

The relationship between mean platelet volume and severity of acute ischemic brain stroke

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ABSTRACT

الأهداف: تحديد فيما إن كان هنالك علاقة بين معدل كثافة الصفائح وشدة الجلطة الإقفارية الحادة ودراسة قوة معدل كثافة الصفائح للتفرقة بين الجلطة الإقفارية الحادة والبسيطة.

الطريقة: قمنا بتقسيم 100 مريض مصاب بجلطة مقارنة في قسم العلوم العصبية بمستشفى فاطمة، سمنان، إيران خلال الفترة من يناير 2010م حتى يناير 2011م. تم تقسيم المجموعتين على أساس درجات رانكلين (المجموعة الأولى درجة (0-2)، المجموعة الثانية 3 وأكثر). تم تحليل عينات الدم لقياس معدل كثافة الصفائح وقياس شدة الجلطة الإقفارية باستخدام مقياس رانكلين المحدث.

النتائج: أظهرت الدراسة أن قيمة معدل كثافة الصفائح أعلى بشكل إحصائي في المجموعة الثانية من المجموعة الأولى (9.36±0.95) مقابل (8.55±0.65) $p<0.001$. كما كان متوسط الصفائح أقل بشكل إحصائي في المجموعة الثانية (238.8±89.2) مقابل (283.7±59.2) $p=0.020$. بعد السيطرة على المخاطر اللازمة للجلطة الإقفارية في نموذج الإنحدار اللوجستي المتعدد، أستمثر أثر المعدل الإحصائي لمعدل كثافة الصفائح ($p=0.012$). أشارت المنطقة أسفل منحنى ROC والتي كانت قيمتها 0.77 إلى أثر مختلف لمعدل كثافة الصفائح لتشخيص الجلطة الإقفارية الحادة وذلك بالإعتماد على درجات رانكلين أعلى من أو تساوي 3 للجلطة المتوسطة.

خاتمة: أن معدل كثافة الصفائح مصاحب لشدة الجلطة الإقفارية وله أثر قوي في التفرقة بين الجلطة الإقفارية الحادة والمتوسطة.

Objective: To determine whether an association exists between mean platelet volume (MPV) and severity of acute ischemic stroke. Also, to investigate the power of MPV for discriminating more severe ischemic stroke from mild events.

Methods: We divided 100 patients with first ischemic stroke presenting to the Neurology Department, Fatemeh Hospital, Semnan, Iran between January 2010 and January 2011 into 2 groups based on Rankin score (group 1: score 0-2, and group 2: score 3 or more). Blood samples were taken to measure MPV. Severity of ischemic stroke was assessed by the Modified Rankin scale.

Results: The MPV value was higher and more significant in group 2 than group 1 (9.36±0.95 versus 8.55±0.65, $p<0.001$). Also, the mean platelet count was significantly lower in group 2 (238.8±89.2 versus 283.7±59.2, $p=0.020$). After controlling for the risk profile associated with ischemic stroke in the multivariate logistic regression model, the effect of MPV in ischemic stroke remained statistically significant ($p=0.012$). The area under the ROC curve was 0.77, indicating the high discriminative value of MPV for predicting severe ischemic stroke based on Rankin score ≥ 3 from mild stroke.

Conclusion: The MPV is associated with ischemic stroke severity and has a high value for discriminating severe from mild ischemic stroke.

Neurosciences 2013; Vol. 18 (2): 147-151

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Received 31st July 2012. Accepted 6th January 2013.

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Platelets play a major role in maintaining vessel integrity through hemostasis. The hemostatic efficiency of these circulating cells is directly dependent

on some vasoactive factors and prothrombotic agents including thromboxane A₂, and serotonin secreted from platelet granules.¹ It is clear that the larger platelets contain more granules and therefore produce and secrete greater amounts of these stimulators. In fact, platelet volume is associated with shorter bleeding time, and the mean platelet volume (MPV) has been considered as a determinant for the level of platelet activity.² An increase of MPV has been confirmed after acute ischemic heart diseases. The MPV is directly associated with the risk of acute myocardial infarction, and subsequent life-threatening events.^{3,4} Some authors reported an association between MPV measurement and ischemic ECG changes.^{5,6} The MPV and MPV/platelet is also used for assessing the prognosis of coronary diseases and different cardiac interventions.⁷⁻⁹ However, the relationships between MPV with cerebrovascular accidents and their prognosis have already been questioned. Some studies detected an increased MPV in different subtypes of brain stroke, both in the acute phase and long after disease occurrence.¹⁰⁻¹² An increased MPV could also predict the risk of a second stroke event in those with a history of cerebrovascular events.¹³ The role of elevated MPV for predicting poor outcome of brain stroke was reported as independent to other clinical parameters such as lipid profile and other biochemical parameters.¹⁴ These findings lead to the hypothesis that the increase of MPV might have a critical role for genesis or worsening of brain stroke. Therefore, we aimed to determine whether an association exists between MPV and severity of ischemic brain stroke. Also, to determine the power of MPV measurement for discriminating more severe brain stroke from mild stroke events.

Methods. One hundred consecutive patients with first-ever ischemic stroke presenting to the Neurology Department of Fatemeh Hospital in Semnan, Iran between January 2010 and January 2011 were included in this cross-sectional study. The diagnosis of ischemic stroke was made according to the evidence of acute infarction determined by cranial CT or MRI within the first 24 hours of the disease appearance. Those with transient symptoms of cerebrovascular diseases, peripheral vascular disease, acute infection, positive C-reactive protein or inflammatory conditions, prior stroke, pregnancy, acute myocardial infarction, malignancies, cranial traumas, intracranial hemorrhage or hematomas, or arteriovenous malformation were excluded. Those who were administered medications including anti-lipids, angiotensin-converting enzyme inhibitors, and anticoagulants were also excluded. All

participants gave informed consent to participate in the study, and we obtained ethical approval from the ethical committee of Semnan University of Medical Sciences.

All baseline data were collected from the hospital files or by face-to-face interview if required. The data included demographics, vascular risk profile, medical history especially previous history of ischemic heart disease or cerebrovascular accidents, biochemical parameters, medications, echocardiographic data, and neuroimaging studies. After overnight fasting, blood samples were taken in the supine position for MPV measurement within the first 24 hours of hospitalization. The samples were collected into EDTA tubes (Terumo Italia SRL, Rome, Italy) and transported at 4°C for analysis at a single laboratory in the hospital and analyzed using an EDTA3K kit and by a Sysmex SE 9000 analyzer (Roche Diagnostics, Munich, Germany).

Severity of ischemic stroke was assessed by Modified Rankin scale that scores patients on a scale from 0 to 6, with 0 being asymptomatic and 6 being dead. Scores of 0-2 are considered "good" stroke outcomes; in that these patients are able to lead fairly independent lives and are able to return to work in almost all cases. Scores of 3 or greater indicate that the patient will need considerable help with their daily activities. On the 7th day following stroke, the patients were divided into 2 groups based on the Modified Rankin scale: group 1 included patients with Rankin scale 0-2, and group 2 patients with Rankin scale 3 and more.¹⁵

The results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups with the different ischemic stroke severity scores were compared using the Student's t-test for the continuous variables and the chi-square test for the categorical variables. Predictors exhibiting a statistically significant relation with more severe ischemic stroke (Rankin score ≥ 3) were taken for multivariate logistic regression analysis to investigate their independence as predictors. The area under the receiver operating characteristic (ROC) curve was used to evaluate the performance of MPV for discriminating severe ischemic stroke from a mild event. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Statistical significance was determined at $p < 0.05$. All statistical tests and analysis including chi-square, t-test, and logistic regressions were performed using the Statistical Package for Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA).

Results. A total of 100 patients with first-ever ischemic stroke with a mean age of 69.3±12.2 years,

and age range between 40-89 years old (52 males and 48 females) were included to the study. Among those, 85 participants were categorized as poor stroke outcome (Rankin score ≥ 3) and others had lower outcome score. Demographic characteristics and baseline factors of the 2 groups are presented in Table 1. There were no significant differences according to gender distribution ($p=0.501$). But, those with higher Rankin scale were older and had more prevalence of previous ischemic heart disease.

The mean (\pm SD) MPV was 9.36 ± 0.95 in the group with Rankin score ≥ 3 , and 8.55 ± 0.65 in the subjects

Table 1 - Baseline characteristics and clinical data according to the severity of CVA.

Characteristics	CVA score 0-2 (n=15)	CVA score ≥ 3 (n=85)	P-value
Male gender, n (%)	9 (60.0)	43 (50.6)	0.501
Age (years +/-SD)	61.9 \pm 11.6	70.6 \pm 11.9	0.015
History of ischemic heart disease, n (%)	2 (13.3)	41 (48.2)	0.012
Platelet count (x 10 ³ /ul)	283.7 \pm 59.2	238.8 \pm 89.2	0.020

CVA - cerebrovascular accident, SD - standard deviation

Table 2 - Relationship between MPV and CVA severity.

MPV	CVA score 0-2 (n=15)	CVA score ≥ 3 (n=85)
	n (%)	
≤ 8 fL	2 (13.3)	2 (2.4)
8.1-9.0 fL	11 (73.3)	36 (42.4)
9.1-10.0 fL	1 (6.7)	29 (34.1)
10.1-11.0 fL	1 (6.7)	15 (3.5)
>11.0 fL	0 (0.0)	3 (3.5)

CVA - cerebrovascular accident, MPV - mean platelet volume

Table 3 - Multivariate logistic regression analysis for determining the role of MPV in predicting CVA severity.

Characteristics	Regression coefficients (β)	SE (β)	Odds Ratio	95% CI	P-value
Age (year)	0.047	0.025	1.05	0.998-1.101	0.058
MPV	1.43	0.530	4.18	1.48-11.80	0.007
Constant coefficient	-14.10	4.84	--	--	0.004

CVA - cerebrovascular accident, MPV - mean platelet volume, SE - standard error, CI - confidence interval, Hosmer-Lemeshow test of goodness of fit ($p=0.218$)

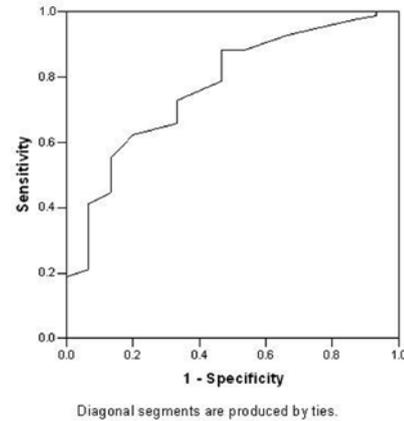


Figure 1 - Specificity and sensitivity of mean platelet volume in predicting ischemic stroke severity. Area under the curve: 0.77, standard error: 0.064.

with lower scores, which was statistically different ($p=0.002$). The distribution of MPV is presented in Table 2.

After controlling risk profiles associated with ischemic stroke in the multivariate logistic regression model (Table 3), the effect of MPV in ischemic stroke remained statistically significant (OR: 4.58, 95% CI: 1.38-15.13, $p=0.012$). The area under the ROC curve was 0.77 (95% CI: 0.65-0.90, $p=0.001$), indicating the high discriminative value of MPV for predicting severe ischemic stroke based on Rankin score ≥ 3 from a mild stroke event (Figure 1).

Discussion. The MPV can be used for assessing changes in the level of platelet stimulation and rate of its function, and is very useful in various clinical conditions. In vascular disorders, severity and extension of disease are associated with stimulated platelet production, and therefore MPV has broader clinical applications in detecting and monitoring these disorders.¹⁶ High MPV has been shown to be associated with more platelet

reactivity and aggregation and therefore, can be an important factor in hemostasis.¹⁷ Some studies that have measured platelet volume in acute ischemic stroke have shown inconsistent results.¹⁸⁻²⁰ However, some other studies could not confirm this predictive role for MPV, this might be due to the number of enrolled patients and to the utilization of different outcomes.^{18,21} Also, an increase in platelet aggregation in the acute phase is already conflicting. The current study assessed the role of MPV for predicting severer and extensive acute ischemic brain stroke from its mild status. We showed that measuring MPV within the first 24 hours of brain stroke appearance was strongly related to the severity of disease, and could effectively discriminate a severer situation from a milder degree of the disorder. In this study, increased MPV was associated with a poorer outcome in patients suffering an acute ischemic cerebrovascular event. Patients within the higher MPV range had more than 4-fold risk of suffering a severe stroke compared with patients within the lower range of MPV. The association of high MPV with severe stroke remained significant after adjustment for confounding factors. Similarly, Pikiija et al²² indicated that higher MPV was independently associated with larger infarct size, and higher risk of early and mid-term death after stroke. Furthermore, in a study by Mayda-Domaç,¹⁰ MPV was observed as independent risk factor for ischemic stroke and correlated with poorer outcome. In fact, according to these results, an increase in MPV is a feature of both the acute and non-acute phases of cerebral ischemia.

There are some possible explanations for MPV fluctuations during the acute phase of ischemic stroke. According to the results of the West Birmingham Stroke Project,²³ the pathophysiology of ischemic stroke potentially involves the platelet and its morphology. In fact, patients presenting with an acute ischemic stroke have activated platelets, as evident by the increased levels of soluble and platelet P-selectin. Also, platelet size is determined at the level of the progenitor cell (namely, the megakaryocyte), and some studies reported that cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets.²⁴ It is, therefore, reasonable to speculate that a proinflammatory state before the cerebrovascular event may confer a higher MPV and a prothrombotic condition. In addition, it has been suggested that patients with large platelets are more susceptible to some risk factors such as diabetes,²⁵ and obesity,²⁶ and therefore have an increased risk of ischemic stroke.

This study has some limitations that should be taken into account in assessing the results. We measured MPV only at admission, and did not perform further serial measurements during the evolution of stroke. Secondly, MPV was measured in stroke patients, but not against a control group; we cannot estimate whether these values are different from healthy subjects and confirm that MPV increases in acute ischemic stroke. Today, by using the new blood cell counters we can become easily informed of platelet indices. Therefore, according to our results, we recommended further studies to investigate the role of this index as a predictive factor in the severity of ischemic stroke.

In conclusion, MPV and platelet count are associated with stroke severity and have a high predictive value for discriminating severe from mild ischemic stroke. Thus, we can use the MPV and platelet count as a prognostic marker in acute ischemic stroke.

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ETHICAL CONSENT

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed. Research papers not involving human or animal studies should also include a statement that approval/no objection for the study protocol was obtained from the institutional review board, or research ethics committee.