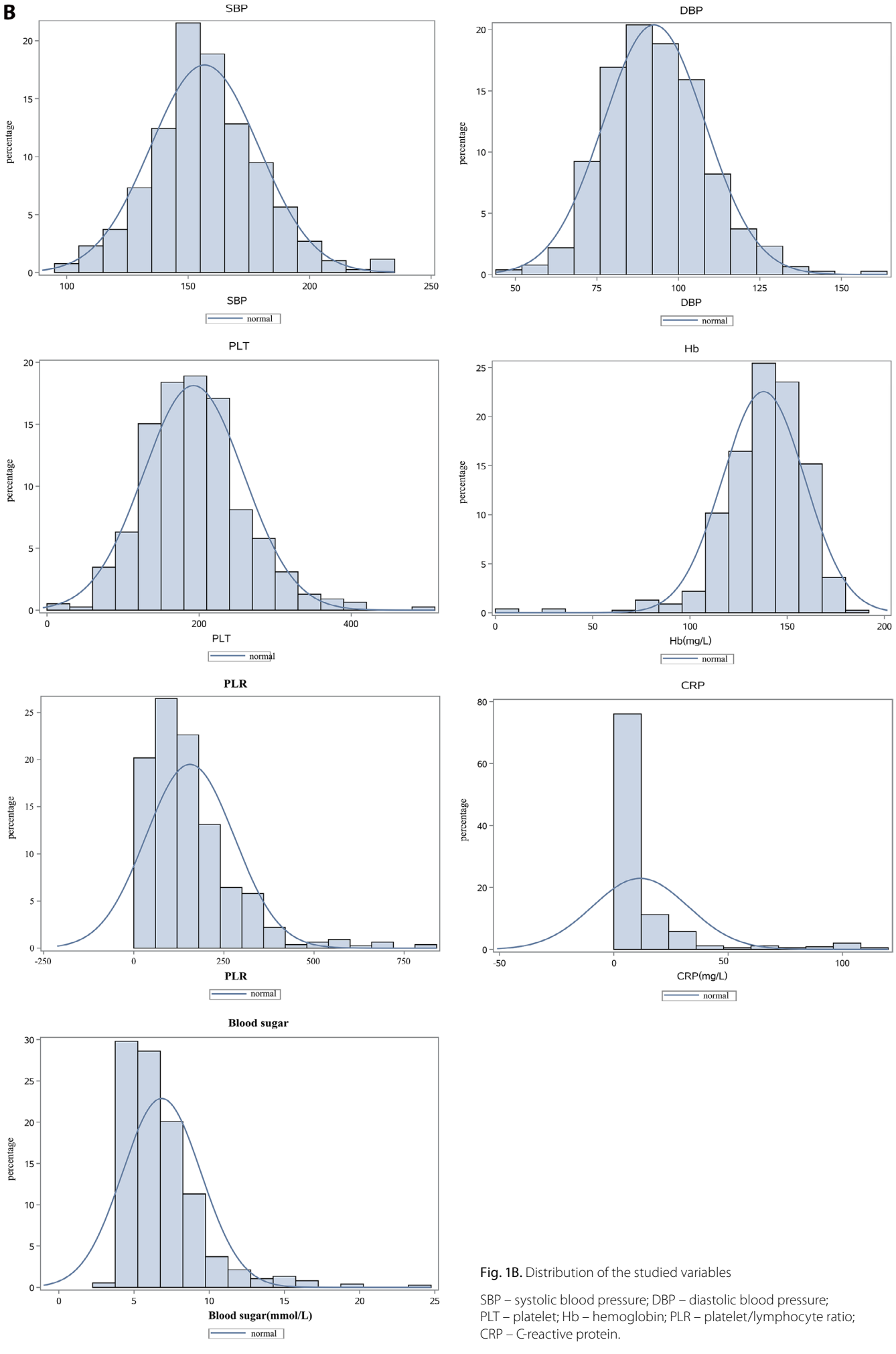


**Fig. 1B.** Distribution of the studied variables

SBP – systolic blood pressure; DBP – diastolic blood pressure; PLT – platelet; Hb – hemoglobin; PLR – platelet/lymphocyte ratio; CRP – C-reactive protein.

**Table 2.** The influencing factors' colinearity of multivariable logistic regression for HE in ICH patients

| Variables | TOL | VIF |
|---|---|---|
| Midline shift [cm] | 0.924 | 1.082 |
| ICH location: basal ganglia | 0.930 | 1.076 |
| ICH location: hypothalamus | 0.933 | 1.072 |
| SIRS | 0.863 | 1.159 |
| Neutrophils [$10^9$/L] | 0.855 | 1.170 |
| CRP [mg/L] | 0.961 | 1.041 |
| FBG [mmol/L] | 0.947 | 1.056 |

HE – hematoma expansion; SIRS – systemic inflammatory response syndrome; ICH – intracerebral hemorrhage; CRP – C-reactive protein; FBG – fasting blood glucose; TOL – tolerance; VIF – variance inflation factor.

**Table 3.** The influencing factors' colinearity of multivariable logistic regression for SIRS in ICH patients

| Variables | TOL | VIF |
|---|---|---|
| Midline shift [cm] | 0.899 | 1.112 |
| ICH location: basal ganglia | 0.917 | 1.091 |
| ICH location: hypothalamus | 0.920 | 1.087 |
| Body temperature (>38°C or <36°C) | 0.876 | 1.142 |
| Respiratory rate (>20 breaths/min) | 0.927 | 1.078 |
| WBC (>12 × $10^9$/L or <4 × $10^9$/L) | 0.960 | 1.042 |
| Heart rate (>90 beats/min) | 0.699 | 1.430 |
| Neutrophils [$10^9$/L] | 0.680 | 1.472 |
| CRP [mg/L] | 0.926 | 1.080 |
| FBG [mmol/L] | 0.937 | 1.067 |

SIRS – systemic inflammatory response syndrome; ICH – intracerebral hemorrhage; WBC – white blood cell; CRP – C-reactive protein; FBG – fasting blood glucose; TOL – tolerance; VIF – variance inflation factor.

**Table 4.** Baseline characteristics of HE and non-HE groups

| Variables | df | Non-HE group (n = 629) | HE group (n = 151) | Statistics | p-value |
|---|---|---|---|---|---|
| Age, years, M ($Q_1$, $Q_3$) | 1 | 63.00 (53.00, 71.00) | 61.00 (51.00, 75.00) | Z = –0.488 | 0.6257[a] |
| Gender, n (%)<br>Male<br>Female | 1 | 405 (64.4)<br>224 (35.6) | 93 (61.6)<br>58 (38.4) | $\chi^2$ = 0.413 | 0.5204[b] |
| Smoke history, n (%)<br>No<br>Yes | 1 | 424 (67.4)<br>205 (32.6) | 116 (76.8)<br>35 (23.2) | $\chi^2$ = 5.065 | 0.0244[b] |
| Drinking history, n (%)<br>No<br>Yes | 1 | 458 (72.8)<br>171 (27.2) | 113 (74.8)<br>38 (25.2) | $\chi^2$ = 0.253 | 0.6147[b] |
| Medical history, n (%) | | | | | |
| Hemorrhagic stroke, n (%)<br>No<br>Yes | 1 | 598 (95.1)<br>31 (4.9) | 140 (92.7)<br>11 (7.3) | $\chi^2$ = 1.327 | 0.2493[b] |
| Ischemic stroke, n (%)<br>No<br>Yes | 1 | 587 (93.3)<br>42 (6.7) | 136 (90.1)<br>15 (9.9) | $\chi^2$ = 1.906 | 0.1674[b] |
| Hypertension, n (%)<br>No<br>Yes | 1 | 184 (29.3)<br>445 (70.7) | 44 (29.1)<br>107 (70.9) | $\chi^2$ = 0.001 | 0.9780[b] |
| Diabetes mellitus, n (%)<br>No<br>Yes | 1 | 555 (88.2)<br>74 (11.8) | 121 (80.1)<br>30 (19.9) | $\chi^2$ = 6.919 | 0.0085[b] |
| Hematoma volume [mL], M ($Q_1$, $Q_3$) | 1 | 12.86 (6.14, 28.17) | 12.00 (5.21, 29.00) | Z = 0.019 | 0.9849[a] |
| Midline shift [cm], n (%)<br>≤0.5<br>>0.5 | 1 | 517 (82.2)<br>112 (17.8) | 108 (71.5)<br>43 (28.5) | $\chi^2$ = 8.708 | 0.0032[b] |
| ICH location, n (%)<br>Basal ganglia<br>Hypothalamus<br>Other brain parts | 2 | 336 (53.4)<br>215 (34.2)<br>78 (12.4) | 101 (66.9)<br>36 (23.8)<br>14 (9.3) | $\chi^2$ = 9.000 | 0.0111[b] |
| SBP [mm Hg], M ($Q_1$, $Q_3$) | 1 | 155.00 (145.00, 170.00) | 156.00 (137.00, 170.00) | Z = –0.662 | 0.5080[a] |

PLR, CRP, and FBG values were included in the multivariate logistics regression analysis, and the final regression model included midline shift, ICH location, respiratory rate, WBC and neutrophils count, CRP and FBG. The results of logistic regression analysis (Table 5) revealed that the risk of HE in ICH patients with midline shift >0.5 cm was 2.076 times higher than in ICH patients with midline shift ≤0.5 cm (odds ratio (OR) = 2.076, 95% confidence interval (95% CI): [1.274; 3.381], p = 0.0034). The risk of HE in ICH patients with basal ganglia hemorrhage and

**Table 4.** Baseline characteristics of HE and non-HE groups – cont.

| Variables | df | Non-HE group (n = 629) | HE group (n = 151) | Statistics | p-value |
|---|---|---|---|---|---|
| DBP [mm Hg], M ($Q_1$, $Q_3$) | 1 | 92.00 (82.00, 102.00) | 90.00 (78.00, 102.00) | Z = –0.485 | 0.6278[a] |
| SIRS, n (%)<br>No<br>Yes | 1 | 535 (85.1)<br>94 (14.9) | 108 (71.5)<br>43 (28.5) | $\chi^2$ = 15.401 | <0.0001[b] |
| Body temperature [°C], n (%)<br>36–38<br>>38 or <36 | 1 | 566 (90.0)<br>63 (10.0) | 125 (82.8)<br>26 (17.2) | $\chi^2$ = 6.249 | 0.0124[b] |
| Heart rate [beats/min], n (%)<br>≤90<br>>90 | 1 | 132 (21.0)<br>497 (79.0) | 31 (20.5)<br>120 (79.5) | $\chi^2$ = 0.015 | 0.9015[b] |
| Respiratory rate [breaths/min], n (%)<br>≤20<br>>20 | 1 | 63 (10.0)<br>566 (90.0) | 45 (29.8)<br>106 (70.2) | $\chi^2$ = 39.959 | <0.0001[b] |
| WBC count [$10^9$/L], n (%)<br>4–12<br>>12 or <4 | 1 | 475 (75.5)<br>154 (24.48) | 98 (64.9)<br>53 (35.1) | $\chi^2$ = 7.039 | 0.0080[b] |
| Graeb score, n (%)<br>No intraventricular hemorrhage<br>Mild intraventricular hemorrhage<br>Moderate intraventricular hemorrhage<br>Severe intraventricular hemorrhage | 3 | 448 (71.2)<br>98 (15.6)<br>64 (10.2)<br>19 (3.0) | 108 (72.0)<br>23 (15.3)<br>13 (8.7)<br>6 (4.0) | $\chi^2$ = 0.645 | 0.886[b] |
| GCS score, M ($Q_1$, $Q_3$) | 1 | 12.00 (9.00, 14.00) | 13.00 (11.00, 14.00) | Z = 1.507 | 0.1317[a] |
| INR, M ($Q_1$, $Q_3$) | 1 | 0.99 (0.95, 1.04) | 0.98 (0.95, 1.02) | Z = –0.333 | 0.7388[a] |
| PLT [$10^9$/L], M ($Q_1$, $Q_3$) | 1 | 187.00 (150.00, 235.00) | 184.00 (136.00, 215.00) | Z = –1.930 | 0.0536[a] |
| Hb [mg/L], M ($Q_1$, $Q_3$) | 1 | 140.00 (127.00, 154.00) | 140.00 (126.00, 150.00) | Z = –0.237 | 0.8129[a] |
| Neutrophils count [$10^9$/L], M ($Q_1$, $Q_3$) | 1 | 7.20 (4.80, 9.60) | 5.40 (3.40, 8.90) | Z = –4.403 | <0.0001[a] |
| LC count [$10^9$/L], M ($Q_1$, $Q_3$) | 1 | 1.20 (0.81, 1.70) | 1.27 (0.80, 1.91) | Z = 1.146 | 0.2518[a] |
| NLR (%), M ($Q_1$, $Q_3$) | 1 | 5.64 (3.12, 10.33) | 3.53 (1.69, 11.88) | Z = –3.377 | 0.0007[a] |
| PLR (%), M ($Q_1$, $Q_3$) | 1 | 136.54 (81.00, 206.80) | 98.57 (62.59, 207.35) | Z = –2.488 | 0.0128[a] |
| CRP [mg/L], M ($Q_1$, $Q_3$) | 1 | 0.00 (0.00, 2.30) | 1.00 (0.00, 8.60) | Z = 4.270 | <0.0001[a] |
| FBG [mmol/L], M ($Q_1$, $Q_3$) | 1 | 5.90 (4.93, 7.50) | 7.02 (5.13, 8.31) | Z = 2.831 | 0.0046[a] |

[a] – derived from Mann–Whitney U test; [b] – derived from $\chi^2$ test; M – median; HE – hematoma expansion; df – degrees of freedom; ICH – intracerebral hemorrhage; SBP – systolic blood pressure; DBP – diastolic blood pressure; SIRS – systemic inflammatory response syndrome; WBC – white blood cell; LC – lymphocytes; GCS – Glasgow Coma Score; INR – international normalized ratio; PLT – platelet; Hb – hemoglobin; NLR – neutrophil/lymphocyte ratio; PLR – platelet/lymphocyte ratio; CRP – C-reactive protein; FBG – fasting blood glucose.

hypothalamus hemorrhage was respectively 2.512 and 2.121 times higher than in those with bleeding occurring in other parts of brain (OR = 2.512, 95% CI: [1.496; 4.218], p = 0.0005; OR = 2.121, 95% CI: [1.007; 4.466], p = 0.0479). The association between SIRS patients and the risk of HE was significant (OR = 2.549, 95% CI: [1.497; 4.342], p = 0.0006). The HE risk in patients decreased by 15.5% for every 1×$10^9$/L increase in neutrophils count (OR = 0.845, 95% CI: [0.792; 0.902], p < 0.0001), increased by 1.3% for every 1 mg/L increase in CRP (OR = 1.013, 95% CI: [1.002; 1.024], p = 0.0184), and increased by 9.9% for every 1 mmol/L increase in FBG (OR = 1.099, 95% CI: [1.026; 1.178], p = 0.0074). The value of goodness-of-fit was 7.704, p = 0.463 and $R^2$ was 0.136 in the multivariable logistic regression model.

After adjusting midline shift, ICH location, neutrophils count, CRP and FBG, the further analysis demonstrated that the risk of HE in ICH patients with respiratory rate >20 breaths/min was 3.436 higher than in patients with respiratory rate ≤20 breaths/min (OR = 3.436, 95% CI: [1.981; 5.690], p < 0.0001). The risk of HE in ICH patients with WBC count >12($10^9$/L) or ≤4($10^9$/L) is 2.489 times higher than in those with WBC count 4–12 ($10^9$/L) (OR = 2.489, 95% CI: [1.494; 4.149], p = 0.0005) (Table 6). The value of goodness-of-fit was 10.953, p = 0.204 and $R^2$ was 0.179.

## Discussion

Intracerebral hemorrhage is associated with poor prognosis and high mortality. Its morbidity in China is far higher than in Europe or in the USA.[14] Hematoma expansion is a leading cause of poor prognosis and neurological deterioration in patients with ICH, as well as an important therapeutic goal of ICH.[15] In this study, the results showed that SIRS was significantly associated with the risk of HE. The logistic regression analysis was performed to analyze

**Table 5.** Multivariate logistic regression analysis for HE in ICH patients

| Variables | df | β | SE | Wald | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| Constant | – | –2.218 | 0.365 | 36.966 | <0.0001 | – |
| Midline shift [cm] | 1 | | | | – | |
| ≤0.5 | | | – | | | Ref |
| >0.5 | – | 0.730 | 0.249 | 8.601 | 0.0034 | 2.076 [1.274; 3.381] |
| ICH location | 2 | | | | – | |
| Other brain parts | | | – | | | Ref |
| Basal ganglia | – | 0.921 | 0.264 | 12.126 | 0.0005 | 2.512 [1.496; 4.218] |
| Hypothalamus | – | 0.752 | 0.380 | 3.912 | 0.0479 | 2.121 [1.007; 4.466] |
| SIRS | 1 | 0.936 | 0.272 | 11.863 | 0.0006 | 2.549 [1.497; 4.342] |
| Neutrophils count [$10^9$/L] | 1 | –0.168 | 0.033 | 25.411 | <0.0001 | 0.845 [0.792; 0.902] |
| CRP [mg/L] | 1 | 0.013 | 0.006 | 5.555 | 0.0184 | 1.013 [1.002; 1.024] |
| FBG [mmol/L] | 1 | 0.095 | 0.035 | 7.185 | 0.0074 | 1.099 [1.026; 1.178] |

HE – hematoma expansion; df – degrees of freedom; SE – standard error; SIRS – systemic inflammatory response syndrome; ICH – intracerebral hemorrhage; CRP – C-reactive protein; FBG – fasting blood glucose; OR – odds ratio; 95% CI – 95% confidence interval.

**Table 6.** Multivariate logistic regression analysis for SIRS in ICH patients

| Variables | df | β | SE | Wald | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| Body temperature (>38°C or <36°C) | 1 | 0.259 | 0.337 | 0.591 | 0.4422 | 1.295 [0.669; 2.507] |
| Respiratory rate (>20 breaths/min) | 1 | 1.234 | 0.281 | 19.287 | <0.0001 | 3.436 [1.981; 5.960] |
| WBC count (>12 × $10^9$/L or <4 × $10^9$/L) | 1 | 0.912 | 0.261 | 12.249 | 0.0005 | 2.489 [1.494; 4.149] |
| Heart rate (>90 beats/min) | 1 | –0.326 | 0.287 | 1.289 | 0.2563 | 0.722 [0.411; 1.267] |

SIRS – systemic inflammatory response syndrome; ICH – intracerebral hemorrhage; df – degrees of freedom; SE – standard error; WBC – white blood cell; OR – odds ratio; 95% CI – 95% confidence interval. The model with adjustment of midline shift, ICH location, neutrophils, C-reactive protein (CRP) and fasting blood glucose (FBG).

the risk factors for HE and the results indicated that midline shift >0.5 cm, basal ganglia hemorrhage, hypothalamus hemorrhage, respiratory rate >20 breaths/min, WBC count >12($10^9$/L) or ≤4($10^9$/L), high CRP, and hyperglycemia were the risk factors for HE in patients with ICH.

Inflammation, which is the main pathological feature of ICH and the leading factor of HE, plays a key role in the development of hemorrhage-induced brain injury and perihematomal edema.[16] A number of studies have shown that inflammatory markers such as interleukin 6 (IL-6), neutrophils count and CRP were significantly associated with a short-term poor prognosis of ICH.[8,17,18] The neutrophils, as the biomarkers of the severity of systemic inflammation, generally promote the production of chemokines, cytokines, reactive oxygen species (ROS), and extracellular proteases in the brain.[19] In addition, the inflammatory response after ICH does not only occur in a given part of the brain, but also causes systemic inflammation: the neutrophils promote the rapid recruitment of peripheral cytokines and chemokines within a few hours of the onset.[20,21] Interestingly, our study indicated that the HE risk in patients with ICH decreased by 15.5% for every 1×$10^9$/L increase in neutrophils count. This may be attributed to the small sample size, whereas well-designed and larger sample studies for verification are still required.

Multiple researches reported that higher WBC count is associated with more serious ICH in the case of decreased consciousness, increased baseline hematoma volume and existing intraventricular hemorrhage.[22,23] Morotti et al.[24] conducted a retrospective analysis to investigate the relationship between WBC count and HE using multivariate logistic regression. The results showed that a higher WBC count was associated with a lower risk of HE. Subsequently, the inflammation was not only a nonspecific stress-related response, but was also beneficial to ICH patients in improving the coagulation response and limiting HE. Conversely, our study found that WBC count >12($10^9$/L) or ≤4($10^9$/L) was associated with an increased risk of HE in patients with ICH. This may have occured due to the different admission year of the selected patients.[24] The medical equipment and conditions of patients admitted early may not be as good as they are now, which means that our research is more accurate and convincing.

Little research was available on the association between respiratory rate and HE in ICH patients. Previous studies showed that acute respiratory distress syndrome (ARDS) normally occurred in 20% of patients with ICH.[25,26] The ARDS is a type of acute respiratory failure with severe hypoxemia and extremely difficult breathing as typical symptoms, and is associated with a high morbidity

and mortality burden.[27] Our study further investigated the relationship between the respiratory rate and HE using multivariate logistic regression analysis. The results demonstrated that the respiratory rate >20 breaths/min was related to the increased risk of HE in patients with ICH.

To our knowledge, there were few studies investigating the association of SIRS with HE after ICH. A retrospective study of ICH patients at New York University (NYU) Langone Medical Center Manhattan Campus (New York, USA) found that SIRS was associated with HE within the first 24 h of the onset of symptoms,[28] which was consistent with our findings. The SIRS is an immune-related aseptic inflammatory response common in various critically ill patients.[10] The possible mechanisms of SIRS include: a pro-inflammatory response of inflammatory cytokines; an increased release of toxic substances such as excitatory amino acids, nitric oxide and free radicals; and an increased production of thrombin, which induces glial in neuronal apoptosis of cells.[11,29,30] Previous studies focused on the association between SIRS and the outcomes after ICH. Boehme et al.[12] found that patients with SIRS were at an increased risk of poor prognosis, but SIRS was not an independent predictor of poor functional outcomes after ICH. Melmed et al. suggested that the relationship between SIRS and poor clinical outcome was mediated by HE.[28] An another study conducted by Hagen et al.[11] explored the associations of SIRS with long-term functional outcome and contributing factors after ICH, the results of which showed independent associations of SIRS with larger hematoma volumes. The present study investigated the relationship between the risk of HE in ICH patients and body temperature, heart rate, respiratory rate, and WBC count. The findings suggested that respiratory rate >20 breaths/min and WBC count >12($10^9$/L) or ≤4($10^9$/L) were related to an increased risk of HE in patients with ICH.

## Limitations

The strength of our study was a large sample size, which made the results more powerful and convincing. Unfortunately, it was a retrospective study and some clinical data were missing, such as the information on the use of antiplatelet drugs and anticoagulant drugs before the admission.

# Conclusions

We have established that in patients with ICH, SIRS was positively associated to the risk of HE, especially regarding the indicators of respiratory rate and WBC count, which may help indentify the ICH patients. This finding may achieve the early prevention of HE in ICH patients and open targeted therapeutic regimens for improving the prognosis of patients with ICH.

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