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A high neutrophil-to-platelet ratio is associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage: a retrospective study

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Abstract

Background Early hematoma expansion (HE) occurs in 20 to 40% of spontaneous intracerebral hemorrhage (ICH) patients and is a primary determinant of early deterioration and poor prognosis. Previous studies have shown that inflammation is a major pathological feature of ICH, and the neutrophil-to-platelet ratio (NPR) is a marker of systemic inflammation. Therefore, we aimed to assess the association between the NPR and HE in ICH patients.

Methods We retrospectively collected and analyzed data from ICH patients who received treatment at our institution from January 2018 to November 2019. The NPR was calculated from the admission blood test. Brain computed tomography (CT) scans were performed at admission and repeated within 24 h. Hematoma growth was defined as relative growth > 33% or absolute growth > 6 ml.

Results A total of 317 patients were enrolled in our study. Multivariate logistic regression analysis indicated that the NPR was an independent predictor of HE [odds ratio (OR) = 1.742; 95% CI: 1.508–2.012, $p < 0.001$]. Receiver operating characteristic (ROC) curve analysis revealed that the NPR could predict HE, with an area under the curve of 0.838 (95% CI, 0.788–0.888, $p < 0.001$). The best predictive cut-off of the NPR for HE was 5.47 (sensitivity, 75.3%; specificity, 77.6%).

Conclusions A high NPR was associated with an increased risk of HE in patients with ICH.

Keywords Hematoma expansion, Inflammation, Intracerebral hemorrhage, Neutrophil-to-platelet ratio, Predictor

Background

Spontaneous intracerebral cerebral hemorrhage (ICH) comprises approximately 10 to 20% of all strokes, with high rates of disability and mortality [1]. Early hematoma expansion (HE) occurs in 20 to 40% of ICH patients and is a primary determinant of early deterioration and poor prognosis [2]. Previous studies have shown that inflammation is a major pathological feature of ICH [3–5]. In addition, systemic inflammatory responses have been found to be associated with the pathological process of active bleeding in ICH patients [6]. The neutrophil-to-platelet ratio (NPR) is a marker of systemic inflammation. A previous study indicated that the interaction

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between neutrophils and platelets plays a role in vascular injury after cerebral infarction [7]. Moreover, He et al. conducted a retrospective study of 279 ischemic stroke patients with hemorrhagic transformation and found that a high NPR was an independent predictor of hemorrhagic transformation [8].

However, the literature regarding the relation between the NPR and HE in ICH patients is infrequent. Therefore, this study aimed to explore the association between the NPR at admission and early HE after spontaneous ICH.

Methods

Patients and definitions

We performed a retrospective review of patients with ICH who visited West China Hospital from January 2018 to November 2019. The study protocol was approved by the ethics committee of our hospital. Informed consent was obtained from all patients or family members. We defined the inclusion criteria as follows: 1) a diagnosis of intracranial hemorrhage by computed tomography (CT); 2) patient underwent the first CT scan on admission and the second CT scan at 24 h after the onset of symptoms; 3) routine examinations and laboratory blood tests were conducted within 24 h after admission; and 4) patient age ≥ 18 years. We excluded patients with 1) ICH attributable to aneurysm, arteriovenous malformation or moyamoya disease; 2) ICH attributable to acute cerebral infarction, thrombolysis of cerebral or myocardial infarction; 3) prior systemic diseases such as cancer, hematological diseases, immunological disease, neurological disease, recent infectious disease, severe hepatic dysfunction, renal dysfunction and coagulation dysfunction; 4) a medical history of anticoagulant use or antiplatelet treatments; 5) patients who underwent surgery before the 24-h CT; and 6) isolated intraventricular hemorrhage.

Clinical manifestation assessment

Baseline clinical and demographic parameters were collected at hospital arrival, including age; sex; Glasgow Coma Scale (GCS) score on admission; National Institutes of Health Stroke Scale (NIHSS) score on admission; blood pressure; cigarette consumption and alcohol use; and the medical history, including that of ischemic stroke, ICH, hypertension and diabetes mellitus.

Laboratory examinations

Radiological data were recorded, including hematoma location, hematoma size and the presence of intraventricular hemorrhage (IVH). Laboratory variables were also recorded, including red blood cell (RBC) count, hemoglobin, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), platelet count, prothrombin time (PT), activated

partial thromboplastin time (APTT), international normalized ratio (INR) and blood glucose level. Admission NPR was calculated as the ratio of the $ANC \times 100$ to the platelet count.

Outcome assessments

Two reviewers independently evaluated all the head CT scans. Any disagreement between the two reviewers was resolved by consensus. All patients underwent the first CT scan at admission, and the follow-up CT scan was performed within 24 h of symptom onset. Hematoma volume was measured by the ABC/2 method as described previously [9]. HE was defined as absolute growth of >6 ml or relative growth of $>33\%$ from the first CT to the follow-up CT [10].

Statistical analysis

The clinical data, laboratory parameters and imaging characteristics of ICH patients with and without HE were compared. Continuous variables are expressed as mean \pm standard deviation or median with interquartile range (IQR) for normally distributed and non-normally distributed variables, respectively, whereas categorical variables are expressed as frequency and percentage. Univariate analyses were conducted by independent t-test, Mann–Whitney U-test, chi-square (χ^2) test, or Fisher's exact test. Independent t-tests or Mann–Whitney U-tests were applied to compare continuous variables. The chi-square (χ^2) test or Fisher's exact test was used to compare categorical data. Variables with a p -value < 0.10 on univariate analysis were entered into a multivariate regression model. To facilitate interpretation, some variables were classified as follows: GCS score as "13–15 points", "9–12 points" and "3–8 points" and hematoma location as "infratentorial hematoma" and "supratentorial hematoma". Receiver operating characteristic (ROC) curve analysis was performed to indicate the value of the NPR for the prediction of HE in ICH patients. The cut-off value of the NPR was set by the Youden index from the ROC curve. A value of $p < 0.05$ was considered to be significant. All the above mentioned statistical analyses were carried out with SPSS version 21.0 (SPSS, Chicago, IL, USA).

Results

A total of 317 consecutive ICH patients (230 males and 87 females) meeting the inclusion criteria were enrolled in this study (Fig. 1). The median age, median baseline hematoma volume and median NPR were 56 years (IQR, 45–67.5), 24.00 ml (IQR, 10.15–41.84) and 4.79 (IQR, 2.70–6.63), respectively. HE was detected in 89 (28%) patients. For these patients, the median age was 58 (IQR, 49–70) years, 61 (68.5%) were men and 28 (31.5%)

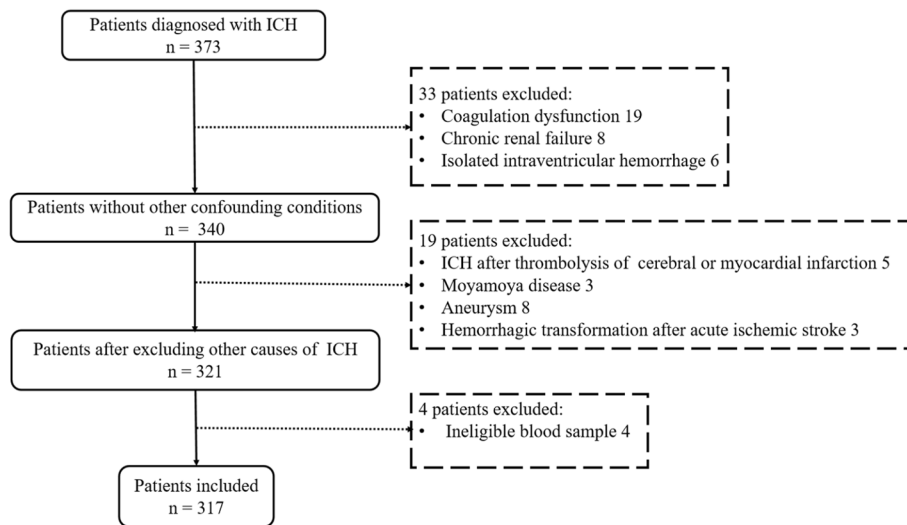


Fig. 1 Flowchart of study enrollment

were women. The median NPR of the HE group was significantly higher than that of the group without HE ($p < 0.001$) (Table 1).

Univariate analysis showed significant associations between HE with age ($p = 0.028$), GCS score on admission ($p < 0.001$), NIHSS score on admission ($p = 0.019$), baseline hematoma volume ($p < 0.001$), RBC count

($p = 0.03$), ANC ($p < 0.001$), ALC ($p < 0.001$), AMC ($p = 0.003$), Platelet ($p < 0.001$), NPR ($p < 0.001$), PT ($p = 0.009$), INR ($p = 0.005$) and blood glucose ($p < 0.001$) (Table 1).

The multivariate analysis indicated that GCS score (3–8 points) [OR=3.387, 95% CI: 1.443–7.949, $p = 0.005$], NPR (OR=1.742; 95% CI: 1.508–2.012, $p < 0.001$) and

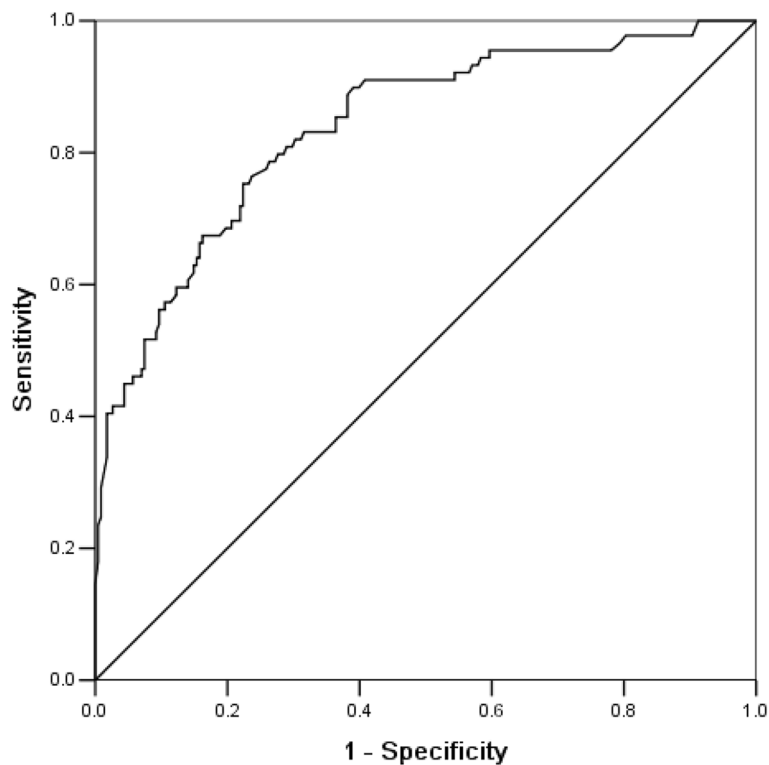


Fig. 2 Receiver operating characteristic curve for the value of the NPR for the prediction of HE in ICH patients

Table 1 Univariate analysis of clinical characteristics related to HE in patients with ICH

Characteristic	Total (n = 317)	HE (n = 89)	No HE (n = 228)	p-Value
Age(years)	56(45,67.50)	58(49,70)	54(43,66)	0.028*
Sex (male)	230(72.6%)	61(68.5%)	169(74.1%)	0.329
Hypertension	258(81.4%)	76(85.4%)	182(79.8%)	0.335
Diabetes mellitus	26(8.2%)	6(6.7%)	20(8.8%)	0.653
Prior ischemic stroke	10(3.2%)	2(2.2%)	8(3.5%)	0.826
Prior ICH	11(3.5%)	4(4.5%)	7(3.1%)	0.779
Smoking	98(30.9%)	23(25.8%)	75(32.9%)	0.279
Alcohol consumption	83(26.2%)	19(21.3%)	64(28.1%)	0.256
Onset-to-first-CT time(hours)	7(4,15)	8(5,14.5)	7(4,15)	0.249
SBP(mmHg)	163 ± 27	162 ± 26	164 ± 27	0.664
DBP(mmHg)	96 ± 18	96 ± 16	97 ± 19	0.578
GCS score on admission	-	-	-	< 0.001**
13-15	114(36.0%)	15(16.9%)	99(43.4%)	-
9-12	104(32.8%)	29(32.6%)	75(32.9%)	-
3-8	99(31.2%)	45(50.6%)	54(23.7%)	-
NIHSS on admission	12(9,14)	12(10,14)	10(9,13)	0.019*
Infratentorial hematoma	67(21.1%)	20(22.5%)	47(20.6%)	0.760
Hematoma size (ml)	24.00(10.15,41.84)	35.24(14.98,52.20)	21.23(8.36,38.18)	<0.001**
Presence of IVH	133(42.0%)	42(47.2%)	91(39.9%)	0.256
RBC, x10 ¹²	4.58 ± 0.72	4.44 ± 0.75	4.63 ± 0.70	0.031*
Hemoglobin(g/L)	139 ± 20	135 ± 21	140 ± 19	0.061
Neutrophil, x10 ⁹	8.12(5.25,11.33)	10.86(8.56,13.74)	6.85(4.74,9.93)	<0.001**
Lymphocyte, x10 ⁹	1.22(0.79,1.83)	0.91(0.65,1.29)	1.31(0.87,1.93)	<0.001**
Monocyte, x10 ⁹	0.51(0.38,0.73)	0.63(0.40,0.81)	0.50(0.35,0.69)	0.003*
Platelet, x10 ⁹	185 ± 64	159 ± 60	195 ± 62	<0.001**
NPR	4.79(2.70,6.63)	7.37(5.46,9.67)	3.85(2.50,5.40)	<0.001**
PT (s)	10.9(10.5,11.4)	11.1(10.7,11.5)	10.9(10.4,11.3)	0.009*
APTT (s)	26.1(24.4,27.6)	25.4(24.2,27.6)	26.3(24.6,27.6)	0.224
INR	0.93(0.89,0.97)	0.95(0.91,1.00)	0.92(0.89,0.97)	0.005*
Blood glucose (mmol/L)	7.85(6.37,9.69)	8.68(7.08,11.87)	7.60(6.31,9.23)	<0.001**

Values are n (%) and median (25,75%)

HE hematoma expansion, ICH intracerebral hemorrhage, SBP systolic blood pressure, DBP diastolic blood pressure, GCS Glasgow coma scale, NIHSS National Institutes of Health stroke scale, IVH intraventricular hemorrhage, RBC red blood cells, NPR neutrophil to platelet ratio, PT prothrombin time, APTT activated partial thromboplastin time, INR international normalized ratio

* $p < 0.05$. ** $p < 0.001$

larger hematoma size (OR = 1.015, 95% CI: 1.002–1.028, $p = 0.022$) were significantly correlated with HE (Table 2).

The area under the ROC curve was 0.838 (95% CI, 0.788–0.888, $p < 0.001$) for HE (Fig. 2). The best predictive cut-off value of HE was 5.47 (sensitivity, 75.3%; specificity, 77.6%).

Discussion

This study, to the best of our knowledge, is the first to analyze the relationships between the NPR and HE in spontaneous ICH patients. The present study found that a high NPR was related to HE after spontaneous ICH.

The occurrence of HE could be detected within 3 h of symptom onset in approximately 73% of ICH patients, and clinically obvious expansion was present in 35% of patients [11–13]. Accumulating evidence suggests that inflammation caused by HE accelerates brain injury in patients with ICH [4, 14–16]. Although the relationship between WBC count and outcome in ICH patients has been well demonstrated [3, 17], the correlation between early HE and leukocyte subsets remains disputed [4, 16, 18, 19]. In our study, the univariate analysis showed significant associations between HE and ANC, ALC, AMC and NPR, and multivariate logistic regression analysis showed that all those biomarkers mentioned above

Table 2 Multivariate analysis of predictors for HE

Predictors	OR (95% CI)	p-Value
Age(years)	0.998 (0.975-1.021)	0.857
NPR(per 1 increase)	1.742 (1.508-2.012)	<0.001**
GCS score on admission	-	-
GCS (13-15 points)	Reference	-
GCS (9-12 points)	1.796 (0.772-4.183)	0.174
GCS (3-8 points)	3.387 (1.443-7.949)	0.005*
NIHSS on admission	1.020(0.927-1.122)	0.688
PT (s)	0.929 (0.354-2.441)	0.882
RBC, x10 ¹²	0.967 (0.446-2.098)	0.932
Hemoglobin(g/L)	1.003 (0.985-1.020)	0.772
Lymphocyte, x10 ⁹	0.727 (0.457-1.158)	0.180
Monocyte, x10 ⁹	2.003 (0.616-6.508)	0.248
Neutrophil, x10 ⁹	0.926 (0.715-1.199)	0.561
Platelet, x10 ⁹	1.001 (0.994-1.007)	0.842
INR	3.230 (0.024-430.0)	0.639
Blood glucose (mmol/L)	1.073 (0.981-1.174)	0.125
Hematoma size (per 1 ml increase)	1.015 (1.002-1.028)	0.022*

OR odds ratio, CI confidence interval, HE hematoma expansion, NPR neutrophil to platelet ratio, GCS Glasgow coma scale, NIHSS National Institutes of Health stroke scale, PT prothrombin time, RBC red blood cells, INR international normalized ratio

* $P < 0.05$. ** $P < 0.001$

could not independently predict early HE, except for the NPR. However, the exact underlying mechanism of the associations between routine blood variables and HE remains unclear and needs further study.

Neutrophils play a basic defensive role in both infection-related diseases and aseptic inflammation, which are indicators of inflammation and immune response [20]. Neutrophils appear first in the hematoma [21], delivering pro-inflammatory factors, oxygen free radicals and proteases, which could have an effect on blood–brain barrier (BBB) disruption and brain damage [22, 23]. Previous studies have reported that neutrophils are the primary cellular source of metalloproteinases (MMPs), specifically MMP-9, working on the BBB [24]. Moreover, it has been shown that in ischemia–reperfusion injury, the increase in BBB permeability induced by WBC-derived MMP-9 is associated with peak neutrophil infiltration [25]. Furthermore, accumulating studies have reported that HE is associated with changes in the basal membrane of the BBB induced by MMP [4, 26, 27]. Therefore, it is reasonable to believe that neutrophils are associated with HE.

Several studies have reported the relationship between neutrophil count and hematoma size. Neutrophil count at admission was positively associated with intracerebral hemorrhage volume [28], and it was found in another study that the inhibition of neutrophil recruitment could reduce the amount of bleeding [29]. One study

reported that neutrophil count was negatively related to an increased risk of HE during the hyperacute phase of ICH [19]. One possible explanation for this paradoxical finding is that the injury to blood vessels caused by neutrophils may be mediated by platelets, and neutrophil-platelet interactions may play different roles in vascular inflammation at different stages of ICH [30]. Despite activated neutrophils having a procoagulant role [31], the mutual relationship between neutrophils and platelets could increase the formation of reactive oxygen species and aggravate vascular damage [32]. In addition, platelets, as a considerable contributor to some pro-inflammatory factors, could enhance the aggregation of activated neutrophils [30, 33].

In a review of neutrophil-platelet interplay, activated platelets were found to be connected with the release of inflammatory mediators, the accumulation of neutrophils, and increased vascular permeability [7]. By locally releasing soluble vascular protective factors, platelet-endothelial interplay may prevent or treat neutrophil-induced vascular damage [34]. The hemostatic role of platelets depends on embolization and coagulation at the location of vascular injury [35], which contributes to the preservation the integrity of the BBB [36]. Systemic inflammation is often accompanied by thrombocytopenia, which may be attributed to the immune response in the blood circulation [30]. According to the above, it can be speculated that in patients with ICH, the higher the NPR, the more serious the BBB damage may be, resulting in the higher occurrence of HE.

The NPR may be more stable as a ratio than individual blood parameters, such as neutrophils or thrombocytes, because of the mutual relationship between neutrophils and platelets. Recent studies have shown a correlation between the NPR and other diseases, such as ischemic stroke [8, 37–40], ST-elevation myocardial infarction [41] and infective endocarditis [42]. For example, a high NPR was related to an increased risk of hemorrhagic transformation in acute ischemic stroke patients [8]; the platelet-to-neutrophil ratio (PNR) was found to be an independent protective predictor of 90-day prognosis in patients with acute ischemic stroke [38]. Moreover, the PNR on admission could independently predict poor functional prognosis in ischemic stroke patients undergoing intravenous thrombolysis [39]. Consistent with these findings, we found a significant association between the NPR and ICH, and a high NPR on admission was an independent predictor of HE in ICH patients.

In addition, previous studies have reported that a larger baseline ICH volume and lower GCS score on admission were associated with HE [43, 44]. In our study, the initial hematoma volume and GCS score on admission were predictors of HE in both univariate analysis and

multivariate regression analysis. The results were consistent with Zhang's study [44] and Li's study [45]. On the other hand, an onset-to-first-CT time of less than 6 h was independently associated with HE [19, 46]. However, in our study, the median onset-to-first-CT time was 7 h and the median for the group with HE was 8 h. One possible explanation may be that West China Hospital of Sichuan University is an upper-level hospital in Southwest China, and many patients request to be transferred to our hospital for treatment from lower-level hospitals in this region or other regions. Therefore, the median onset-to-first-CT time in our study was longer.

Given HE being the independent risk factor for disability and death in ICH patients, it is crucial to timely identify HE [2, 13]. In this case, NPR has its clinical implications. Firstly, in clinical practice, as a routine indicator of blood test, it is easy and convenient to obtain NPR. Moreover, the predictability of NPR here can help clinicians initially estimate the risk of HE in ICH patients, and then conduct appropriate treatment and follow-up CT for that population. In addition, since single predictor for HE has its limitation, there are currently a variety of prediction scores containing several predictors [47]. Similarly, the combination of NPR and other predictive factors can form new prediction scores with higher specificity and sensitivity. However, the potential clinical implications of NPR should be further investigated.

Several limitations should be noted in this study. First, the data were recorded in a single center, and the sample size was limited. Second, although the results of this retrospective study may be influenced by confounding factors, multivariate analysis was used to address this problem. Third, given the complex role of inflammation in HE, more studies that record more inflammatory biomarkers are necessary in future studies.

Conclusions

This present study showed that a high NPR was related to the risk of HE in ICH patients. These findings may assist clinicians in identifying ICH patients who have increased risk for HE and then in conducting appropriate treatment and follow-up CT for that population. In view of the limitations of the study, future well-designed studies are needed to confirm our findings.

Abbreviations

ICH	Intracerebral cerebral hemorrhage
HE	Hematoma expansion
NPR	Neutrophil-to-platelet ratio
CT	Computed tomography
GCS	Glasgow Coma Scale
NIHSS	National Institutes of Health Stroke Scale
IVH	Intraventricular hemorrhage

RBC	Red blood cell
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
ALC	Absolute lymphocyte count
PT	Prothrombin time
APTT	Activated partial thromboplastin time
INR	International normalized ratio
IQR	Interquartile range
ROC	Receiver operating characteristic
BBB	Blood-brain barrier
MMPs	Metalloproteinases
PNR	Platelet-to-neutrophil ratio

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Authors' contributions

Y.L. and J.Z. designed the project. Y.L. and X.Y. did the statistical analyses and wrote the manuscript draft. Y.L., H.Z., J.Z., X.Y., X.H. and H.L. prepared Figures 1, 2 and Tables 1, 2. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving the patient included were in accordance with the ethical standards of the institutional board and with the 1964 Helsinki Declaration. This study is approved by the Medical Ethics Committee of the West China Hospital of Sichuan University. At admission, the subjects or the guardians of patients with cognitive impairment provided written informed consent for research and publication.

Consent for publication

We have obtained consent to publish from the participant to report individual patient data.

Competing interests

The authors declare that they have no competing interests.

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