Hindawi
Acta Neurologica Scandinavica
Volume 2023, Article ID 6642768, 7 pages
https://doi.org/10.1155/2023/6642768

Research Article

Relationship between Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Hyperhomocysteinemia in Patients with Ischemic Stroke: A Proof-of-Concept Randomized Trial

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Received 11 June 2023; Revised 1 August 2023; Accepted 29 August 2023; Published 19 September 2023

Academic Editor: Gessica Sala

Background. This study is aimed at investigating the relationship between neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hyperhomocysteinemia (HHCY) in patients with ischemic stroke (IS). *Methods*. This study retrospectively analyzed the clinical data and laboratory results of 110 IS patients. According to the cut-off value of HCY = 15 μmol/L, the included patients were divided into the normal HCY (NHCY, $n = 69$) and the high HCY (HHCY, $n = 41$) groups. The relationship between NLR, PLR, and HCY between these groups was then compared. *Results*. NLR and PLR levels in IS patients with HHCY were significantly higher than those in IS patients without HHCY ($P < 0.05$). Correlation analysis showed that NLR and PLR were positively correlated with hs-CRP, RDW, N, L, and HCY ($P < 0.05$). NLR and PLR were the largest predictors of IS-related HHCY, followed by WBC, hs-CRP, RDW, VLDL, and TG. Additionally, NLR and PLR were independent risk factors for IS-related HHCY. *Conclusions*. NLR and PLR may be fast, cheap, and easy-to-analyze biomarkers for predicting IS-related HHCY.

1. Introduction

Ischemic stroke (IS), also known as cerebral infarction, is the leading cause of death and disability worldwide [1]. Hyperhomocysteinemia (HHCY) is a major complication in patients with ischemic stroke. Moreover, HHCY is considered a high-risk factor for fatal and nonfatal cerebrovascular events [2] and has also been shown to be significantly associated with increased long-term mortality in IS patients [3]. Although HHCY can be treated, studies have shown that the treatment of HHCY does not improve the clinical outcome of cardiovascular disease in IS patients with mildly elevated homocysteine (HCY) [4]. At the same time, Lehotsky et al. showed that preventing HHCY may have therapeutic significance for IS [5]. Therefore, early and accurate prediction of HHCY in IS patients is essential for optimizing treatment.

The role of HHCY in the development of IS has not been clearly defined. However, many studies have shown that HHCY pathogenesis is closely related to inflammation [6–8]. Pathogenic levels of circulating HCY are associated with the induction of inflammatory determinants, including expression of adhesion molecules, leukocyte adhesion, endothelial dysfunction, oxidative stress, and reduced nitric oxide bioavailability [9]. Additionally, studies have shown that inflammation plays an important role in the progression of IS [10]. Previous studies have shown that HHCY can induce inflammatory responses in the brain [11]. Together, these lines of evidence suggest that the pathogenesis of HHCY is

Table 1: The clinical data and laboratory indexes of the HHCY group and the NHCY group were compared (mean ± SD).

Indexes	NHCY(69)	HHCY(41)	t/χ^2	*P*-value
Gender, male (female)	55 (14)	32 (9)	0.043	0.836
Age, (year)	71.72 ± 11.37 (47-95)	72.05 ± 12.93 (43-95)	0.137	0.891
History of diabetes, yes (no)	23 (46)	8 (33)	2.427	0.119
History of hypertension, yes (no)	55 (14)	34 (7)	0.172	0.678
History of smoking, yes (no)	19 (50)	14 (27)	0.535	0.464
History of drinking, yes (no)	18 (51)	12 (29)	0.131	0.717
WBC ($10^9 \cdot L^{-1}$)	5.63 ± 1.38 (2.55-8.37)	7.54 ± 3.21 (3.37-16.39)	3.616	0.001
N ($10^9 \cdot L^{-1}$)	3.27 ± 0.94 (1.65-5.64)	5.48 ± 3.08 (2.5-14.8)	4.457	<0.001
L ($10^9 \cdot L^{-1}$)	1.72 ± 0.49 (0.57-2.64)	1.39 ± 0.51 (0.50-2.72)	-3.256	0.002
NLR	1.98 ± 0.53 (0.82-3.04)	4.65 ± 3.81 (1.36-18.63)	4.464	<0.001
PLT ($10^9 \cdot L^{-1}$)	168.16 ± 50.29 (75-322)	198.85 ± 62.77 (84-404)	2.818	0.006
PLR	104.18 ± 36.84 (38.78-234.17)	153.87 ± 51.92 (62.22-288.24)	5.377	<0.001
RDW (%)	12.97 ± 0.59 (11.60-14.50)	13.5 ± 1.48 (11.4-19.0)	2.184	0.034
RBC ($10^{12} \cdot L^{-1}$)	4.20 ± 0.51 (3.01-5.25)	4.33 ± 0.54 (3.20-5.68)	1.318	0.190
Hb ($g \cdot L^{-1}$)	129.39 ± 15.14 (98-159)	130.85 ± 15.98 (96-168)	0.480	0.632
ALB($g \cdot L^{-1}$)	38.46 ± 3.84 (25.0-47.1)	38.36 ± 4.62 (28.6-46.0)	-0.123	0.902
GLU ($mmol \cdot L^{-1}$)	5.63 ± 2.37 (3.75-16.71)	5.80 ± 1.95 (3.96-12.27)	0.368	0.713
TG ($mmol \cdot L^{-1}$)	1.33 ± 0.59 (0.41-2.99)	1.90 ± 1.46 (0.46-7.92)	2.411	0.020
CHOL ($mmol \cdot L^{-1}$)	4.06 ± 1.01 (2.50-6.41)	4.25 ± 1.15 (2.56-6.79)	0.919	0.360
HDL ($mmol \cdot L^{-1}$)	1.14 ± 0.27 (0.65-1.87)	1.10 ± 0.28 (0.68-1.95)	-0.715	0.476
LDL ($mmol \cdot L^{-1}$)	2.49 ± 0.89 (0.93-4.29)	2.55 ± 0.96 (1.14-4.60)	0.345	0.730
VLDL ($mmol \cdot L^{-1}$)	0.60 ± 0.27 (0.19-1.36)	0.86 ± 0.66 (0.21-3.60)	2.412	0.020
ApoA1 ($g \cdot L^{-1}$)	1.00 ± 0.21 (0.65-1.67)	0.98 ± 0.24 (0.65-1.70)	-0.525	0.601
ApoB ($g \cdot L^{-1}$)	0.74 ± 0.22 (0.33-1.29)	0.80 ± 0.26 (0.40-1.41)	1.208	0.230
Lpa ($mg \cdot L^{-1}$)	174.86 ± 148.68 (8.2-679.2)	168.13 ± 193.41 (2.10-932.22)	-0.205	0.838
hs-CRP ($mg \cdot L^{-1}$)	5.32 ± 10.07 (0.27-60.79)	13.45 ± 21.79 (0.43-113.04)	2.250	0.029
D-D ($mg \cdot L^{-1}$)	0.78 ± 1.22 (0.01-8.97)	1.43 ± 2.25 (0.01-9.86)	1.695	0.096
HCY ($\mu mol \cdot L^{-1}$)	10.83 ± 2.07 (6.44-14.92)	25.49 ± 16.97 (15.09-109.94)	5.509	<0.001

related to inflammation. Therefore, this vicious cycle of HHCY and inflammation indicates that there may be an association between inflammatory markers and HHCY.

NLR and PLR are new and recognized indicators of systemic inflammation [12], which have good application prospects in evaluating SLE disease activity and mortality of COVID-19 patients and establishing the prognosis of acute pulmonary embolism, laryngeal cancer, and elderly adults with community-acquired pneumonia [13–17]. NLR and PLR have also been shown to indicate the prognosis of IS patients and are biomarkers for predicting poststroke delirium and depression [18–20]. However, no study has investigated the relationship between NLR, PLR, and HHCY in IS patients. This study is aimed at exploring the relationship between NLR, PLR, and HHCY in IS patients.

2. Material and Methods

2.1. Ethics. This study met the requirements of the Ethics Committee of Anhui No.2 Provincial People's Hospital and was approved.

2.2. Data of the Subjects. The clinical data of IS patients admitted to the Department of Neurology, Anhui No.2 Provincial People's Hospital, from January 2022 to June 2023, were retrospectively collected. All patients were diagnosed with IS according to the World Health Organization criteria [21]. Only IS patients over 18 years and who were admitted within 4.5 hours of disease onset were included in this study. IS patients with severe inflammatory diseases, autoimmune diseases, malignant tumors, severe cardiac dysfunction, and severe liver and kidney dysfunction were excluded. After screening, 115 patients with IS met the requirements of our study, including 41 patients with HHCY and 74 patients with NHCY. Finally, 41 patients with HHCY and 69 patients with NHCY were included in this study matched by age and sex randomly. NLR (power = 0.6) and PLR (power = 0.68) were calculated as the ratio between absolute neutrophil and lymphocyte count and platelet and lymphocyte count.

2.3. Diagnostic Criteria for Hyperhomocysteinemia. The upper limit of the HCY reference range was taken as the critical value (cut – off = 15 μmol/L). The 110 IS patients were divided into two groups, namely, the hyperhomocysteinemia

(HHCY) ($n = 41$) and the normal homocysteinemia (NHCY) ($n = 69$) groups.

2.4. Clinical Assessments and Laboratory Data. Next, the clinical evaluation and laboratory data of all patients were collected. These data included patient age, gender, history of diabetes, history of hypertension, history of drinking, history of smoking, leukocytes (WBC), neutrophils (N), lymphocytes (L), platelets (PLT), red blood cell distribution width (RDW), red blood cell (RBC), haemoglobin (Hb), albumin (ALB), glucose (GLU), triglyceride (TG), total cholesterol (CHOL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), lipoprotein a (Lpa), hypersensitive C-reactive protein (hs-CRP), D-dimer (D-D), and homocysteine (HCY). After admission, the patients were collected and tested according to the requirements of various detection indicators. All operations were completed within 2 hours per the instrument's standard operating procedures and the reagent instructions' requirements (Sysmex automatic blood cell analyzer XN-1001, Japan; Hitachi automatic biochemical analyzer 008AS, Japan; and Siemens automatic biochemical analyzer XPT).

2.5. Statistical Analysis. SPSS21.0 and R software (version 4.0.3, Vienna, Austria) (packages: pwr) were used for statistical analysis. The Kolmogorov-Smirnov test was used to assess data normality. The χ^2 test was used to analyze the enumeration data. An independent sample t-test was used to compare the measurement data. The Pearson correlation analysis was used for linear correlation analysis. The correlation between laboratory indicators and HCY was analyzed by binary logistic regression, and the statistical level was $\alpha = 0.05$. P values less than 0.05 were considered significant.

3. Results

3.1. The Clinical Data and Laboratory Indexes of the HHCY Group and the NHCY Group Were Compared. The clinical data and laboratory parameters of the 41 patients in the HHCY group and 69 patients in the NHCY group were evaluated. Significant differences in WBC, N, L, NLR, PLT, PLR, RDW, TG, VLDL, hs-CRP, D-D, and HCY were observed between the two groups ($P < 0.05$) (Table 1). Compared with the NHCY group, WBC, N, NLR, PLT, PLR, RDW, TG, VLDL, hs-CRP, D-D, and HCY in the HHCY group showed an upward trend, while L showed a downward trend.

3.2. ROC Curve of Laboratory Inflammatory Markers for Predicting HHCY in IS Patients. Inflammatory markers (NLR, PLR, WBC, hs-CRP, and RDW) were used as test variables, and NHCY and HHCY were used as state variables. The value of the state variable was 0 in the NHCY group and 1 in the HHCY group. Using these data, the ROC curve was drawn. The AUC of inflammatory indicators was compared. The AUC analysis revealed that NLR had the largest AUC, followed by PLR, WBC, hs-CRP, and RDW (Figure 1 and Table 2).

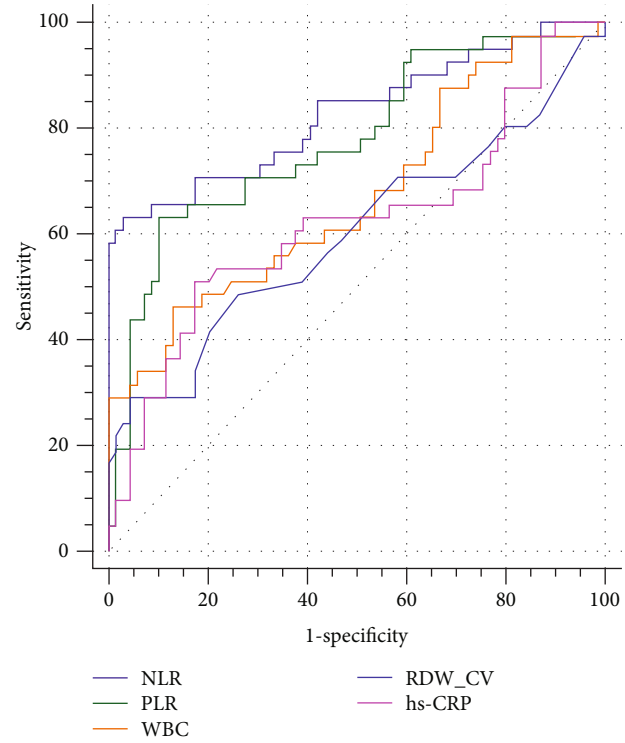

Figure 1: ROC curve of laboratory inflammatory markers for predicting HHCY in IS patients.

3.3. Correlation Analysis of NLR, PLR, and HCY in Patients with Ischemic Stroke. Next, a bivariate Pearson correlation analysis was performed to assess any associations between NLR, PLR, and HCY (Figure 2). NLR, PLR, and HCY were positively correlated.

3.4. Correlation between NLR, PLR, and Other Laboratory Parameters. A bivariate Pearson correlation analysis was also used to analyze the linear correlation between NLR, PLR, and other laboratory indicators. NLR was positively correlated with RDW and hs-CRP and negatively correlated with L (Table 3). Additionally, PLR was positively correlated with N, RDW, and hs-CRP (Table 3).

3.5. Multivariate Logistic Regression Model Was Used to Analyze IS-Related HHCY. Next, we aimed to identify independent risk factors associated with hyperhomocysteinemia (HHCY) in IS patients. Initially, univariate regression analysis was performed to screen for significant variables using a standard P value threshold of <0.05. Subsequently, multivariate logistic regression analysis was conducted, where TG and VLDL were excluded due to collinearity diagnosis (VIF > 10). As a result, two models were established, model 1 (NLR, PLR, WBC, RDW, hs-CRP, and TG) and model 2 (NLR, PLR, WBC, RDW, hs-CRP, and VLDL). The multivariate logistic regression analysis revealed that high NLR, PLR, TG, and VLDL levels were independent risk factors for HHCY in IS patients ($P < 0.05$) (Table 4). Together, these findings underscore the importance of considering

Table 2: ROC curve of laboratory inflammatory markers for predicting HHCY in IS patients.

Markers	AUC	Standard error	*P* value	95% CI
NLR	0.829	0.044	<0.05	0.745-0.894
PLR	0.781	0.047	<0.05	0.692-0.854
WBC	0.673	0.055	<0.05	0.577-0.760
hs-CRP	0.625	0.060	<0.05	0.527-0.715
RDW	0.603	0.060	<0.05	0.505-0.695

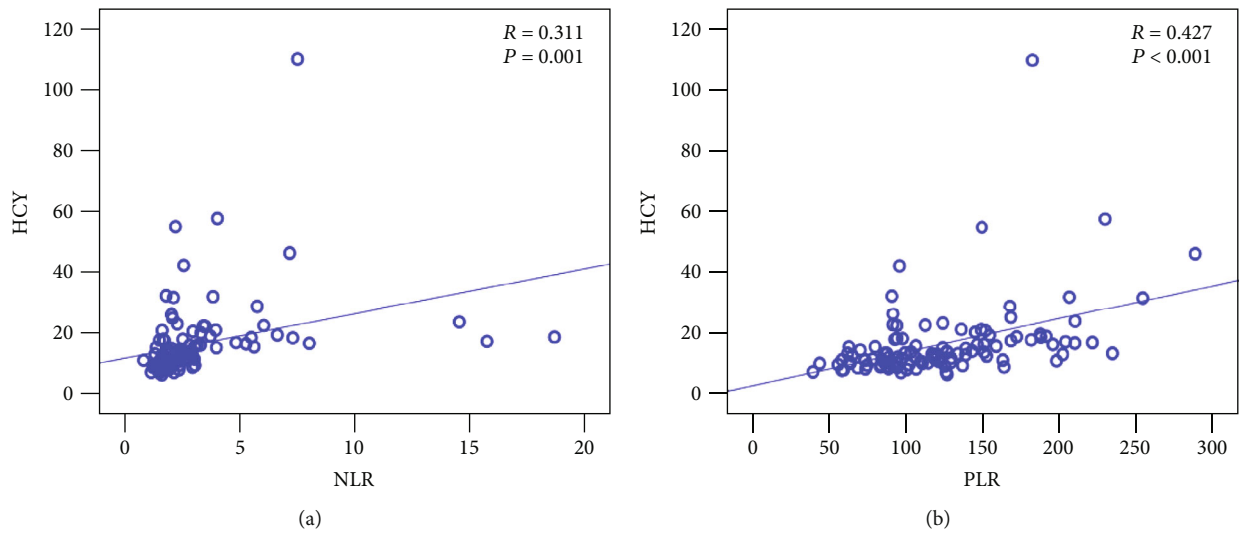

Figure 2: Correlation analysis of NLR, PLR, and HCY in patients with ischemic stroke.

Table 3: Correlation between NLR, PLR, and other laboratory parameters.

Laboratory indicators	NLR		PLR	
	r	*P* value	*r*	*P* value
WBC ($10^9 \cdot L^{-1}$)	/	/	0.127	0.186
N ($10^9 \cdot L^{-1}$)	/	/	0.295	0.002
RDW (%)	0.289	0.002	0.314	0.001
PLT ($10^9 \cdot L^{-1}$)	0.006	0.951	/	/
hs-CRP ($mg \cdot L^{-1}$)	0.559	<0.001	0.338	<0.001
TG ($mmol \cdot L^{-1}$)	-0.127	0.186	0.010	0.914
VLDL ($mmol \cdot L^{-1}$)	-0.127	0.186	0.011	0.910

these variables when evaluating the risk for HHCY in this patient population.

4. Discussion

This is the first clinical study to explore the relationship between NLR, PLR, and HHCY with IS. Our main findings show that NLR and PLR levels are significantly increased and positively correlated with HCY in IS-related HHCY patients relative to IS patients without HHCY. Compared with other indicators, NLR was the largest predictor of IS-related HHCY. PLR was also considered to have a high predictive value ($ROC_{AUC} > 0.7$). Together, these data indicate that compared with other indicators, NLR and PLR were independent risk factors for IS-related HHCY.

Increasing evidence has shown that neuroinflammatory mechanisms play a crucial role in the pathogenesis and progression of IS [22–24]. A high lymphocyte count is believed to be neuroprotective and improves neurological function [25], while a high neutrophil count can result in increased free oxygen free radical release and brain damage [26]. Additionally, it has been shown that AIS can lead to abnormal platelet function and excessive platelet activation and accumulation, hindering stroke recovery [27]. NLR and PLR are a combination of the above three indicators that are stable and easy to obtain and can provide more information

Table 4: Multivariate logistic regression model was used to analyze IS-related HHCY.

Indicators	Model 1 OR (95% CI)	*P* value	Model 2 OR (95% CI)	*P* value
NLR	5.696 (1.983-16.360)	0.001	5.689 (1.981-16.339)	0.001
PLR	1.020 (1.002-1.039)	0.032	1.020 (1.002-1.039)	0.033
WBC	1.429 (0.865-2.359)	0.163	1.427 (0.864-2.356)	0.164
RDW	1.290 (0.669-2.487)	0.448	1.288 (0.668-2.484)	0.450
hs-CRP	0.956 (0.878-1.040)	0.292	0.956 (0.879-1.040)	0.291
TG	4.645 (2.112-10.215)	<0.001	/	/
VLDL	/	/	29.269 (5.167-165.787)	<0.001

about immune activity in the pathogenesis of IS. Previous studies have shown that NLR and PLR can predict the clinical outcome of AIS patients [28, 29] and the neurological outcome after thrombolysis and reperfusion and prognosis after endovascular treatment [30, 31]. However, the relationship between NLR, PLR, and IS-related HHCY has not been reported. Our study shows that NLR and PLR levels were significantly higher in IS patients with HHCY than in IS patients without HHCY and were significantly positively correlated with HCY. Compared with other indicators, NLR and PLR are independent risk factors for IS-related HHCY. Therefore, our study complements the role of NLR and PLR in cerebrovascular diseases and provides new ideas for clinical practice. NLR is considered an emerging marker between the immune system and disease including IS and thyroid function dysfunction [32, 33]; the results of our study are a further proof underscoring the involvement of immune system in the pathogenetic chain of IS. A previous study showed inconsistent trends in NLR and CRP levels in patients with COVID-19 [34], whereas our study found that both NLR and CRP levels increased simultaneously in IS-related HHCY patients, This may be due to COVID-19 patients being infected by the novel corona virus.

Lee et al. indicated insufficient evidence to support the hypothesis that hs-CRP was associated with long-term functional outcomes in AIS patients [35]. In agreement with this finding, another study showed insufficient evidence to recommend the detection of CRP in the routine evaluation of primary stroke prevention [36]. In contrast to these studies, our study found that compared to cases of IS without HHCY, the hs-CRP of patients with HHCY was significantly increased. These data are consistent with the current literature reporting that HHCY may aggravate cerebral inflammation in IS [11] and that the pathogenesis of HHCY is related to inflammation [6–8]. These results further validate the speculation that there may be a possible association between inflammatory markers and IS-related HHCY. Previous studies have shown that oral administration of homocysteine thiolactone induces increased plasma triglyceride levels in rats [37]. Therefore, elevated serum HCY may inhibit VLDL lipolysis, leading to hypertriglyceridemia. Our study is the first to find that TG and VLDL are increased in patients with HHCY related to ischemic stroke and are independent risk factors for HHCY. It is well known that hyperlipidemia is a high-risk factor for carotid atherosclerotic plaque, which is a high-risk factor for IS; NLR was shown in a pioneer study to be a strong predictor of the presence and the number of carotid atherosclerotic plaques. Its use could therefore be useful to identify the risk of harboring carotid plaques, whereas CRP, although performed well, did so to a lesser extent [38]; our research is consistent with these reports.

Several limitations in our study need to be discussed. First, this study was a retrospective case-control study, and the patient's medical histories, such as NIHSS scores, were not adequately assessed. Second, the sample size was relatively small, and the incidence of selection bias is possible. Third, other suggestive inflammatory markers, such as procalcitonin and interleukin, were not assessed. Finally, we did not dynamically evaluate the relationship between NLR, PLR, and HHCY.

This is the first clinical study to explore the relationship between NLR, PLR, and HHCY associated with IS. NLR and PLR significantly correlate with HHCY in IS patients and are independent risk factors for IS-related HHCY. Therefore, NLR and PLR may be two biomarkers for predicting IS-related HHCY. These biomarkers would be fast, cheap, easy to analyze and detect, and thus worthy of clinical application.

5. Conclusions

HHCY is considered a high-risk factor for fatal and nonfatal cerebrovascular events. Although HHCY can be treated, studies have shown that the treatment of HHCY does not improve the clinical outcome of cardiovascular disease in IS patients with mildly elevated homocysteine (HCY). NLR and PLR levels are significantly increased and positively correlated with HCY in IS-related HHCY patients relative to IS patients without HHCY. Therefore, NLR and PLR may be two biomarkers for predicting IS-related HHCY. These biomarkers would be fast, cheap, easy to analyze and detect, and thus worthy of clinical application.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

All authors declare that they have no conflict of interest in conducting this study and publishing the results of this article.

Authors' Contributions

Bing Luo and Yun Wang contributed equally to this work.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (no. 81803938) and the Natural Science Key Project Foundation of Anhui Province Education Department (no. KJ2019A1099).

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