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%).

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.

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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. 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 cardiovascular diseases such as myocardial infarction. 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. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or current therapy for hypertension. Dyslipidaemia was defined as a serum total cholesterol concentration ≥220 mg/dL, low-density lipoprotein cholesterol concentration ≥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, thrombocytopaenia, blood transfusion or major operation or trauma during the last 3 months, patients who were receiving drugs that could cause thrombocytopaenia 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 μg/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).
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 inhospital 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 ≤8.7 fL (tertile 1), group II (n=406) comprised patients with an MPV value of >8.7 fL and ≤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 χ² 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 to 9.1 fL; mean 9.17(SD 1.0 fL) and 162 (13.4%) had MPV levels ≤8.7 fL and ≥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 χ² 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).

Table 1 Baseline characteristics of study population

| Age, mean (SD) | MPV tertile 1 (n=434) | MPV tertile 2 (n=406) | MPV tertile 3 (n=366) | p Value |
|----------------|------------------------|------------------------|------------------------|---------|
| Men            | 55 (10.87)             | 57 (10.87)             | 56 (11.46)             | 0.06    |
| Dyslipidaemia  | 336 (77.4)             | 326 (80.3)             | 272 (74.3)             | 0.14    |
| Diabetes       | 81 (18.7)              | 110 (27.1)             | 94 (25.7)              | 0.01    |
| Hypertension   | 120 (27.6)             | 124 (30.5)             | 118 (32.2)             | 0.35    |
| Stroke         | 134 (30.9)             | 144 (35.5)             | 140 (38.3)             | 0.08    |
| Coronary artery disease | 22 (5.1)      | 18 (4.4)               | 14 (3.8)               | 0.70    |
| 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 (x10^12/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 (44.94) | 122.12 (44.09) | 0.005 |
| Creatinine (mg/dL), mean (SD) | 106 (0.33) | 109 (0.39) | 118 (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.
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±0.99 vs 9.19±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. Several studies have found that high

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

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

*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. 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 inhospital 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.

Many studies have shown a negative correlation between platelet count and MPV, and no relation between MPV and antiplatelet use. 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. 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. Previous studies have reported that MPV increases in a time-dependent manner when EDTA is used as an anticoagulant. However, a more recent study demonstrated that this increase of platelet size amounts to approximately 0.5 fL when the analysis was performed 2 h after sample collection. 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 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 | | | | | | |
| Tertile 2 | 84 (25.9) | 0.002† | 1 | 1 | 0.003 |
| Tertile 3 | 116 (35.8) | 1.75 1.22 to 2.51 | 1.76 1.22 to 2.56 | 0.001 |
| Cardiovascular mortality at 1 year | | | | | | |
| Tertile 2 | 16 (4.9) | 1 | 1 | 0.046 |
| Tertile 3 | 42 (13.0) | 2.87 1.58 to 5.21 | 2.85 1.5 to 5.41 |
| Inhospital mortality | | | | | | |
| Tertile 2 | 10 (2.5) | 1 | 1 | 0.36 |
| 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 | | | | | | |
| Tertile 2 | 51 (15.7) | 0.107† | 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 | | | | | | |
| Tertile 2 | 39 (12) | 0.28† | 1 | 1 | 0.129 |
| Tertile 3 | 44 (13.6) | 1.29 0.82 to 2.03 | 1.45 0.90 to 2.34 |
| Stroke | | | | | | |
| Tertile 2 | 6 (1.9) | 0.048† | 1 | 1 | 0.074 |
| Tertile 3 | 14 (4.3) | 2.65 1.01 to 6.97 | 2.44 0.92 to 6.51 |

| 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.

Contributors All the authors contributed to planning, conducting of the study and preparing the article for publication.

Competing interests None declared.

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