Original Article

Mean Platelet Volume (Mpv) as a Predictor of Venous Thromboembolism (Vte) in Colorectal Cancer

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Background: Platelet activity is a major devilish atherothrombotic events and cancer. Mean platelet volume (MPV), which is widely available as a routine parameter of the complete blood count, is a potentially useful biomarker of platelet activity in the setting of venous thrombosis. Recent studies showed that high-MPV levels are associated with an increase VTE risk in cancer patients.

Objective: To investigate the role of MPV in VTE and colorectal-cancer.

Materials and Methods: A retrospective study was performed to analyze differences of MPV between patients with VTE, VTE and colorectal-cancer, and control.

We identified comparative studies that compared the effect of MPV in VTE from PubMed and Scopus databases up to December 2017. Two reviewers independently extracted data for meta-analysis. Differences in MPV were expressed as unstandardized mean difference.

Results: Among 170 patients, 58-control, 54-VTE, and 58-VTE with colorectal-cancer, MPV was significantly higher in VTE groups. From 403 articles, 10 studies (5 cohorts and 5 case-controls) comprising 2,265 patients. MPV was significantly higher in those with VTE (mean difference 0.61 fL, 95% CI 0.34 to 0.88, $p<0.001$). Elevated MPV increased the relative risk of VTE (RR 1.319, 1.061 to 1.641, $I^2 = 82.5\%$).

Conclusion: Our evidence suggests that elevated MPV is associated with VTE and VTE with colorectal-cancer. A mechanistic study and RCT are required in order to use antiplatelet therapy.

Keywords: Deep vein thrombosis, Meta-analysis, Pulmonary embolism

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Platelet activity is a major devilish (unclear use of word, devilish, Ed) in atherothrombotic events and cancer. Many studies have suggested that increase platelet activity is a risk factor for cardiovascular disease and associated with cigarette smoking, dyslipidemia, hypertension, and diabetes, all of which are associated with increased risk for atherothrombotic in arterial and venous diseases[1-3]. Mean platelet volume (MPV), which is widely available as a routine parameter of the complete blood count, is a potentially useful biomarker of platelet activity in the setting of venous thrombosis. Recent studies showed that high-MPV levels are associated with an increase VTE risk in cancer[2,4].

Mean platelet volume (MPV) is an accurate measurement of the size of platelets. Larger platelets are metabolically and enzymatically more active and have higher homeostasis property than smaller platelets, containing more pro-thrombotic material with increased thromboxane B2 per unit volume and glycoprotein IIb/IIIa receptor expression. Larger platelets possess greater aggregability in response to ADP and decreased inhibition of aggregation by prostacyclin in vitro. Larger platelets are denser which contain more alpha granules, which release prothrombotic factors[5].

MPV is associated with platelet function and activation and has emerged as a potential marker of atherothrombotic in arterial and venous diseases[6]. When measuring complete blood count (CBC), the MPV is routinely measured and reported. It is increasingly recognized as an important marker of platelet activity. Large platelets are more active, contain more prothrombotic material, and are more likely to aggregate compared with smaller platelets. Platelet volume has been found to increase in patients with myocardial infarction, cerebrovascular disease, VTE, and cancer[7-9]. However, some studies have shown controversial results, high MPV levels might associated with a decreased VTE risk in cancer patients[10]. In the present study, the authors aim to investigate the role of MPV in VTE and colorectal-cancer.

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Materials and Methods

Cohort study

A retrospective study was performed to analyze differences of MPV between patients with VTE, VTE and colorectal-cancer, and control. Retrospective analysis was performed in 170 patients who were diagnosed and treated in out-patient surgical unit of Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University between 2012 and 2017. All participants who had MPV results were eligible for inclusion in the present study. The participants with history of hematologic disease or abnormal CBC results were excluded. Patients were divided into 3 groups according to the diagnosis. Group I, 58 patients who were diagnosed as varicose veins without underlying diseases, VTE, or cancer. Group 2, 54 patients who were diagnosed as VTE without cancer. Group 3, 58 patients who were diagnosed as VTE with colorectal-cancer. MPV values were analyzed from the laboratory records (CBC) of patient data.

Meta-analysis

A literature search of the MEDLINE and Scopus was performed from January 1946 to December 2017. Search terms used were ("Venous thromboembolism" or "deep vein thrombosis" or "pulmonary embolism") and ("mean platelet volume" [Mesh] or "platelet") with limited to comparative studies, English, and human for Medline; English, medicine, article, article in press for Scopus. List of references of previous meta-analyses and all eligible studies were also explored for eligibility. If studies were duplicated, the one with the most complete data was chosen. For studies which reported insufficient data, the corresponding authors were contacted and invited to provide more information. Two attempts were made to contact authors and those who did not respond were excluded from the review.

Outcomes

The outcome of interest was mean platelet volume (MPV) which was routinely measured and reported in CBC. A normal range of mean platelet volumes is between 9.7 to 12.8 fL.

Data extraction

Two reviewers (CW and NP) independently extracted the data from each study using a standard data extraction form. Information extracted included general data (i.e. author, year of publication, journal), study characteristics (i.e. study design, setting), patient characteristics (i.e. age, underlying diseases, surgical procedures, diagnosis, investigations, follow-up period), and outcome as described above. Any disagreement was discussed and resolved by consensus with the third party (BS).

Risk of bias assessment

The quality of studies was independently assessed by CW, NP, and BS on the basis of representativeness of studied subjects, information bias (*i.e.*, ascertainment of outcome and surgical technique), and confounding bias. Each item was graded as "yes" for low risk of bias, "no" for high risk of bias, and "unclear" if there was insufficient information to judge. Any disagreement between the reviewers was discussed and resolved by consensus.

Statistical analysis

The continuous variables were expressed as mean $\pm$ standard deviation while the categorical variables were expressed as number and percentage (%). Normally distributed variables were compared across groups by means of student t test. The non-parametric variables were compared using the Mann-Whitney U test. Logistic regression analyses were performed to rule out the confounding effect of imbalance clinical features between two groups. Categorical variables were compared via Chi-square test. A p-value <0.05 was considered to be statistically significant. Odds ratios and 95% confidence intervals were estimated by logistic regression.

A mean difference of MPV between patients with VTE and without VTE was estimated for each study. Data were then pooled using non-standardised mean differences using Der-Simonian and Laid random effect model if heterogeneity was present; otherwise, the fixed-effect model was used. If the study did not report mean and standard deviation (SD), these parameters were estimated from median and range in the study using method described by Hozo et al[11].

Meta-regression analysis was used to assess the source of heterogeneity by fitting age, and type of wound in the meta-regression model. Funnel plot with or without contour-enhancement was applied to detect publication bias due to small study effects. Egger's test was used for assessing the asymmetry of the funnel plot. All analyses were performed using STATA version 14.0. A p-value <0.05 was considered statistically significant, except for the heterogeneity test for which p<0.1 was used.

Results

Cohort study

There was no significant difference in demographic data between 3 groups of patients (age, gender, and underlying diseases). The mean platelet volume values (fl) were 7.0$\pm$0.6, 8.2$\pm$1.0, and 9.0$\pm$0.9 in the control group (patients with varicose veins), the VTE group, and VTE with colo-rectal cancer group, respectively. The MPV values were significantly higher in VTE group when compared to the control group (7.0$\pm$0.6 vs. 8.2$\pm$1.0, p = 0.04). The MPV values were significantly higher in VTE with colo-rectal cancer group when compared to the control group (7.0$\pm$0.6 vs. 9.0$\pm$0.9, p<0.001). The MPV values were significantly higher in VTE with colo-rectal cancer group when compared to the VTE group (8.2$\pm$1.0 vs. 9.0$\pm$0.9, p = 0.04) (Table 1). The significant association between MPV and VTE was unchanged when MPV was used as a categorical variable (mean tertile 1 to 7.10%, mean tertile 2 to 8.20%, mean tertile 3 to 9.00%).

Table 1. MPV values in the control, VTE, and VTE with colorectal cancer

Treatment	Mean ± SD (fl)	*p*-value
Control-varicose veins vs. VTE	7.0±0.6 vs. 8.2±1.0	0.04
Control-varicose veins vs. VTE with colorectal cancer	7.0±0.6 vs. 9.0±0.9	<0.001
VTE vs. VTE with colorectal cancer	8.2±1.0 vs. 9.0±0.9	0.04

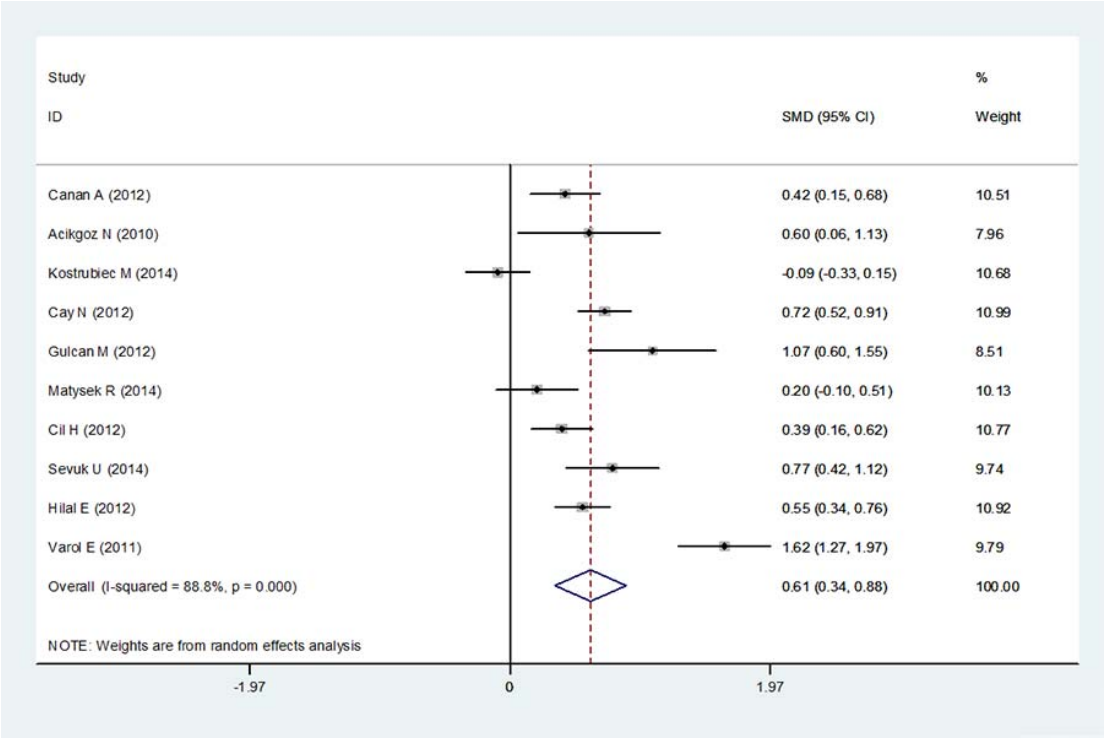

Figure 1. Forest plot for risk of venous thromboembolism (VTE) and increase mean platelet volume (MPV).

Meta-analysis

From 403 articles, 10 studies (5 cohorts and 5 case-controls) comprising 2,265 patients. MPV was significantly higher in those with VTE (mean difference 0.61 fL, 95% CI 0.34 to 0.88, $p<0.001$). Elevated MPV increased the relative risk of VTE (RR 1.319, 1.061 to 1.641, $I^2 = 82.5\%$) (Figure 1).

Assessment of risk of bias was done. The agreement between two reviewers was 94.6 percent with a statistic of 0□94($p<0$□001). Among 10 studies, the risk of selection bias from the use of non-representative cases was low in 8 and unclear in 2 studies. The ascertainment of all outcomes was clearly described in 7 studies. Ascertainment of MPV measurement technique was clear in 7 studies. Confounding bias was likely to be present in 8 studies.

Discussion

There is growing evidence of a relationship between cancer biology, platelet, and the clotting system[12]. Tissue factor (TF), the initiator of the clotting pathway, promotes cancer via clotting dependent and independent mechanism. Thrombocytosis is associated with reduced survival in several cancers, such as lung cancer, ovary cancer, endometrium cancer, rectal cancer, kidney cancer, gastric cancer, pancreatic cancer, and breast cancer[13]. Increased platelets facilitate cancer progression and metastasis by promoting angiogenesis and tumor cell establishment at distant sites[14].

Prior studies support that MPV is a measure of platelet activity. Larger platelets are metabolically and enzymatically more active than smaller platelets, containing more pro-thrombotic material with increased thromboxane B2 and glycoprotein IIb/IIIa receptor expression. Larger platelets possess greater aggregability in response to ADP and decreased inhibition of aggregation by prostacyclin in vitro. Larger platelets are denser which contain more alpha granules, which release prothrombotic factors. Larger platelets

are associated with increasing reticulated platelets, an independent predictor of poor response to dual antiplatelet therapy[15]. Nevertheless, the role of platelet size, as a biological marker of platelet activation, remains debated in the setting of venous thrombosis. A decreased MPV value in active cancer patients was associated with the highest risk of diagnosing thrombosis in emergency department and inverse association between MPV and the risk of venous thrombosis was found at diagnosis[16].

The present study found that MPV is correlated with the risk of VTE and colorectal cancer. Our findings indicted the potential importance of assessing CRC prognosis by combining clinicopathological characteristics with platelet index. However, our study has several limitations. First is the small sample size, second is we cannot establish causal relations between MPV and PAD, third is the variability in MPV remains unexplained by clinical factors, and fourth is the uncertain measurement of MPV at a single time point.

In conclusion, VTE in CRC continues to be a challenging clinical entity for patients and clinicians, and its health burden, in the form of death, chronic pain and venous ulceration, is likely underestimated. Robust strategies for the prevention of VTE in CRC are essential. Our evidence suggests that elevated MPV is associated with VTE and VTE with colorectal-cancer. A mechanistic study and RCT are required in order to use antiplatelet therapy.

What is already known on this topic?

According to the results in our study related to the results in previous studies in terms of association between MPV and VTE, it confirmed the role as we know it about high-MPV levels associated with an increase in VTE risk.

What this study adds?

The present study added new knowledge to solve the controversy over association and the role between MPV with a decreased VTE risk in colorectal cancer patients. The results showed statistics significantly higher for MPV levels in colorectal cancer than the control group.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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