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Original Article

Correlation between peripheral blood inflammatory markers and delayed cerebral ischemia after intracerebral hemorrhage

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Abstract: Objective: To assess the predictive value of peripheral blood inflammatory markers for delayed cerebral ischemia (DCI) in patients with intracerebral hemorrhage (ICH) and explore methods for early intervention. Methods: This single-center retrospective study reviewed medical records of ICH patients admitted to Cangzhou People's Hospital over a 12-month period from January 2022 to December 2023. Of the 150 identified patients with ICH, including 80 patients without DCI (control group) and 70 with DCI (observation group). Demographics and blood biochemical markers during hospitalization were recorded. Binary logistic regression was used to identify independent factors influencing DCI occurrence. Results: Significant differences were observed between the two groups in neutrophil percentage, lymphocyte percentage, lymphocytes absolute and neutrophil-to-lymphocyte ratio (NLR) (all $P<0.05$). Logistic regression analysis identified mRS score, lymphocyte percentage, educational level, uric acid, neutrophils percentage, and NLR as independent risk factors for DCI. Conclusion: Neutrophil percentage and NLR are independent factors influencing delayed cerebral ischemia after intracerebral hemorrhage. These markers are readily accessible and may provide valuable insights for early ICH management.

Keywords: Peripheral blood inflammatory, delayed cerebral ischemia, intracerebral hemorrhage

Introduction

Intracerebral hemorrhage (ICH) is the second most common type of stroke, accounting for 8%-15% of all strokes in western countries, with an annual incidence of 10-25 per 100,000 people [1]. In China, ICH accounts for 17.1%-55.4% of all strokes, with a much higher incidence compared to western countries. The mortality rate from ICH is 30%-50%, with 74% of patients remaining disabled 12 months after the onset [2]. ICH progresses rapidly and has the highest disability and mortality rates among all stroke types, imposing significant economic and social burdens on society [3].

Delayed cerebral ischemia (DCI) is a possible yet severe complication following ICH [4]. DCI not only brings mental stress to patients, but also imposes substantial financial burden on families and society. The incidence of DCI after ICH ranges from 1.8% to 20% [5, 6]. It is characterized by reduced cerebral blood flow, leading to neurologic deficits and poor outcomes [7]. Studies have shown that DCI is a complex, multifactorial process involving various mechanisms such as cerebral vasospasm, microthrombosis, inflammation, and impaired autoregulation [8-10]. An in-depth understanding of these mechanisms plays a crucial role in elucidating DCI progression and provides a key theoretical basis for advancing research and clinical interventions.

Immune dysregulation is a condition where the immune system malfunctions, leading to an imbalance in immune response [11]. This can result in various health problems, including an increased risk of developing DCI [12], a brain injury that may occur after a stroke or neurologic event. Studies have shown that immune dysregulation can trigger an inflammatory response in the brain, causing damage to the blood-brain barrier and promoting the develop-

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ment of DCI [13]. Elevated levels of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, observed in patients with DCI, further highlight the role of immune dysregulation in this condition [14]. Previous studies have shown the predictive value of biomarkers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and red cell distribution width (RDW) for adverse outcome in patients with ischemic stroke or intracranial hemorrhage [15-17]. However, the association between these biomarkers and outcome in patients with DCI is insufficiently established in these studies.

Therefore, our study aimed to evaluate the predictive potential of peripheral blood inflammatory markers for DCI in patients with ICH. Our goal is to identify methods for early intervention in ICH patients at risk of developing DCI, providing scientific evidence to enhance clinical decision-making and guide personalized treatment strategies.

Methods

Study design and standard protocol approvals

This single-center retrospective study involved a 12-month review of medical records of patients with ICH admitted to Cangzhou People's Hospital from January 2022 to December 2023. From a total cohort of 150 ICH patients identified in the database, 80 patients without DCI comprised the control group and the other 70 patients with DCI served as the observation group. The study was approved by the Ethics Board of Cangzhou People's Hospital.

Patient selection

Inclusion criteria: 1) Patients aged 18 years or older with confirmed ICH; 2) Patients who underwent cerebrovascular magnetic resonance examination (CTA, MRA, or DSA), with no attributable arterial aneurysms, arteriovenous malformations, etc.; 3) Admission within 7 days of initial symptom onset; and 4) Complete clinical data.

Exclusion criteria: 1) Patients with trauma, tumors, hemorrhagic transformation, primary intraventricular hemorrhage, or subarachnoid hemorrhage; 2) Patients with subcortical brain hemorrhage, including cerebellar and brainstem hemorrhage; 3) Premature death within 3 days of hospitalization; 4) History of previous brain hemorrhage or stroke with a modified Rankin Scale (mRS) score >3; 5) Prior treatment with antiepileptic drugs or a history of epilepsy; 6) Severe liver or kidney function impairment; 7) Patients without a repeat head CT within 24 hours of admission or before surgery.

Data collection

Demographic and blood biochemical data during hospitalization were collected. The demographics included sex, history of disease, age, smoking history, alcohol consumption, educational level, systolic and diastolic pressure, and modified Rankin Scale (mRS) score. The blood biochemical indicators included cystatin C, fasting blood glucose, triglyceride, total cholesterol, HDL-C, LDL-C, uric acid, and homocysteine. Upon admission, 5 ml of blood was drawn from the cubital vein using EDTA-K2 anticoagulant vacuum blood collection tubes. The collected venous blood was divided, labeled, and stored at 4°C. Samples were then centrifuged at 4000 r/min for 10 minutes, with serum stored at -70°C. After specimen collection, an ELISA method was used to detect serum levels of cystatin C, fasting blood glucose, triglyceride, total cholesterol, HDL-C, LDL-C, uric acid and homocysteine. The detection methods followed the protocols for each indicator using the following kits: cystatin C (JINGMEI Co., Ltd., Cat. No. JM-00652R1), triglyceride (Andygene Co., Ltd., Cat. No. AD0023Ra), total cholesterol (Solarbio Co., Ltd., Cat. No. BC1985-100T/96S), uric acid (Macklin Co., Ltd., Cat. No. U820317-25g-69-93-2), and homocysteine (JINGMEI Co., Ltd., Cat. No. E031-1-1).

Outcome assessment

The primary outcome measure was the development of DCI. DCI was defined using the following criteria: 1) Clinical assessment: Patients with DCI may present with hemiparesis, aphasia, apraxia, hemianopia, or neglect. 2) Transcranial Doppler (TCD) ultrasound: TCD ultrasound, a non-invasive technique, was used to monitor intracranial blood flow velocity. Changes in flow velocity may suggest vasospasm, a frequent contributor to DCI. 3) Cerebral perfusion monitoring: Monitoring cerebral perfusion pressure (CPP) and regional cerebral oxygen saturation (rSO_2) can help in assessing the adequacy of blood flow to the brain. Decreased CPP or rSO_2 levels may indicate

Table 1. Comparison of baseline data between the two groups

	Control group (n=80)	Observation group (n=70)	χ^2/Z/T	P
Female	20 (25.00%)	22 (31.43%)	0.585	0.444
Hypertension	48 (60.00%)	46 (65.71%)	0.521	0.470
DM	24 (30.00%)	23 (32.86%)	0.142	0.707
Heart disease	14 (17.50%)	11 (15.71%)	0.086	0.770
Smoke	43 (53.75%)	34 (48.57%)	0.401	0.527
Drinking	38 (47.50%)	30 (42.86%)	0.325	0.569
Age	63 (56-69)	63 (59-69)	1.728	0.086
Educational level	12 (9-15)	9 (6-12)	-7.892	0.000
Systolic pressure	149 (134-163)	154 (138-169)	3.721	0.000
Diastolic pressure	87 (79-95)	89 (78-98)	1.361	0.176
mRS score	2 (0-3)	3.5 (2-6)	14.735	0.000

Note: DM: diabetes mellitus. mRS score: Modified Rankin Scale score.

Table 2. Comparison of blood biochemical markers between the two groups

	Control group (n=80)	Observation group (n=70)	χ^2/Z/T	P
Cystatin C	0.96 (0.84-1.08)	0.98 (0.89-1.12)	1.941	0.054
Fasting blood glucose	5.60 (5.06-6.89)	6.07 (5.22-7.69)	0.617	0.538
Triglyceride	1.70 (1.20-2.15)	1.65 (1.18-2.04)	-1.089	0.278
Total cholesterol	4.56 (3.88-5.17)	4.62 (3.88-5.27)	1.017	0.311
Uric acid	336 (286-383)	301 (258-346)	-7.852	0.000

impaired cerebral perfusion and an elevated risk of DCI. 4) Functional outcome assessment: The mRS [18], a measure for evaluating functional outcomes post-stroke or brain ischemia, was also used. The scale ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death.

Sample size estimation

The sample size was calculated by power analysis and calculated as: corrected sample size = sample size/(1 - [% attrition/100]) [19]. This led to a final estimated sample size of approximately 150. Patient group assignments were based on a detailed screening and statistical review of our medical database. Using the defined inclusion and exclusion criteria, we reviewed and classified eligible cases, resulting in 70 cases in the observation group and 80 in the control group.

Statistical analysis

The data were statistically analyzed using SPSS 23.0 software. Continuous variables following a normal distribution were reported as mean ± standard deviation, and group differences were tested using t-tests or one-way analysis of variance. Continuous variables that did not follow a normal distribution were expressed as median and interquartile range, and group differences were determined using Mann-Whitney U test or Kruskal-Wallis H test. Categorical and ordinal data were described using frequency (%) and group comparisons were made using chi-square test or rank sum test. First, a one-way analysis was conducted, and variables with a significance level (P<0.1) were included in a binary logistic regression analysis. A *P*-value of <0.05 was considered significant.

Results

General data of the two groups

Significant differences were observed between the two groups in terms of hypertension, education level, systolic blood pressure, and mRS score (all P<0.05) (**Table 1**).

Comparison of blood biochemical markers between the two groups

The blood biochemical markers are summarized in **Table 2**. Results demonstrated a signifi-

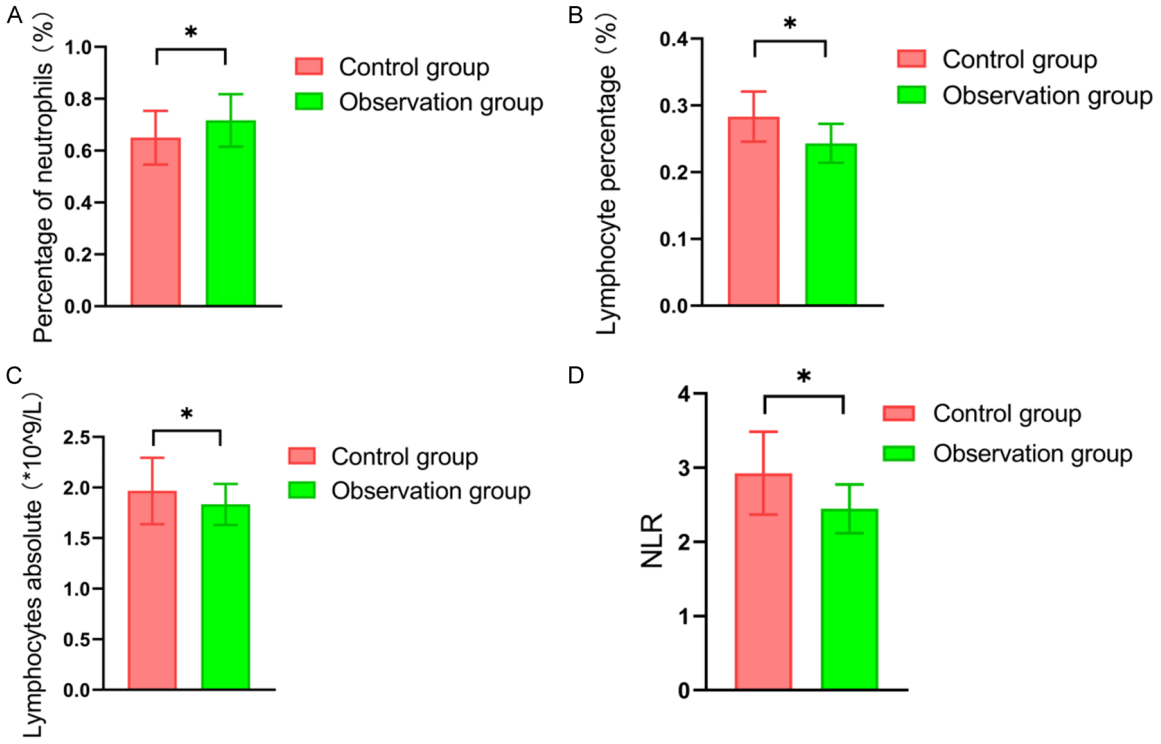

Figure 1. Comparison of the peripheral blood inflammatory markers between the two groups. A: Neutrophil percentage; B: Lymphocyte percentage; C: Lymphocytes absolute; D: NLR. Note: NLR: Neutrophil-to-Lymphocyte Ratio. Compared to control group, *$P<0.05$.

cant difference in uric acid between the two groups (P=0.003). However, no significant differences were found for cystatin C, fasting blood glucose, triglyceride, total cholesterol and homocysteine (all P>0.05).

Comparison of peripheral blood inflammatory indicators between the two groups

Figure 1 illustrates the peripheral blood inflammatory profiles of the two groups. Analysis revealed significant differences between the groups in terms of neutrophil percentage, lymphocyte percentage, lymphocytes absolute, and NLR (all P<0.05). These findings suggest differences in peripheral blood inflammation between the two groups, warranting further investigation.

Logistic regression analysis

Table 3 presents the logistic regression analysis incorporating neutrophil and lymphocyte percentages. Results showed that mRS score, lymphocyte percentage, and neutrophils percentage were independent risk factors for DIC.

Table 4 shows logistic regression analysis incorporating lymphocytes absolute. The results showed that educational level, mRS score, and uric acid were independent risk factors for DIC. Furthermore, we also conducted logistic regression analysis incorporating NLR. The results showed that NLR, and education level were independent risk factors for DIC (**Table 5**).

Discussion

This study found that neutrophil percentage and neutrophil-to-lymphocyte ratio (NLR) in the observation group were significantly higher than those of the control group. Both neutrophil percentage and NLR were identified as independent risk factors for the occurrence of DCI. After adjusting for other factors, each 0.056 increase in neutrophil percentage was associated with a 1.054-fold increase in the likelihood of DCI. For NLR, the risk of DCI occurrence was 2.168 times higher for patients with NLR value of (2.73-4.04) compared to those with NLR≤1.62, and similarly, an NLR≥4.05 increased the risk by 2.187 times relative to

Table 3. Logistic regression analysis incorporating neutrophil and lymphocyte percentages

	B	P	OR	95% CI of OR	
				Lower limit	Upper limit
Age	-0.286	0.217	0.751	0.478	1.182
Educational level	1.210	0.067	3.354	0.921	12.217
Hypertension					
Yes	-0.754	0.571	0.470	0.035	6.383
No	0		1		
mRS score	-3.919	0.016	0.020	0.001	0.479
Lymphocyte percentage	185.388	0.005	0.000	0.045	0.068
Uric acid	0.027	0.343	1.028	0.971	1.087
Percentage of neutrophils	-36.788	0.017	0.000	0.000	0.001
Constant	-15.293	0.463	0.000		

Note: mRS score: Modified Rankin Scale score.

Table 4. Logistic regression analysis incorporating lymphocytes absolute

	B	P	OR	95% CI of OR	
				Lower limit	Upper limit
Gender					
Female	0		1		
Male	-0.001	0.999	0.999	0.264	3.775
Age	0.016	0.860	1.016	0.852	1.211
Educational level	0.607	0.001	1.835	1.292	2.606
Hypertension					
Yes	0.352	0.572	1.422	0.419	4.828
No	0		1		
mRS score	-1.544	0.000	0.213	0.109	0.420
Uric acid	0.043	0.001	1.044	1.017	1.071
Lymphocytes absolute	0.559	0.791	1.749	0.028	108.751
Constant	-18.038	0.058	0.000		

Note: mRS score: Modified Rankin Scale score.

Table 5. Logistic regression analysis incorporating NLR

	B	P	OR	95% CI of OR	
				Lower limit	Upper limit
NLR	8.399	0.000	4442.596	147.352	1339.905
Lymphocytes absolute	2.464	0.221	11.746	0.228	604.726
Hypertension					
Yes	0.127	0.826	1.135	0.366	3.517
No	0		1		
Age	-0.097	0.261	0.908	0.767	1.074
Educational level	0.672	0.000	1.958	1.352	2.835
Constant	-28.035	0.001	0.000		

Note: mRS score: Modified Rankin Scale score.

NLR≤1.62. International studies have shown that elevated NLR in the acute phase of stroke is independently associated with an increased risk of ICH after 3 months [20]. In addition, while lymphocyte percentage and lymphocytes absolute differed significantly between the DCI group and the non-DCI group, they were not independent risk factors for DCI. The associa-

tion between NLR and DCI appears robust. Furthermore, in another study in China focusing on the ICH population, NLR was significantly higher in individuals with cognitive impairment, and the risk for individuals with NLR≥2.07 was nearly 6 times higher than for those with NLR<2.07 [21]. While the diagnostic threshold for NLR in predicting DCI may vary, a consistent relationship between NLR and DCI suggests that systemic inflammation may play an important role in the pathogenesis of DCI.

Systemic inflammation activates inflammatory cells, such as neutrophils and macrophages, which can infiltrate the brain and contribute to neuronal damage. These inflammatory cells release pro-inflammatory cytokines and chemokines, exacerbating the inflammatory response in the brain and leading to tissue damage [22, 23]. Another possible mechanism involves disruption of the blood-brain barrier (BBB) due to systemic inflammation [24]. Normally, the BBB functions as a protective barrier, regulating the movement of molecules and cells between the blood and the brain. Systemic inflammation can compromise BBB integrity, allowing inflammatory mediators and immune cells to enter the brain, which promotes neuroinflammation and tissue damage [25]. Furthermore, systemic inflammation can activate the coagulation cascade, leading to microthrombi formation that restricts blood flow to the brain, exacerbating ischemic injury [26]. Furthermore, systemic inflammation can impair endothelial function and vasoreactivity, further contributing to cerebral ischemia.

Neutrophil percentage and NLR are two important inflammatory markers with potential predictive value for DCI. Neutrophils, a type of white blood cell, play a key role in the body's inflammatory response [27, 28]. An elevated neutrophil percentage can indicate an active inflammatory process, which has been associated with DCI [29]. NLR, calculated by dividing the absolute neutrophil count by the lymphocytes absolute, is often elevated in states of increased systemic inflammation [30]. Studies have shown that an elevated NLR may be associated with a higher risk of DCI in patients with brain injury [31-33]. Therefore, monitoring neutrophil percentage and NLR can provide valuable information for predicting DCI onset, enabling early intervention and management to prevent further brain damage.

There are several limitations to this study. First, this research lacked a prospective and multicenter design. Second, outcome analyses were based on chart reviews and were limited by the data available to the investigators. Furthermore, lack of long-term follow-up prevented assessment of the biomarkers' predictive value over time. Despite these limitations, our findings are relevant since they offer a foundation and direction for further research. Further prospective and multicenter studies could refine the predictive value of these markers for DCI in ICH patients.

Our study suggests that the neutrophil percentage and NLR are promising indicators for identifying ICH patients at risk of developing DCI. These peripheral blood inflammatory makers are readily available and practical, and they may provide substantial clinical value for ICH management.

Disclosure of conflict of interest

None.

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