

# Associations Between Mean Platelet Volume and Risk of Deep Vein Thrombosis: A Mendelian Randomization Study and a Retrospective Study

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**Objective:** In this study, it was intended to explore the causal association between mean platelet volume (MPV) and risk of deep vein thrombosis (DVT) using a two-sample Mendelian randomization (MR) analysis and a retrospective study.

**Methods:** This study applied two-sample MR analysis to estimate the causal association between MPV and risk of DVT. Twenty-one single nucleotide polymorphisms (SNPs) were selected as genetic variants from two independent consortiums cohorts (p-value  $< 5 \times 10^{-8}$ , linkage disequilibrium  $r^2 < 0.1$ ). Inverse variance weighted (IVW), MR-egger method and weighted median were performed. A retrospective study was also conducted to verify the associations identified from the MR study.

**Results:** The MR analysis demonstrated that genetically predicted higher MPV was associated with significantly lower risk of DVT (OR 0.982, 95% CI = 0.967–0.998,  $P = 0.023$ ), with the consistent result in weighted median and MR-Egger. There was no directional horizontal pleiotropy in the method of MR-Egger regression (intercept =  $2.9 \times 10^{-4}$ ,  $P = 0.194$ ). There was no single SNP was found to strongly drive the combined causal effect in the leave-one-out sensitivity analysis. Additionally, the similar result was observed in the retrospective study.

**Conclusion:** This study suggested that MPV was negatively associated with the risk of DVT. More basic researches are needed in the future to explore its specific mechanism.

**Keywords:** mean platelet volume, deep vein thrombosis, Mendelian randomization, causal association

## Introduction

Deep venous thrombosis (DVT) is a substantial cause with severe complications in nearly all hospitalized patients, which increases the potential incidence both for morbidity and mortality. While a lot of efforts are performed in the DVT prevention, delay diagnosis of DVT still contributed to a high risk of pulmonary embolism and post-thrombotic syndrome, seriously affecting the quality of life of patients and bringing a heavy global health burden. As a result, timely and accurate prediction of DVT is of significant importance.<sup>1,2</sup> D-dimer is the most common clinical indicator to diagnosis or rule out the DVT events in clinical practice.<sup>3</sup> Due to the lack of specificity,<sup>4</sup> the diagnostic value of D-dimer is not clinically recognized, thus to identify more effective diagnosis marker has become imperative.

Platelet plays an essential role in the process of thrombosis formation.<sup>5</sup> As a common marker to measure the size of platelet in clinical practice, mean platelet volume (MPV) is expected to be a potential predictor of the diagnosis of DVT, while there is still controversy on the effect of MPV on DVT.<sup>6</sup> Higher MPV was observed with increased risk of DVT in several retrospective studies. However, increasing researches reported different opinions on the effect of MPV towards the risk of DVT, indicating that the relationship has not been systematically examined and further studies are needed to explore the casual relationship between MPV and risk of DVT.<sup>7,8</sup>

Considering that most previous reports belonging to traditional observation research, the result was inevitably disturbed by confounding factors and reverse causation.<sup>11</sup>

As a new approach, Mendelian randomization (MR) has been widely performed to the casual inference, while it remained blank about MPV on the risk of DVT.

In the present study, we aimed to investigate a potentially causal association between MPV and risk of DVT by using MR as well as a retrospective study to verify the result.

## Materials and Methods

### Study Design

A two-sample MR analysis was performed to investigate the causal association between MPV and risk of DVT, in which the summary data of genetic variants associated with MPV and genetic variants associated with DVT were obtained from two independent consortiums cohorts.<sup>12</sup> The analysis was based on three hypotheses.<sup>13</sup> Firstly, to serve as instruments, genetic variants are robustly related to MPV. Secondly, genetic variants should be strictly independent of confounding factors between DVT and MPV. At last, genetic variants must affect the risk of DVT only through the way of MPV. The study complied with the Declaration of Helsinki.

### Summary Statistics for MPV

As shown in Table 1, the publicly available summary data on MPV were extracted from the study conducted by Gieger et al in 2011.<sup>14</sup> The study included 66,867 participants and all of them were Europeans. Single nucleotide polymorphism (SNP). To avoid the bias caused by strong linkage disequilibrium (LD), the selection threshold was set as p-value  $<5 \times 10^{-8}$ , linkage disequilibrium  $r^2 < 0.1$ , as previous study.<sup>15</sup> Twenty-eight SNPs (rs10076782, rs10512627, rs10813766, rs10876550, rs10914144, rs11601356, rs11734132, rs11789898, rs1354034, rs1558324, rs1668871, rs1790931, rs2015599, rs2227831, rs2950390, rs3000073, rs329003, rs342293, rs4305276, rs4521516, rs4812048, rs4814776, rs649729, rs7075195, rs7317038, rs7961894, rs8076739, rs997482) closely associated with MPV were identified from the dataset.

### Summary Statistics for DVT

The summary data on DVT were obtained from MRC Integrative Epidemiology Unit Consortium (MRC-IEU) in 2018, which was included in UK Biobank (<http://www.bristol.ac.uk/integrative-epidemiolog>) with 462933 participants (18818 DVT patients and 444115 controls). Seven SNPs were not found in the MRC-IEU Consortium (rs10512627, rs11734132, rs1790931, rs342293, rs4305276, rs4521516, rs649729). Finally, the rest 21 SNPs were included, explaining 0.011% of the variations in the final analysis. The F statistic, an essential tool to assess the weak instrument bias, was 134 and well over 10.<sup>16</sup> It was generally believed that the result was not affected from the bias caused by weak instruments. For the heterogeneity test among the 21 SNPs, there was no heterogeneity for causal inference of MPV on the risk of DVT (Q statistic, 29.95;  $P > 0.05$ ). At last, 21 independent SNPs associated with DVT were included as instrumental variables for

**Table 1** Details of Studies and Datasets Used for MR Analysis

Exposure/ Outcomes	ID	PMID	Category	Sample Size (No. Cases/ No. Controls)	First Author	Consortium	Year	Population
Mean platelet volume	ieu-A-1006	22139419 <sup>14</sup>	Risk factor	66,867	Gieger C	Gieger C	2011	European
Deep vein thrombosis	ukb-b-12040	<a href="http://www.bristol.ac.uk/integrative-epidemiology/">http://www.bristol.ac.uk/integrative-epidemiology/</a>	Binary	462,933(18,818/ 444,115)	Ben Elsworth	MRC-IEU	2018	European

the final MR analysis. The detailed information, effect allele (EA), effect allele frequency (EAF), effect sizes ( $\beta$ ), standard errors (SE) and P values were recorded and shown in Table 2.

## Statistical Analyses

Three methods, inverse variance weighted (IVW), weighted median and MR-egger method were the classical method of MR analysis and performed to explore the causal association between MPV and risk of DVT.<sup>12,17</sup> The result was presented as Results of MR of were expressed as odds ratios (OR) and confidence interval (CI) and visualized as forest plot and scatter plot. Sensitivity analysis was evaluated by pleiotropy test from the method of Egger regression and the leaving-one-out method. The MR analysis was performed by using the R (version 3.4.2) package “TwoSampleMR” (version 0.3.4).<sup>18</sup> The P value less than 0.05 was considered as differences with statistically significant.

**Table 2** Characteristics of the SNPs Associated with Mean Platelet Volume and Risk of Deep Vein Thrombosis

SNPs	Chr:Position	Nearest Gene	EA /NEA	EAF	Mean Platelet Volume			Deep Vein Thrombosis		
					$\beta$	SE	P	$\beta$	SE	P
rs10076782	5:159,177,955	RNF145	A/G	0.25	6.70E-03	1.20E-03	4.48E-08	-2.73E-05	3.35E-04	0.94
rs10813766	9:331,490	DOCK8	G/T	0.66	-7.40E-03	1.10E-03	3.68E-12	1.20E-04	3.06E-04	0.69
rs10876550	12:54,318,524	COPZ1	A/G	0.56	-8.00E-03	1.00E-03	1.86E-14	-8.09E-04	2.93E-04	5.70E-03
rs10914144	10:12,265,895	DNM3	C/T	0.80	1.43E-02	1.40E-03	1.11E-24	1.00E-04	3.91E-04	0.78
rs11601356	11: 249,131	NA	A/G	0.23	-1.05E-02	1.30E-03	1.18E-15	-9.51E-05	3.48E-04	0.78
rs11789898	9:13,406,054	BRD3	T/G	0.17	-7.50E-03	1.30E-03	2.46E-08	-1.57E-04	3.91E-04	0.69
rs1354034	3:56,815,721	ARHGEF3	C/T	0.60	-2.25E-02	1.30E-03	3.31E-69	7.16E-04	2.96E-04	0.02
rs1558324	12:6,180,053	CD9, VWF	A/G	0.43	9.90E-03	1.00E-03	1.55E-21	-5.77E-04	2.93E-04	0.05
rs1668871	1:205,268,009	TMCC2	C/T	0.38	-1.20E-02	1.10E-03	1.17E-29	1.34E-04	2.99E-04	0.65
rs2015599	12:29,282,547	FAR2	A/G	0.46	8.20E-03	1.00E-03	5.55E-16	-1.59E-04	2.92E-04	0.59
rs2227831	5:76,727,669	F2R	G/A	0.05	2.09E-02	2.60E-03	9.65E-16	-5.98E-05	7.01E-04	0.93
rs2950390	12:56,661,507	ATP5F1B, PTGES3	T/C	0.34	-7.80E-03	1.00E-03	7.45E-14	-5.08E-04	3.07E-04	0.10
rs3000073	14:105,263,455	BRF1	A/G	0.30	-7.20E-03	1.10E-03	3.27E-11	3.12E-04	3.17E-04	0.33
rs329003	18:9,570,320	NA	G/A	0.10	9.50E-03	1.70E-03	3.24E-08	1.09E-04	4.96E-04	0.83
rs4812048	20:59,012,716	CTSZ, TUBB1	T/C	0.18	-7.90E-03	1.30E-03	1.30E-09	2.88E-04	3.77E-04	0.45
rs4814776	20:1,940,877	SIRPA, PDYN-AS1	A/C	0.33	-8.30E-03	1.10E-03	3.59E-14	2.97E-04	3.10E-04	0.34
rs7075195	10:63,290,899	JMJD1C	G/A	0.42	-1.42E-02	1.00E-03	2.39E-44	8.09E-04	2.95E-04	0.006
rs7317038	13:113,358,583	GRTPI, GRTPI-AS1	T/C	0.35	-6.40E-03	9.00E-04	8.27E-12	6.13E-05	3.04E-04	0.84
rs7961894	12:121,927,677	CFAP251	T/C	0.11	2.96E-02	1.40E-03	1.42E-103	-4.00E-04	4.57E-04	0.38
rs8076739	17:29,387,569	RNU4-34P, RPL35AP35	T/C	0.52	1.30E-02	1.00E-03	4.59E-38	-7.06E-04	2.91E-04	0.02
rs997482	1:10,213,121	KIF1B	T/C	0.13	8.80E-03	1.60E-03	2.09E-08	8.13E-04	4.36E-04	0.062

**Abbreviations:** SNPs, single nucleotide polymorphisms; Chr., chromosome; EA, effective allele; NEA, non-effective allele; EAF, effect allele frequency;  $\beta$ , effect sizes; SE, standard errors.

## Retrospective Study

A retrospective cohort study was conducted at the adult patients with newly confirmed diagnosis of DVT from January 2020 to December 2021. The retrospective study was approved by the Ethics Committee of Foshan Hospital of Traditional Chinese Medicine and informed consent has been obtained from all the included participants. In the present study, the participants with the following were excluded: (1) acute infections; (2) already receiving anticoagulation or anti-platelet treatment; (3) Lacking of MPV value. The participants were divided into the DVT group and the non-DVT group. The diagnosis of DVT was based on the screening through color Doppler ultrasonography (iU 22, Philips, The Netherlands). The following variables were collected, such as age, sex, body mass index, related comorbidities, smoking status and laboratory examination. Continuous variables were represented as the mean  $\pm$  standard deviation and categorical variables were expressed as counts (percentages). Comparison of quantitative variables was performed by using Student's *t*-test or Mann–Whitney *U*-test while the Chi-squared Test was utilized in categorical variables. Threshold probability value of  $P < 0.05$  was used in this study.

## Results

### Effect of MPV on the Risk of DVT

As shown in Table 3, the present two-sample MR analysis demonstrated that genetically predicted higher MPV was associated with significantly lower risk of DVT (OR 0.982, 95% CI = 0.967–0.998,  $P = 0.023$ ). In term of orientation and magnitude, there was the consistent result observed in the method of the weighted median and MR-Egger. Each single causal estimate from each SNP and the 95% CI are demonstrated in Figure 1 while the combined causal effect of all the included 21 SNPs using three different methods was also presented. Three SNPs (rs1354034, rs8076739 and rs7075195) showed clear negative associations between MPV and the risk of DVT for the causal effect. Figure 2 illustrates the regression slopes of causal effect between MPV and risk of DVT.

### Sensitivity Analysis

Little evidence was observed with directional horizontal pleiotropy in the method of MR-Egger regression, in which the *P* value was larger and suggested null effects (intercept =  $2.9 \times 10^{-4}$ ,  $P = 0.194$ ). As shown in Figure 3, no single SNP was found to strongly drive the combined causal effect of MPV on the risk of DVT in the leave-one-out sensitivity analysis.

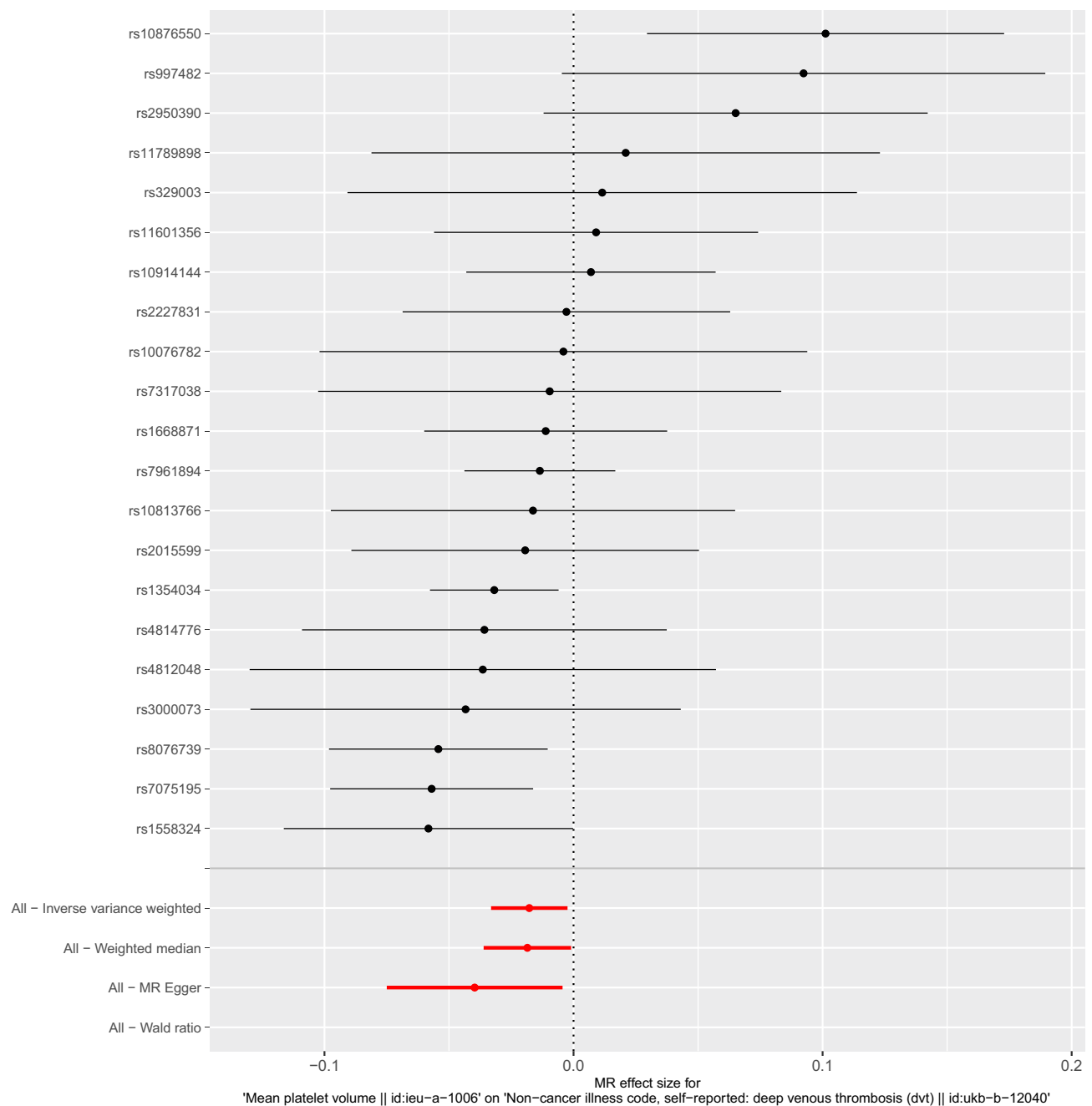
### Replication Study

There were 343 participants in this study, among which the mean age was  $77.2 \pm 9.0$  years while about one-third of the patients are male. Forty-eight patients were diagnosed with DVT, and the incidence of was 14.0%. Compared with the non-DVT group, higher body mass index was observed in the DVT group ( $P < 0.05$ ). There were no significant differences with regard to age, sex, smoking status, major comorbidities. For laboratory finding, the mean level of MPV was  $12.0 \pm 2.6$  fL while the lower level of MPV was significantly associated with patients with DVT. The other laboratory result failed to reach a significant association. The detailed information is presented in Table 4.

**Table 3** Mendelian Randomization Estimates of the Associations Between Mean Platelet Volume and Risk of Deep Vein Thrombosis

Outcome	IVW Method		MR-Egger		Weight Median	
	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value
Deep vein thrombosis	0.982 (0.967–0.998)	0.023	0.961 (0.928–0.996)	0.040	0.982 (0.965–0.999)	0.040

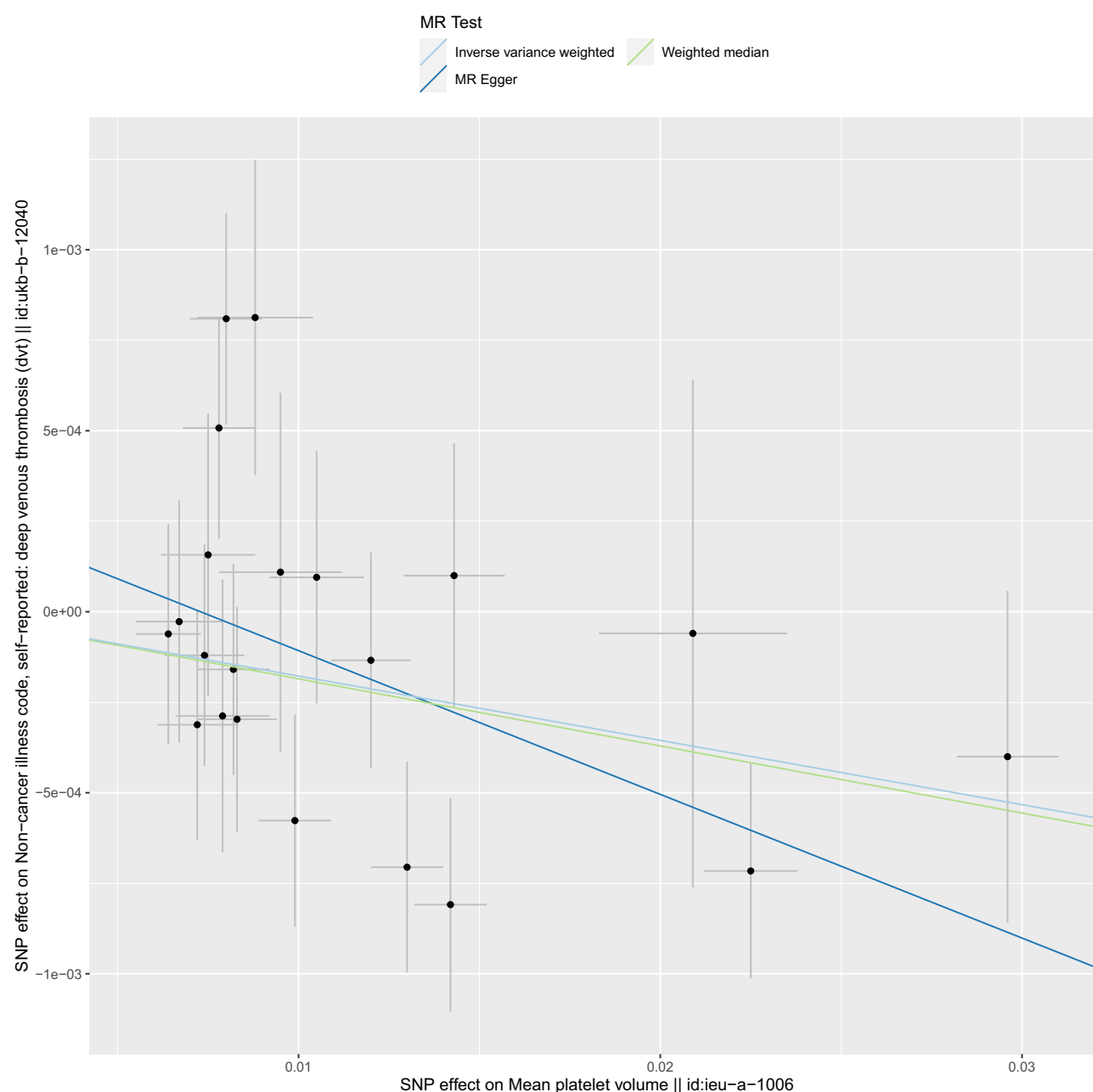
**Abbreviations:** IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval.



**Figure 1** Forest plot of single nucleotide polymorphisms (SNPs) associated with MPV and risk of DVT. Each black point represented the MR estimates for treatment of MPV on risk of DVT. Red points showing the overall causal effect including all SNPs using three different methods (IVW method, weighted median method and MR-Egger method). The horizontal lines represent 95% confidence intervals of the MR estimates.

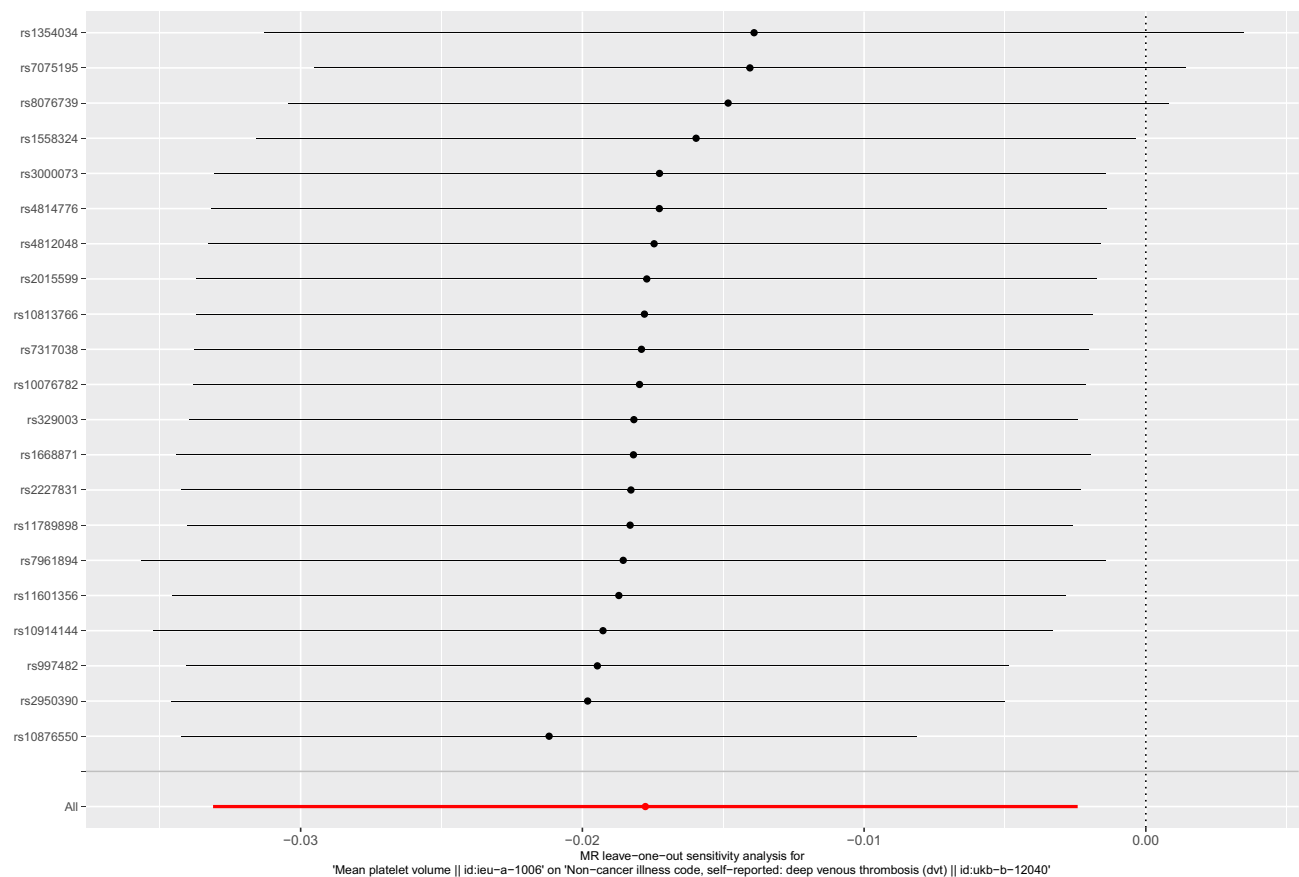
## Discussion

DVT is an important cause of cardiovascular disease, significantly associated morbidity, mortality and health cost worldwide.<sup>1</sup> Accurate diagnosis and timely elimination of DVT is essential to reduce the risk of complications and improve the quality of life for patients. As a result, there is an urgent need to accurately assess the risk factor of DVT patients. Platelet plays an essential role in the complex process of thrombosis development in a complex process, while the specific causal between MPV and risk of DVT is still not clear. In the present study, the major finding demonstrated that MPV was negatively associated with the risk of DVT both in the two-sample MR analysis and retrospective study.



**Figure 2** Scatter plot of SNPs associated with MPV and the risk of DVT. The plot relating the effect sizes of the SNP-MPV association (x-axis, SD) and the SNP-DVT associations (y-axis, log (OR)) with 95% confidence intervals. The regression slopes of the lines correspond to causal estimates using three MR methods including the IVW approach, Weighted median and MR-Egger method.

In this study, the incidence of DVT was 14% and negative association between MPV and the risk of DVT was reported, which was consistent with several previous studies. A research in China reported that the incidence was 15.1% and found that low MPV was associated with DVT in Older Patients with Hip Fracture.<sup>9</sup> Ferroni et al<sup>19</sup> demonstrated that low level of MPVs in cancer patients before chemotherapy was a predictor of increased risk venous thromboembolism risk while the similar result was confirmed in another research in cancer patients from Australia.<sup>20</sup> In the emergency department, a retrospective study conducted in Italy supported an inverse association between MPV and the risk of DVT.<sup>10</sup> However, the role of MPV for the risk of DVT remained controversial while different results have been also reported.<sup>21,22</sup> Considering that most previous studies were conventional retrospective studies, it is particularly important to adopt new research methods for these clinical issues. Two



**Figure 3** Leave-one-out (LOO) sensitivity analysis of SNPs associated with MPV and risk of DVT. Each black point represents the effect size ( $\beta$ ) excluding one SNP estimated by the IVW method. The red point presented the MR estimate including all resting SNPs. The line represents 95% confidence interval of MR estimates. The leave-one-out analysis shows no single SNP was strongly or reversely driving the overall effect of MPV on the risk of DVT.

sample MR analysis has been widely performed in the exploration of risk factors for DVT.<sup>23,24</sup> Recently, focus on the size of blood cells on the risk of DVT, there was a report through the method of MR analysis. He et al<sup>25</sup> found that the distribution width and volume of red blood cells were associated with a higher risk of VTE. However, it has not yet been investigated exploring the size of the platelets on the risk of DVT through the MR analysis. In the present study, the causal estimates between MPV and risk of DVT were similar both in terms of direction and magnitude among IVW, weighted median and Egger regression, with great power to support the causal relationship.

The exact mechanisms of low MPV and increased risk of DVT have not been clarified. Compared with the larger platelets, the small platelets with lower MPV were observed with greater propensity to thrombosis formation. It should be noted that the result was observed in the cancer patients. Thus, the generalizability of the finding toward non-cancer participants needs to be confirmed. In vitro, platelets with a smaller size secreted more P-selectin, which played an important role in the surface adhesion in the thrombosis formation.<sup>26</sup> Considering the few studies at present, more basic researches are needed in the future to explore its specific mechanism.

The study had several essential advantages. To the best of our knowledge, this was the first MR study to investigate the causality between MPV and risk of DVT. Depending on genetic instruments, MR analysis can effectively prevent the usual pitfalls of confounders and reverse causality, which are commonly present in traditional observational studies and an important cause of conflicting results. With the genetic instrument associated with MPV and DVT extracted from two different large consortiums, the study had included more than 450,000 participants and robustly instrumental variables (F statistics over larger than 10). Moreover, the result

**Table 4** Demographic Characteristics and Laboratory Data of the Included Patients with DVT and Without DVT

	All Patients (n=343)	DVT Group (n=48)	Non-DVT Group (n=295)	P value
Age (Year)	77.2±9.0	79.5±8.2	76.8±9.1	0.540
Sex n (%)				0.529
Male	121 (35.3)	15 (31.2)	106 (35.9)	
Female	222 (64.7)	33 (68.8)	189 (64.1)	
Body mass index	21.0±4.3	22.2±3.2	20.7±4.4	0.009
Comorbidities n(%)				
Diabetes	65 (19.0)	7 (14.6)	58 (19.7)	0.405
Hypertension	140 (40.8)	16 (33.3)	124 (42.0)	0.255
Coronary heart disease	47 (13.7)	5 (10.4)	42 (14.2)	0.475
Malignant tumor	12 (3.5)	3 (6.3)	9 (3.1)	0.263
Surgery	142 (41.4)	10 (20.8)	132 (44.7)	0.002
Trauma	32 (9.3)	5 (10.4)	27 (9.2)	0.780
Smoking	39 (11.4)	6 (12.5)	33 (11.2)	0.790
Erythrocyte ( $\times 10^9/L$ )	4.9±1.6	4.9±1.1	5.2±1.9	0.109
Hemoglobin (g/dl)	11.2±2.3	10.2±1.5	11.5±2.2	0.124
Platelet ( $\times 10^9/L$ )	138.0±26.0	154.1±21.7	135.4±25.7	0.394
MPV (fL)	12.0±2.6	11.4±1.9	12.1±2.7	0.006
D-dimer (mg/L)	4.0±1.1	4.2±1.0	4.0±1.1	0.806
Fibrinogen (g/L)	3.9±1.1	3.2±1.2	3.3±1.4	0.961

was further confirmed by the retrospective study, because of which the study had higher credibility for causal estimates. Early diagnosis is of great significance for improving the treatment effect of DVT and reducing complications. This study emphasizes the significance of the MPV. For patients with increased MPV, more attention should be paid the occurrence of DVT. Further, to well improve the diagnostic accuracy, more studies should be performed to combine MPV with the other clinical markers.

Inevitably, there were also some limitations to be desired. First, all the included participants in MR analysis were of European origin. Though the result was verified in our center, the retrospective study was a single-center study with the small sample size. As a result, it was still questionable whether our findings could generalizable to Asian populations. Further prospective studies with a larger sample in Asian population are needed to confirm the conclusion. Because of the limitation from the summary data, detailed information was not able to be obtained in the individual level, for which the MR analysis provided a linear relationship between MPV and risk of DVT. In a real-world study, the relationship between risk factor and outcome might be J- or U-shaped. More researches are needed to explore the MPV cut-off points in DVT based on the clinical studies with large sample.

## Conclusion

In this study, we found the negatively casual association between MPV and risk of DVT by using the two-sample Mendelian randomization method and retrospective study. But further researches are demanded to add to the findings and explore the potential mechanism of the size of platelets on the formation of DVT.

## Ethics Approval and Consent to Participate

There were no patients involved in the MR analysis, so the ethical approval was waived by the ethic committee of Foshan Hospital of Traditional Chinese Medicine. The retrospective study was approved by the Ethics Committee of Foshan Hospital of Traditional Chinese Medicine.

## Funding

There is no funding to report.



## Disclosure

The authors report no conflicts of interest in this work.

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