Neurology Asia 2023; 28(4) : 817 – 824

Mean platelet volume-to-lymphocyte ratio predicts poor functional outcome of acute ischemic stroke patients

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Abstract

Background & Objective: The mean platelet volume-to-lymphocyte ratio (MPVLR) is a novel and easily available marker of poor short-term prognosis in myocardial infarction patients. The present study was to investigate the association between MPVLR and clinical outcome of patients with acute ischemic stroke. *Methods:* A total of 494 acute ischemic stroke patients were included in this study and received 3-months follow-up. Blood samples for MPVLR were obtained at admission and at 7 days after acute ischemic stroke. Poor functional outcome was defined as a modified Rankin Scale (mRS) score of 3-6 at 3 months after stroke. *Results:* Compared with good prognosis group, MPVLR level at admission and at 7 days in poor prognosis group was significantly higher, the difference between these two groups was statistically significant ($P < 0.001$). In multivariate logistic regression analysis, both MPVLR as a continuous (OR 1.13; 95%CI, 1.064-1.190, P=0.001) and categorical variable (OR 3.05; 95%CI, 1.85-5.05, P<0.001) were independently associated with poor outcome at 3 months. ROC analysis revealed the predictive value of MPVLR was better than that of platelet-to lymphocyte ratio (PLR). The nomogram was used for predicting 3-months unfavourable outcome after an acute ischemic stroke. *Conclusions:* MPVLR at admission and at 7 days after stroke were found to be independently associated with poor functional outcome. MPVLR may serve as an activity marker for poor prognosis in patients with acute ischemic stroke.

Keywords: Mean platelet volume-to-lymphocyte ratio, acute ischemic stroke, prognosis, inflammation, thrombosis

INTRODUCTION

Stroke has becomes one of the major causes of adult disability and mortality worldwide today.[1] Most stroke survivors live with residual impairments, which decline quality and independence of life.[2] Ischemic stroke, which accounts for about 80–85% of all strokes, is mostly caused by cerebral embolism or arterial thrombosis and result in brain ischemic injury.[3] Although a few factors related to functional outcome of ischemic stroke patients has been well identified,[4,5] detection of new risk factors are still important and necessary.

Platelets play a central role in the formation and progression of atherosclerosis, as well as ischemic stroke.[6] Platelet size, measured as mean platelet volume (MPV), could indicate the activation and functions of platelet. Larger-size platelets are metabolically and enzymatically more active.[7] It has been reported that elevated MPV predict the mortality and functional outcome after 1 year in patients with acute ischemic stroke.[8] Inflammatory process links to pathogenesis and poor prognosis of ischemic stroke.[9] The main pathophysiological path of early brain injury were immune response, neuroinflammation and leukocytes accumulation, involving lymphocyte, monocytes and neutrophils.[4,10] Numerous studies have shown that lower lymphocyte counts concentrations were correlated with worse outcomes in AIS patients.[11] Recently, mean platelet volume-to-lymphocyte ratio (MPVLR) was considered as a novel marker of poor short-term prognosis in myocardial infarction patients who underwent primary percutaneous coronary intervention.[12] This prompted us to explore the prognostic value of MPVLR in acute ischemic stroke. Therefore, the objective of our study was to explore whether MPVLR was associated with functional outcome of acute ischemic stroke patients.

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Date of Submission: 5 July 2023; Date of Acceptance: 8 July 2023

https://doi.org/10.54029/2023thw

METHODS

Population

We included consecutive patients with ischemic stroke who were accepted by Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University from Jan 2021 to Apr 2022. The inclusion criteria for patients were as follows: (1) older than 18 years old; (2) diagnosis of acute ischemic stroke by neurologists according to the recommendations from World Health Organization[1]; (3) admitted to the hospital within 24 hours of onset. Exclusion criterion included: (1) an antithrombotic treatment after onset of AIS; (2) a stroke history; (3) late admission (> 24 hours after stroke onset). Besides these, patients with incomplete medical records and a missing 3-month prognostic information were also excluded. The present study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province.

Clinical protocol and laboratory tests

Baseline information on the age, gender, smoking status, alcohol consumption, systolic pressure and diastolic pressure, hypertension, diabetes, dyslipidemia and atrial fibrillation at admission were collected. The severity of neurological impairment was assessed by the National Institutes of Health Stroke Scale (NIHSS) at admission.
Blood samples within 24 hours of admission and at 7 days after stroke were collected for all patients. Complete blood count was analyzed by the automated hematology analyzer (Sysmex Company, XE-2100, Japan). MPVLR was calculated as mean platelet volume divided by lymphocyte count (fL/10^9). And the platelet-to-lymphocyte ratio (PLR)was calculated as platelet count divided by lymphocyte count.

Clinical outcome measures and prognosis

The prognosis of all patients was evaluated on the basis of the modified Rankin Scale (mRS) through outpatient department or telephone follow-up by trained neurologists. Poor functional outcome was defined as an mRS score of 3-6 at 3 months after stroke.

Statistical analysis

The data managements and analyses were applied with SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC). A value of P <0.05 was considered significant for all analyses. Categorical variables were presented as counts and percentages, and Fisher's exact test or chi-square tests were used as appropriate. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges. Statistical analyses were performed using Student's t-test, and Kruskal-Wallis for continuous data, chi-square test or Fisher exact test for categorical data. Logistic regression was carried out to find the association between unfavorable clinical outcome and MPVLR. We determined the sensitivity and specificity of MPVLR and PLR levels to serve as a prognosis for AIS by using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated as a criterion for the accuracy of the test. The method of optimal cutoff was applied to transform MPVLR into a categorical variable. A nomogram is a conventionally clinical tool which interpolates different data to generate a scoring system reflecting the risk probability. In this study, we generate a specific nomogram aimed to predict the likelihood of 3-months unfavourable outcome after stroke.

RESULTS

Basic characteristics of the study population

Among 718 consecutive stroke patients, 632 were diagnosed with the first-ever ischemic stroke. From the 632 patients, we excluded 44 patients because the onset to admission time was over 24h, 32 patients due to receiving antithrombotic therapy, and 62 patients because of a loss to follow up. Finally, a total of 494 patients with ischemic stroke were enrolled.

The baseline characteristics of the two groups based on the mRS scores in the study population were summarized in Table 1. There were no statistically significant differences between the two groups in sex, diabetes, alcohol drinking, systolic BP and diastolic BP. Patients with a poor clinical outcome showed a higher MPVLR (median 7.6 versus median 5.5, P <0.001), PLR (median 150.3 versus median 119.8, P <0.001), NIHSS score (median 6 versus median 3, P <0.001) at admission than patients with a good clinical outcome. Moreover, age, hypertension, smoking, total cholesterol and fibrinogen was significantly different between patients with good and poor outcome. At 7 days after stroke, MPVLR were significantly higher in patients with poor functional outcome than those without. In addition, lymphocyte was also lower in the

Table 1: Comparison of the baseline characteristics between patients with poor and good functional outcome

Characteristics	Good outcome (n =339)	Poor outcome (n =155)	*p*-value
Age (y), mean±SD	65.0(55.5,73.0)	73.0(63.0,80.0)	<0.001
Gender, male, n (%)	106(32.3)	50(34.7)	0.609
Baseline NIHSS, median (IQR)	3.0(1.0,4.0)	6.0(3.0,9.0)	<0.001
Hypertension, n (%)	269(82.0)	130(90.3)	0.022
Diabetes, n (%)	112(34.1)	48(33.3)	0.864
Hyperlipidemia, n (%)	166(50.6)	55(38.2)	0.013
Atrial fibrillation, n (%)	35(25.7)	44(41.9)	0.008
Systolic BP (mmHg), mean ± SD	149.8±18.8	152.6±21.5	0.277
Diastolic BP (mmHg), mean ± SD	86.3±13.6	85.1±15.7	0.510
Smoking (n)	157(47.9)	53(36.8)	0.026
Cell count at admission			
Lymphocytes, x10^9/L, mean± SD	1.8(1.39.2.27)	1.4(0.99,1.74)	0.000
MPV, fL, mean±SD	9.9(9.1,10.8)	10.1(9.3,10.9)	0.143
PLT, x10^9/L, mean± SD	222..8±58.4	222.1±69.0	0.024
MPVLR, fL/10^9/L, median (IQR)	5.5(4.3,7.3)	7.6(5.8,10.0)	<0.001
PLR, median (IQR)	119.8(93.1,158.6)	150.3(107.7,201.5)	<0.001
Cell count at 7 days after stroke			
Lymphocytes, x10^9/L, mean± SD	1.8(1.4,2.2)	1.4(1.1,1.8)	<0.001
MPV, fL, mean±SD	10.5(10,11.2)	10.7(10.1,11.5)	0.015
MPVLR, fL/10^9/L, median (IQR)	5.8(4.7,7.50)	7.8(5.9,10.0)	<0.001

NIHSS: National Institute of Health stroke scale; BP: blood pressure; MPV: mean platelet volume; PLT: Platelet; MPVLR: mean platelet volume-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation; IQR: interquartile range.

poor functional outcome group than in the good functional outcome group.

The ROC curve analyses

The ROC curves of MPVLR and PLR at admission to prediction of an unfavorable clinical outcome are shown in Table 2. According to the ROC curve, the optimal cut off value of MPVLR level predicted 3-months prognosis of AIS patients was 6.57, the sensitivity was 65.97%, specificity was 67.07%, the area under the curve (AUC) was 0.7(95%CI, 0.64–0.75; P < 0.001). ROC analysis revealed good diagnostic value of MPVLR in predicting three months poor outcome. The predictive value of MPVLR was better than that

Table 2: Receiver operating characteristics curves identifying the discrimination thresholds of MPVLR and PLR for three-month outcome

	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	P
MPVLR at admission	0.7	0.64-0.75	65.97	67.07	46.8	81.78	<0.001
PLR at admission	0.63	0.58-0.69	57.64	64.02	41.29	77.49	<0.001
Difference between areas MPVLR vs. PLR at admission							0.07
95% Confidence interval							0.002-0.126
p							0.043

PLR: platelet-to-lymphocyte ratio; AUC: area under the curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

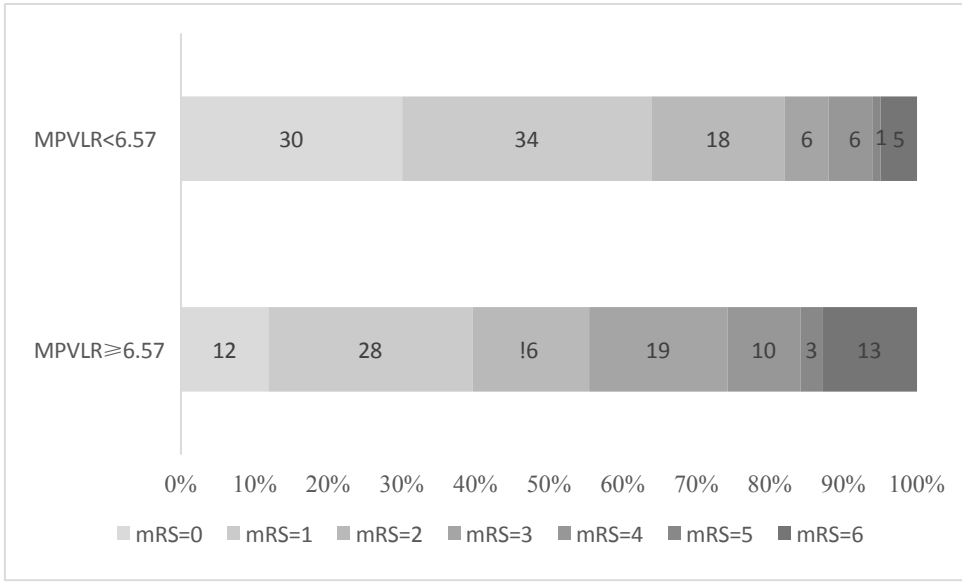

Figure 1. Functional outcome at 3 months stratified for the cut-off value of MPVLR at admission

of PLR (Table 2).

The distribution of functional outcome at 3 months stratified for MPVLR cut-off value is shown in Figure 1 and Figure 2. Whether at admission or at 7 days after stroke, poor functional outcome was more common in the higher MPVLR group stratified by cut-off value (Table 3).

The correlation between MPVLR and 3-month outcome

The results of the binary logistic regression analysis between MPV, lymphocyte, MPVLR and poor outcome were shown in Table 4. At admission, the MPVLR level as a dichotomous variable was independently associated with a higher risk of poor outcome at 3 months with an adjusted odds ratio (OR) of 3.88 (95 % confidence interval (CI), 2.57-5.87; P<0.001) with adjustment for age, sex and baseline NIHSS (model 1) and 3.05 (95 % CI, 1.85-5.05, P<0.001) with further adjustment for age, sex, National Institutes of Health Stroke Scale score, hypertension, diabetes, hyperlipidemia, Atrial fibrillation (model2). The predictive of MPVLR as a continuous variable

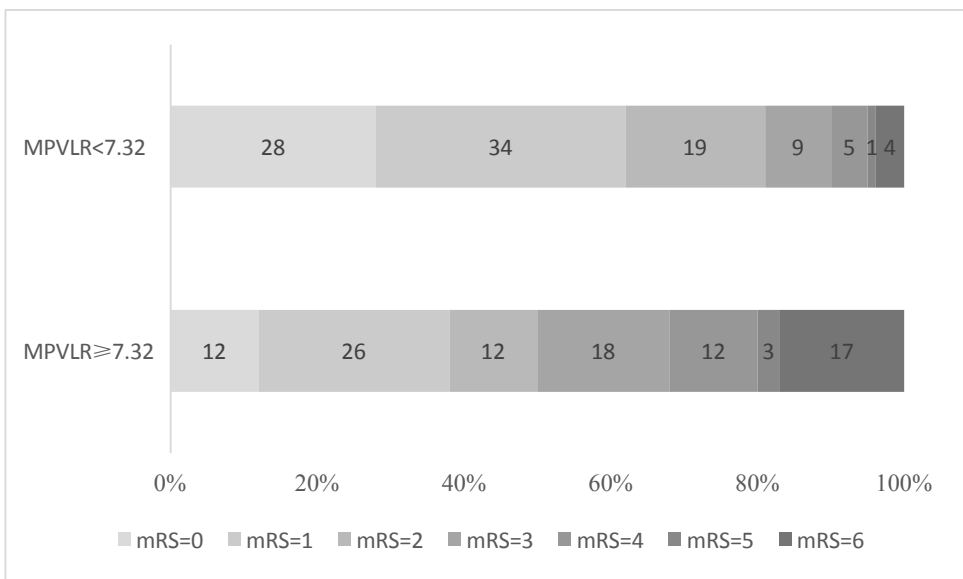

Figure 2: Functional outcome at 3 months stratified for the cut-off value of MPVLR at 7days after stroke

Table 3: Comparison of outcomes between subgroups based on MPVLR cutoff

Outcomes	Cell count at admission		*p*-value	Cell count at 7-10 days after stroke		*p*-value
	MPVLR<6.57 (n =286)	MPVLR≥6.57 (n =208)		MPVLR<7.32 (n =314)	MPVLR≥7.32 (n= 180)	
mRS, median (IQR)	1(0,2)	3(1,4)	0.001	1(0,2)	3(1,5)	0.000
mRS3-6, n(%)	52(18)	93(45)	0.000	60(19)	90(50)	0.000

mRS: modified Rankin Scale.

at admission for poor outcome were trend to become significant whether in Model 1 or Model 2. At 7 days after stroke, whether in Model 1 or Model 2, increased MPVLR level maintained its predictive accuracy as either continuous or categorical variable.

Patients were then further subdivided into four groups and logistic regression analysis was performed again. Notably, there was a trend of incremental OR when compared higher quarter of MPVLR with lower ones (second quarter, adjusted OR 2.59, 95% CI: 1.16-5.75, P = 0.019; third quarter, adjusted OR 3.07, 95% CI:1.41-6.68, P = 0.005, fourth quarter adjusted OR 5.44, 95% CI:2.53-11.68, P<0.001) (Table 5).

The nomogram used for predicting 3-month unfavourable outcome after an acute ischemic stroke

Based on the independent risk factors which were statistically significant in multivariate analysis, nomograms were constructed to predict the risk of the poor outcome after three months (Figure 3). The final output was an individual risk probability of 3-months adverse outcome expressed in percentage, thus ranging from 0 to 100%. Predictably, a higher score of the nomogram would be associated with a higher likelihood of unfavourable outcome, whereas a lower score would be associated with a lower likelihood of unfavourable outcome. This can be explained by two paradigmatic examples. A 52-year-old (20 points) stroke patient, admitted with a NIHSS score of 4 (15 points), a MPVLR value of 5 (8 points) and without HBP (0 points) would have a total score of 45 reflecting probability of adverse outcome <10%. Conversely, a 70-year-old (30points) stroke patient, admitted with a NIHSS score of 6 (25 points), MPVLR value of 15 (22 points) and with HBP (28 points) would have

Table 4: Multivariate logistic regression of association between MPV, lymphocyte, MPVLR and poor outcome

	Multivariate Adjusted (Model 1)		*p*-value	Multivariate Adjusted (Model 2)		*p*-value
	OR	95% CI		OR	95% CI	
Cell count at admission						
MPV	1.09	0.912-1.302	0.344	1.07	0.89-1.28	0.48
lymphocyte	0.39	0.266-0.577	0.000	0.372	0.247-0.558	<0.001
MPVLR	1.13	1.064-1.190	0.000	1.13	1.067-1.202	<0.001
MPVLR≥6.57	3.88	2.57-5.87	0.000	3.05	1.85-5.05	<0.001
Cell count at 7 days after stroke						
MPV	1.26	1.00-1.58	0.05	1.22	0.97-1.29	0.08
lymphocyte	0.35	0.219-0.542	0.000	0.34	0.213-0.537	<0.001
MPVLR	1.17	1.088-1.267	0.000	1.17	1.084-1.265	<0.001
MPVLR≥7.32	3.79	2.543-5.646	0.000	3.16	1.97-5.07	<0.001

Model 1 = adjusted for age, sex, National Institutes of Health Stroke Scale score.
Model 2 = adjusted for age, sex, National Institutes of Health Stroke Scale score, hypertension, diabetes, hyperlipidemia, Atrial fibrillation.

Table 5: Univariate and multivariate logistic regression analysis between MPVLR and clinical outcome

MPVLR	N	Number of Poor prognosis(%)	Crude		Adjusted	
			OR(95%CI)	*P*	OR(95%CI)	*P*
2.08~	124	16(13.0)	1.00(1.00,1.00)	Ref.	1.00(1.00,1.00)	Ref.
4.53~	124	27(21.7)	1.89(0.96,3.73)	0.066	2.59(1.16,5.75)	0.019
5.97~	124	39(31.5)	3.15(1.64,6.04)	0.001	3.07(1.41,6.68)	0.005
8.30~	122	62(50.8)	7.06(3.73,13.37)	<0.001	5.44(2.53,11.68)	<0.001
Trend test				<0.001		<0.001

Adjusted for age, sex, National Institutes of Health Stroke Scale score, hypertension, diabetes, hyperlipidemia, Atrial fibrillation.

a total nomogram score of 87 and a following probability of adverse outcome approximating 70%.

DISCUSSION

In the present study, we first demonstrated an independent association between MPVLR and 3-months unfavorable clinical outcomes in patients with acute ischemic stroke. High level of mean platelet volume-to-lymphocyte ratio could predict 3-month worse outcome. In addition, we found an optimal cut-off point for MPVLR at admission of at least 6.57. It predicted the presence of poor three-months outcome with a good sensitivity and specificity. This study also showed that the level of MPVLR on admission was more accurate in predicting the prognosis of AIS than that of PLR.

Thrombosis and inflammatory are vital in the progression of acute ischemic stroke. The relationship between thrombosis and inflammation is complicated. Thrombosis could increase inflammation, while inflammation in return contributes to thrombosis.[13] Platelet plays an important role in the thrombosis and inflammation.[14,15] In the formation of atherosclerotic plaque, platelets can adhere to endothelial cells and contribute to the recruitment of leukocytes involved in the vascular inflammation.[16] Elevated platelet count may indicate a higher propensity to form platelet-rich thrombi, which in turn may worsen the prognosis.[17,18] Moreover, the evidence suggests

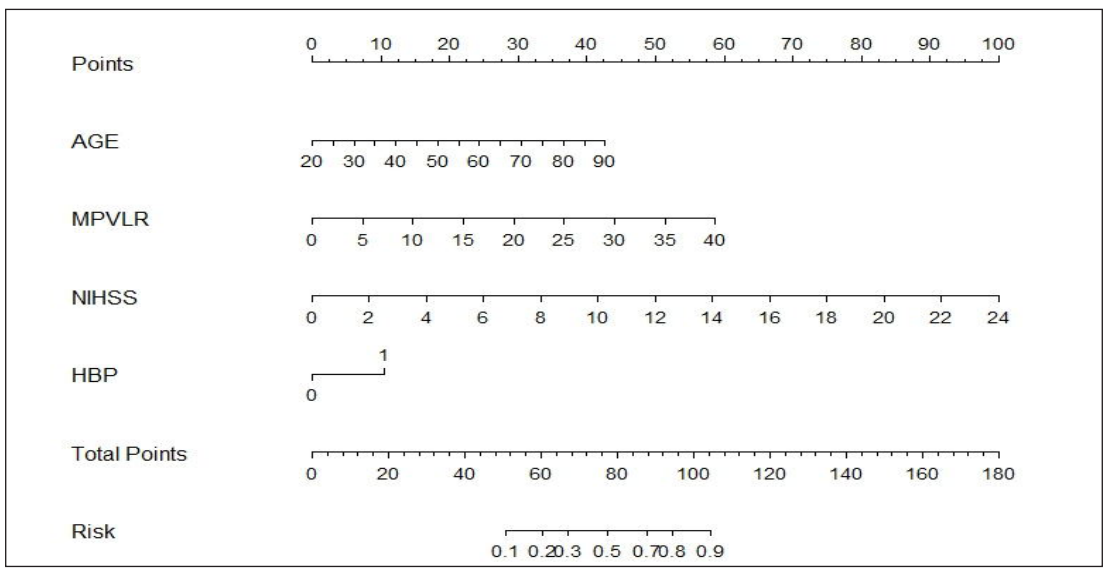

Figure 3. The nomogram used for predicting 3-month unfavourable outcome after an acute ischemic stroke. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total points axis to determine the risk of the poor outcome at the lower line of the nomogram.

that it is platelet size, rather than the count itself, that is associated with platelet function and activation.[19] Mean platelet volume is a marker of platelet size and reflect the activation and functions of platelet because large platelets contain more dense granules and produce more prothrombotic substance such as thromboxaneB2, serotonin.[20,21] Previous studies have shown that the levels of MPV is higher in patients with acute ischemic stroke than in control commons. Other studies have shown patients with high MPV is associated with an increase in morbidity and poor clinical outcome in patients with ischemic stroke.[8,22]

Inflammatory process exists in all stage of the acute ischemic stroke. The ischemic condition could release the proinflammatory cytokines and recruit the immune cells, which represent an important mechanism of secondary progression of brain lesion.[23] When ischemic stroke occurs, a large quantity of leukocytes infiltrate in peripheral blood in immediately.[24] Each subtype of leukocytes has a specific inflammatory function and may contribute differently to the process of ischemic stroke.[25] As a subtype of leukocyte, lymphocytes counts decreased after AIS and lower lymphocyte counts owing to poor functional outcome.[26] Subsets of lymphocyte, specific T cell lymphocytes, may have a regulatory function in inflammation inducing neuroprotection.[27] Our clinical evidence indicated that lower lymphocyte counts were associated with poor functional outcome in patients with acute ischemic stroke, which is in line with the results from Kim *et al*.[25]

In the event of acute ischemic stroke, platelets become active due to thrombosis, resulting in a increase in MPV[28], lymphocyte decrease due to inflammation.[29] Both of these lead to an increase in MPVLR. In a recent study, high level of MPVLR has been found to be a marker of poor short-term and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction.[30] Our study showed that having a high MPVLR values increased the 3-months poor prognosis, suggesting that increased platelet activity and inflammation may contribute to poor prognosis. We presume that MPVLR may reflect the degree of thrombosis and inflammation. The potential mechanisms may be that MPVLR activate platelets by releasing platelet activators from ischemic/necrotic tissue.[12] MPVLR is a combined indices and high MPVLR could reflect the burden of high-risk plaques and systemic inflammation in comparison with MPV or lymphocyte levels alone. As a ratio, MPVLR is more stable than individual blood parameters that can be altered by several variables such as over-hydration, dehydration, and blood specimen handling. However, further studies are needed to gain a better understanding of the specific mechanism of this phenomenon.

This study has several limitations. First, this study was carried out in a single center, the sample size is limited, which may lead to selection bias. Second, other platelet markers and inflammatory markers were not evaluated in the study. Finally, MPVLR level and follow-up data were not acquired in 62 patients included in this study.

In conclusion, to the best of our knowledge, this is the first study that has investigated the association between MPVLR and the 3-months prognosis. We assessed MPVLR at admission and at 7 days after stroke, and both were found to be independently associated with poor functional outcome. Monitoring of MPVLR is easy to achieve and may serve as an activity marker for unfavorable prognosis in patients with acute ischemic stroke.

DISCLOSURE

Conflict of interest: None

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