

Elevated Neutrophil-to-Lymphocyte Ratio Predicts Depression After Intracerebral Hemorrhage

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Purpose: Inflammation plays a critical role in the development of depression after intracerebral hemorrhage (ICH), while neutrophil-to-lymphocyte ratio (NLR) has been identified as a novel comprehensive inflammatory indicator in recent years. The aim of this study was to examine the association between NLR and depression after ICH.

Patients and Methods: From January 2016 to December 2018, ICH patients were prospectively enrolled. NLR was measured at admission. Depression at 3 months after ICH was diagnosed according to the Hamilton Depression Scale (HAMD).

Results: Of the 372 enrolled patients, 107 (28.8%) were diagnosed with depression at 3 months after ICH. Patients with depression had a higher NLR (6.15 vs 3.55, $P < 0.001$). Logistic regression analysis detected that after adjusting for major confounders, NLR remained independently associated with depression after ICH (OR = 2.25, 95% CI: 1.45–3.49, $P < 0.001$). Moreover, NLR acted as the optimal variable for prediction, with the optimal predictive threshold of 4.53 in ROC analysis.

Conclusion: Elevated NLR is associated with depression at 3 months after ICH, suggesting that NLR may be a significant biomarker to predict depression after ICH.

Keywords: inflammation, neutrophil-to-lymphocyte ratio, depression, intracerebral hemorrhage

Introduction

Post-stroke depression (PSD) is one of the most frequently seen psychosomatic disorders that occurs in almost 20% intracerebral hemorrhage (ICH) survivors.^{1–3} Patients with PSD bear increased risk for cognitive impairment, stroke recurrence and death.^{4–6} Hence, it is vital to identify and understand the pathogenesis of PSD early.

Inflammation may play an important role in the development of PSD.⁷ Higher levels of tumor necrosis factor- α (TNF- α), interleukin (IL)-6 and IL-18 have been shown to be associated with PSD.^{8,9} In another study, TNF- α and IL-1 β genes polymorphism were reported to be correlated with increased risk for PSD.¹⁰ A recent review also indicated that inflammation may promote the occurrence of depression after intracerebral hemorrhage through a series of signaling pathways.¹¹

The neutrophil-to-lymphocyte ratio (NLR) has been reported as a credible, simple and convenient marker of inflammation recently, which is a more potent indicator than neutrophils or lymphocytes themselves.^{12,13} Previous studies have been conducted to examine the relationship between NLR and depression after ischemic stroke.¹⁴ However, the association of NLR and depression after ICH has

not been clarified. Thus, this study aimed to investigate the predictive value of NLR in depression at 3 months after ICH.

Patients and Methods

Study Population

Patients with ICH were enrolled consecutively from Huainan First People's Hospital from January 2016 to December 2018. Patients were included if they: (1) were diagnosed with ICH verified by CT scans within 24 h from symptom onset; (2) aged ≥ 18 years. The patients were excluded if they: (1) had secondary hemorrhage as a result of tumor, trauma, vascular malformation, aneurysm, hemorrhagic transformation of cerebral infarct and blood coagulation abnormalities; (2) had concurrent disease that might affect the value of NLR, such as active infection (fever, cough, or diarrhea), chronic inflammatory disease or malignancy; (3) had severe cognitive impairment, a history of major depression or other psychiatric disorders; (4) with severe aphasia so that could not complete the psychological measurement; (5) had severe heart, renal or liver diseases. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethic committee of Huainan First People's Hospital. Informed consent was obtained from each patient.

Clinical Data

Demographic characteristics, clinical variables and vascular risk factors were all collected from medical records. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score.¹⁵ The extent of coma was determined by Glasgow Coma Scale (GCS) score. Fasting venous blood was collected in the next morning for routine blood test and NLR was defined as the ratio of neutrophil counts to lymphocyte counts.

Assessment of Outcomes

All patients were followed up through telephone interviews or clinical visits at 3 months after ICH, unless they died or were lost. The functional outcomes were assessed using modified Rankin Scale (mRS) score and Barthel Index (BI) score. Cognitive functions were measured through Mini-Mental State Examination (MMSE). The 17-item Hamilton Depression Scale (HAMD) was used to assess depression.¹⁶ Patients with a HAMD score of >7 were diagnosed with depression after ICH.¹⁴

Statistical Analysis

Continuous variables were presented as mean $\pm$ SD or median (interquartile range). Categorical variables were presented as numbers (percentages). Independent *t*-test or Mann–Whitney U-test was applied for continuous variables. Chi-square test or Fisher exact test were employed for categorical data. Multivariable regression analyses were performed using 3 models to recognize the predictive factors of PSD, among which, model 1 was adjusted for age and sex; model 2 was adjusted for age, sex and risk factors (history of smoking, history of drinking, hypertension, diabetes, hyperlipidemia, atrial fibrillation); whereas model 3 was further adjusted for variables with $P < 0.05$ upon univariate analysis. Besides, the association was indicated as odds ratio (OR) with 95% confidence interval (CI). In addition, the predictive accuracy of NLR in depression after ICH was assessed through the receiver operating characteristic (ROC) curve and area under the curve (AUC). DeLong test was employed to compare the AUC between groups. Results were considered as statistically significant if $P < 0.05$. The R software package (version 3.0) was utilized for all statistical analyses for DeLong test, while SPSS 22.0 (IBM, New York, USA) was used for other statistical analyses.

Results

A total of 372 ICH patients were enrolled in this study, including 232 (62.4%) males and 140 (37.6%) females. The median patient age was 66 (56–75) years. Among them, 107 (28.8%) patients were eventually diagnosed with depression at 3 months after ICH.

Compared with subjects without depression after ICH, those with depression had higher NIHSS score ($P < 0.001$), mRS score ($P < 0.001$), total white blood cells (WBC) ($P = 0.006$), absolute neutrophil count (ANC) ($P < 0.001$), NLR ($P < 0.001$) and higher proportions of basal ganglia lesions ($P = 0.036$); besides, the levels of GCS score ($P < 0.001$), BI score ($P < 0.001$) and absolute lymphocyte count (ALC) ($P < 0.001$) were lower (Table 1).

Table 2 shows ascending tertiles of NLR was associated with older age ($P = 0.030$), male sex ($P = 0.002$), lower education years ($P = 0.048$) and smoking ($P = 0.038$), also with higher NIHSS score ($P = 0.001$), mRS score ($P < 0.001$) and lower GCS score ($P < 0.001$) and BI score ($P < 0.001$). The numbers of patients with depression after ICH were 15 (14%), 30 (28%) and 62 (58%) in

Table I Comparisons of Baseline Characteristics According to the Presence or Absence of Depression After ICH

Variables	Total (n=372)	Depression After ICH		P value
		Depression	Non-Depression	
Demographics				
Age, years, median (IQR)	66 (56, 75)	70 (57, 76)	65 (56, 74)	0.100
Gender, Male, n (%)	232 (62.4)	63 (58.9)	169 (63.8)	0.378
Education years, median (IQR)	5 (4, 9)	5 (4, 9)	6 (4, 10)	0.117
Married, n (%)	322 (86.6)	92 (86.0)	230 (86.8)	0.347
Medical history, n (%)				
Hypertension	255 (68.5)	74 (69.2)	181 (68.3)	0.872
Diabetes	50 (13.4)	16 (15.0)	34 (12.8)	0.587
Hyperlipidemia	138 (37.1)	44 (41.1)	94 (35.5)	0.307
Coronary heart disease	34 (9.1)	12 (11.2)	22 (8.3)	0.377
Atrial fibrillation	9 (2.4)	3 (2.8)	6 (2.3)	0.759
Prior stroke	127 (34.1)	39 (36.4)	88 (33.2)	0.551
Smoking	91 (24.5)	31 (29.0)	60 (22.6)	0.355
Drinking	94 (25.3)	24 (22.4)	70 (26.4)	0.636
Hematoma volume, mL, median (IQR)	12 (8, 18)	14 (8, 20)	12 (8, 16)	0.102
Hematoma location, n (%)				
Frontal lobe	9 (2.4)	5 (4.7)	4 (1.5)	0.072
Parietal lobe	22 (5.9)	10 (9.3)	12 (4.5)	0.075
Temporal lobe	34 (9.1)	9 (8.4)	25 (9.4)	0.757
Occipital lobe	24 (6.5)	8 (7.5)	16 (6.0)	0.609
Basal ganglia	290 (78.0)	91 (85.0)	199 (75.1)	0.036
Cerebellum	22 (5.9)	5 (4.7)	17 (6.4)	0.519
Brainstem	10 (2.7)	2 (1.9)	8 (3.0)	0.535
Concurrent ventricular hemorrhage	61 (16.4)	21 (19.6)	40 (15.1)	0.285
Hematologic parameters				
WBC, $\times 10^9/L$, median (IQR)	7.94 (6.35, 10.04)	8.55 (6.84, 10.49)	7.73 (6.11, 9.82)	0.006
ANC, $\times 10^9/L$, median (IQR)	5.80 (3.99, 7.70)	6.95 (5.43, 9.04)	5.33 (3.50, 7.22)	<0.001
ALC, $\times 10^9/L$, median (IQR)	1.35 (1.01, 1.70)	1.17 (0.85, 1.51)	1.40 (1.09, 1.79)	<0.001
NLR, median (IQR)	4.14 (2.63, 6.36)	6.15 (4.22, 9.87)	3.55 (2.42, 5.89)	<0.001
Neuropsychological function				
NIHSS score, median (IQR)	6 (3, 11)	12 (9, 15)	5 (3, 8)	<0.001
GCS score, median (IQR)	15 (15, 15)	14 (14, 15)	15 (15, 15)	<0.001
mRS score, median (IQR)	2 (1, 4)	4 (3, 4)	2 (0, 3)	<0.001
BI score, median (IQR)	90 (20, 100)	20 (20, 65)	100 (65, 100)	<0.001
MMSE score, median (IQR)	25 (24, 26)	25 (24, 26)	25 (24, 26)	0.249

Abbreviations: ICH, intracerebral hemorrhage; IQR, interquartile range; WBC, white blood cells; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; BI, Barthel Index; MMSE, Mini-Mental State Examination.

Q1, Q2 and Q3, respectively. The proportion of subjects with depression in the highest tertile was higher than those in the two lower tertiles ($\chi^2 = 45.37$, $P < 0.001$).

In the unadjusted multivariable logistic regression analysis, NLR was independently associated with depression after ICH (OR 1.50, 95% CI 1.35–1.66, $P < 0.001$). The association remained significant after adjusting for the potential confounders (OR 2.25, 95% CI 1.45–3.49, $P < 0.001$) (Table 3).

ROC curve analysis showed that NLR was the best discriminating variable, with the best predictive threshold of 4.53 (sensitivity 73.8%, specificity 66.0%, positive likelihood ratio 2.17, and negative likelihood ratio 0.40). DeLong test indicated that the AUC of NLR was evidently greater than those of the other groups ($Z = -4.76$, $P < 0.001$, compared with WBC; $Z = -2.34$, $P = 0.02$, compared with ANC; $Z = -4.19$, $P < 0.001$, compared with ALC) (Figure 1).

Table 2 Comparisons of Baseline Characteristics According to NLR Tertiles

Variables	NLR			P value
	Q1 (≤ 3.18 , n=124)	Q2(3.18–5.91, n=124)	Q3 (>5.91 , n=124)	
Demographics				
Age, years, median (IQR)	64 (54, 72)	65.5 (56, 75)	69 (60, 76)	0.030
Gender, Male, n (%)	62 (50)	83 (66.9)	87 (70.2)	0.002
Education years, median (IQR)	6.0 (4.0, 11.8)	5 (4, 9)	5 (4, 8)	0.048
Married, n (%)	112 (90.3)	106 (85.5)	104 (83.9)	0.490
Medical history, n (%)				
Hypertension	86 (69.4)	91 (73.4)	78 (62.9)	0.200
Diabetes	19 (15.3)	18 (14.5)	13 (10.5)	0.489
Hyperlipidemia	52 (41.9)	43 (34.7)	43 (34.7)	0.393
Coronary heart disease	7 (5.6)	15 (12.1)	12 (9.7)	0.205
Atrial fibrillation	2 (1.6)	5 (4.0)	2 (1.6)	0.359
Prior stroke	42 (33.9)	45 (36.3)	40 (32.3)	0.454
Smoking	29 (23.4)	21 (16.9)	40 (32.3)	0.038
Drinking	32 (25.8)	29 (23.4)	33 (26.6)	0.635
Hematoma volume, mL, median (IQR)	12 (8, 17)	12 (8, 16)	12 (7, 20)	0.942
Hematoma location, n (%)				
Frontal lobe	3 (2.4)	2 (1.6)	4 (3.2)	0.711
Parietal lobe	8 (6.5)	3 (2.4)	11 (8.9)	0.094
Temporal lobe	10 (8.1)	12 (9.7)	12 (9.7)	0.879
Occipital lobe	4 (3.2)	8 (6.5)	12 (9.7)	0.118
Basal ganglia	98 (79.0)	95 (76.6)	97 (78.2)	0.896
Cerebellum	8 (6.5)	7 (5.6)	7 (5.6)	0.953
Brainstem	2 (1.6)	6 (4.8)	2 (1.6)	0.193
Concurrent ventricular hemorrhage	16 (12.9)	23 (18.5)	22 (17.7)	0.430
Hematologic parameters				
WBC, $\times 10^9/L$, median (IQR)	6.37 (5.11, 8.33)	8.31(6.88, 10.18)	9.02 (7.43, 10.70)	<0.001
ANC, $\times 10^9/L$, median (IQR)	3.51 (2.80, 4.71)	6.00 (4.99, 7.68)	7.69 (6.36, 9.75)	<0.001
ALC, $\times 10^9/L$, median (IQR)	1.66 (1.34, 2.06)	1.40 (1.15, 1.69)	1.00 (0.82, 1.23)	<0.001
NLR, median (IQR)	2.26 (1.87, 2.64)	4.14 (3.69, 5.24)	7.31 (6.35, 9.47)	<0.001
Neuropsychological function				
NIHSS score, median (IQR)	5 (3, 9)	6 (4, 11)	8 (3, 12)	0.001
GCS score, median (IQR)	15 (15, 15)	15 (15, 15)	15 (14, 15)	<0.001
mRS score, median (IQR)	2 (0, 3)	2 (1, 4)	3 (1, 4)	<0.001
BI score, median (IQR)	100 (60, 100)	90 (20, 100)	60 (20, 100)	<0.001
MMSE score, median (IQR)	25 (24, 26)	25 (24, 26)	25 (24, 26)	0.910

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range; WBC, white blood cells; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; BI, Barthel Index; MMSE, Mini-Mental State Examination.

Discussion

This study observed a 2.25-fold higher risk of depression after ICH among individuals with the highest tertiles of NLR compared to those with the lowest NLR tertiles after adjusting for major confounders. To the best of our knowledge, this is the first study to investigate the association between NLR and depression after ICH.

In the current study, we observed that the incidence of depression at 3 months after ICH was 28.8%, which was almost consistent with that of previous report.² In addition, our study found that patients with depression after ICH had a more severe condition and a poorer prognosis, which were in agreement with previous studies on the risk factors of PSD.^{17,18} The frontal lobe and

Table 3 Logistic Regression Model of NLR and Depression After ICH at 3 Months

	β	SE	OR	95% CI for OR		P value
				Lower	Upper	
Unadjusted model	0.40	0.05	1.50	1.35	1.66	<0.001
Adjusted model						
Model 1	0.41	0.06	1.51	1.35	1.67	<0.001
Model 2	0.43	0.06	1.53	1.37	1.71	<0.001
Model 3	0.81	0.23	2.25	1.45	3.49	<0.001

Notes: Model 1: adjusted for age and sex. Model 2: adjusted for age, sex and risk factors (history of smoking, history of drinking, hypertension, diabetes, hyperlipidemia, atrial fibrillation). Model 3: further adjusted for variables with $p < 0.05$ in univariate analysis (basal ganglia lesions, baseline NIHSS score, baseline GCS score, mRS score, BI score, WBC, ANC, NLR and ALC).

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; ICH, intracerebral hemorrhage; OR, odds ratio; CI, confidence interval.

basal ganglia are the core brain areas of the emotional network, and any damage in these brain areas will result in depressive symptoms.¹⁹ A similar result was found in our study, that patients with depression were more likely to have basal ganglia lesions. However, there was no significant difference of frontal lobe lesion between patients with and without depression after ICH, which might be ascribed to a small number of injuries at frontal

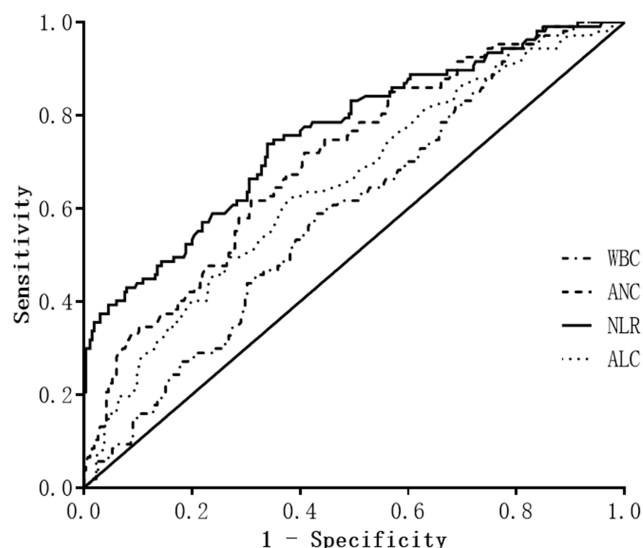


Figure 1 Receiver operating characteristic curves for predicting of depression following ICH. Predictive values of WBC, ANC and NLR for depression after ICH at 3-month and ALC for non-depression. Area under the curve 0.592 (95% CI, 0.530–0.653; $P = 0.006$) for WBC; 0.704 (95% CI, 0.647–0.761; $P < 0.001$) for ANC; 0.758 (95% CI, 0.702–0.814; $P < 0.001$) for NLR; and 0.649 (95% CI, 0.588–0.711; $P < 0.001$) for ALC.

Abbreviations: ICH, intracerebral hemorrhage; WBC, white blood cells; ANC, absolute neutrophil count; NLR, neutrophil-to-lymphocyte ratio; ALC, absolute lymphocyte count; CI, confidence interval.

lobe in our research. Therefore, it needs to be further verified in a larger sample size.

The association between NLR and depression after ICH could be explained by the following mechanisms. Firstly, the biological mechanism. Numerous studies have shown that NLR may play an important role in the development of ICH and depression. Once ICH occurs, blood components, such as leukocytes, red blood cells (RBCs) and macrophages, immediately infiltrate into the surrounding brain tissues to activate the inflammatory cells. Notably, numerous animal studies on ICH demonstrate the presence of neutrophil infiltration into the hematoma.^{20,21} Afterwards, the neutrophils can induce neurotoxicity through a multitude of inflammatory signaling pathways, including the release of cytokines, free radicals, chemokines and other toxic chemicals, ultimately exacerbating the ICH-induced brain injury.²² In contrast, lymphocyte was shown to decrease inflammation in ICH patients.²³ Moreover, many studies have shown a close relationship between NLR and depression. Demircan and Aydin et al found that NLR levels were significantly higher in depressive patients.^{24,25} Inflammation induces the dysfunction of synaptic plasticity by mediating alterations in neurotransmitter, especially the synthesis and metabolism of 5-hydroxytryptamine and glutamine, and eventually leads to depression.²⁶ Therefore, an elevated NLR may represent high levels of inflammation which probably promotes the occurrence of depression after ICH. The second one is the psychological mechanism. Stroke is a serious and highly disabling disease, which is a heavy blow to the mental health of patients. The decline in self-care ability of daily living and the lack of working capacity have rendered unavoidable serious psychological defect in stroke patients, eventually leading to depression.

Some limitations should be noted in this study. Firstly, the NLR level was detected only once on admission, but not dynamically monitored during the course of disease. The combination of baseline and dynamic changes of NLR could provide better prognostic information. Secondly, the connections between NLR and some other inflammatory mediators had not been investigated. Finally, several studies report that some risk factors are related to PSD, including economic status and social support.^{27,28} However, the influence of these factors was not examined in our research.

Conclusions

To sum up, a higher NLR is independently associated with depression at 3-month after ICH, which suggests that NLR on

admission can serve as a significant biomarker of systemic inflammation to predict the occurrence of depression after spontaneous ICH. Further studies regarding the immune mediators will contribute to determining the therapeutic strategies.

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Disclosure

All authors declare that they have no conflicts of interest for this work.

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