

# Mean platelet volume and cardiovascular outcomes in acute myocardial infarction

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## ABSTRACT

**Objective** High levels of mean platelet volume (MPV) may be associated with adverse outcomes in patients with myocardial infarction (MI). We examined the association between MPV and the risk of death and adverse cardiovascular outcomes in patients with MI.

**Methods** We studied consecutive patients with MI admitted to a tertiary-care hospital during a period of 1 year. MPV was measured at admission and at third month. Patients were followed up for 1-year primary composite outcome of cardiovascular death, stroke, fatal or non-fatal MI and cardiac failure. Patients were classified according to tertile of baseline MPV.

**Results** A total of 1206 patients with MI, including 934 men (77.4%) and 272 women (22.6%) were studied. The mean age of the study population was 56 years. At 1-year follow-up, 292 (28.57%) primary outcome occurred: cardiovascular mortality 78 (7.6%), fatal or non-fatal MI 153 (15.0%), stroke 30 (2.9%) and cardiac failure 128 (12.52%). Patients with the highest tertile MPV had higher primary outcome as compared with those with MPV in the lowest tertile (adjusted OR=2.31; 95% CI 1.60 to 3.35;  $p<0.001$ ). Total mortality was also more in high-MPV group (adjusted OR 2.62; 95% CI 1.47 to 4.70;  $p<0.001$ ). There were no significant changes in mean MPV values at admission from those at third month interval (9.15, (SD 0.99) vs 9.19 (SD 0.94);  $p=0.2$ ).

**Conclusions** Elevated MPV was associated with worse outcome in patients with acute MI. Elevated MPV in these patients may be due to inherently large platelets.

**Trial registration number** <http://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=5485&EncHid=98036.61144&modid=1&compid=19>; CTRI/2012/12/003222.

## INTRODUCTION

Mean platelet volume (MPV) is an indicator of mean size of the platelet population. Activated platelets have an important role in the initiation of atherosclerotic lesions and subsequent complications.<sup>1</sup> Previous studies have shown MPV as an independent variable for prognosis in patients with cardiovascular diseases such as myocardial infarction (MI), heart failure or stroke, and also in patients undergoing coronary bypass surgery or coronary angioplasty.<sup>2–9</sup> Other studies have suggested increased MPV as an indicator of larger, more reactive platelets resulting from an increased platelet turnover as potential mechanism linking MPV to outcome.<sup>10–11</sup> But a few studies have shown no correlation between MPV and prognosis in MI.<sup>12</sup> There are conflicting reports regarding the prognostic value of MPV in MI; there are no studies assessing the prognostic value of MPV in

MI among Asian population. We tested the hypothesis that higher levels of MPV were associated with risk of all-cause mortality and adverse cardiovascular outcomes in a population with MI.

## METHODS

### Study design and patients

In a single-centre prospective cohort study, we included consecutive patients admitted to the coronary care unit of a large tertiary hospital with a diagnosis of non-ST-elevation MI (NSTEMI) and ST-elevation MI (STEMI) from December 2011 to November 2012. The American College of Cardiology diagnostic criteria were used for making the diagnosis of MI.<sup>13</sup> Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg or current therapy for hypertension. Dyslipidaemia was defined as a serum total cholesterol concentration  $\geq 220$  mg/dL, low-density lipoprotein cholesterol concentration  $\geq 140$  mg/dL or ongoing lipid-lowering therapy. Patients whose platelet indices could not be estimated within 12 h of presentation or before revascularisation were excluded. Patients with previous MI in 6 months or with history of bleeding disorders, pre-eclampsia, sepsis, thrombocytopenia, blood transfusion or major operation or trauma during the last 3 months, patients who were receiving drugs that could cause thrombocytopenia were also excluded. Patients were followed up for a period of 1 year by telephonic interview; those who had a suspected outcome event were reviewed by examining hospital admission reports or during outpatient visits.

The ethics committee of study centre approved the study in accordance with ethical standards of the Declaration of Helsinki, and all patients gave their informed consent. Full clinical evaluation was performed. Baseline investigations included complete blood count, blood sugar, serum urea and creatinine, serum lipid profile, serum troponin-I and creatine phosphokinase myocardial band (CPK-MB), ECG and comprehensive echocardiography. Troponin I  $>0.11$  ng/L and CPK-MB  $>7.0$   $\mu$ g/L were taken as positive. Estimation of platelet count and MPV was performed in all patients. Venous blood samples were drawn from all subjects after admission (within 30 min) before initiation of treatment. For sample collection, standardised EDTA sample tubes were used, and all samples were processed within 30 min after blood collection, using a Sysmex KX21-N autoanalyser (Sysmex, Kobe, Japan).



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## Study outcomes

The primary outcome for this study was a composite of cardiovascular mortality, stroke, non-fatal MI and cardiac failure requiring hospitalisation at 1-year follow-up. All deaths were considered as cardiac unless a clear non-cardiac cause could be established. Secondary outcomes were in-hospital mortality, fatal or non-fatal MI, the development of symptomatic heart failure, ischaemic or non-ischaemic stroke and cardiovascular mortality at 1 year. MI and stroke were defined according to the American Heart and Stroke Association criteria. Patients admitted with a discharging diagnosis of heart failure were counted as cardiac failure event.

## Statistical analysis

The continuous variables were presented as means and SDs. Categorical variables were presented as percentages. Patients were divided into subgroups according to MPV tertile. The cut-offs for tertile taken were 33.33 and 66.66 percentiles of baseline MPV values. Group I (n=434) comprised patients with an MPV  $\leq 8.7$  fL (tertile 1), group II (n=406) comprised patients with an MPV value of  $>8.7$  fL and  $\leq 9.5$  fL (tertile 2) and group III (n=366) comprised patients with MPV values of  $>9.5$  fL (Tertile 3). To test for differences across all groups, the  $\chi^2$  and one-way analysis of variance tests were used. Multivariate regression analysis was done and variables which were likely to affect the outcome were included in the model. Outcome was adjusted for age, dyslipidaemia, stroke, hypertension, coronary artery disease, diabetes, history of antiplatelet consumption, smoking, ejection fraction  $<50\%$  and creatinine. Analyses were performed with the SPSS statistical software (V.18.0; SPSS, Chicago, Illinois, USA).

## RESULTS

### Baseline characteristics

A total of 1206 patients with MI including 934 men (77.4%) and 272 women (22.6%) were studied. The mean age of the study population was 56 years. Among the population, 797 (66.09%) were diagnosed as STEMI and rest of them as NSTEMI. The MPV ranged from 6.3 fL to 13.2 fL. (Median 9.1 fL; mean 9.17(SD 1.0 fL) and 162 (13.4%) had MPV levels outside the normal range of 8–11 fL with MPV  $<8$  fL (n=108

(8.96%)) and  $>11$  fL (n=54 (4.48%).) Among the total population, 84.7% completed 1-year follow-up (first tertile 86.2%, second tertile 79.8%, third tertile 88.5%; p for trend 0.453). There was no significant difference in MPV values between those patients taking antiplatelets and those not taking ( $9.29 \pm 1$  vs  $9.15 \pm 0.99$ ; p=0.082). The baseline characteristics of patients are shown in [table 1](#).

### Association between MPV and primary outcome

At 1-year follow-up, primary outcome occurred in 292 (28.57%) of which cardiovascular mortality comprised of 78 (7.6%), fatal or non-fatal MI in 153 (15.0%), stroke in 30 (2.9%) and cardiac failure in 128 (12.52%). When participants were divided into three categories on the basis of tertile of baseline MPV level, a graded relation between MPV and primary outcome was observed (p=0.01). Participants with MPV in the highest tertile had fully adjusted OR for experiencing the primary outcome of 1.71 (95% CI 1.18 to 2.45) compared with those with MPV in the lowest tertile ([table 2](#), [figure 1](#)). When the second and third tertiles of MPV were compared similar results were obtained (adjusted OR-1.76; 95% CI 1.22 to 2.56; p=0.003) ([table 3](#))

### Association between MPV and cardiovascular mortality

The incidence of cardiovascular mortality was 7.6% among those who completed 1 year of follow-up. There was a graded relation between MPV and cardiovascular mortality at 1-year follow-up among the MPV tertile groups (p=0.001). For example, the fully adjusted risk of cardiovascular mortality in the highest category of MPV was 2.83 (95% CI 1.49 to 5.35) compared with the referent group and 2.85 (95% CI 1.5 to 5.41) as compared with second tertile ([tables 2 and 3](#)).

### Association between MPV and secondary outcome

Higher levels of MPV were associated with an increased risk of fatal or non-fatal MI after adjustment for different clinical variables (p=0.025). Participants with MPV in the highest tertile had fully adjusted OR for developing fatal or non-fatal MI of 1.91 (95% CI 2.2 to 3.04) compared with those with MPV in the lowest tertile. In-hospital mortality, incidence of new symptomatic heart failure and stroke were high in the third tertile

**Table 1** Baseline characteristics of study population

	MPV tertile 1 (n=434)	MPV tertile 2 (n=406)	MPV tertile 3 (n=366)	p Value
Age, mean (SD)	55 (10.87)	57 (10.87)	56 (11.46)	0.06
Men	336 (77.4)	326 (80.3)	272 (74.3)	0.14
Dyslipidaemia	81 (18.7)	110 (27.1)	94 (25.7)	0.01
Diabetes	120 (27.6)	124(30.5)	118 (32.2)	0.35
Hypertension	134 (30.9)	144 (35.5)	140 (38.3)	0.08
Stroke	22 (5.1)	18 (4.4)	14 (3.8)	0.70
Coronary artery disease	48 (11.1)	40 (9.9)	48 (13.1)	0.35
Current smoker	180 (41.5)	188 (46.3)	130 (35.5)	0.01
History of antiplatelet consumption	60 (13.8)	55 (13.5)	67 (18.3)	0.12
Platelet count ( $\times 10^9/L$ ), mean (SD)	259.39 (66.23)	238.69 (57.37)	213.50 (65.09)	$<0.001$
Total cholesterol (mg/dL), mean (SD)	188.58 (53.60)	181.44 (36.82)	186.48 (43.09)	0.08
Triglycerides (mg/dL), mean (SD)	111.35 (44.94)	115.46 (44.84)	122.12 (44.09)	0.005
LDL cholesterol (mg/dL), mean (SD)	121.21 (44.96)	118.29 (71.70)	119.35 (40.46)	0.76
Creatinine (mg/dL), mean (SD)	1.06 (0.33)	1.09 (0.39)	1.18 (0.58)	$<0.001$
Ejection fraction (%), mean (SD)	57.50 (10.74)	57.01 (10.15)	58.12 (10.60)	0.35

Values are n (%) unless otherwise indicated.  
LDL, Low-density lipoprotein; MPV, mean platelet volume.

**Table 2** Adjusted association between tertile of MPV and clinical outcomes

	Unadjusted				Adjusted*		
	Events, n (%)	OR	95% CI	p Value	OR	95% CI	p Value
Primary outcome				0.001†			<0.001
Tertile 1	92 (24.6)	1			1		
Tertile 2	84 (25.9)	1.28	0.86 to 1.90		1.31	0.89 to 1.95	
Tertile 3	116 (35.8)	2.26	1.57 to 3.24		2.31	1.60 to 3.35	
Cardiovascular mortality at 1 year				<0.001†			<0.001
Tertile 1	20 (5.3)	1			1		
Tertile 2	16 (4.9)	0.92	0.47 to 1.81		0.92	0.46 to 1.86	
Tertile 3	42 (13.0)	2.64	1.51 to 4.59		2.62	1.47 to 4.70	
Inhospital mortality				0.096†			0.196
Tertile 1	8 (1.8)	1			1		
Tertile 2	10 (2.5)	1.35	0.53 to 3.44		1.51	0.57 to 3.98	
Tertile 3	16 (4.4)	2.43	1.03 to 5.76		2.26	0.92 to 5.52	
Fatal or non-fatal myocardial infarction				0.01†			0.01
Tertile 1	41 (11.0)	1			1		
Tertile 2	51 (15.7)	1.38	0.89 to 2.13		1.29	0.83 to 2.00	
Tertile 3	61 (18.8)	1.92	1.26 to 2.93		1.92	2.25 to 2.95	
New symptomatic heart failure				0.542†			0.41
Tertile 1	45 (12)	1			1		
Tertile 2	39 (12)	0.92	0.59 to 1.44		0.85	0.54 to 1.36	
Tertile 3	44 (13.6)	1.18	0.76 to 1.84		1.18	0.74 to 1.86	
Stroke				0.12†			0.183
Tertile 1	10 (2.7)	1			1		
Tertile 2	6 (1.9)	0.64	0.23 to 1.78		0.66	0.24 to 1.87	
Tertile 3	14 (4.3)	1.69	0.74 to 3.84		1.61	0.69 to 3.75	

\*Adjusted for age, dyslipidaemia, stroke, hypertension, coronary artery disease, diabetes, history of antiplatelet consumption, smoking, ejection fraction <50% and creatinine.  
†p for linear trend.  
MPV, mean platelet volume.

MPV group as compared with first tertile (4.4% vs 1.8%, 13.6% vs 12%, 4.3% vs 2.7%). However, after adjustment for clinical variables, this difference was not statistically significant (table 2).

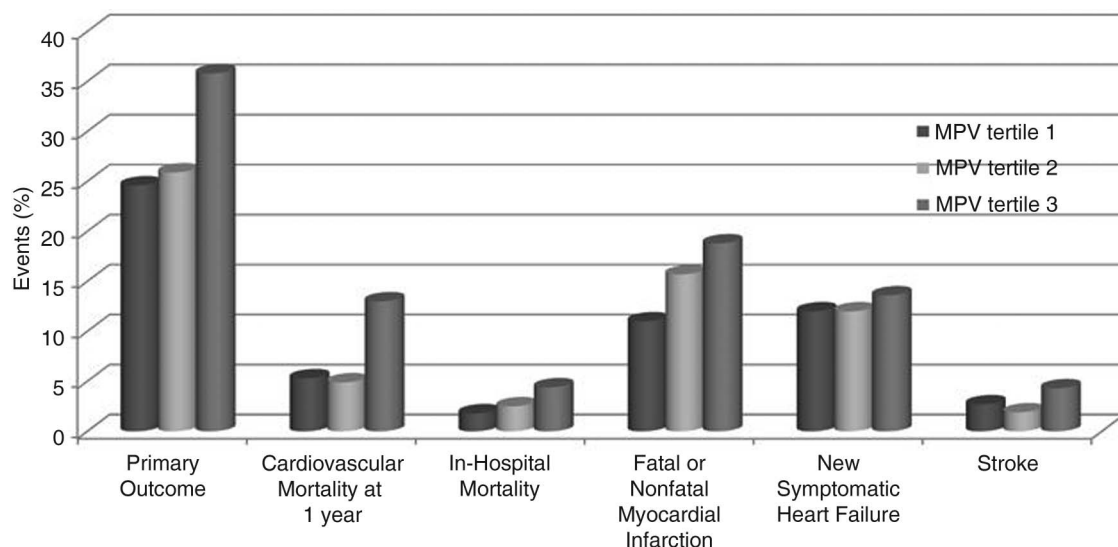
### Relation of MPV with baseline characteristics

The MPV value repeated at third month did not show significant changes from baseline MPV values (mean;  $9.15 \pm 0.99$  vs  $9.19 \pm 0.94$ ;  $p=0.2$ ). There was a significant correlation between

age and MPV values ( $r=0.69$ ;  $p=0.016$ ). Even though weak, serum creatinine also showed a positive correlation with MPV ( $r=0.131$ ;  $p<0.001$ ). There was a negative correlation between MPV and platelet count ( $r=-0.339$ ;  $p<0.001$ ) (table 4).

### DISCUSSION

Larger platelets, characterised by high MPV, was associated with increased platelet reactivity which represents a major risk factor for atherothrombosis.<sup>14</sup> Several studies have found that high

**Figure 1** Association of mean platelet volume (MPV) with various cardiovascular events.

**Table 3** Adjusted association between second and third tertile of MPV and clinical outcomes

	Unadjusted				Adjusted*		
	Events, n (%)	OR	95% CI	p Value	OR	95% CI	p Value
Primary outcome				0.002†			0.003
Tertile 2	84 (25.9)	1			1		
Tertile 3	116 (35.8)	1.75	1.22 to 2.51		1.76	1.22 to 2.56	
Cardiovascular mortality at 1 year				0.001†			0.001
Tertile 2	16 (4.9)	1			1		
Tertile 3	42 (13.0)	2.87	1.58 to 5.21		2.85	1.5 to 5.41	
Inhospital mortality				0.147†			0.36
Tertile 2	10 (2.5)	1			1		
Tertile 3	16 (4.4)	1.81	0.81 to 4.04		1.50	0.63 to 3.56	
Fatal or non-fatal myocardial infarction				0.107†			0.046
Tertile 2	51 (15.7)	1			1		
Tertile 3	61 (18.8)	1.39	0.93 to 2.08		1.52	1.01 to 2.3	
New symptomatic heart failure				0.28†			0.129
Tertile 2	39 (12)	1			1		
Tertile 3	44 (13.6)	1.29	0.82 to 2.03		1.45	0.90 to 2.34	
Stroke				0.048†			0.074
Tertile 2	6 (1.9)	1			1		
Tertile 3	14 (4.3)	2.65	1.01 to 6.97		2.44	0.92 to 6.51	

\*Adjusted for age, dyslipidaemia, stroke, hypertension, coronary artery disease, diabetes, history of antiplatelet consumption, smoking, ejection fraction <50% and creatinine.

†p for linear trend.

MPV, mean platelet volume.

MPV levels were associated with overall increased vascular mortality and other cardiovascular events, including MI.<sup>5 15 16</sup> Therefore, MPV has been suggested as a simple marker of functional status of platelets and may represent a risk factor for vascular adverse events. Our study found a graded, independent association between baseline MPV level and the risk of a composite of cardiovascular mortality, stroke, fatal or non-fatal MI and cardiac failure. This association was primarily driven by fatal or non-fatal MI and cardiovascular mortality at 1 year, while symptomatic heart failure, ischaemic or non-ischaemic stroke did not independently show any association with MPV values. Also, MPV did not show any significant independent association with in-hospital mortality.

Adjustment for multiple potential confounders did not eliminate the association between higher MPV levels and the occurrence of primary outcome, cardiovascular mortality or reinfarction. In addition to reaching statistical significance, the magnitude of the increased risk associated with higher levels of MPV was clinically relevant. For example, the risk of cardiovascular mortality at 1 year in participants with MPV in the highest tertile was nearly 120% higher than those in the lowest tertile. This was comparable with the adjusted risk of recurrent cardiovascular events among Cholesterol and Recurrent Events study participants with high and low C reactive protein.<sup>17</sup> These findings are notable given that MPV is widely available to clinicians as part of the complete blood count and therefore incurs no additional cost, in contrast to other novel markers of cardiovascular risk.

Many studies have shown a negative correlation between platelet count and MPV, and no relation between MPV and antiplatelet use.<sup>3 18 19</sup> These results were replicated in our study, but our study showed a positive correlation between MPV and age or serum creatinine.

The mechanisms for an increased platelet volume are not fully understood. There are several theories that may explain the increase in MPV in acute coronary syndrome (ACS). One

explanation for this is the consumption of platelets and release of larger and more immature platelets from bone marrow into the circulation.<sup>20 21</sup> Another hypothesis is that in some patients, platelets are larger and metabolically more active and hence predisposing them for ACS. But if the increase in platelet volume is a transient phenomenon occurring during ACS, it has to normalise by few months after the event. In our study, when the MPV was repeated after 3 months, there was no significant change from the baseline.

Strengths of our analysis include relatively large sample size and the use of a central laboratory for all assays. However, we could not exclude the presence of heterotypic platelet aggregates in the high-MPV group as such phenomenon would only be determined by flow cytometry, which is currently costly, time-consuming and needs specialised equipment.<sup>22</sup> Previous studies have reported that MPV increases in a time-dependent manner when EDTA is used as an anticoagulant.<sup>23</sup> However, a more recent study demonstrated that this increase of platelet size amounts to approximately 0.5 fL when the analysis was performed within 2 h after sample collection.<sup>24</sup> The reported platelet swelling with EDTA may have been due to varying concentrations of EDTA used in the blood tubes; therefore to minimise the effect of EDTA on platelet size in the present study, standardised sample tubes were used, and all samples were processed within 30 min after blood collection.

**Table 4** Correlation between mean platelet volume and other variables

	r	p Value
Age	0.69	0.016
Platelet count	-0.339	<0.001
Serum creatinine	0.131	<0.001

## CONCLUSION

The current study found that MPV values at admission is a strong and independent predictor of composite of cardiovascular mortality, stroke, fatal or non-fatal MI and cardiac failure at 1-year follow-up among patients with MI. This effect was primarily driven by occurrence of cardiovascular mortality and reinfarction. Elevated MPV in these patients may be due to inherently large platelets.

## Key messages

**What is already known about this subject?**

Mean platelet volume (MPV) is an indicator of mean size of the platelet population. Activated platelets have an important role in the initiation of atherosclerotic lesions and subsequent complications. The association between MPV and prognosis has been studied in patients with coronary artery disease. There are conflicting reports regarding the prognostic value of MPV in myocardial infarction (MI).

**What does this study add?**

This study found a graded, independent association between baseline MPV level and the risk of composite of cardiovascular mortality; stroke, fatal or non-fatal MI and cardiac failure at 1-year follow-up among patients with MI. Elevated MPV in these patients may be due to inherently large platelets.

**How might this impact on clinical practice?**

Stratification using MPV helped to predict the adverse cardiac events in patients with MI. So, MPV can be used as a prognostic indicator in Asian population with MI.

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**Competing interests** None declared.

**Ethics approval** Medical College, Kozhikode, Ethics Committee.

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