Neutrophil-to-lymphocyte ratio predicts hematoma growth in intracerebral hemorrhage

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Abstract

Objective: Early hematoma growth is a major determinant of early neurological deterioration and poor clinical outcome in patients with spontaneous intracerebral hemorrhage (ICH). Inflammation plays a major role in the pathophysiology of ICH. This study aimed to evaluate the potential of the neutrophil-to-lymphocyte ratio (NLR) for predicting early hematoma growth after ICH.

Methods: A retrospective review was performed of patients with acute spontaneous ICH who were admitted to the Stroke Center of the First People’s Hospital of Jingmen between January 2014 and January 2017. The NLR was computed from admission blood work. Brain computed tomography scans were performed at admission and repeated within 24 hours. Hematoma growth was defined as absolute growth >6 mL or relative growth >33%.

Results: A total of 123 patients were included and early hematoma growth occurred in 30 (24%) patients. Multivariate analysis showed that the NLR (odds ratio, 1.22; 95% confidence interval, 1.09–1.38) was independently associated with early hematoma growth. The best predictive cut-off of the NLR for early hematoma growth was 6.49 (sensitivity, 50%; specificity, 69%).

Conclusions: A high NLR is independently predictive of early hematoma growth and may aid in risk stratification of patients with ICH on admission.

Keywords
Neutrophils, lymphocytes, intracerebral hemorrhage, hematoma, inflammation, stroke

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Introduction
Spontaneous intracerebral hemorrhage (ICH) accounts for 10% to 20% of all strokes and remains a significant cause of morbidity and mortality worldwide.1 Early hematoma growth occurs in 20% to 40% of patients with ICH and is a major determination of early deterioration and poor outcome.2 Increasing evidence has shown that inflammation is a major feature of ICH pathology.3–5 Inflammation progresses in response to various stimuli produced after ICH. A previous study showed that systemic inflammatory responses might be involved in the pathological process of active bleeding in patients with ICH.6 The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation. The NLR is associated with short-term and 3-month outcome in patients with ICH, but its relationship with early hematoma growth is unknown.7–14 Therefore, this study aimed to determine the association between the NLR at admission and early hematoma growth after spontaneous ICH.

Methods

Patients and methods
We performed a retrospective review of patients with ICH from the stroke unit of the First People’s Hospital of Jingmen (Jingmen, China) from January 2014 to January 2017. All information was extracted from the hospital medical records. The study protocol was approved by the Ethics Committee of our hospital. All of the patients provided informed consent. We included all patients with ICH aged >18 years who had undergone the first noncontrast computed tomographic (CT) scan on admission and the second CT scan at 24 hours after onset of symptoms. We excluded patients with secondary causes of ICH (e.g., trauma, brain tumor, aneurysms, and arteriovenous malformations), infection on admission, and hematological diseases. Baseline clinical data were recorded for each patient, including demographics, medical history, risk factors, Glasgow Coma Scale (GCS) score on admission, examination findings, routine laboratory testing, CT scan findings, and treatment. The total number of white blood cells (WBC), absolute neutrophil count, and absolute lymphocyte count were collected from admission blood work. The NLR was computed as the ratio of the absolute neutrophil count to absolute lymphocyte count values. Blood samples were collected within 6 hours of onset in all of the patients.

The initial CT scan was reviewed to identify the location of ICH (basal ganglia, thalamus, lobar, brainstem, cerebellum), hematoma volume, midline shift, and intraventricular extension. All of the patients underwent a second CT scan at 24 hours or earlier if clinically indicated. All of the CT scans were reviewed by consultant radiologists of the Department of Radiology who were blinded to clinical information. The volume of the hematoma was calculated by the formula $A \times B \times C/2$, where $A$ represents the greatest hemorrhage diameter by axial CT, $B$ represents the diameter 90° to $A$, and $C$ represents the thickness of the lesion.15 Hematoma growth was defined as absolute growth $>6$ mL or relative growth $>33\%$ from the initial CT to follow-up CT.16 All of the patients were evaluated and treated according to standard guidelines for stroke.17

Statistical analysis
The statistical package SPSS, Version 17.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. Values are expressed as the proportion (%), median (interquartile range [IQR]), or mean ± standard deviation (SD). The associations between early
hematoma growth and clinical variables, radiological findings, and routine laboratory testing at the univariate level were evaluated using the Mann–Whitney U test, the chi-squared test, or where appropriate, Fisher’s exact test. To evaluate the effect of the NLR on hematoma growth, multivariate logistic regression analysis was used and adjusted for sex, age, medical and drug history, GCS score on admission, glucose levels, systolic blood pressure, diastolic blood pressure, international normalized ratio (INR), white blood cells, NLR, location, midline shift, hematoma volume, and intraventricular hemorrhage. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For all analyses, \( P \) values < 0.05 were considered to indicate statistically significant differences. Receiver operating characteristic analysis was used to evaluate the ability of the NLR to predict early hematoma growth.

**Results**

A total of 123 patients with ICH met the inclusion criteria and were included in the analysis. The patients’ age ranged from 41 to 88 years, with a mean age of 63.01 ± 10.34 years. A total of 91 (74%) patients were men and 32 (26%) were women. The median baseline hematoma volume was 9.94 mL (IQR, 0.97–67.47). The median NLR was 4.98 (IQR, 1.13–23.16). Hematoma growth was detected in 30 (24%) patients. The mean age of these patients was 62.90 ± 11.49 years, and 26 (86.7%) were men and four (13.3%) were women. The median NLR was significantly higher in the hematoma growth group than in the non-hematoma growth group \( (P = 0.007) \) (Table 1). Two (6.67%) patients died in the hematoma growth group and no patients died in the non-hematoma growth group.

Univariate analysis showed significant associations between early hematoma growth and vitamin K antagonist/antiplatelet use \( (P = 0.019) \), diastolic blood pressure \( (P = 0.014) \), white blood cells \( (P = 0.009) \), and the NLR \( (P = 0.007) \). Multivariable analysis did not significantly reduce the association between early hematoma growth and the NLR \( (OR, 1.22; 95\% CI, 1.09–1.38; P = 0.001) \) (Table 2). The area under the receiver operating characteristic curve was 0.655 (95% CI, 0.541–0.769, \( P = 0.011 \)) for early hematoma growth. The best predictive cut-off value was 6.49 (sensitivity, 50%; specificity, 69%).

**Discussion**

This study showed that a high NLR value within the first few hours of ICH was independently associated with early hematoma growth. The NLR represents a composite index of systemic inflammation that integrates information of innate and adaptive pathways. Apart from resulting in peripheral leukocytosis,\(^{18}\) the inflammatory response after ICH can directly cause blood–brain barrier disruption and brain edema formation.\(^{19}\) Post-ICH inflammation affecting coagulation function and vessel wall pathophysiology might contribute to persistent vessel leakage.\(^{20}\)

Because inflammatory pathways may play a potential role in the pathogenesis of ICH and early hematoma growth, these may be potential therapeutic targets. The peripheral leukocyte count can be easily determined with a simple and low-cost analysis, and interpreted without specific expertise. Therefore, rapid measurement of the NLR, shortly after onset in ICH, may be a practical method of stratifying the risk of early hematoma growth at the time of presentation.

There are several limitations to our study that should be considered when interpreting the results. First, the generalizability of our results may be limited by the retrospective nature, selection bias, and small sample size.
of this study. Second, exclusion of patients who died early after onset or underwent surgical evacuation before the second CT scan might have led to underestimation of early hematoma growth. Finally, we cannot exclude potential clinical care confounders, such as blood pressure and body temperature control, osmotherapy, and intensive care unit care, which might affect the association between leukocytes and early hematoma growth.

Table 1. Baseline characteristics of the patients at admission

| Variables                | EHG (n = 30) | Non-EHG (n = 93) | P value |
|--------------------------|--------------|------------------|---------|
| Demographics             |              |                  |         |
| Age (years [mean, SD])   | 62.90 ± 11.49| 63.04 ± 10.01    | 0.948   |
| Sex (n, %)               |              |                  | 0.069   |
| Male                     | 26 (86.7)    | 65 (69.9)        |         |
| Female                   | 4 (13.3)     | 28 (30.1)        |         |
| Medical and drug history (n, %) | | | |
| Hypertension             | 30 (100)     | 86 (92.5)        | 0.274   |
| Hyperlipidemia           | 14 (46.7)    | 40 (43.0)        | 0.726   |
| Diabetes mellitus        | 3 (10.0)     | 14 (15.1)        | 0.694   |
| Antihypertensive drugs   | 20 (66.7)    | 58 (62.4)        | 0.671   |
| VKA/antiplatelet use     | 6 (20.0)     | 4 (4.3)          | 0.019   |
| Clinical and laboratory variables (median, IQR) | | | |
| GCS score                | 14.5 (4–15)  | 15 (4–15)        | 0.435   |
| SBP (mmHg)               | 169 (110–234)| 165 (105–220)    | 0.151   |
| DBP (mmHg)               | 100 (63–170) | 98 (60–130)      | 0.014   |
| Glucose (mmol/L)         | 6.35 (4.50–14.50) | 6.50 (4.00–14.65) | 0.694 |
| INR                      | 0.92 (0.79–3.46) | 0.93 (0.82–1.09) | 0.308   |
| WBC (×10³ cells/L)       | 8.34 (3.68–17.24) | 7.02 (3.44–17.67) | 0.009   |
| NLR                      | 6.28 (3.38–23.16) | 4.97 (1.13–17.19) | 0.007   |
| Imaging                  |              |                  |         |
| Volume (mL [median, IQR]) | 10.19 (0.97–37.31) | 9.94 (1.45–67.47) | 0.743   |
| IVH (n, %)               | 6 (20.0)     | 27 (29.0)        | 0.332   |
| Location (n, %)          |              |                  | 0.718   |
| Lobar                    | 5 (16.7)     | 9 (9.7)          |         |
| Basal ganglia            | 17 (56.7)    | 56 (60.2)        |         |
| Thalamus                 | 4 (13.3)     | 10 (10.8)        |         |
| Brain stem               | 1 (3.3)      | 8 (8.6)          |         |
| Cerebellum               | 3 (10.0)     | 10 (10.8)        |         |
| Midline shift (>5 mm) (n, %) | 1 (3.3)     | 9 (9.7)          | 0.471   |

SD = standard deviation; IQR = interquartile range; EHG = early hematoma growth; VKA = vitamin K antagonist; GCS = Glasgow Coma Scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; INR = international normalized ratio; WBC = white blood cells; NLR = neutrophil-to-lymphocyte ratio; IVH = intraventricular hemorrhage

Table 2. Multivariate analysis of predictors of early hematoma growth

| OR       | 95% CI        | P value |
|----------|---------------|---------|
| VKA/antiplatelet use | 8.35 (1.95–35.76) | 0.004   |
| NLR      | 1.22 (1.09–1.38) | 0.001   |
| DBP      | 1.03 (1.00–1.06) | 0.026   |

OR = odds ratio; CI = confidence interval; VKA = vitamin K antagonist; NLR = neutrophil-to-lymphocyte ratio; DBP = diastolic blood pressure

The final model was adjusted for age, sex, Glasgow Coma Scale score, white blood cells, volume, and midline shift of this study. Second, exclusion of patients who died early after onset or underwent surgical evacuation before the second CT scan might have led to underestimation of early hematoma growth. Finally, we cannot exclude potential clinical care confounders, such as blood pressure and body temperature control, osmotherapy, and intensive care unit care, which might affect the association between leukocytes and early hematoma growth.
In conclusion, our study shows that a high NLR value in the first few hours after onset of symptoms is independently associated with early hematoma growth and could aid in the risk stratification of patients. Further larger prospective studies are required to confirm the role of leukocytes in early hematoma growth.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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