Mean platelet volume as a risk stratification tool in the Emergency Department for evaluating patients with ischaemic stroke and TIA

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Abstract
Objective: To investigate the variations of mean platelet volume in patients with ischaemic cerebrovascular complaints, and to find out its diagnostic utility in an acute setting to help risk stratification in patients with ischaemic stroke and transient ischaemic attacks.
Methods: The prospective cross-sectional study was conducted at the Gazi University Hospital, Ankara, Turkey, from November 2009 to June 2010. It comprised 143 consecutive patients of acute ischaemic stroke, 39 patients of transient ischaemic attacks and 60 healthy volunteers. SPSS 13 was used for statistical analysis, and so were t-test, one-way analysis of variance test and correlation analysis. Statistical significance was accepted at $p < 0.05$.
Results: Mean platelet volume results were significantly higher in patients with cortical infarction and transient ischaemic attack compared to the control group ($p < 0.001$ and $p < 0.002$). A statistically significant increase was also noted in hospitalised patients when compared with discharged patients from the emergency department ($p < 0.036$). A weak positive correlation was identified between the National Institute of Health Stroke Scores and mean platelet volume levels ($r=0.207$; $p < 0.001$). A significant relationship was identified between mean platelet volume levels and previous stroke ($p < 0.005$).
Conclusion: The measurement of mean platelet volume levels may provide useful diagnostic and prognostic information to emergency physicians caring for patients with transient ischaemic attack and ischaemic stroke. In patients with suspected neurological ischaemic symptoms, high levels may be considered as an atherosclerotic risk factor.
Keywords: Blood platelets, Stroke, Transient ischaemic attack, Emergency department. (JPMA 63: 581; 2013).

Introduction

Platelets play an important role in the pathogenesis of ischaemic events. Large platelets are more reactive, produce more prothrombotic factors, and show greater aggregation to adenosine diphosphate (ADP), collagen or adrenaline and secrete more thromboxane A2 (TxA2).[1,2] Increased platelet size has been reported in patients with vascular risk factors such as diabetes mellitus (DM), hypercholesterolaemia, myocardial infarction, ischaemic stroke and smoking.[3]
Moreover, an elevated mean platelet volume (MPV) is associated with a poor outcome among survivors of myocardial infarction and stroke.[4] MPV remained elevated for 3 months in a study in the post-stroke period and this was limited to patients with cortical infarction.[2]
Cortical events are usually related to atherosclerotic events that occur in the heart, aorta, carotid arteries or large intracranial arteries; all conditions that are likely to involve platelet activation. However, many white-matter lacunar strokes are considered to be a consequence of small vessel lipohyalinosis.[2]

Therefore, MPV values may change by these different mechanisms.
Though the relationship between MPV and ischaemic stroke is well known, the diagnostic value of MPV in the emergency department (ED) to distinguish between ischaemic stroke and transient ischaemic attack (TIA) has not been studied.
The cortical infarctions, which are usually easy to diagnose with imaging techniques, could be smoothly managed in EDs. However, there are still patients who are classified as undetermined ischaemic strokes. Cardiovascular risk factors may help the decisions about these undetermined ischaemic events or TIAs. The current study aimed to investigate the value of MPV in an acute setting.

Patients and Methods

The cross-sectional study was conducted at the ED of Gazi University Hospital, Ankara, Turkey, from November 2009 to June 2010 and comprised 143 consecutive patients with acute ischaemic stroke and 39 consecutive patients with TIA. The control group consisted of 60 healthy volunteers.
All patients who had ischaemic cerebrovascular complaints and presented to the adult ED (over 18 years old) were included. Patients were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[5] and the stroke subtype (cortical or lacunary) was confirmed via computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients with acute coronary syndrome, pulmonary thromboembolism, acute renal failure, chronic renal failure, known thyroid disease, known haematological malignancy, known or newly detected cardiac thrombus (to exclude cardioembolic sources), intracranial mass lesion and intracranial aneurysm were excluded. Patients whose complaints lasted over 7 days were also excluded.
The study was approved by the relevant ethics committee, and informed consent was obtained from all patients (or relatives in case patients who were unable to give consent) and control subjects.
Venous blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) (BD Vacutainer® Plastic K3 EDTA). All the samples were analysed on a Sysmex KX-21N haematological analyser. They were processed within a maximum of 15 minutes after venipuncture to avoid platelet swelling due to EDTA.
Statistical analysis was performed using SPSS 13.0. Analysis of variance (ANOVA) test was used to compare MPV between stroke subtypes and to compare MPV between the admission status of patients. Student\'s t test was performed to compare MPV with medical history characteristics of patients. Correlation analysis was used to compare MPV with Glasgow Coma Scores and NIHSS scores. Results were expressed as mean±Standard deviation. Statistical significance was taken at $p < 0.05$. The literature did not reveal any exact cutoff values for MPV in ischaemic cerebrovascular diseases. Therefore, Receiver Operating Characteristic (ROC) curve analysis was done for the determination of sensitivity and specifity of the cutoff values of all patients.

Results

A total of 259 patients were initially enrolled in the study. Of them, 48 (18.5%) with ischaemic stroke and 29 (11.2%) with haemorrhagic stroke (intraparenchymal haematoma, subdural haematoma and subarachnoidal haemorrhage) were excluded from the study due to other concomitant diagnoses and excluding criteria, respectively.
Eventually, 182 (70.27%) patients represented the final study sample; 143 (78.57%) with ischaemic stroke; 88 (61.53%)with cortical infarction; 55 (38.46%) with lacunar infarction); and 39 (21.42%) patients with TIA. Besides, 60 control subjects were also enrolled in the study. General clinical characteristics of all the participants were noted down (Table-1).

Table-1: Demographic characteristics.

	Ischaemic stroke (n=143)	TIA (n=55)	Control group (n=60)	p-value*
Mean age (years)	67.7 ± 13.6	59.3 ± 15.7	57.7 ± 16.7	<0.01
Male gender	75 (52.4%)	16 (29.1%)	26 (43.3%)	<0.83
Diabetes Mellitus	52 (36.4%)	6 (10.9%)	22 (36.7%)	<0.35
Hypertension	111 (77.6%)	23 (41.8%)	24 (40.0%)	<0.01
Hyperlipidaemia	32 (22.4%)	7 (12.7%)	9 (15.0%)	<0.52
Coronary artery disease	53 (37.1%)	6 (11.0%)	8 (13.3%)	<0.02
Smoking habitus	60 (42.0%)	18 (32.7%)	10 (16.7%)	<0.01
Previous ischaemic stroke	46 (32.2%)	8 (14.6%)	2 (3.3%)	<0.01
Previous TIA	11 (7.7%)	2 (3.6%)	0 (0.0%)	<0.09
MPV	9.9 ± 0.9 fL	9.9 ± 0.9 fL	9.4 ± 0.8 fL	<0.01

Values are mean ± SD or number/percentage.

*Statistical significance for comparison of control group and ischaemic stroke/TIA group

TIA: Transient ischaemic attack. MPV: Mean platelet volume.

In terms of MPV levels, there was no statistically significant difference between male and female patients ($p<0.307$). There was a weak positive correlation between the ages of the patients and MPV levels ($r=0.143$; $p<0.026$).

Patients with a history of previous stroke and DM had significantly higher MPV values ($p<0.005$ and $p<0.044$, respectively). There was no statistically significant difference between MPV values and hypertension, and previous TIA. MPV levels were also higher in the patients with non-sinus electrocardiogram (ECG) rhythms (atrial fibrillation, atrial flutter, junctional rhythm) compared to sinus rhythms ($p<0.011$), (Table-2).

Table-2: Relationship between historical characteristics of patients and MPV levels.

	MPV*	MPV**	P-value***	95% CI
Hypertension	9.85 ± 0.93	9.62 ± 0.91	<0.059	-0.0094 - 0.4815
Diabetes Mellitus	9.94 ± 0.96	9.69 ± 0.90	<0.044	-0.0074 - 0.5023
Previous stroke	10.08 ± 0.93	9.68 ± 0.91	<0.005	0.1213 - 0.6688
Previous TIA	9.99 ± 0.83	9.76 ± 0.93	<0.398	-0.2964 - 0.7434

*Patients with history of the disease, mean (femtoliter) ± standard deviation.

**Patients without history of the disease, mean (femtoliter) ± standard deviation.

***t test.

TIA: Transient ischaemic attack. MPV: Mean platelet volume. CI: Confidence interval.

To determine the association between neurological impairment and MPV levels, NIHSS scores and Glasgow Coma Scores (GCS) were calculated. The GCS of cortical strokes, lacunar strokes and TIAs were 13.02±2.75, 14.65±1.00 and 14.82±0.60 respectively. Also the NIHSS scores of the patients were 10.98±8.57, 5.02±3.84 and 2.38±3.30 respectively. MPV values positively correlated with NIHSS scores (r=0.207; p<0.001). NIHSS scores also showed a strong negative correlation with GCS (r =-0,818; p <0.001).

Cortical infarction group and TIA group differed from the control group with respect to MPV levels. There was no statistically significant difference between lacunar infarction group and control group (p<0.377) (Table-3).

Table-3: MPV values in stroke and TIA patients compared to control group.*

Diagnosis	n (%)	MPV**	P-value
Cortical infarction	88 (48.4%)	10.09 ± 0.87	<0.001
Lacunar infarction	55 (30.2%)	9.66 ± 0.98	<0.377
TIA	39 (21.4%)	9.89 ± 0.94	<0.020
Control group	60	9.35 ± 0.77	

*ANOVA test with Bonferroni correction.

**Mean (femtoliter) ± standard deviation.

TIA: Transient ischaemic attack. MPV: Mean platelet volume.

TIA group only differed from the control group (p<0.020), but there was no statistically significant difference between the TIA group and the two stroke subtypes.

Patients were also divided into three subgroups according to their admission status: 72 (39.6%) were discharged from ED, 93 (51.1%) were admitted to service, and 17 (9.3%) were admitted to Intensive Care Unit (ICU). The MPV levels among the three subgroups were also investigated. No statistically significant difference was found between admissions to service (9.89±0.94fL) and ICU (10.29±0.93 fL) ($p<0.284$). The MPV levels of discharged patients were 9.84±0.92fL and there was a statistically significant difference between discharged patients and the patients, who were admitted to service ($p<0.036$) and ICU ($p<0.009$).

For all patients\' ROC curve analysis, the area under the curve for MPV was 0.674 (95% confidence interval [CI], 0.559-0.748) ($p<0.0001$) (Figure).

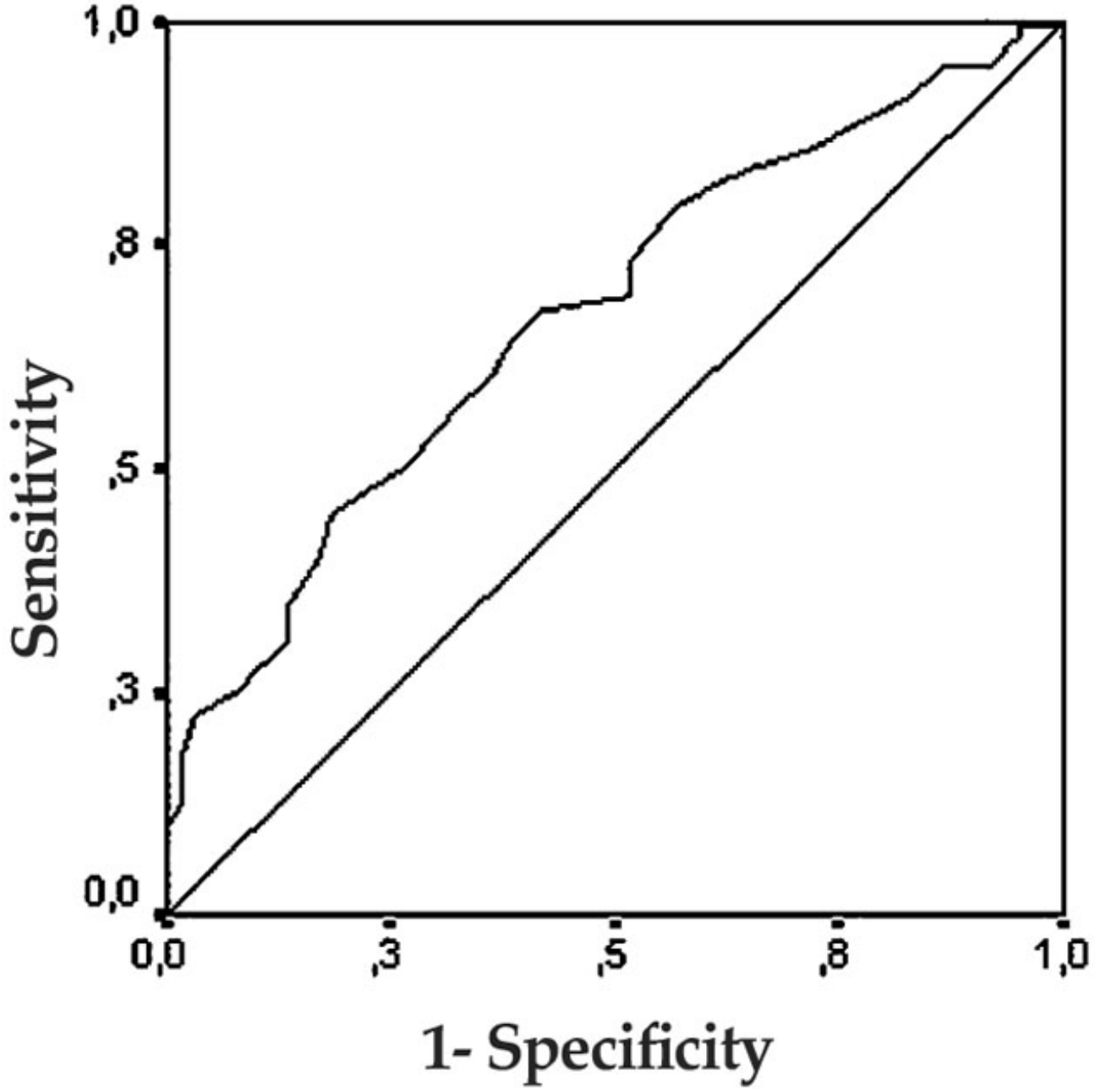

Figure: Receiver operating characterstic (ROC) curve for ischaemic stroke and Transient ischaemic attack (TIA) patients.

When MPV level was taken as 9.95 femtoliter, a sensitivity of 46.2% and a specifity of 80.0% was

found.

Discussion

The relationship between ischaemic stroke and MPV to date has been well studied in many publications.[1-3] Previous studies reported that lacunar strokes, which are associated with small vessel lipohyalinosis, do not cause increase in MPV values. Conversely, cortical events are usually related to atherothrombotic events that occur in the heart, aorta, carotid arteries or large intracranial arteries, which are all conditions that are likely to involve platelet activation.[2,6,7] The relationship between TIA and MPV levels were not evaluated yet, although TIA patients were associated with significant proximate risks for stroke. Almost half of TIAs result in cerebral infarction on diffusion-weighted imaging; the chance of infarction increases with increasing duration of symptoms.[8]

One study grouped the patients with stroke subtypes (cortical infarction, lacunar infarction, brainstem infarction) and compared the MPV values. It stated that patients with cortical and brainstem events had largest platelets, while patients with lacunar events had MPV values similar to that of the control group.[2] Our results are also in line with these findings. MPV levels of the TIA group were higher than the control group, but there was no significant difference between the TIA group and cortical infarction group in our study.

MPV increases in systemic conditions such as DM, obesity, metabolic syndrome and acute myocardial infarction.[9] We found a relationship between MPV and DM history. However, DM is one of the systemic diseases, which showed a strong relationship with MPV. In these patients, MPV increase might contribute to the diabetes-associated vascular damage. In DM, platelets are not only larger, but also circulate in an activated state, as demonstrated by the presence of markers of platelet activation, and by an increased spontaneous platelet aggregation.[10,11] In our study, 58 (29.3%) patients had DM previously. Consistent with the literature, MPV values in diabetic patients were significantly higher than the non-diabetic patients.

One set of researchers argued that there was no significant difference in MPV in those patients with previous stroke compared to the ones with no previous stroke.[1] Nevertheless, previous stroke was the most affecting variable in MPV levels in our study. We found a strong relationship between MPV levels and previous stroke ($p<0.005$). Although platelet life is limited to approximately 7 days, a study reported that MPV levels remain elevated for 3 months following cortical ischaemic stroke.[2]

Moreover, an important question about the relationship between MPV and stroke severity arises. Higher MPV was independently associated with larger infarct volume, greater risk of death/dependence 7 days post-stroke, and greater risk of death/dependence 3 months post-stroke.[12] A study determined the stroke severity by the modified Rankin Scale. It found that patients with a severe stroke had experienced MPV significantly more often on admission in the highest quintile (MPV between 11.3-15.3fL). Compared to patients with MPV in the lowest quintile (MPV between 6.7-9.2fL), those within the highest quintile had a 2.6-times unadjusted risk of suffering a severe stroke.[3] In our study, we evaluated the stroke severity by the NIHSS score in the ED. MPV values were positively correlated with NIHSS scores ($r= 0,207$; $p< 0.001$).

Hospitalisation and discharge decisions are sometimes critical for ischaemic stroke and TIA patients in the ED. In two studies analysing TIA evaluation, 19% to 42% of TIA patients did not receive a computed tomography scan; 75% of patients were discharged from the ED; and only 29% received a neurology consultation.[13,14] Although TIA diagnosis in the ED is primarily a clinical diagnosis,15 risk assessment tools may be useful for evaluating patients with ischaemic complaints. In our study, we found a statistical difference in discharged and hospitalised patients according to MPV levels. This might reflect on the stroke severity, which would be more serious in the group of hospitalised patients.

MPV levels may help clinicians to assess cardiovascular risk status of patients with TIA and ischaemic stroke.
Our study had several limitations: We measured MPV only in the ED and did not perform further serial measurements during the following days. Serial measurements might be helpful in investigating prognosis of the patients. We did not aim to investigate the source of embolus, therefore our study did not include cardioembolic sources of stroke. Furthermore, investigations to classify the subtypes of stroke (echocardiographic studies) are not always possible in the ED.

Conclusion

MPV may be a warning sign in ED to detect risk factors, particularly in stroke and TIA patients. MPV values can provide additional information about atherosclerotic risk profile in patients with TIA, who are sometimes difficult to diagnose. As the MPV levels cannot determine the diagnosis or discharge decisions exactly, they may help the clinicians in making a risk stratification.

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