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Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease

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HIGHLIGHTS

- This study aimed to evaluate the impact of mean platelet volume (MPV) in patients following elective percutaneous coronary intervention (PCI).
- Patients with low MPV values showed higher incidences of cardiovascular events.
- A decrease in MPV was significantly associated with poor clinical outcomes.
- The results were contrary to the report from previous studies on acute coronary syndrome (ACS) patients.

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ABSTRACT

Background and aims: Although an elevated mean platelet volume (MPV) has been associated with poor clinical outcomes after acute coronary syndrome (ACS), the association between MPV and long-term outcomes in patients with stable coronary artery disease (CAD) remains uncertain. We aimed to investigate the impact of pre-procedural MPV levels in patients following elective percutaneous coronary intervention (PCI).

Methods: We studied 2872 stable CAD patients who underwent their first PCI and who had available data on pre-procedural MPV between 2002 and 2016. Patients were divided into quartiles based on their MPV. The incidences of major adverse cardiac events (MACE), including all-cause death and non-fatal myocardial infarction, were evaluated.

Results: The median MPV was 10.4 fL (interquartile range: 9.8–11.0). During a median follow-up of 5.6 years, 498 (17.3%) MACE were identified, with a cumulative incidence significantly higher in the lowest MPV group than in other groups ($p < 0.01$). After adjustment for platelet count and the other cardiovascular risk factors, the lowest MPV group had a significantly higher risk of MACE compared with the highest MPV groups (hazard ratio: 1.43, 95% confidence interval 1.10–1.86, $p = 0.009$). Decreasing MPV as a continuous variable was associated with the incidence of MACE (hazard ratio: 1.16 per 1 fL decrease, 95% confidence interval 1.04–1.30, $p = 0.007$).

Conclusions: Contrary to previous studies on ACS patients, this study showed that a low MPV was associated with worse clinical outcomes among stable CAD patients.

1. Introduction

Cardiovascular disease is one of the leading causes of mortality and disability, and remains a major concern despite improved clinical outcomes with evidence-based treatment [1]. Therefore, identification of the residual risk for cardiovascular disease is essential for more effective management and prevention.

Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the pathogenesis of atherosclerosis and arterial thrombosis [2,3]. Mean platelet volume (MPV) is a major parameter of platelet size that is routinely determined by complete blood count analyzers at a relatively low cost. Compared with

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smaller platelets, larger platelets are more readily stimulated to release chemical mediators and are recognized as being more active and likely to aggregate [4]. Increased MPV levels have been reported to be associated with coronary artery disease (CAD), peripheral arterial disease, and cerebrovascular disease [5–7]. In addition, the correlation between a high MPV and poor clinical outcomes after myocardial infarction (MI) has been previously demonstrated [8,9]. However, the association between MPV levels and clinical outcomes in patients with stable CAD remains uncertain. Therefore, in the present study, we aimed to investigate the impact of pre-procedural MPV levels in stable CAD patients after elective percutaneous coronary intervention (PCI).

2. Patients and methods

2.1. Patients and data collection

In this observational study, the data of consecutive patients, who underwent their first-time elective PCI at Juntendo University from January 2002 to December 2016, were analyzed. Patients missing MPV values and those with known malignancy or active inflammatory disease were excluded from the study. Patients were divided into 4 groups according to MPV values (< 9.8, 9.8–10.3, 10.4–10.9 and 10.9 <).

The demographic data and information on coronary risk factors, medications, revascularization-related factors, and co-morbidities were prospectively collected and analyzed. Hypertension was defined as blood pressure of > 140/90 mmHg on admission or receiving antihypertensive drugs. Patients with low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dl, high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dl, triglycerides ≥150 mg/dl) or current treatment with statins and/or lipid-lowering agents were regarded as dyslipidemic [10]. Diabetes mellitus was defined when hemoglobin A1c was ≥6.5% or when oral hypoglycemic drugs or insulin were taken. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2, as calculated using the equation of the modification of the diet in renal disease, modified with a Japanese coefficient using baseline serum creatinine [11]. A current smoker was defined as a person who smoked at the time of PCI or who had stopped smoking within 1 year before PCI. Left ventricular ejection fraction (LVEF) was assessed using echocardiography or left ventricular angiography before admission. All patients had symptoms of effort angina, documented myocardial ischemia, or both.

Blood samples were collected in the early morning after an overnight fasting. All samples were obtained in standardized dipotassium ethylenediaminetetraacetic acid tubes. The blood counts were determined using automated hematology analyzers [XE-2100 (2002–2008) and XE-5000 (2008–2016); Sysmex Corporation, Kobe, Japan]. We used the continuous variable MPV values as the test variable and all-cause death and non-fatal MI as the state variables.

This study was performed in accordance with the Declaration of Helsinki and with the approval of our institutional review board. Written informed consent was obtained from all patients before undergoing PCI.

2.2. Primary endpoints

The primary outcome was major adverse cardiac events (MACE), which was defined as a composite of all-cause death and non-fatal MI. MI was defined as clinical evidence of myocardial necrosis that was consistent with myocardial ischemia. Clinical follow-up comprised analyses of office visit charts, as well as the responses to the questionnaires sent to the patients or their families and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated at our institution; the details and causes of death were obtained from the other hospitals where the patients had been admitted.

2.3. Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Continuous variables were compared across groups using One-way analysis of variance or Kruskal-Wallis test. The Chi-squared test was used for categorical variables. Simple linear regression analysis was used for MPV and biochemical and clinical measurements. Pearson's correlation coefficients were used to examine the relationships between MPV and the other variables. The unadjusted cumulative event rates were compared across groups using Kaplan–Meier curves and log-rank test. The effects of MPV values on clinical outcomes after PCI were determined using multivariate Cox proportional hazard regression analysis. Model 1 was adjusted for age, sex, and platelet count. Model 2 was adjusted for the variables in model 1 plus body mass index (BMI), beta blocker use, CKD, diabetes mellitus, HDL-C level [12], hypertension and statin use on admission. Model 3 was adjusted for age, BMI, CKD, family history of CAD, fasting blood glucose, hemoglobin, insulin use, LVEF, statin use and white blood cell counts. These variables in model 3 were selected by univariate Cox hazard analysis ($p < 0.10$) and using backward and forward stepwise method. The MPV values were included in the multivariate model, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Differences were considered significant at $p < 0.05$. Statistical analyses were carried out using JMP version 12.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline and procedural characteristics

Of the 2882 patients who underwent elective PCI, pre-procedural MPV values were available for 2872 patients (99.7%). The median and mean MPV values were 10.4 fL (IQR, 9.8–11.0 fL) and 10.5 ± 0.9 fL, respectively. The clinical and procedural characteristics of these patients are shown in Table 1. Patients in the lowest MPV group were significantly older and had lower baseline hemoglobin, higher platelet count, and higher concentration of high-sensitivity C-reactive protein (hs-CRP); whereas patients in the higher MPV groups had higher prevalence of diabetes mellitus, higher BMI, and lower HDL-C levels on admission. No significant differences were found among groups in terms of medications, with the exception of β-blockers, and characteristics of the lesion or procedure.

Table 2 shows the association between the logarithm (log) of MPV and the clinical parameters. A significant inverse correlation was found between MPV level and platelet count ($r = -0.31$, $p < 0.0001$). Likewise, the correlations of MPV levels with hemoglobin ($r = 0.15$, $p < 0.0001$) and hemoglobin A1c ($r = 0.11$, $p < 0.0001$) were significant but relatively weak.

3.2. Clinical outcomes

The median duration of follow-up was 5.6 years (IQR, 2.2–10.4 years). In total, 498 (17.3%) MACE were identified during follow-up, including 446 (15.5%) deaths and 64 (2.2%) MIs. Table 3 shows the cumulative incidences of the cardiac events. MACE, all-cause death, and MI were significantly higher in the lowest MPV group than in other groups (all $p < 0.05$). The Kaplan–Meier curves (Fig. 1) show that the patients in the lowest MPV group clearly had significantly higher incidence of MACE (log-rank $p = 0.0002$). Furthermore, Kaplan-Meier curves for MACE showed significant differences in the incidences of events among groups, even stratified by platelet counts of 200×10^3/μL (Supplementary Fig. 1).

Table 4 shows the Cox proportional hazard analyses for MACE. In the unadjusted Cox model, the lowest MPV group was significantly associated with cardiac events compared with patients in the highest groups ($p = 0.001$). In model 3, patients in the lowest MPV group had

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