Heliyon 10 (2024) e28554

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Association between white blood cells and ultra-early hematoma growth in patients with spontaneous intracerebral hemorrhage

Hui Zhang [a,b,c], Jian Deng [a,b,c], Zhili Cai [a,b,c], Yitao He [a,b,c,*]

[a] Department of Neurology, The Second Clinical Medical College of Jinan University, Shenzhen, Guangdong, China
[b] Department of Neurology, The First Affiliated Hospital of Southern University of Science and Technology (Shenzhen People's Hospital), Shenzhen Guangdong, China
[c] Shenzhen Clinical Research Centre for Geriatrics, Shenzhen People's Hospital, Shenzhen, Guangdong, China

ARTICLE INFO

Keywords:
Ultra-early hematoma growth
Spontaneous intracerebral hemorrhage
White blood cells
Risk factor

ABSTRACT

Background: Ultra-early inflammatory reaction after spontaneous intracerebral hemorrhage (sICH) plays an important role in the coagulation process and is closely related to early hematoma expansion. However, the relationship between ultra-early hematoma growth (uHG) and ultra-early inflammatory reaction remains unknown.
Objective: To evaluate the association between ultra-early inflammatory indicators and uHG in patients with sICH.
Methods: We retrospectively included 225 patients with acute sICH who were divided into the uHG ≤4.7 ml/h group and the uHG >4.7 ml/h group, respectively. The uHG was defined as hematoma volume (milliliter) at the primary computed tomography (CT) scan divided by time (hour) from onset to the performance of primary CT within 6 h after onset. The white blood cells (WBC), blood hypersensitive C-reactive protein, National Institutes of Health Stroke Scale (NIHSS) score and other related baseline data were collected and compared between the two groups. The multivariate regression analysis and receiver operating characteristic (ROC) curve were used to evaluate the independent risk factors for uHG >4.7 ml/h.
Results: NIHSS score and WBC were independent risk factors for uHG in patients with acute sICH (OR 1.188, 95% *CI*: 1.111–1.271, $p < 0.001$; OR 1.151, 95% *CI*: 1.018–1.300, $p = 0.024$; respectively). The area under curve of ROC for WBC and NIHSS score was 0.658 and 0.754, respectively (all $p < 0.001$), while the WBC combined with NIHSS score was 0.773 ($p < 0.001$).
Conclusion: WBC count within 6h after onset might be an independent risk factor for the increase of uHG in patients with sICH.

1. Introduction

Ultra-early hematoma growth (uHG) was defined as hematoma volume (milliliter) at the primary computed tomography (CT) scan divided by time (hour) from onset to the performance of primary CT within 6 h after onset [1]. In recent years, numerous studies have proposed that uHG was closely associated with early neurological deterioration and poor prognosis after three months in patients with acute spontaneous intracerebral hemorrhage (sICH) [1–3]. The uHG has been reported to be affected by many factors such as age,

* Corresponding author. No.1017 of Dongmen North Road, Luohu District, Shenzhen, Guangdong Province, China.
E-mail addresses: zhangzhenghuizi@126.co (H. Zhang), jian6cathy@163.com (J. Deng), caizhili002@sina.com (Z. Cai), heyitaovv@126.com (Y. He).

https://doi.org/10.1016/j.heliyon.2024.e28554
Received 8 September 2023; Received in revised form 12 March 2024; Accepted 20 March 2024
Available online 27 March 2024

hypertension, type 2 diabetes, National Institutes of Health Stroke Scale (NIHSS) score, blend sign and black hole sign on baseline non-contrast computed tomography, and lobar hemorrhage [2,4,5]. Ultra-early inflammatory reaction after sICH plays an important role in the coagulation process and is closely related to early hematoma expansion (HE) [6]. However, the relationship between uHG and ultra-early inflammatory reaction remains unknown. Hence, this study aimed to evaluate the predictive value of ultra-early inflammatory indicators on the uHG in patients with sICH.

2. Methods

2.1. Participants

We retrospectively enrolled consecutive patients with acute sICH who were admitted to the Department of Neurology of our Hospital between January 2015 and December 2022.

The inclusion criteria were as follows: (1) patients diagnosed with acute sICH [7], with the bleeding site located in the basal ganglia; (2) head CT and the observed blood indicators were performed within 6 h after onset; (3) the hematoma volume on the initial head CT were less than 30 mL; (4) no fever before admission (body temperature $<37.3\ ^{\circ}C$).

The exclusion criteria were as follows: (1) age <18 years; (2) bleeding secondary to tumor, trauma, vascular malformation; (3) a history of infection within two weeks before admission; (4) received antibiotic treatment within one week before admission; (5) treated with glucocorticoid before admission; (6) incomplete data; (7) patients who underwent hematoma removal surgery.

2.2. Observed data

The following clinical data of the enrolled patients were collected: age, gender, initially measured systolic blood pressure (BP) and diastolic BP at the first visit to the hospital after onset, NIHSS score, white blood cells (WBC), blood hypersensitive C-reactive protein (CRP), platelet (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), times from onset to hospital, times from onset to performance of the primary CT, and use of antiplatelet or anticoagulant drugs within 2 week prior to sICH.

If the systolic and diastolic BP were higher than 140/90 mmHg, the intravenous antihypertensive drug such as urapidil was used, with lower than 140/90 mmHg as the target BP.

Nosocomial pneumonia was defined as pneumonia that developed at least 48 h after hospitalization and was generally divided into hospital-acquired pneumonia and ventilator-associated pneumonia [8].

2.3. Evaluation of uHG

Hematoma volume was measured by semiautomated multislice and voxel threshold techniques using MIStar software (version 3.2, Apollo Medical Imaging Inc, Melbourne, VIC, Australia). The uHG = baseline hematoma volume (milliliter)/time (hour) from onset to performance of the primary CT [1].

2.4. Sample size estimation

In this study, we used events per variable (EPV) method to conduct sample size estimation. The sample size was calculated according to the formula: $m = n \times EPV$ (n was the number of independent variables, and EPV was generally 15–20). The number of independent variables was 13, thus the sample size of the study should be > 195.

2.5. Grouping

Based on previous relevant studies, we used uHG = 4.7 ml/h as the cutoff value [2,3,9], and divided the enrolled patients into the uHG $\leq$4.7 ml/h group and the uHG $>$4.7 ml/h group.

2.6. Statistical analysis

SPSS 25.0 software was used to analyze all the data. Count data were expressed as percentage, and Chi-square test was used for comparison between the two groups. Measurement data were indicated as means $\pm$ standard deviation, and compared by independent sample *t*-test. Multivariate logistic regression analysis and receiver operating characteristic (ROC) curve were used to evaluate the independent risk factors for uHG $>$4.7 ml/h in patients with acute sICH. A p value < 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

We included 225 patients with acute sICH admitted to our Hospital between January 2015 and December 2022. The roadmap of our study was showed as Fig. 1. There were 151 men and 77 women, with an average age of 59.92 $\pm$ 12.62 years (range 25–90 years).

The enrolled patients were divided into the uHG ≤4.7 ml/h group (n = 158) and the uHG >4.7 ml/h group (n = 67). The incidence of uHG >4.7 ml/h was 29.77%, and the average value of uHG was 5.10 ± 7.67 ml/h. Other baseline data between the two groups are shown in Table 1. The values of NIHSS score, WBC, systolic BP and the proportion of diabetics were all significantly higher in the uHG >4.7 ml/h group than in the uHG ≤4.7 ml/h group ($p < 0.001$, $p < 0.001$, $p = 0.019$, $p = 0.001$, respectively), while the age and TT were significantly lower in the uHG >4.7 ml/h group than in the uHG ≤4.7 ml/h group ($p = 0.048$, $p = 0.028$, respectively). There were no significant differences in gender, diastolic BP, PLT, PT, INR, APTT and CRP between the two groups (all $p > 0.05$).

3.2. Logistic regression for uHG in patients with acute sICH

The NIHSS score, WBC, systolic BP, age, TT and whether combined with diabetes were set as independent variables, and uHG >4.7 ml/h as the dependent variable for conducting the multivariate logistic regression analysis. The result showed that the NIHSS score and WBC were independent risk factors for uHG in patients with sICH (OR 1.188, 95% *CI*: 1.111–1.271, $p < 0.001$; OR 1.151, 95% *CI*: 1.018–1.300, $p = 0.024$; respectively. Table 2).

3.3. Baseline characteristics of the normal and higher WBC groups

We divided the enrolled cases into the normal WBC group (WBC $\leq 10 \times 10^9$/L) and the higher WBC group (WBC $>10 \times 10^9$/L). The clinical data of the two groups were compared, which showed that NIHSS score, baseline hematoma volume and the incidence of nosocomial pneumonia were significantly higher in the higher WBC group than in the normal WBC group ($p = 0.001$, $p = 0.002$, $p = 0.005$, respectively. Table 3).

3.4. ROC curve for uHG>4.7 mL/h

Based on the multivariate logistic regression, ROC curve was plotted to evaluate the predictive value of risk factors for uHG >4.7 ml/h. It showed that the area under curve (AUC) of WBC combined with NIHSS score was 0.773 ($p < 0.001$), which was larger than the AUC of WBC (0.658, $p < 0.001$) or NIHSS score (0.754, $p < 0.001$), respectively. The sensitivity of combined prediction was 77.6%, which was better than WBC (71.6%) or NIHSS score (61.2%) alone, and the specificity was 70.3%, which was higher than WBC (58.9%) and lower than NIHSS score (81%). When we increased the systolic BP into the predictive model, the AUC of combining systolic BP with NIHSS score and WBC was 0.773 ($p = 0.034$), and the sensitivity was 77.6% and the specificity was 69%. Compared with the combined prediction of NIHSS and WBC, there was no benefit from increasing systolic BP in the combined prediction model (Table 4, Fig. 2). Thus, in patients with acute sICH, although WBC was independent risk factor for uHG, the predictive value of WBC for

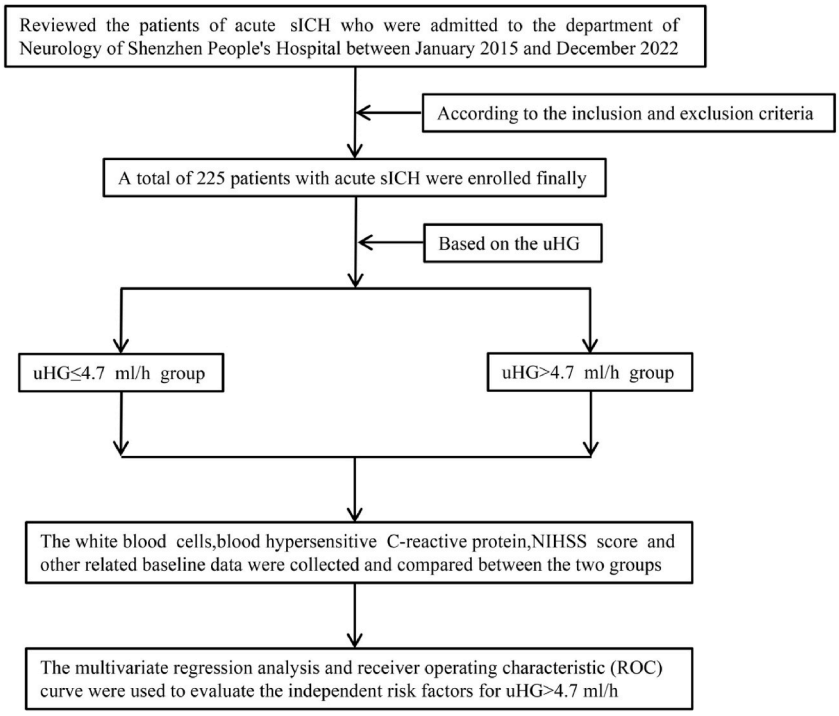

Fig. 1. The roadmap of study. **Note:** sICH, spontaneous intracerebral hemorrhage; uHG, ultra-early hematoma growth; NIHSS, National Institutes of Health Stroke Scale.

Table 1
Comparison of baseline characteristics between the uHG >4.7 ml/h group and the uHG ≤4.7 ml/h group.

	uHG >4.7 ml/h group	uHG ≤4.7 ml/h group	*t* or *Z* or x^2 value	*p* value
Number of cases (n)	67	158		
Age (years)	57.37 ± 12.18	61.00 ± 12.69	1.984 [a]	0.048
Gender (male/female)	45/22	106/52	<0.001 [b]	0.991
Diabetes, n (%)	34 (50.7%)	44 (27.8%)	10.892 [b]	0.001
Systolic BP (mmHg)	174.99 ± 23.67	166.85 ± 23.63	−2.358 [a]	0.019
Diastolic BP (mmHg)	100.69 ± 15.34	96.70 ± 14.84	−1.826 [a]	0.069
Times from onset to hospital (hours)	1.00 (0.75,1.90)	2.50 (1.33,3.68)	−5.489 [c]	<0.001
NIHSS score	9 (5, 12)	3 (1, 6)	−6.043 [c]	<0.001
WBC (10^9/L)	9.64 ± 3.14	8.12 ± 2.39	−3.946 [a]	<0.001
PLT (10^9/L)	227.33 ± 67.66	229.81 ± 68.48	0.249 [a]	0.803
PT (s)	11.56 ± 1.48	11.68 ± 2.81	0.334 [a]	0.738
INR	0.97 (0.94, 1.02)	0.97 (0.93, 1.03)	−0.203 [c]	0.839
APTT (s)	29.74 ± 4.33	29.14 ± 4.52	−0.913 [a]	0.362
TT (s)	15.09 ± 1.97	15.87 ± 2.59	2.206 [a]	0.028
CRP (umol/L)	3.00 (1.22, 6.39)	2.38 (1.03, 5.94)	−1.245 [c]	0.213
Use of antiplatelet drugs within 2 weeks prior to sICH (n, %)	7 (10.4%)	18 (11.4%)	0.430 [b]	0.837
Use of anticoagulant drugs within 2 weeks prior to sICH (n, %)	5 (7.5%)	6 (3.8%)	0.685 [b]	0.408

Abbreviations: BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cells; PLT, platelet; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, hypersensitive C-reactive protein; uHG, ultraearly hematoma growth.
[a] Conduct *t*-test.
[b] Conduct Chi-square test.
[c] Conduct Mann Whitney *U* test.

Table 2
Multivariate logistic regression analysis of risk factors for uHG.

	B	SE	Wald	*p* value	OR	95%*CI*
NIHSS score	0.172	0.034	25.051	<0.001	1.188	1.111–1.271
WBC	0.140	0.062	5.070	0.024	1.151	1.018–1.300

Conduct multifactor logistic regression analysis. Whether uHG >4.7 ml/h was set as dependent variable, and NIHSS score, WBC, age, Systolic BP, and TT as independent variables, with stepwise forward method was adopted.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cells; CI, confidence interval; OR, odds ratio; uHG, ultraearly hematoma growth.

Table 3
Comparison of characteristics between the normal WBC group and the higher WBC group.

	Normal WBC group	Higher WBC group	*Z* or x^2 value	*p* value
Number of cases (n)	168	57		
NIHSS score	4 (1, 7)	8 (2, 11.50)	−3.241 [b]	0.001
Nosocomial pneumonia, n (%)	29 (17.3%)	20 (35.1%)	7.939 [a]	0.005
Baseline hematoma volume (ml)	5.40 (2.40, 10.45)	10.00 (4.65, 14.5)	−3.066 [b]	0.002

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.
[a] Conduct Chi-square test.
[b] Conduct Mann Whitney *U* test.

Table 4
The AUC of related predictive factors for uHG >4.7 ml/h in actue sICH.

	AUC	*p* value	95%CI
WBC	0.658	<0.001	0.580–0.736
NIHSS score	0.754	<0.001	0.684–0.823
WBC + NIHSS score	0.773	<0.001	0.706–0.840
WBC + NIHSS score + systolic BP	0.773	<0.001	0.706–0.841

Abbreviations: AUC, Area Under Curve; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cells; BP, blood pressure; uHG, ultraearly hematoma growth; sICH, spontaneous intracerebral hemorrhage.

uHG was mediocre, even combining with NIHSS and systolic BP.

4. Discussion

This study revealed that WBC and NIHSS score were independent risk factors for uHG in patients with acute sICH. WBC are considered as a marker of central nervous system inflammation [10], and histopathological evidence showed infiltrating WBC in and around the hematoma within a few hours after sICH [11]. The immune response caused by the release of neuroendocrine hormones during acute stress events [12] and the increased activity of interleukins released in plasma and cerebrospinal fluid might lead to the increase in WBC count [13]. The mechanism of leukocytosis after sICH remains unclear, but the role of WBC in secondary brain injury of sICH has been confirmed [13–15]. The increase in initial WBC count was reported to be independently associated with larger baseline hematoma volume [16] and early HE [10]. In addition, the increase in WBC count, especially in the first 72 h of onset, could predict early neurological deterioration in patients with sICH [15]. It was also reported that the higher the WBC count one day before and on the day of neurological deterioration, the more severe was the brain damage after sICH, due to the enhancement of inflammatory state [14]. WBC was increased in the first 4–48 h in traumatic cerebral injury animal model [17], which indicated that the accumulation of WBCs might influence the cerebral circulation and cause cerebral damage. WBC could cause secondary cerebral damage via destroying the blood-brain barrier [18]. Consequently, higher WBC count after sICH might be associated with the increase of uHG.

Previous studies confirmed that the increase of uHG was associated with higher baseline and 24-h NIHSS scores [3], especially when NIHSS score was larger than 14 [1,2]. The results of our study were in accordance with the previous studies. Kwan et al. [19]and Yu et al. [12]confirmed that higher baseline NIHSS score was associated with the increase in WBC count in patients with sICH at early stage. These studies indicated that patients with severe clinical syndromes might have higher levels of systemic inflammatory response. In our study, we also found that the higher WBC group had larger baseline hematoma volume and higher baseline NIHSS score. Besides, our study revealed that the higher WBC count at baseline was independently associated with the increase of uHG, which was not confirmed in any other previous study. However, although the predictive value was mediocre, the WBC count within 6 h after onset was an independent risk factor for uHG in patients with acute sICH.

In this study, we excluded patients with infection or receiving hormone therapy, which could influence the level of WBC. Thus, we considered that the increase of WBC count in early stage after sICH was related to systemic inflammatory response, rather than infection or drug. Besides, in our study, higher WBC count on admission could predict greater possibility of nosocomial pneumonia, which was also consistent with the study of Sun et al. [15].

In our study, elevated BP was not an independent risk factor for uHG. Acute hypertension is common when acute sICH occurs, and elevated BP was found to be related to an increased risk of HE [20,21]. However, there were very few studies on the relationship between BP and uHG. Sato et al. reported that antihypertensive therapy was beneficial to HE, but had no significant effect on uHG [1], and our study showed similar conclusion. Meanwhile, we considered it might result from the BP monitoring method in our study. The BP at admission was collected as the statistical indicator of BP in our study, and it could not represent the average BP level and variability. However, in our study, we emphasized the influence of BP at admission for the uHG.

4.1. Limitations

This study had certain limitations. First, the intracranial hemorrhage of some patients had stopped when the first head CT was conducted, which might cause incorrect evaluation of uHG. Second, the bleeding site was limited to basal ganglia, and hematoma volume was set at less than 30 mL, thus the conclusion might not suitable for patients with cerebral hemorrhage in other sites, hematoma volume greater than 30 mL in the basal ganglia or requiring surgical treatment. Finally, although we eliminated the potential influence of other factors on WBC count, it could be affected by some factors related to insufficient pre-hospital diagnosis.

5. Conclusion

Our study showed that the WBC count within 6 h after onset might be an independent risk factor for the increase of uHG in patients with sICH of basal ganglia, despite being of limited value as a predictor of uHG. Our study limited the bleeding site and hematoma volume. Thus, the results of this study may be more applicable to patients with a hematoma volume of less than 30 mL in the basal ganglia without surgery. In addition, well-designed clinical and basic studies are needed to further understand the association between WBC and uHG.

Ethical declarations

This study was reviewed and approval by the Ethics Committee of Shenzhen People's Hospital. The data in the study was anonymous, thus the requirement for informed consent was waived, which was approved by the Ethics Committee. The study was registered in the Chinese Clinical Trial Registry center (registration number: ChiCTR1900021729).

Funding

This research has been supported by the National Natural Science Foundation of China (grant number: 82071463), the clinical

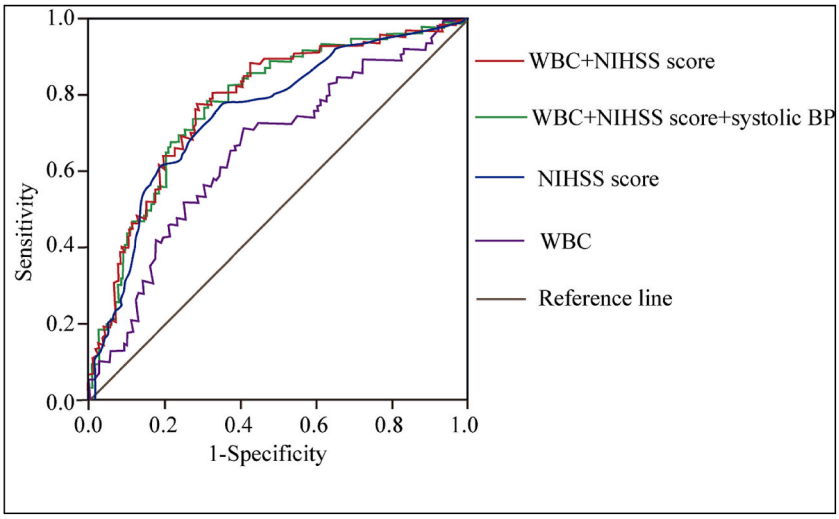

Fig. 2. ROC curve for uHG >4.7 ml/h in patients with actue sICH.
Note: The AUC of WBC and NIHSS score was 0.658 and 0.754, respectively (all $p < 0.001$), while the AUC of WBC combined with NIHSS score was 0.773 ($p < 0.001$). The AUC and sensitivity of WBC and NIHSS score combined with systolic BP was the same as WBC combined with NIHSS score (AUC = 0.733, and sensitivity = 77.6%), but the specificity is lower (70.3% vs. 69%).
Abbreviations: AUC, Area Under Curve; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cells; BP, blood pressure; uHG, ultraearly hematoma growth; sICH, spontaneous intracerebral hemorrhage.

research cultivation project of Shenzhen People's Hospital (grant number: SYLCYJ202117), and the Science and Technology Program of Shenzhen Science and Technology Innovation Committee (grant number: JCYJ20230807112400001).

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Hui Zhang: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Jian Deng:** Methodology, Investigation, Data curation. **Zhili Cai:** Methodology, Investigation, Data curation. **Yitao He:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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