A new marker of short-term mortality and poor outcome in patients with acute ischemic stroke
Mean platelet volume-to-lymphocyte ratio

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Abstract

Background: The mean platelet volume-to-lymphocyte ratio (MPVLR), as a novel marker of thrombosis and inflammation, has been demonstrated to be closely linked to poor cardiovascular disease prognosis. However, the correlation between MPVLR and acute ischemic stroke (AIS) remains unclear. This study, therefore, aimed to clarify the relationship between MPVLR and the short-term prognosis of AIS.

Methods: A total of 315 patients with first-time AIS diagnoses were recruited and divided into 3 groups based on the tri-sectional quantiles for MPVLR on admission: group 1 (N = 105) with a MPVLR ≤ 4.93, group 2 (N = 105) with a MPVLR of 4.94 to 7.21, and group 3 (N = 105) with a MPVLR ≥ 7.22. All patients were followed-up for 3 months, and death within 3 months was defined as the endpoint. Baseline characteristics, stroke severity, and functional outcomes were evaluated.

Results: The Spearman’s correlation coefficient test showed that MPVLR was significantly positively correlated with the National Institutes of Health Stroke Scale score (R = 0.517, P < .001). Multivariate analysis revealed that MPVLR was an independent predictor of both short-term mortality (adjusted odds ratio [OR] 1.435, P < .001) and poor outcome (adjusted OR 1.589, P < .001). The receiver operating characteristic (ROC) curve analysis showed that the best cutoff value of MPVLR for short-term mortality and poor outcome were 6.69 (sensitivity: 86.4%, specificity: 68.6%) and 6.38 (sensitivity: 78.8%, specificity: 72.3%), respectively.

Conclusions: MPVLR on admission was positively associated with stroke severity. An elevated MPVLR is an independent predictor of short-term mortality and poor outcome after AIS.

Abbreviations: AIS = acute ischemic stroke, CI = confidence interval, MPV = mean platelet volume, MPVLR = mean platelet volume-to-lymphocyte ratio, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, ROC = receiver operating characteristic.

Keywords: acute ischemic stroke, lymphocyte count, mean platelet volume, mean platelet volume-to-lymphocyte ratio, platelet, prognosis

1. Introduction

Acute ischemic stroke (AIS), the most common type of stroke, remains a major cause of disability and mortality worldwide.[1] Despite a slight decline in the incidence rate in developed Western countries,[2] there is still a significant population of patients with new-onset cerebral infarction in developing countries each year, particularly in China.[1,4]

Platelets play a vital role in the formation of thrombi, as well as in the development and destabilization of atherosclerotic plaques.[1,6] Activated platelets can also produce rich reactive oxygen species in the cyclooxygenase-1 pathway to accelerate rupture in vulnerable plaques.[1] Mean platelet volume (MPV) is the most useful parameter reflecting platelet activity and function.[1] Elevated MPV has been shown to be associated with large infarct size and short-term unfavorable prognosis in AIS.[14-16] Inflammation plays an important role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury. Recently, some studies have reported that the lymphocyte count in patients with AIS was significantly lower than that in healthy people, which may be closely related to stroke-induced immunodepression syndrome.[11,12] Kim et al studied 779 patients with AIS and found that a decrease in lymphocytes had a negative effect on early neurologic recovery and functional outcome.[13] Mean platelet volume-to-lymphocyte ratio (MPVLR), a marker that is economical and readily available, has been linked to poor prognosis in patients with stable angina pectoris and myocardial infarction.[14-16] Increased MPV and decreased lymphocyte count are common manifestations of stroke; however,

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How to cite this article: Wu F, Wang Q, Qiao Y, Yu Q, Wang F. A new marker of short-term mortality and poor outcome in patients with acute ischemic stroke: Mean platelet volume-to-lymphocyte ratio. Medicine 2022;101:40(e30911). Received: 7 July 2022 / Received in final form: 31 August 2022 / Accepted: 1 September 2022
http://dx.doi.org/10.1097/MD.0000000000030911
few studies have been conducted to investigate the role of MPVLR in AIS. Thus, this study was performed to investigate whether MPVLR could be associated with short-term prognosis after AIS.

2. Methods

2.1. Study population

We included 315 consecutive patients with a first episode of AIS who were admitted to the Stroke Unit between August 2020 and December 2021. The diagnostic criteria for AIS were based on medical history, symptoms and signs, and computed tomography/magnetic resonance imaging findings. Patients were excluded if they: were younger than 18 years of age or older than 80 years of age; were admitted to the hospital >24 hours from symptom onset; had an infection within 2 weeks prior to the stroke; were diagnosed with tumor, autoimmune disease, hypersplenism, or severe liver and kidney dysfunction; had a history of stroke or brain trauma; took immunosuppressive drugs such as steroids. The Ethics Committee of Central China Cardiovascular Hospital of Fu-wai approved this study. All participants or their relatives signed informed consent forms.

2.2. Data collection

Eligible patients' baseline clinical data including demographic characteristics (age, sex), risk factors (history of hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, smoking, alcohol consumption), stroke etiologic subtypes, and treatments (anti-coagulation agents, antiplatelet agents, statins) were collected. The etiologies of AIS were classified based on the Trial of Org 10172 in Acute Stroke Treatment rating system.[17] All patients were subjected to routine blood tests within 6 hours of admission. The complete blood counts were measured using a Unicel DxH800 (Beckman Coulter, Brea, CA); lipid profiles, which were measured using a Cobas E702 automatic biochemical analyzer (Roche, Basel Switzerland), were also collected. MPVLR was calculated as the ratio of MPVLR (10^9/mm^3).

2.3. Stroke severity and short-term outcomes

Stroke severity on admission was assessed by certified neurologists according to the National Institutes of Health Stroke Scale (NIHSS) score. According to the NIHSS score, patients were divided into those with mild stroke (NIHSS ≤ 8), moderate stroke (NIHSS 9-15) and severe stroke (NIHSS ≥ 16).[18] All patients attended clinical follow-up for 3 months. Functional outcome at 3 months was evaluated according to the modified Rankin Scale (mRS) and the results were categorized into good outcomes (mRS 0-2) and poor outcomes (mRS 3-6). Poor outcomes included major disabilities (mRS 3-5) and death (mRS 6).[19] Prognosis information was obtained during follow-up via telephone or in person interview. The endpoint of this clinical study was death within the follow-up period.

2.4. Statistical analyses

All statistical analyses were performed using SPSS 20.0 (IBM Corp, Armonk, NY) and GraphPad Prism 5.0 (GraphPad, San Diego, CA). P values <.05 were considered statistically significant. The Kolmogorov–Smirnov test was used to identify normally distributed data before the analysis. For continuous variables, the data are presented as means ± standard deviation. For categorical data, they were presented as frequencies (percentages). A one-way analysis of variance model was used to compare the normally distributed data for the 3 groups and the Mann–Whitney U test was used to compare the skewed data. Categorical data were compared using the chi-squared or Kruskal-Wallis tests. Correlations between the MPVLR and NIHSS score were evaluated using Spearman’s correlation coefficient test.

The overall survival curve was analyzed using the Kaplan-Meier method and the log-rank test was used to compare the differences in survival among the 3 groups. Moreover, comparisons for differences for every 2 groups were performed using log-rank tests combined with Bonferroni corrections. Logistic regression was used to assess the effects of the different variables on clinical outcomes. Any significant variables for which the P value <.10 in the univariate analysis were further incorporated into the multivariate models to investigate potential independent predictors.

Receiver operating characteristic (ROC) curve analyses were performed to investigate the prognostic value of MPVLR with respect to short-term mortality and poor outcomes. The best cutoff value and the corresponding sensitivities and specificities were estimated according to the Youden index.

3. Results

3.1. Study population characteristics

A total of 332 patients with AIS who fulfilled the inclusion criteria were screened. Among them, 17 patients were lost to follow-up. Ultimately, 315 patients were enrolled in this study.

The baseline and clinical characteristics of the 315 patients are summarized in Table 1. The mean age of the patients was 59.21 ± 11.11 years and 209 patients (66.3%) were male. According to the tri-sectional quantile MPVLR values on admission, the study population was divided into 3 groups: group 1 (N = 105) with MPVLR ≤ 4.93, group 2 (N = 105) with MPVLR 4.94-7.21, and group 3 (N = 105) with MPVLR ≥ 7.22. The age of group 3 was higher and the hemoglobin concentration was lower than the other 2 groups (P <.05). Patients from group 3 had significantly higher MPVs and MPVLRs, with lower lymphocyte counts compared to the other groups (P <.001). No significant differences were found among the groups in terms of sex, smoking status, alcohol consumption, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, stroke subtypes, medications (anti-coagulation agent, antiplatelet agent, and statin), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, white blood cell count, neutrophil count, or platelet count.

3.2. Stroke severity in 3 groups

As shown in Table 2, the patients in group 3 had more moderate and severe strokes compared to the other groups (P <.001). Figure 1 shows that MPVLR positively correlated with stroke severity, as revealed by the Spearman’s correlation coefficient test (R = 0.517; P <.001).

3.3. Short-term clinical outcome in 3 groups

During the 3-month follow-up period, 44 (14%) patients died and 113 (35.9%) patients suffered poor outcomes (Table 3). The mortality rate was 1.9% in group 1, 10.5% in group 2, and 29.5% in group 3 (P <.001). The poor outcome rate was 15.2% in group 1, 28.6% in group 2, and 63.8% in group 3 (P <.001) (Fig. 2). The patients with high MPVLRs had a higher frequency of mortality and poor outcomes.

The Kaplan–Meier overall survival curves are shown in Figure 3. The log-rank analysis showed a significant difference in survival among the 3 groups (P <.001). We used the log-rank tests combined with Bonferroni corrections to explore the differences between 2 groups (P <.017 was defined as statistically significant). We found that the log-rank value for groups 1 and 2 was 6.512 (P = .011), the log-rank value for groups 1 and 3...
was 29.760 ($P<.001$), and the log-rank value for groups 2 and 3 was 11.463 ($P=.001$). Shorter 3-month overall survival was more prevalent in the high MPVLR groups.

### 3.4. Short-term mortality and poor outcome prediction evaluation

The variables with $P<.05$ from the comparison of baseline characteristics and selected variables (hypertension, atrial fibrillation, triglyceride, WBC, platelet count) were included in the regression analysis for short-term mortality and poor outcome, respectively. As shown in Table 4, MPVLR, age, and monocyte count were associated with short-term mortality ($P<.1$) in the initial univariable logistic regression analysis. After adjusting for potential confounders, MPVLR (adjusted odds ratio [OR]: 1.435, 95% confidence interval [CI]: 1.280-1.609, $P<.001$) and age (adjusted OR: 1.047, 95% CI: 1.006-1.090, $P=.025$) were independent prognostic variables for 3-month mortality. Table 5 shows that MPVLR, hemoglobin, platelet count, and monocyte count were associated with poor 3-month outcomes ($P<.1$) in the univariable logistic regression analysis. After adjusting for potential confounders, MPVLR remained an independent predictor of poor 3-month outcome (adjusted OR: 1.589, 95% CI: 1.393-1.811, $P<.001$).

In Figure 4, the ROC curve shows that the best MPVLR cutoff value was 6.69 as a predictor of 3-month mortality, with a sensitivity of 86.4% and specificity of 68.6% and an area under the curve of 0.834 (95% CI: 0.777-0.898). Similarly, in

### Table 1

Baseline characteristics.

|                          | Total                      | Group 1                  | Group 2                  | Group 3                  |
|--------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
| Age (yr)                 | 59.21 ± 11.11              | 56.87 ± 12.06            | 59.72 ± 10.65            | 61.04 ± 10.23            |
| Males                    | 209(66.3)                  | 71(67.6)                 | 66(62.9)                 | 72(68.6)                 |
| Smoking                  | 89(28.3)                   | 24(22.9)                 | 20(27.6)                 | 35(34.3)                 |
| Alcohol consumption      | 59(18.7)                   | 19(18.1)                 | 19(18.1)                 | 21(20.0)                 |
| Hypertension             | 182(57.8)                  | 52(49.5)                 | 63(60.0)                 | 67(63.8)                 |
| Diabetes mellitus        | 92(29.2)                   | 30(28.6)                 | 31(29.5)                 | 31(29.5)                 |
| Atrial fibrillation      | 33(10.5)                   | 5(4.8)                   | 13(12.4)                 | 15(14.3)                 |
| Coronary artery disease  | 61(19.4)                   | 17(16.2)                 | 19(18.1)                 | 25(23.8)                 |
| Stroke etiology          |                            |                          |                          |                          |
| Large-vessel occlusive   | 70(66.7)                   | 64(61.0)                 | 73(69.5)                 |                          |
| Small-vessel occlusive   | 16(15.2)                   | 21(20.0)                 | 17(16.2)                 |                          |
| Cardioembolic            | 13(12.4)                   | 8(7.6)                   | 11(10.5)                 |                          |
| Other                    | 2(1.9)                     | 5(4.7)                   | 1(0.9)                   |                          |
| Unknown                  | 4(3.8)                     | 7(6.7)                   | 3(2.9)                   |                          |
| Laboratory tests         |                            |                          |                          |                          |
| TC(mmol/L)               | 4.17 ± 1.07                | 4.09 ± 1.07              | 4.23 ± 0.89              | 4.21 ± 1.22              |
| TG(mmol/L)               | 1.43 ± 0.93                | 1.37 ± 1.09              | 1.58 ± 0.74              | 1.34 ± 0.91              |
| HDL(mmol/L)              | 1.11 ± 0.34                | 1.07 ± 0.34              | 1.12 ± 0.29              | 1.13 ± 0.38              |
| LDL(mmol/L)              | 2.60 ± 0.92                | 2.52 ± 0.94              | 2.68 ± 0.77              | 2.61 ± 1.03              |
| HB (g/L)                 | 136.48 ± 16.72             | 139.58 ± 14.80           | 136.28 ± 18.22           | 133.57 ± 16.58           |
| WBC(10^9/L)              | 7.71 ± 2.66                | 8.16 ± 2.23              | 7.60 ± 1.64              | 7.37 ± 3.67              |
| Neutrophils(10^9/L)      | 5.39 ± 2.60                | 5.05 ± 2.04              | 5.30 ± 1.55              | 5.84 ± 3.67              |
| Lymphocytes(10^9/L)      | 1.63 ± 0.63                | 2.31 ± 0.44              | 1.56 ± 0.21              | 1.00 ± 0.27              |
| Monocytes(10^9/L)        | 0.48 ± 0.19                | 0.53 ± 0.18              | 0.49 ± 0.16              | 0.42 ± 0.20              |
| Platelet count (10^12/L) | 206.04 ± 51.89             | 207.30 ± 52.94           | 213.64 ± 49.83           | 197.28 ± 52.05           |
| MPV(FL)                  | 9.15 ± 1.22                | 8.46 ± 0.99              | 9.26 ± 0.94              | 9.73 ± 1.35              |
| MPVLR (10^3/mm³)         | 6.03 (4.36, 7.76)          | 3.68 (3.24, 4.38)        | 6.03 (5.28, 6.54)        | 8.81 (7.68, 12.30)       |
| Treatment                |                            |                          |                          |                          |
| Antiplatelet agent       | 283 (89.8)                 | 97 (92.4)                | 91 (86.7)                | 95 (90.5)                |
| Anticoagulation agent    | 37 (11.7)                  | 9 (8.6)                  | 13 (12.4)                | 15 (14.3)                |
| Statin                   | 20 (6.3)                   | 4 (3.8)                  | 6 (4.8)                  | 11 (10.5)                |

HB = hemoglobin, HDL = high density lipoprotein, LDL = low density lipoprotein, MPV = mean platelet volume, MPVLR = mean platelet volume-to-lymphocyte ratio, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count.

### Table 2

Comparison of stroke severity among the 3 groups based on the mean platelet volume-to-lymphocyte ratio.

|                          | Total                      | Group 1                  | Group 2                  | Group 3                  |
|--------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
| NIHSS category           |                            |                          |                          |                          |
| Mild (<8)                | 182 (57.8)                 | 76 (72.4)                | 64 (61.0)                | 42 (40.0)                |
| Moderate (9-15)          | 77 (24.4)                  | 21 (20.0)                | 24 (22.9)                | 32 (30.5)                |
| Severe (≥16)            | 56 (17.8)                  | 8 (7.6)                  | 17 (16.1)                | 31 (29.5)                |

NIHSS = National institutes of health stroke scale.
Figure 5, the ROC curve shows that the optimal MPVLR cutoff value for 3-month poor outcome was 6.38, with a sensitivity of 78.8%, specificity of 72.3%, and area under the curve of 0.800 (95% CI: 0.748-0.852).

4. Discussion

Our study showed that MPVLR positively correlated with stroke severity. MPVLR on admission was an independent predictor of both short-term mortality and poor clinical outcome in patients after AIS.

MPVLR, as a novel composite indicator of thrombosis and inflammation, has received intense interest.\[14–16\] Several reports demonstrated that MPVLR was closely related to cardiovascular disease prognosis. Ornek et al reported that MPVLR could predict the development of coronary collateral circulations in patients with stable coronary artery disease.\[14\] Kurtul et al found, in an analysis of 1206 patients, that MPVLR was a strong independent predictor of angiographic “no-reflow” and short-term mortality in patients with ST-segment elevation myocardial infarction.\[15\] MPVLR is reported to have potential diagnostic value in patients with deep vein thrombosis.\[16\]

Stroke is the second leading cause of mortality and represents the third major cause of long-term disability worldwide.\[20,21\] Ischemic strokes account for nearly 87% of all strokes and contribute to the development of severe brain dysfunction.\[22\] Stroke prevention requires management of the major risk factors, including hypertension, hyperlipidemia, diabetes mellitus, and tobacco use, as well as antithrombotic therapy.\[23,24\] Despite sustained efforts to improve treatment methods for patients after AIS, the incidence of disability and death continues to rise in China.\[4\] Thus, it is critical to have an in-depth understanding of

| Mean platelet volume-to-lymphocyte ratio | Total | Group 1 (≤4.93, n = 105) | Group 2 (4.94-7.21, n = 105) | Group 3 (≥7.22, n = 105) | P |
|-----------------------------------------|-------|--------------------------|-----------------------------|--------------------------|---|
| Poor outcome (mRS 3-6)                  | 113 (35.9) | 16 (15.2) | 30 (28.6) | 67 (63.8) | <.001 |
| Death (mRS 6)                           | 44 (14.0) | 2 (1.9) | 11 (10.5) | 31 (29.5) | <.001 |

mRS = modified rankin scale.

Figure 2. Comparison of death and poor outcomes among the 3 groups based on MPVLR. MPVLR = mean platelet volume-to-lymphocyte ratio.
the pathogenic mechanisms of stroke and identify an effective prognostic indicator.

In most cases, stroke results from the rupture of atherosclerotic plaques and thrombus formation. Platelets not only play a critical role in arterial thrombosis, but also have important functions in promoting atherogenesis and plaque vulnerability. MPV is a biological index that describes the average size of circulating platelets in the peripheral blood. Compared to the platelet count, MPV might better reflect platelet activity and function. Large platelets, which contain more granules and high-density granules, are more active and more liable to form thrombi than those with smaller volumes. Peng et al reported that an elevated MPV was an independent predictor of poor outcomes in patients with acute anterior circulation stroke after mechanical thrombectomy. Finally, it has been reported that high MPV levels upon admission may be a predictor of post-stroke depression. We also observed that large platelets were produced before stroke onset. The size of platelets does not change once they are produced and released into the circulatory system, thus elevations of MPV may be the cause of the stroke rather than the result.

Inflammation participates in the brain damage produced by ischemia, and the damaged brain, in turn, exerts an immunosuppressive effect promotes fatal infection after stroke. Lymphocytes are a major type of leukocyte that participate in the development of innate and adaptive immune responses following acute stroke. Previous studies have suggested that immunologic reactions were associated with protection from, and delay of, ischemic brain insults. Although helper T-cells, cytotoxic T-cells, and B-cells function differently in cerebral ischemia, reduced lymphocyte counts as a whole have a negative effect on early neurologic recovery and 3-month clinical outcomes. Recently, stroke-induced immune-depression syndrome has been intensely studied. Growing evidence has shown that injured brain tissues induce rapid and long-lasting suppression of cell-mediated immunity responses after the onset of stroke. The precise pathophysiology of stroke-induced immune-depression syndrome remains unclear. Some studies have reported that locally injured brain tissue could release a large amount of TNF-α, IL-6, IL-1β, and other

**Table 4**

| Variables       | Univariate analysis     | Multivariate analysis |
|-----------------|-------------------------|-----------------------|
|                 | Unadjusted OR (95% CI)  | P         | Adjusted OR (95% CI) | P     |
| Age             | 1.035 (1.003-1.067)     | .032*     | 1.047 (1.006-1.090)  | .025  |
| Hypertension    | 1.189 (0.619-2.283)     | .610      |                       |       |
| Atrial fibrillation | 1.783 (0.722-4.400)   | .210      |                       |       |
| MPVLR           | 1.447 (1.300-1.611)     | <.001*    | 1.435 (1.280-1.609)  | <.001 |
| TG              | 0.729 (0.469-1.132)     | .159      |                       |       |
| HB              | 0.994 (0.976-1.013)     | .562      |                       |       |
| Platelet count  | 0.998 (0.992-1.004)     | .531      |                       |       |
| WBC             | 1.065 (0.957-1.184)     | .247      |                       |       |
| Monocyte        | 0.007 (0.001-0.078)     | <.001*    | 0.141 (0.012-1.624)  | .116  |

*P<0.10; candidate variables were further incorporated into the multivariate logistic regression model.

CI = confidence interval, HB = hemoglobin, MPVLR = mean platelet volume-to-lymphocyte ratio, OR = odds ratio, TG = triglyceride, WBC = white blood cell.

**Table 5**

| Variables       | Univariate analysis     | Multivariate analysis |
|-----------------|-------------------------|-----------------------|
|                 | Unadjusted OR (95% CI)  | P         | Adjusted OR (95% CI) | P     |
| Age             | 1.017 (0.996-1.039)     | .120      |                       |       |
| Hypertension    | 1.041 (0.653-1.660)     | .866      |                       |       |
| Atrial fibrillation | 1.565 (0.756-3.239)   | .228      |                       |       |
| MPVLR           | 1.615 (1.419-1.837)     | <.001*    | 1.589 (1.393-1.811)  | <.001 |
| TG              | 0.838 (0.638-1.101)     | .204      |                       |       |
| HB              | 0.983 (0.969-0.997)     | .017      | 0.989 (0.972-1.006)  | .208  |
| Platelet count  | 0.996 (0.991-1.001)     | .082*     | 0.997 (0.992-1.003)  | .355  |
| WBC             | 0.967 (0.884-1.058)     | .469      |                       |       |
| Monocyte        | 0.138 (0.034-0.563)     | .006*     | 1.144 (0.241-5.428)  | .866  |

*P<0.10; candidate variables were further incorporated into the multivariate logistic regression model.

CI = confidence interval, HB = hemoglobin, MPVLR = mean platelet volume-to-lymphocyte ratio, OR = odds ratio, TG = triglyceride, WBC = white blood cell count.
inflammatory cytokines, which stimulate the hypothalamic-pituitary-adrenal axis. The activation of the axis produces increased levels of cortisol, which results in apoptosis and functional deactivation of peripheral lymphocytes.\cite{16,21} Urra et al. suggested that lymphopenia or increased lymphocyte apoptosis is an early sign in patients with stroke.\cite{16,21} Animal experiments have supported the concept that focal cerebral ischemia gives rise to apoptosis of lymphocytes and atrophy of the spleen and thymus.\cite{16,21} Moreover, a study conducted by Hug et al. showed that changes in immune function could be associated with poorer clinical outcomes and higher mortality.

Several limitations of this study need to be acknowledged. First, this was a single-center analysis. Second, the sample size was relatively small; thus, there may be some level of bias in patient selection. Third, the MPVLR was measured only once, at the time of admission. We lacked dynamic variation data with respect to potential changes in MPVLR with time. Further multicenter, large-scale studies are required to better elucidate the predictive role of MPVLR in stroke prognosis.

5. Conclusion
According to our results, a higher MPVLR at the time of admission is an independent prognostic factor for short-term mortality and poor short-term outcome following AIS. MPVLR is a novel index that simultaneously reflects both thrombosis and inflammation and may be of high prognostic value in patients after AIS.

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