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Original Article

Influence of neutrophil-to-lymphocyte ratio and mean platelet volume on severity and short-term prognosis of acute ischemic stroke

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Abstract: Objective: To investigate the influence of neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) on the severity and short-term prognosis of acute ischemic stroke (AIS). Methods: A retrospective analysis was made on 188 AIS patients treated in our hospital from June 2019 to June 2021. They were divided into mild stroke group and severe stroke group based on NIHSS score. In view of the modified Rankin score (mRS) on 14th day after stroke, patients were divided into good prognosis group and bad prognosis group. The clinical data, NLR and MPV data of each group were compared, and the independent risk factors of short-term poor prognosis of AIS patients were analyzed by multivariate Logistic regression. Results: NLR and MPV in patients with mild stroke were lower than those with severe stroke ($P<0.05$). In addition, NLR and MPV of patients with good prognosis were lower than those with poor prognosis ($P<0.05$). Regression analysis revealed that high NLR and MPV were independent predictors of short-term poor prognosis of AIS patients. The AUC of NLR in predicting the poor prognosis of patients after 14 days of stroke was 0.904, and the specificity and sensitivity were 70.55% and 97.62%. A. AUC of MPV was 0.904, and the specificity and sensitivity were 92.47% and 85.71%. B. Pearson correlation analysis revealed that NLR was positively correlated with MPV ($r=0.452$, $P<0.001$). Conclusion: The elevation of NLR and MPV may be independent risk factors of AIS, but it is related to the severity of stroke and short-term prognosis.

Keywords: Neutrophil-to-lymphocyte ratio, mean platelet volume, acute ischemic stroke, severity of disease, short-term prognosis

Introduction

When blood circulation in the brain is blocked, it causes stroke, a very serious brain injury disease [1]. With the aging of society and unhealthy modern social habits, cerebrovascular diseases are increasing annually [2]. Among them, acute stroke has a rapid onset. If rescue doesn't occur in time, it will often results in serious sequelae or even death [3]. Acute ischemic stroke (AIS) is the main type of acute stroke, accounting for about 85% of all types of stroke [4]. AIS has become the main cause of permanent disability in adults, the second most common reason for dementia, and the third major cause of mortality worldwide [5]. Epidemiological statistics from the United States reveal that 610,000 new stroke cases occur every year. As our society develops, the morbidity of stroke is still increasing annually. In the past 30 years, the morbidity of stroke in low-income countries has increased by 12%, and the affected population is gradually becoming younger [6-8]. It can be found that even if AIS patients are treated pertinently, about 3.7% of them will die directly during in-hospital treatment, 20% of AIS patients will have cardiac obstruction and 76% will have obvious autonomic dysfunction [9-12].

Prognostic testing predictors are currently lacking in AIS, while hematological tests are more rapid and affordable [12]. Among them, neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) have been shown in many studies to be associated with an increased risk of cardiovascular disease [13]. AIS often causes a series of inflammatory reactions in patients, so many inflammatory indicators are relevant to disease progression [14]. NLR is a parameter used to reflect inflammation, and has also been found to be a predictor of many cardiovascular and tumor diseases [15, 16]. Meanwhile, some studies have begun to pay attention to the pre-

dictive effect of NLR in cerebrovascular diseases. For example, NLR has a good predictive value for the prognosis of patients with intracranial hemorrhage [17]. Platelets also play a role in the process of thrombosis. Activated platelets will release inflammatory mediators to block blood vessels, which may lead to AIS formation. MPV can effectively reflect the activation and size of platelets [18]. PLR and MPV are associated with inflammation in AIS, and can help assess the prognosis of patients by reflecting the inflammation of patients. Thus, this research measured the NLR and MPV levels in AIS patients with different severities and investigated the value of NLR and MPV in prognosis, so as to provide direction and basis for clinical practice.

Data and methods

Patient data

A retrospective analysis was made on 188 AIS patients treated in our hospital from June 2019 to June 2021. They were divided into mild stroke group and severe stroke group based on admission NIHSS score. Specifically, 102 patients (67 males and 35 females), (49.9±9.1) years old on average, were enrolled into mild stroke group (NIHSS score ≤7). The NIHSS scale was compiled by the National Institutes of Health: <7 points were mild neurological impairment, and ≥7 were moderate and severe neurological impairment [19]. While 86 patients (50 males and 36 females), with an average age of (50.4±10.3), were regarded as severe stroke group. The study was approved by the Medical Ethics Committee and all patients provided an informed consent form in accordance with the Declaration of Helsinki. Approval number: 2019018.

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed with AIS according to imaging and pathology, and the diagnostic criteria were in line with the guidelines issued by the Stroke Committee of American Heart Association in 2013 [20]. All patients were hospitalized within 6 hours of onset, with age ≥18 years, and had complete clinical data with telephone follow-up.

Exclusion criteria: Patients with other abnormal coagulation diseases, estimated survival time less than 7 days, and severe liver and renal insufficiency; Patients with other malignancies; Patients with severe inflammation; Pregnant or lactating women.

Detection methods

On admission, 5 mL of fasting peripheral venous blood was collected from patients and put into anticoagulation tubes. The NLR and MPV levels in venous blood of anticoagulation tubes were tested by flow cytometry. A 100 μL sample was transferred to the measuring room of MACS Quant flow cytometry (Miltenyi Biotec GmbH, Bergisch-G Ladbach, Germany), using 405 nm, 488 nm and 640 nm air-cooled lasers. The flow cytometry was calibrated with MACSQuant calibration beads with a size of 3 μm; 460 nm microspheres were used as the reference for the sample to analyze the gated population based on the definition of forward scattering (FSC) and side scattering (SSC) characteristics.

Outcome measures

The NLR and MPV levels in patients with mild and severe stroke were observed. In view of the modified Rankin score (mRS) on the 14th day of stroke [21], patients were divided into good prognosis group and poor prognosis group, in which mRS score >2 was poor prognosis, and ≤2 was good prognosis [22]. The NLR and MPV levels of patients with poor and good prognosis were assessed. ROC curve was employed to detect the predictive value of NLR and MPV levels in predicting short-term poor prognosis of AIS patients. Pearson test was conducted to assess the relationship between MPV and NLR, and multivariate Logistic regression was used to analyze the independent risk factors of short-term poor prognosis.

Statistical methods

SPSS 20.0 software (SPSS Co., Ltd., Chicago, USA) was applied to statistical analysis. Continuous variables were expressed by the number of cases, average value and standard deviation. Independent t-test was conducted to test data between two groups, marked by T. For classification variables, the data were expressed as the number or percentage of classification cases; those variables were tested through chi-square analysis, represented as X^2. ROC curve was used to predict the poor prognosis of NLR and MPV after 14 days of stroke. Pearson test was conducted to analyze the relationship between MPV and NLR. $P<0.05$ was considered as statistically significant.

Table 1. Clinical data of patients

Factor	Mild stroke group (n=102)	Severe stroke group (n=86)	T/χ^2 value	*P*-value
Gender			1.131	0.288
Man	67 (65.69)	50 (58.14)		
Woman	35 (34.31)	36 (41.86)		
Age (years)	49.9±9.1	50.4±10.3	0.353	0.724
BMI (kg/m^2)	23.75±1.68	23.30±1.88	1.733	0.085
Past medical history				
Hypertension	39 (38.24)	31 (36.05)	0.096	0.757
Diabetes	23 (22.55)	17 (19.77)	0.216	0.643
Hyperlipemia	15 (14.71)	10 (11.63)	0.383	0.536
History of smoking			0.765	0.382
Yes	37 (36.27)	26 (30.23)		
No	65 (63.73)	60 (69.77)		
History of alcoholism			0.104	0.747
Yes	16 (15.69)	15 (17.44)		
No	86 (84.31)	71 (82.56)		
Place of residence			0.152	0.697
Cities	77 (75.49)	67 (77.91)		
Countryside	25 (24.51)	19 (22.09)		
Blood glucose (mmol/L)	6.56±1.98	6.68±2.33	0.382	0.703
Total cholesterol (mmol/L)	6.63±0.88	6.52±0.91	0.841	0.402
Triglyceride (mmol/L)	3.36±0.68	3.46±0.73	0.971	0.333

BMI: Body Mass Index.

Results

Clinical data of patients

We divided the patients into mild stroke group and severe stroke group in light of the NIHSS score. We collected the clinical data of both groups and compared them. This revealed that there was no statistical difference in gender, age, BMI, previous medical history (hypertension, diabetes and hyperlipidemia), smoking history, alcoholism history, place of residence, blood glucose, total cholesterol and triglyceride between the observation group and control group (P>0.05) (**Table 1**).

NLR and MPV expression in different severity

It was found that NLR and MPV of patients with severe stroke were significantly higher than those with mild stroke (**Figure 1**).

NLR and MPV expression in patients with different prognosis

Altogether 188 AIS patients were divided into a good prognosis group (146 cases) and bad prognosis group (42 cases) based on their mRS on the 14th day after stroke. It was found that the NLR and MPV of patients in the bad prognosis group were significantly higher than those in good prognosis group (**Figure 2**).

Univariate analysis of poor prognosis of AIS patients

The clinical data of the good and poor prognosis group were collected. Univariate analysis confirmed that there was no difference in gender, age, BMI, previous medical history (hypertension, diabetes, hyperlipidemia), smoking history, alcoholism history, place of residence, total cholesterol and triglycerides between both groups, but there were obvious differences in blood glucose, NLR and MPV (**Table 2**).

Multivariate analysis of poor prognosis

We conducted multivariate analysis on the indicators with differences in univariate analysis, and chose the forward multivariate logistic regression (LR) method. The results denoted that blood glucose was not an independent risk factor for patients with poor prognosis in 14 days, but NLR (OR: 2.802, 95% CI: 1.798-4.366), MPV (OR: 1.072, 95% CI: 1.033-1.111),

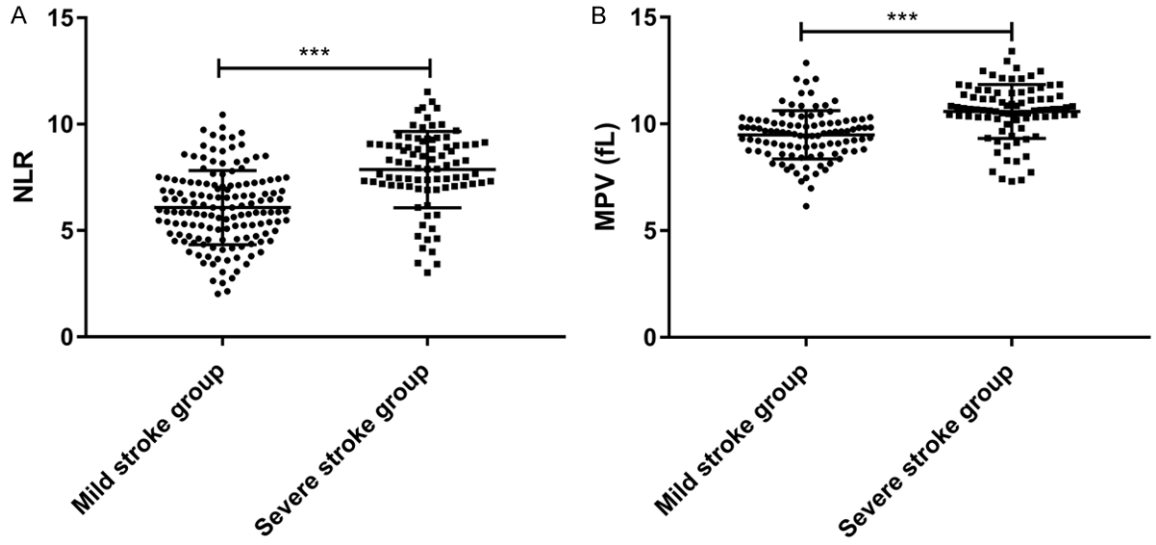

Figure 1. NLR and MPV expression in different severities. A. The NLR of patients with good prognosis is significantly lower than that of those with poor prognosis (t=7.463, P<0.001). B. The MPV of patients with good prognosis is significantly lower than that of those with poor prognosis (t=6.256, P<0.001).

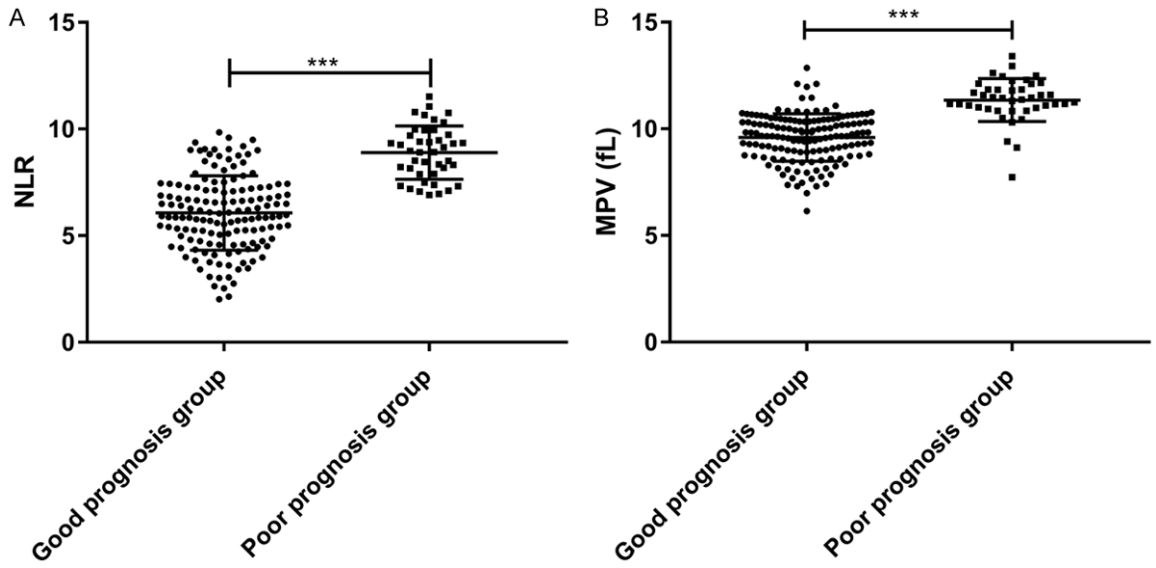

Figure 2. NLR and MPV expression in patients with different prognosis. A. The NLR of patients with good prognosis is significantly lower than that of those with poor prognosis (t=9.842, P<0.001). B. The MPV of patients with good prognosis is significantly lower than that of those with poor prognosis (t=9.215, P<0.001).

Killip rating (OR: 2.802, 95% CI: 1.798-4.366), and PCI operation rate (OR: 3.731, 95% CI: 2.039-6.827) were independent risk factors for poor prognosis (**Table 3**).

Correlation between NLR and MPV and its predictive value in AIS patients with poor prognosis

By drawing ROC curves of NLR and MPV to predict patients' 14-day poor prognosis, we discovered that AUC of NLR and MPV were both greater than 0.7, which indicated that they had good predictive value. Correlation analysis denotes that NLR and MPV in AIS patients are positively correlated (**Figure 3**).

Discussion

Stroke has become one of the main reasons for death and disability among Chinese residents, and the identification of AIS's disease degree

Table 2. Univariate analysis table

Factor	Good prognosis group (n=146)	Poor prognosis group (n=42)	T/χ^2 value	*P*-value
Gender			2.234	0.135
Man	95 (65.07)	22 (52.38)		
Woman	51 (34.93)	20 (47.62)		
Age (years)	50.1±9.6	50.3±10.0	0.118	0.906
BMI (kg/m^2)	23.59±1.75	23.39±1.90	0.640	0.523
Past medical history				
Hypertension	56 (38.36)	14 (33.33)	0.352	0.553
Diabetes	29 (19.86)	11 (26.19)	0.780	0.377
Hyperlipemia	20 (13.70)	5 (11.90)	0.091	0.763
History of smoking			0.641	0.424
Yes	46 (31.51)	16 (38.10)		
No	100 (68.49)	26 (61.90)		
History of alcoholism			0.247	0.620
Yes	22 (15.07)	8 (18.18)		
No	124 (84.93)	36 (81.82)		
Place of residence			0.118	0.732
Cities	111 (76.03)	33 (78.57)		
Countryside	35 (23.97)	9 (21.43)		
Blood glucose (mmol/L)	6.40±2.10	7.37±2.14	2.627	0.009
Total cholesterol (mmol/L)	6.58±0.90	6.60±0.90	0.127	0.899
Triglyceride (mmol/L)	3.39±0.71	3.47±0.69	0.648	0.518
NLR	6.06±1.74	8.89±1.24	9.838	<0.001
MPV (fL)	9.60±1.11	11.35±1.01	9.180	<0.001

Table 3. Multivariate analysis table

Factor	B	S.E.	Wals	Sig.	Exp (B)	EXP (B) of 95% CI	
						Lower limit	Upper limit
Blood glucose	0.124	0.130	0.906	0.341	1.132	0.877	1.462
NLR	1.030	0.226	20.739	<0.001	2.802	1.798	4.366
MPV	1.317	0.308	18.249	<0.001	3.731	2.039	6.827

and prognosis prediction have been the focus of scholars at home and abroad. Many AIS cases are caused by occlusion of large blood vessels. For those with severe stroke, their large blood vessels and collateral vessels often have poor circulation. Because of the high range and severity of ischemia, these patients have high disability rate and serious complications [23, 24].

We have distinguished the severity of patients' illness by NIHSS score. The score can evaluate the degree of neurological impairment of stroke patients and has a good predictive effect on the bleeding transformation of patients, so it is often used as a basis of risk stratification [25].

The two most important pathological mechanisms of stroke are inflammation and oxidative stress. After inflammation is activated, it will further aggravate brain injury, and in this process, there will be activation of inflammatory cells and immunosuppression [26]. Platelets and lymphocytes will take part in these processes; activated platelets will further aggravate the formation of arterial thrombosis or plaque rupture, and then destroy intracranial blood flow [27]. Simultaneously, some studies on AIS show that patients with low platelet count often have poor prognosis [28]. Lymphocytes are considered as the immunomodulator of brain protection, and the lower number of lymphocytes will often cause more severe

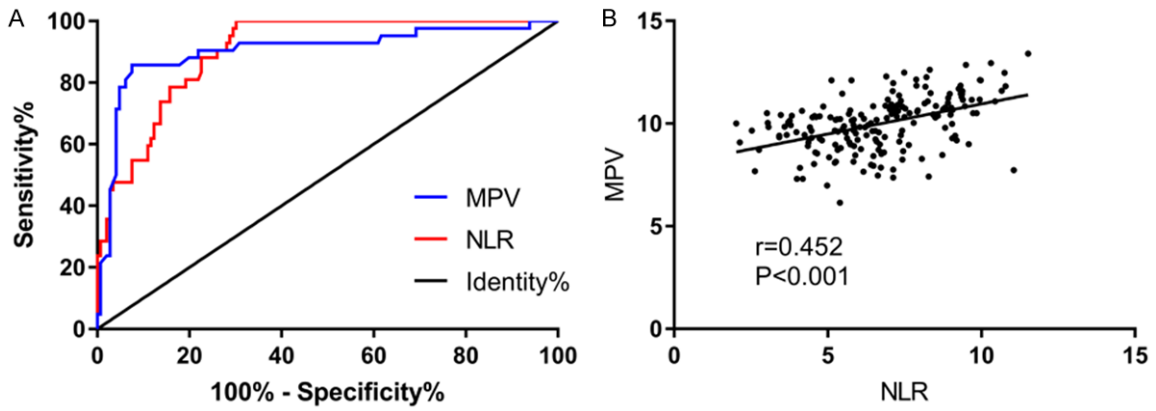

Figure 3. Correlation between NLR and MPV and its predictive value in AIS patients with poor prognosis. A. The ROC curve AUC of NLR for predicting the poor prognosis of patients with stroke after 14 days is 0.904, and the best specificity and sensitivity are 70.55% and 97.62% when it is greater than 6.940. The ROC curve AUC of MPV is 0.904, and the best specificity and sensitivity are 92.47% and 85.71% when it is greater than 10.830. B. NLR is positively correlated with MPV (r=0.452, P<0.001).

brain injury. As a subtype of leukocytes, neutrophils will cause active inflammation and gather in the cerebral vessels in the early stage of stroke, which may not only increase the infarct area but also block the peripheral capillaries [29]. Our study also indicates that AIS is more serious in patients with higher NLR, and MPV is also higher in patients with higher NIHSS score. Elsaid et al. [30] have mentioned that patients with higher NIHSS will have poorer prognosis if they adopt the treatment scheme of delayed intravenous thrombolysis. We evaluated the prognosis of patients according to the mRS score on the 14th day, so we also found that compared with patients with good and poor prognosis, their NLR and MPV were higher. NLR and MPV have good prognostic value for some cardiovascular and cerebrovascular diseases in the past studies. Kahraman et al. [31] have found that NLR is an independent predictor of higher residual SYNTAX scores in patients with ST-segment elevation myocardial infarction after operation through multivariate logistics regression analysis, and there is a positive correlation between NLR and residual SYNTAX scores after operation. Xu et al. [32] have discussed that higher MPV will lead to increased inflammation and oxidative stress in stroke patients, which will not only weaken the deformability of red blood cells, but also aggravate their adhesion to endothelial cells, thus causing repeated embolism of small and medium blood vessels in local brain tissue, resulting in secondary brain injury. In the meantime, multivariate logistics regression analysis demonstrated that high NLR and MPV were independent predictors of poor prognosis of AIS patients. The ROC curve drawn to predict the poor prognosis of patients shows that the area under the curve of NLR and MPV is greater than 0.7, indicating that both of them have good predictive value. We also find that there is a positive correlation between NLR and MPV through Pearson correlation test.

Nevertheless, there are still some shortcomings to this work. First of all, for AIS patients, there are many complications and injuries. For these poor complications, we have not made in-depth distinctions or exploration. Hence, we are still vague about the diagnostic and predictive value of NLR and MPV in these complications. It is hoped that relevant content can be added in the follow-up research to further verify our research results. Secondly, there are many new detection methods combined with imaging, such as CT perfusion imaging based on automatic segmentation algorithm. Joint detection can be carried out in subsequent research to improve the clinical value. Finally, this research did not explore the degree of influence of different treatment methods on the outcome of patients. We hope to observe the influence of treatment methods on NLR and MPV in the future.

Given all of that, the increase of NLR and MPV may be independent risk factors of AIS, and they are associated with the severity of stroke and short-term prognosis.

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Disclosure of conflict of interest

None.

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