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Mean platelet volume and coronary artery disease: a systematic review and meta-analysis

Nakarin Sansanayudh [a,b], Thunyarat Anothaisintawee [a,c,*,1], Dittaphol Muntham [a], Mark McEvoy [d], John Attia [d], AmmarinThakkinstian [a]

[a] Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[b] Cardiology Unit, Department of Internal Medicine, Phramongkutklao Hospital, Bangkok, Thailand
[c] Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[d] Centre for Clincial Epidemiology and Biostatistics, School of Medicine and Public Health, Faculty of Health and Medicine, University of New Castle, NSW, Australia

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ABSTRACT

Background: Platelets with high hemostatic activity play an important role in the pathophysiology of coronary artery disease(CAD) and mean platelet volume(MPV) has been proposed as an indicator of platelet reactivity. Thus, MPV may emerge as a potential marker of CAD risk. The aim of this study was to conduct a systematic review and meta-analysis comparing mean difference in MPV between patients with CAD and controls and pooling the odds ratio of CAD in those with high versus low MPV.
Methods: Medline and Scopus databases were searched up to 12 March 2013. All observational studies that considered MPV as a study's factor and measured CAD as an outcome were included. Two reviewers independently selected the studies and extracted the data.
Results: Forty studies were included in this meta-analysis. The MPV was significantly larger in patients with CAD than controls with the unstandardized mean difference of 0.70 fL (95% CI: 0.55, 0.85). The unstandardized mean difference of MPV in patients with acute coronary event and in patients with chronic stable angina was 0.84 fL (95% CI: 0.63, 1.04) and 0.46 fL (95% CI: 0.11, 0.81) respectively. Patients with larger MPV (≥7.3 fL) also had a greater odds of having CAD than patients with smaller MPV with a pooled odds ratio of 2.28 (95% CI: 1.46, 3.58).
Conclusion: Larger MPV was associated with CAD. Thus, it might be helpful in risk stratification, or improvement of risk prediction if combining it with other risk factors in risk prediction models.

1. Introduction

Coronary artery disease (CAD) is the most common cause of death worldwide [1]. Many risk factors for CAD have been reported including diabetes mellitus (DM), hypertension, dyslipidemia, age, gender, family history of CAD, ethnicity, smoking, lack of exercise, emotional stress, obesity, metabolic syndrome, and insulin resistance [2]. However, in the presence of these risk factors, some people do not develop CAD, and in the absence of these risk factors some people still develop CAD. Therefore the search for new risk factors or biomarkers that could improve disease prediction is ongoing, e.g., high-sensitivity C-Reactive protein (hs-CRP) [3], carotid intimal media thickness (IMT) and coronary calcium score [4,5]. However, these factors are either difficult or expensive to measure, unavailable in routine practice, require subspecialty clinicians to perform or interpret the results, or have limited accuracy. Therefore, at present, there is still a need for a simple, easy to measure, minimally invasive, inexpensive, and widely available marker that will improve risk prediction and risk stratification of CAD.

Platelets play an important role in the pathophysiology of CAD [6]. Young platelets are larger and are more active [7], which can lead to more platelet adhesion and aggregation, and result in vascular thromboembolic events. Therefore, platelet volume has been proposed as an indicator of platelet reactivity. Mean platelet volume (MPV) is an accurate measure of platelet size, which is routinely reported during a complete blood count (CBC) analysis. This has received substantial attention in the past few years with numerous studies assessing the association between MPV and CAD risk. Some studies have shown that MPV was larger in stable angina patients than healthy populations [8–11]. In addition, MPV was also larger in acute myocardial infarction (AMI) compared to stable angina patients [12]. Furthermore, larger MPV was also associated with poor prognosis in AMI patients [13–15].

Abbreviations: AMI, acute myocardial infarction; CBC, complete blood count; CAD, coronary artery disease; CSA, chronic stable angina; CS, coronary artery stenosis; DM, diabetes mellitus; fL, femtoliters; hs-CRP, high-sensitivity C-Reactive protein; IMT, intimal media thickness; MPV, mean platelet volume; NSTEMI, non-ST elevation myocardial infarction; OR, odds ratio; STEMI, ST elevation myocardial infarction; SD, standard deviation; UA, unstable angina; USMD, unstandardized mean difference.

* Corresponding author. Tel./fax: +66 22011284.
E-mail address: thunyarat.ano@mahidol.ac.th (T. Anothaisintawee).
[1] Postal address: Department of Family Medicine, Ramathibodi Hospital, Param VI road, Prayathai, Ratchathewi, Bangkok, Thailand, 10400.

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Although many studies have assessed the effect of MPV on CAD risk, their results are conflicting. This may be due to a lack of power in some studies or the use of different thresholds for assessing the association. Subsequently, a systematic review and meta-analysis of 16 studies were conducted [12]. This suggested that mean MPV was approximately 0.92 femtoliters (fL) (95% CI: 0.67, 1.16) higher in AMI than non-AMI patients. However, this review combined studies in which most of the controls were a mixture of ischemic heart disease and unstable angina patients, and only 3/16 studies included healthy controls. Thus, the magnitude of the association between MPV and CAD might be biased towards the null. In addition, studies were identified from only one database and there have been more studies published since their last search in 2010. We therefore conducted a systematic review and meta-analysis with two aims. First, to assess the association between MPV and CAD by estimating the pooled mean difference in MPV between CAD and control groups. Second, to estimate pooled odds ratio (OR) of CAD between high and low MPV groups.

2. Methods

2.1. Search strategy

We searched Medline and Scopus databases from iniations to 12 March 2013 to identify potential relevant studies. The search terms were as follows: cardiovascular disease, coronary blood flow, coronary flow, ejection fraction, mortality, death, re-stenos*, Ventricular Function, Left[Mesh], Heart Failure[Mesh], Coronary Restenosis[Mesh], Death[Mesh], myocardial infarction, Myocardial Infarction[Mesh], Cardiovascular Diseases[Mesh], platelet volume. Search strategies for both databases are described in Supplement appendix A and B. Reference lists of all included studies and previous systematic reviews were additionally explored to identify eligible studies not located using the database search.

2.2. Selection of studies

The selection of eligible studies was performed by 2 independent reviewers (N.S. and T.A.). Inconsistency regarding the selection of studies was resolved by consensus with the senior consultant (A.T.). Studies published in English were selected if they met the following criteria: 1) MPV was a study factor, 2) the outcome of interest was any types of CAD including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), chronic stable angina (CSA), coronary artery stenosis (CS), cardiac syndrome X, and 3) had sufficient data for pooling, i.e., number of subjects, mean MPV and standard deviation(SD) between CAD and control groups for continuous data; frequencies of subjects in a contingency table of high/low MPV and CAD groups for categorical data. Studies were excluded if there were insufficient data for pooling and no response after contacting the authors twice.

2.3. Data extraction

Baseline participant characteristics of included studies (i.e. mean age, sex, smoking status, study settings, methods used for measuring MPV, types of CAD and non-CAD), mean MPV in CAD and non-CAD groups for continuous outcome, and frequency of CAD and non-CAD patients in high and low MPV groups for dichotomous outcome, were extracted by 2 independent reviewers (N.S. and T.A.) using a standardized data extraction from. Disagreement was resolved by consensus with the senior consultant (A.T.). Missing data were obtained by contacting the corresponding authors up to two times.

2.4. Risk of bias assessment

Two authors (N.S. and T.A.) independently assessed risk of bias of each study using the Newcastle and Ottawa risk of bias criteria [16]. Three domains were considered, i.e., selection of study groups (4 items), comparability of groups (2 items), and ascertainment of exposure and outcome (3 items). Each item was graded as 0 to 1 with a total score ranging from 0 to 9; higher total score reflected higher quality or lower risk of bias.

Since the Newcastle and Ottawa risk of bias criteria do not have the criteria to assess risk of bias for cross-sectional study, thus we applied the criteria of cohort study for cross-sectional study. However, two criteria in the domain of ascertainment of outcome (i.e. adequate duration of follow up and adequate follow up of cohort) cannot be applied for cross-sectional study, thus the total score for cross-sectional study ranged from 0 to 7. Disagreement was resolved by consensus after discussion between both authors.

2.5. Statistical analysis

For continuous outcomes, the mean difference in MPV between CAD and control groups was estimated for each study and pooled using an unstandardized mean difference (USMD). For dichotomous outcomes, given that different studies used different thresholds to define high and low MPV, the odds ratio (OR) of having CAD among high and low MPV groups was estimated for each study. In both cases, heterogeneity of the effect measure was assessed using the Q statistic and I^2. If heterogeneity was detected (P value < 0.10 or $I^2 \geq 25\%$), a random-effect model (Dersimonian & Laird method) was applied; otherwise, a fixed-effect model (inverse-variance method) was used.

Bivariate meta-analysis was applied for pooling diagnostic parameters including sensitivity, specificity, and likelihood ratio positive of high MPV effect on CAD using metandi command in STATA [17]. Pre-test probability (i.e., prevalence and incidence of CAD where appropriate) and positive predictive value were pooled using user-provided pmeta command [18]. Only data from cross-sectional and cohort studies were used for pooling pre-test-probability. Post-test probability was also further estimated [19].

Sources of heterogeneity were explored by fitting each of the co-variables (i.e. mean age, study setting, percentage of males, diabetes, hypertension, smoking, type of anticoagulant used (either EDTA or citrate), timing of MPV test, type of cases and type of controls) in a meta-regression model. Publication bias was assessed using an Egger test and funnel plot. All analyses were performed using STATA software, version 12 [20]. A two-sided test with P-value < 0.05 was considered statistically significant except for the test of heterogeneity, in which a P-value < 0.1 was used.

3. Results

We identified 454 publications in Medline and 638 publications in Scopus databases. Of these 1092 studies, 343 were duplicate studies and thus were excluded, leaving 749 studies to be assessed. After applying eligibility criteria, 40 studies met the inclusion criteria and were included in the review. Reasons for exclusion of the studies are presented in Fig. 1.

Of the 40 included studies, 32 (80%) studies reported mean difference in MPV [10,11,21–50], 4 (10%) studies reported ORs of high vs low MPV [51–54], and 4 (10%) studies reported both [8,9,55,56]. Of the 36 studies reporting mean difference in MPV, 30 (83%) studies [8–11,21–31,33–45,55,56] compared mean MPV between CAD patients (which were defined as either STEMI, NSTEMI, MI, ACS, UA, CSA, or CS) and controls, while 5 (14%) studies [46–50] compared mean MPV between patients with slow coronary blood flow versus normal flow, and 1 (3%) study [32] compared both. Most of the studies were case–control (27 studies, 70%), while 12 (28%) studies were cross-sectional, and 1 (2%) study was a cohort. Mean age of study participants ranged from 50 to 75 years, see Table 1. Percentage of males, smokers, and diabetics ranged from 25% to 86%, 19% to 71%, and 4% to 54%, respectively. Most of the studies (21 studies, 52%) included healthy populations as a control group, whereas some included non cardiac chest pain (8 studies, 20%), normal coronary angiogram (7 studies, 18%), and normal coronary blood flow (4 studies, 10%) patients as controls.

3.1. Risk of bias assessment

Results of risk of bias assessment of 40 studies are presented in Supplement Tables 1 and 2. Only 1 cohort study was included in the review and had the total score of 7 out of 9. For 12 cross-sectional studies, total scores ranged from 1 to 5 with a median of 5. For 28 case control studies, the total scores ranged from 5 to 8 with a median of 6. Seven and nineteen studies had score equal or greater than median for cross-sectional and case–control designs, respectively.

3.2. Pooled mean differences

3.2.1. CAD vs controls

Thirty-one studies [8–11,21–45,55,56] reported mean MPV difference between CAD patients (n = 5236) and controls (n = 7049), see Supplement Table 3. For those studies with multiple CAD outcome categories, data were combined to form one CAD group. Mean difference of MPV between CAD and control was estimated for each study and the estimated USMD was 0.70 fL (95% CI: 0.55, 0.85), see Fig. 2. This indicates that mean MPV in CAD patients was 0.70 fL larger than mean MPV of controls. However, this pooling was highly heterogeneous (Chi-square = 544.79, P-value <0.001, I^2 = 94.5%) and thus possible sources of heterogeneity were explored using meta-regression. Neither coefficient was significant or reduction of the I^2 was observed after including each factor. There was no evidence of publication bias using