Prognostic value of rising mean platelet volume during hospitalization in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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Abstract

Background: The prognostic significance of changes in mean platelet volume (MPV) during hospitalization in ST segment elevation myocardial infarction (STEMI) patients underwent primary percutaneous coronary intervention (pPCI) has not been previously evaluated. The aim of this study was to determine the association of in-hospital changes in MPV and mortality in these patients.

Methods: Four hundred eighty consecutive STEMI patients were enrolled in this retrospective study. The patients were grouped as survivors (n = 370) or non-survivors (n = 110). MPV at admission, and at 48–72 h was evaluated. Change in MPV (MPV at 48–72 h minus MPV on admission) was defined as ΔMPV.

Results: At follow-up, long-term mortality was 23%. The non-survivors had a high ΔMPV than survivors (0.37 (−0.1–0.89) vs 0.79 (0.30–1.40) fL, p < 0.001). A high ΔMPV was an independent predictor of all cause mortality (HR: 1.301 [1.070–1.582], p = 0.008). Moreover, for long-term mortality, the AUC of a multivariable model that included age, LVEF, Killip class, and history of stroke/TIA was 0.781 (95% CI:0.731–0.832, p < 0.001). When ΔMPV was added to a multivariable model, the AUC was 0.800 (95% CI: 0.750–0.848, z = 2.256, difference p = 0.0241, Fig. 1). Also, the addition of ΔMPV to a multivariable model was associated with a significant net reclassification improvement estimated at 24.5% (p = 0.027) and an integrated discrimination improvement of 0.014 (p = 0.0198).

Conclusions: Rising MPV during hospitalization in STEMI patients treated with pPCI was associated with long-term mortality.

Keywords: Mean platelet volume, ST segment elevation myocardial infarction, Mortality
change with mortality in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

The aim of the present study was to investigate the relationship of an in-hospital increase in MPV with long-term mortality in STEMI patient underwent primary PCI.

Methods

Study population

We enrolled 514 STEMI patients who were undergoing primary PCI between January 2008 and June 2015. The patients with malignancy or infectious disease or autoimmune disease or hematologic disease and patients with incompleted data were excluded from this study. The final analysis included 480 patients. Permission of study was obtained by a local ethics committee. STEMI diagnosis was established as typical angina pain lasting > 30 min, with increase in levels of cardiac enzymes (troponin I levels) and electrocardiographic evidence of elevation of the ST segment of > 1 mm in two or more consecutive leads or the presence of new left bundle branch block (LBBB) [13]. We defined hypertension (HT) as the previous use of antihypertensive medication, systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg and Diabetes mellitus as the use of insulin or antidiabetic agents or a fasting glucose level > 126 mg/dL. Hypercholesterolemia was diagnosed as total cholesterol of ≥ 200 mg/dL. Smoking was defined as a current smoker or not. This study complied with the Declaration of Helsinki.

We defined total mortality as death due to any cause at follow-up and considered as the primary end point. Moreover, repeat revascularization, heart failure admission, and stroke/transient ischemic attack (TIA), and 30-day mortality were also evaluated. We obtained follow-up data from the hospital records, patients, and their relatives.

Procedures

All patients were treated according to the current guidelines.13 Primary PCI was performed using standard techniques via the transfemoral approach by 2-experienced interventional cardiologists. The treatment strategies for each patient were left to the discretion of interventional cardiologists. We obtained angiographic data from the cardiac catheterization laboratory records. The infarct-related artery (IRA) was evaluated based on the thrombolysis in myocardial infarction (TIMI) classification. We defined invasive success in acute phase as reduction to < 20% in IRA obstruction and stenosis with TIMI-3 flow immediately after primary PCI. After angioplasty, all patients were transferred to intensive care unit. Dual antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor-blocker (ARB), and statins were administered according to current guidelines [13].

The left ventricle ejection fraction (LVEF) was calculated after measuring the end-diastolic and end-systolic left ventricle (LV) volumes in the apical four-chamber and two-chamber views using the modified Simpson’s method.

Blood sampling and hematological and biochemical analyses

Peripheral blood was obtained for MPV analysis at admission prior to administration of antiplatelet drugs and 48–72 h after admission. Blood samples were collected into standardized tubes containing dipotassium ethylenediaminetetraacetate powder as anticoagulant and stored at room temperature. All measurements were analyzed within 1 h after collection. Change in MPV was defined as \(\Delta\)MPV (MPV at 48–72 h minus MPV on admission). An extra blood was collected on admission for biochemical analysis. They were evaluated by standard methods.

Statistical analysis

Statistical analysis was made using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Variables with normal distribution were analyzed using Kolmogorov-Smirnov test and presented as mean ± standard deviation, while those without normal distribution were presented as medians with a range. Categorical variables were presented as number and percentage. The comparisons between groups was carried out using the chi-square test for categorical variables and Student t tests or Mann-Whitney U test for continuous variables. A multivariate cox regression analysis was carried out to evaluate whether \(\Delta\)MPV was an independent predictor of mortality. Factors with a \(p\) value of < 0.1 by univariate analysis were included in multivariate cox regression analysis. The predictive values of a multivariable model and a combination of \(\Delta\)MPV with a multivariable model were estimated by comparing the areas under the receivers operating characteristic (ROC) curve. DeLong’s test was used to compare the AUC from each of models [14], which were analysed by use of NCSS 12 software programme. Moreover, the increased discriminative value after the addition of \(\Delta\)MPV to a multivariable model was also estimated using the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement [15]. Differences were considered significant at the 2-sided \(p < 0.05\) level.

Results

Baseline characteristics

Baseline demographic, and clinical characteristics are shown in Table 1. Median follow-up time was 65.9 (41.9–80.4) months. The non-survivors were significantly older (68 ± 13 vs 58 ± 11, \(p < 0.001\)). The histories of diabetes mellitus, HT, stroke/TIA were more common in non-survivors compared with survivors (Table 1). The
frequency of Killip class $\geq 2$ and multi-vessel disease were higher in non-survivors than survivors. Compared with survivors there was a higher proportion of women in non-survivors. The rates of usage of ACE-I/ARB and beta-blockers after discharge were lower in the non-survivors than survivors.

Laboratory parameters

Laboratory variables are provided in Table 2. Serum creatinine level at admission was higher in the non-survivors. Compared with survivors, admission hemoglobin level was lower in the non-survivors. There was no significant difference between groups in terms of platelet counts both at admission and at 48–72 h. MPV at 48–72 h was higher in non-survivors than survivors. Compared with survivors, non-survivors had a high $\Delta$MPV value [0.79 (0.30–1.40) vs 0.37 (−0.1–0.89), $p < 0.001$]. Baseline MPV was similar between groups.

LVEF was lower in non-survivors than survivors (41 ± 10 vs 45 ± 9, $p < 0.001$).

Clinical outcomes and $\Delta$MPV

Thirty-day mortality rate was 20% in the non-survivors (Table 1). The frequencies of TVR, stroke, and MI were comparable between groups. Non-survivors had a higher incidence of HF admission compared with survivors (14% vs 2%, $p < 0.001$).

$\Delta$MPV (HR: 1.301 [1.070–1.582], $p = 0.008$), Killip class $\geq 2$, LVEF, history of stroke/TIA and age were independent predictors of long-term mortality in multivariate analysis (Table 3).

The ROC curve analysis of $\Delta$MPV revealed an area under the curve (AUC) of 0.646 for the prediction of long-term mortality. (Fig. 1). Moreover, for long-term mortality, the AUC of a multivariable model that included age, LVEF, Killip class, and history of stroke/TIA was 0.781.

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**Table 1** Baseline characteristics of the study population

| Variable                        | Survivors ($n = 370$) | Non-survivors ($n = 110$) | $P$-value |
|---------------------------------|-----------------------|---------------------------|-----------|
| Age (year)                      | 58 ± 11               | 68 ± 13                   | < 0.001   |
| Female n (%)                    | 80 (22)               | 37 (34)                   | 0.010     |
| Hypertension n (%)              | 151 (41)              | 63 (57)                   | 0.002     |
| Diabetes mellitus n (%)         | 78 (21)               | 37 (34)                   | 0.007     |
| Hyperlipidemia n (%)            | 76 (21)               | 24 (22)                   | 0.772     |
| Current smoking n (%)           | 168 (45)              | 40 (36)                   | 0.098     |
| Previous CAD n (%)              | 64 (17)               | 27 (25)                   | 0.089     |
| Prior stroke/TIA n (%)          | 5 (1)                 | 9 (8)                     | < 0.001   |
| Killip class $\geq 2$ n (%)     | 21 (6)                | 20 (18)                   | < 0.001   |
| Multi-vessel disease n (%)      | 132 (36)              | 57 (52)                   | 0.002     |
| GP IIb/IIIa inhibitors n (%)    | 107 (29)              | 37 (34)                   | 0.343     |

**Medication at discharge**

|                          | Survivors ($n = 370$) | Non-survivors ($n = 110$) | $P$-value |
|--------------------------|-----------------------|---------------------------|-----------|
| Beta-blocker n (%)       | 319 (86)              | 82 (73)                   | 0.004     |
| Statin n (%)             | 312 (84)              | 85 (77)                   | 0.086     |
| ACE-I/ARB n (%)          | 315 (85)              | 76 (69)                   | < 0.001   |
| DAPT n (%)               | 365 (99)              | 107 (97)                  | 0.322     |

**Infarct related artery**

|                          | Survivors ($n = 370$) | Non-survivors ($n = 110$) | $P$-value |
|--------------------------|-----------------------|---------------------------|-----------|
| LAD n (%)                | 170 (46)              | 50 (46)                   | 0.097     |
| Cx n (%)                 | 57 (15)               | 8 (7)                     |           |
| RCA n (%)                | 129 (35)              | 49 (45)                   |           |
| Others n (%)             | 14 (4)                | 3 (2)                     |           |

**Outcomes**

|                          | Survivors ($n = 370$) | Non-survivors ($n = 110$) | $P$-value |
|--------------------------|-----------------------|---------------------------|-----------|
| 30-day death n (%)       | 0 (0)                 | 19 (17)                   | < 0.001   |
| Stroke n (%)             | 7 (2)                 | 5 (5)                     | 0.118     |
| HF admission n (%)       | 7 (2)                 | 15 (14)                   | < 0.001   |
| Myocardial reinfarction n (%) | 30 (8) | 8 (7) | 0.776 |
| TVR n (%)                | 45 (12)               | 11 (10)                   | 0.535     |

HF heart failure, CAD coronary artery disease, TIA transient ischemic attack, ACE-I angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blocker, TVR; target vessel revascularization, DAPT dual antiplatelet therapy.
Table 2: The laboratory findings of study population

| Variable                  | Survivor (n = 370) | Non-survivor (n = 110) | P value |
|---------------------------|--------------------|------------------------|---------|
| Total cholesterol (mg/dl) | 181 ± 43           | 163 ± 39               | 0.001   |
| SCr<sub>admi</sub> (mg/dl) | 0.86 (0.76–1.02)   | 0.95 (0.80–1.26)       | 0.048   |
| Hemoglobin (g/dl)         | 14.0 ± 12          | 13.2 ± 2.2             | < 0.001 |
| WBC count (10<sup>3</sup>/mm<sup>3</sup>) | 12 ± 4             | 12 ± 5                 | 0.781   |
| Platelets<sub>admi</sub> (10<sup>3</sup>/mm<sup>3</sup>) | 273 ± 78           | 271 ± 93               | 0.846   |
| Platelets<sub>48-72h</sub> (10<sup>3</sup>/mm<sup>3</sup>) | 241 ± 73           | 235 ± 90               | 0.448   |
| MPV<sub>admi</sub> (fL)   | 9.0 ± 1.6          | 9.0 ± 1.3              | 0.648   |
| MPV<sub>48-72h</sub> (fL) | 9.4 ± 1.6          | 9.8 ± 1.4              | 0.035   |
| ΔMPV<sub>48-72h</sub> (fL) | 0.37 (<−0.1–0.89)  | 0.79 (0.30–1.40)       | < 0.001 |
| LVEF (%)                  | 45 ± 9             | 41 ± 10                | < 0.001 |

Abbreviations: SCr, serum creatinine; MPV, mean platelet volume; LVEF, left ventricular ejection fraction; ΔMPV, change in mean platelet volume.

Discussion

To the best of our knowledge, this is the first study to investigate the association of an in-hospital increase in MPV and long-term mortality in patients with STEMI who were treated with pPCI. In present study, we found that an increase in hospital MPV at 48–72 h was associated with long-term mortality in these patients.

An increase in MPV at 72 h has been shown Grabovac et al. in STEMI patients [16]. The presence of large PLTs are an indicator of the increased platelet activation. These PLTs are functionally predominantly hyperactivated and have a high granule content including intracellular thromboxane A2, procoagulant surface proteins such as P-selectin and GPIIla, which is an indicator of prothrombotic state. Also, aggregation in response to collagen or ADP, thromboxane release and membrane expression of P-selectin or GPIIb, GPIIb/IIIa have increased in these PLTs [17–19]. There is a relationship between MPV and both proinflammatory and prothrombotic conditions where thrombopoietin and various inflammatory mediators.

Table 3: Univariate and multivariate cox proportional hazards analysis for all-cause mortality

| Variables                  | Univariate HR (95% CI) | P-value | Multivariate HR (95% CI) | P-value |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age (year)                 | 1.062 (1.045–1.080)    | < 0.001 | 1.049 (1.030,0010–1.069) | < 0.001 |
| Gender (Male)              | 0.581 (0.391–0.864)    | 0.007   |                          |         |
| History of stroke/TIA      | 4.263 (2.149–8.457)    | < 0.001 | 2.398 (1.148–5.009)      | 0.020   |
| History of DM              | 1.690 (1.138–2.510)    | 0.009   |                          |         |
| History of CAD             | 1.695 (1.162–2.473)    | 0.053   |                          |         |
| History of HT              | 1.538 (0.995–2.377)    | 0.006   |                          |         |
| IRA                        | 0.987 (0.823–1.183)    | 0.888   |                          |         |
| Multi-vessel disease       | 2.001 (1.372–2.915)    | < 0.001 |                          |         |
| Killip ≥2                  | 3.619 (2.228–5.180)    | < 0.001 | 2.791 (1.597–4.876)      | < 0.001 |
| LVEF (%)                   | 0.957 (0.938–0.977)    | < 0.001 | 0.966 (0.945–0.989)      | 0.003   |
| Hemoglobin (g/dl)          | 0.832 (0.763–0.907)    | < 0.001 |                          |         |
| ΔMPV (fL)                  | 1.428 (1.210–1.685)    | < 0.001 | 1.301 (1.070–1.582)      | 0.008   |
| Serum creatinine (mg/dl)   | 1.235 (1.091–1.397)    | 0.01    |                          |         |
| Statin usage at discharge  | 0.413 (0.275–0.619)    | < 0.001 |                          |         |
| Beta-blocker usage at discharge | 0.496 (0.326–0.756) | 0.001   |                          |         |
| ACE/ARB usage at discharge | 0.239 (0.118–0.484)    | < 0.001 |                          |         |

Abbreviations: HR: hazard ratio, CI: confidence interval, TIA: transient ischemic attack, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, HT: hypertension, CAD: coronary artery disease, ΔMPV: change in mean platelet volume, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blockers, IRA: infarct related artery.
Fig. 1 Receiver operating characteristic (ROC) curves for the ΔMPV, multivariable model, and multivariable model plus ΔMPV for predicting all-cause total mortality.

Fig. 2 Kaplan-Meier survival curves of all-cause mortality according to ΔMPV.
cytokines, such as interleukin (IL) 1, IL-3, and IL-6 and tumor necrosis factor (TNF) a, organize thrombosis. Furthermore, MPV has been shown to be a marker of inflammation in active inflammatory disease [20, 21]. The contribution of PLT to inflammation, in which they perform this by binding to and activating to monocyte, was demonstrated in patients with MI [22, 23].

The mechanism for the enlarged circulating platelets at time after admission remains unclear. Newly generated PLTs arised from bone marrow megakaryocyte are usually bigger as size [18]. The time required for differentiation and maturation of megakaryocyte is about 4–5 days [18, 19]. A period of 24 h is needed for de novo PLTs production and release of these from mature megakaryocytes. Therefore, it is less possible that early mortality in patients with acute MI [31]. MPV at baseline, 30, 60, 90 days, and at 1, 2 and 3 years after PCI was evaluated in unselected coronary artery disease patients [36]. In that study, an increase in MPV over time was associated with long term mortality. In contrast to the their study, we investigated the association of in-hospital increase in MPV with mortality in STEMI patients who were undergoing pPCI. We found that an increase in-hospital MPV after admission was associated with mortality in these patients.

Medications including ACE-I/ARB, beta blockers, statins, and antiplatelet drugs may influence MPV [37, 38]. With regard to ΔMPV, we did not find any difference between patients receiving these drugs and those who did not. Moreover, tirofiban usage had no effect on ΔMPV in our study (data not shown). Further research is required to determine the impact of these treatments on ΔMPV.

A high ΔMPV may be indicative of more thrombogenic and active platelets. Also, the presence of it may be a reflection of the increased thrombosis and inflammation. Thus, an increased PLTs size further contribute to the formation of thrombus. Moreover, large size PLTs may lead to vasoconstriction and endotelial dysfunction. Therefore, the abovementioned associations may be possible underlying mechanisms of mortality in STEMI patients who were undergoing pPCI.

The present study has a few limitations. This is a retrospective study with a relatively small size, which precludes determining a definitive relationship between ΔMPV and outcomes. The effect of different oral antiplatelets loading dose on MPV was not evaluated in the present study. Also, we could not investigate previous use of nonsteroidal anti-inflammatory drugs before PCI. The DM patients treated with incretin had a significantly lower rate of major cardiovascular events compared to those were not treated by this treatment [39, 40]. As data regarding incretin usage was not present in many patients, its effect on mortality in present study could not be assessed. Moreover, we did not evaluated effect this agents on molecules involved in atherosclerotic plaque stability. Finally, possible selection bias may have impacted these results.

**Conclusion**

Rising MPV during hospitalization was associated with long-term mortality in STEMI patients treated with pPCI. We suggest that repeated MPV determinations throughout hospitalization may improve risk stratification in these patients.
Abbreviations

ACS: Acute coronary syndrome; CAD: Coronary artery diseases; DM: Diabetes mellitus; HF: Heart failure; HT: Hypertension; IDI: Integrated discrimination improvement; LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; MPV: Mean platelet volume; NRI: Net reclassification improvement; PCI: Primary percutaneous coronary intervention; ROC: Receivers operating characteristic; sCr: Serum creatinine; STEMI: ST-elevation myocardial infarction; TVR: Target vessel revascularization; WBC: White blood cell; ΔMPV: Change in mean platelet volume.

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Availability of data and materials

Data are available from the corresponding author on reasonable request due to privacy or other restrictions.

Authors’ contributions

TK, EA: conception and design of the work; EA, HD: acquisition, analysis, and interpretation of data; AC, EV, FKE: drafting the manuscript and revising it critically for important intellectual content; TK, DK and EA: final approval of the version to be published. All authors agreed to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Authors’ information

Eyup Avci takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Ethics approval and consent to participate

The study was designed retrospectively. Balikesir University Ethics Committee waived the need for informed consent regarding the retrospective data and approved this study.

Consent for publication

Not applicable.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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