

## RESEARCH ARTICLE

# COVID-19 and platelet traits: A bidirectional Mendelian randomization study

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## Abstract

This study aimed to evaluate the host genetic liability of coronavirus disease 2019 (covid-19) with platelet traits using the Mendelian randomization (MR) approach. We conducted a bidirectional two-sample MR using summary statistics from the largest genome-wide association study of three variables, covid-19 severity (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection, covid-19 hospitalization, and severe covid-19,  $N = \sim 1\,059\,456\text{--}1\,557\,411$ ) and four platelet traits (mean platelet volume [MPV], plateletcrit, platelet distribution width, and platelet count;  $N = 408\,112$ ). Inverse-variance weighted (IVW), median weighted, MR-Egger, and contamination mixture methods were used to estimate the causal association. Null and inconsistent associations in the IVW and sensitivity analyses were observed for SARS-CoV-2 infection and covid-19 hospitalization with platelet traits. For severe covid-19, significant associations with MPV and platelet count were observed in the IVW and sensitivity analyses, with the  $\beta_{\text{IVW}}$  of 0.01 (95% confidence interval [CI]: 0.005–0.016,  $p = 3.51 \times 10^{-4}$ ) and  $-0.009$  (95% CI:  $-0.015$  to  $-0.002$ ,  $p = 0.008$ ) per doubling in odds of severe covid-19, respectively. Conversely, null associations were observed for platelet traits with covid-19 traits. In conclusion, host genetic liability to severe covid-19 was causally associated with increased MPV and reduced platelet count, which may provide insights into evaluating hypercoagulability and thromboembolic events in covid-19 patients.

## KEYWORDS

blood, epidemiology, genetics, genetic variation, SARS coronavirus, virus classification

## 1 | INTRODUCTION

The coronavirus disease 2019 (covid-19), first reported at the end of 2019, is a pandemic affecting nearly 500 million people, causing more than 6 million deaths worldwide as of April 6th, 2022.<sup>1</sup> It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. With the availability of vaccines and drugs for treating covid-19, the severe covid-19 and its associated death have been

reduced. The “Living with covid-19” plan has been employed in many countries. However, it is recognized that symptoms can persist long after the acute SARS-CoV-2 infection, which is also known as long covid.<sup>2</sup> It is important to understand the relationship between acute SARS-CoV-2 infection and general health.

Platelet disorders have been widely reported in covid-19 patients.<sup>3–5</sup> For example, it was reported that 58%–95% of covid-19 patients with severe outcomes had mild thrombocytopenia.<sup>6–8</sup>

Likewise, platelet count was shown to be significantly lower in patients with severe covid-19 in a meta-analysis.<sup>9</sup> Another meta-analysis showed that when compared to patients with non-severe covid-19, those with severe covid-19 had a significantly lower platelet count.<sup>10</sup> However, most of the original studies were cross-sectional in nature. Thus, the relationship between platelet disorders and covid-19 is far from clear.

Mendelian randomization (MR) is a robust method for inferring causality, especially between two diseases in which causality is difficult to establish using the conventional observational study. Host genetics has been proven to affect the susceptibility to SARS-CoV-2 infection and the severity of covid-19.<sup>11</sup> Thus, it is now feasible to evaluate if host genetic liability to SARS-CoV-2 infection and severe covid-19 is causally associated with a clinical outcome. In the current study, we aimed to evaluate if the genetic liability to covid-19 had causal effects on four platelet traits, namely mean platelet volume (MPV), plateletcrit, platelet count, and platelet distribution width, using the two-sample MR approach. To exclude the possibility that these four platelet traits are causally associated with covid-19 outcomes, MR analysis was also conducted in the reverse direction (i.e., evaluating the causal association between platelet traits on covid-19).

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and assumption

MR analyses use genetic instrumental variables (IVs) to evaluate the causal relationship between exposure and outcome. MR analyses have three assumptions. IVs are associated with the exposure, and they are independent of the confounder of the exposure-outcome association. IVs influence the outcome only via exposure and there is no alternative pathway for the IVs to affect the outcome (i.e., no pleiotropy). If all these assumptions are met, MR analyses should be able to infer causality that is free of unmeasured confounding and reverse causality. The evidence of causality provided by the MR analyses was reported to lie at the interface between randomized controlled trials (RCTs) and conventional epidemiological studies.<sup>12</sup> Yet, the genetic IVs used in the MR analyses implicate the life-long effect of the exposure, while detecting the life-long impact of the change in the exposure on an outcome is often impossible in an RCT setting. Single-nucleotide polymorphisms (SNPs) are the genetic variation between individuals expected to be randomly assigned within the population, serving as a robust estimator of lifelong effect. They were utilized as instruments for the MR analysis.

### 2.2 | Data source

In this two-sample MR study, genetic association of gene-exposure and gene-outcome data were retrieved from two independent genome-wide association studies (GWAS) with a nonoverlapping

sample to investigate the causal relationship between host genetic liability to COVID-19 on platelet traits. GWAS summary statistics of exposure were obtained from the COVID-19 Host Genetic Initiative (HGI) (Round 5).<sup>11</sup> Data from the European population except the UK Biobank participants were retrieved.<sup>11</sup> Summary statistics of platelet traits were extracted from a GWAS conducted in UK Biobank participants, which comprised 408 112 participants.<sup>13</sup> Ethical approval was not required for this study since the original GWAS previously received appropriate ethics and institutional review board approval.

### 2.3 | Exposure and outcome

The exposures were critical covid-19 (severe covid-19; case: 4792, control: 1054 664), hospitalized covid-19 (case: 8316, control: 1549 095) and covid-19 infection (case: 32 494, control: 1 316 207).<sup>11</sup> The outcomes were four platelet traits, namely MPV, plateletcrit, platelet distribution width, and platelet count.<sup>13</sup> MR analysis in the reverse direction was performed to assess the possibility of reverse causation. Platelet-related traits were treated as exposure, while covid-19 events were treated as the outcome.

### 2.4 | Genetic instruments

Independent SNPs with genome-wide significance (defined as  $p < 5 \times 10^{-8}$ ) with covid-19 phenotypes were used as instruments. The independent SNPs were identified using the SNPclip tool of LDlink, by pruning the list of genome-wide significant SNPs using the  $r^2$  and minor allele frequency thresholds of 0.1 and 0.01, respectively.<sup>14</sup> In the reverse direction, independent instruments of platelet-related traits ( $p < 5 \times 10^{-9}$ ) identified from the original GWAS were used as instruments. Genetic correlation between covid-19 phenotypes and platelet-related traits was estimated through linkage disequilibrium score regression (LDSC)<sup>15</sup> using the summary statistics of GWAS based on the precomputed European LD scores.

Instruments that failed to harmonize with outcome parameters, or the palindromic instruments with minor allele frequency  $>0.3$  were replaced with proxies identified based on the LD information of the European reference panel of the 1000 Genomes project. Proxies were genetic variants in high LD with the original instruments (defined as  $r^2 \geq 0.8$ ) and showed genome-wide significant association with the exposure. MR pleiotropy residual sum and outlier (MR-PRESSO) were performed to detect and remove outlier instruments.<sup>16</sup>

### 2.5 | Power calculation and assumption assessment

To evaluate the strength of instruments, F-statistics was measured using an online calculator.<sup>17</sup> The proportion of variance explained by

instruments on each exposure was calculated using the reported effect estimate, the effect allele frequency of the instruments, and the prevalence of exposures. Concerning the pleiotropic effect, the MR-Egger intercept test and MR-PRESSO global test were used to detect the presence of horizontal pleiotropy.<sup>16,18</sup> Cochran's Q statistics were used to reflect the presence of heterogeneity of instruments.

## 2.6 | Statistical methods

The primary analysis for the MR study was the inverse-variance weighted (IVW) method, which assumed all instruments were valid.<sup>19</sup> Sensitivity analyses including weighted median, MR-Egger, and contamination mixture (ConMix) methods were performed. The weighted median estimator assumed that more than 50% of instruments were valid.<sup>20</sup> The ConMix detected the causal effect with reasonable power and the lowest mean square error, especially when there are invalid instruments.<sup>21</sup> MR-Egger method detects the association when the IV assumptions do not hold, but a weaker assumption is valid. However, this method has the lowest statistical power in detecting the effect.<sup>18</sup> Thus, a significant causal relationship was considered when a significant *p*-value was observed in IVW, weighted median, and ConMix methods. The significant causal relationship should also show an insignificant MR-Egger intercept test and MR-PRESSO global test, suggesting the absence of horizontal pleiotropy.<sup>16,18</sup> As the covid-19 phenotypes were binary while platelet traits were continuous variables, the effect estimates were transformed by multiplying 0.693,<sup>22</sup> which are interpreted as changes in platelet trait (in standard deviation [SD]) per doubling the odds of the covid-19 event. In the reverse direction, the exponential transformation was performed, indicating changes in the odds ratio (OR) of covid-19 event per one SD increase in the platelet trait. All the MR analyses were conducted with R (version 4.1.3). R packages "MendelianRandomization" and "MRPRESSO" were utilized.

## 3 | RESULTS

The LDSC analysis demonstrated the absence of genetic correlation between covid-19 traits and platelet traits, except for hospitalized covid-19 and plateletcrit ( $r_g = -0.096$ ,  $SE = 0.040$ ,  $p = 0.017$ ; Table 1).

To evaluate the causal effects of host genetic liability to covid-19 on platelet traits, MR analyses using the genetic instruments of covid-19 were done. Six, 11, and 12 genetic instruments of covid-19 infection, hospitalization, and severity were identified after LD pruning (Supporting Information: Table 1). After removing outliers identified by MR-PRESSO, the genetic instruments used in each analysis varies, and the numbers of instruments used are provided in Supporting Information: Table 2. For genetic liability to SARS-CoV-2 infection (Table 2; Figure 1), we saw no evidence of a causal relationship with platelet traits. Genetic liability to hospitalized covid-19 (Table 3; Figure 1) was significantly associated with increased

MPV ( $\beta$ : 0.008 per doubling in odds of hospitalized covid-19, 95% confidence interval [CI]: 0.001–0.016,  $p = 0.035$ ) and reduced platelet count ( $\beta$ : -0.013 per doubling in odds of hospitalized covid-19, 95% CI: -0.024 to -0.002,  $p = 0.026$ ), respectively, in the IVW analysis. However, inconsistent associations were observed in the sensitivity analyses. For genetic liability to severe covid-19 (Table 4; Figure 1), significant associations with increased MPV ( $\beta$ : 0.01 per doubling in odds of severe covid-19, 95% CI: 0.005–0.016,  $p = 3.5 \times 10^{-4}$ ) and reduced platelet count ( $\beta$ : -0.009 per doubling in odds of severe covid-19, 95% CI: -0.015 to -0.002,  $p = 0.008$ ) were found in both the IVW analysis and sensitivity analyses (weighted median and ConMix tests). MR-Egger intercept, Cochran's Q heterogeneity, and MR-PRESSO global tests were all statistically insignificant.

The details of instruments used in the reverse direction are provided in Supporting Information: Table 3. The MR was conducted to evaluate if platelet traits were associated with covid-19 outcomes and the results are provided in Table 5 and Figure 2. All platelet traits were not associated with covid-19 outcomes, except that MPV was associated with hospitalized covid-19 in the IVW (OR: 1.067, 95% CI: 1.007–1.13,  $p = 0.028$ ). However, the association was inconsistent in the sensitivity analysis (Supporting Information: Table 4).

## 4 | DISCUSSION

In this two-sample MR study, we found that host genetic liability to severe covid-19 was causally associated with increased MPV and reduced platelet number, while these associations were inconsistent for hospitalized covid-19 in the main IVW and sensitivity analyses. We observed no evidence of causal association for SARS-CoV-2 infection with platelet traits. Conversely, a null association was

**TABLE 1** Genetic correlation between covid traits and platelet traits

Covid trait	Platelet trait	$r_g$	SE	<i>p</i>
Covid-19 infection	MPV	-0.099	0.068	0.144
	Plateletcrit	-0.015	0.066	0.821
	Platelet count	0.037	0.065	0.569
	Platelet distribution width	-0.043	0.072	0.551
Hospitalized covid-19	MPV	-0.071	0.038	0.062
	Plateletcrit	-0.096	0.040	0.017
	Platelet count	-0.034	0.041	0.410
	Platelet distribution width	0.013	0.054	0.814
Severe covid-19	MPV	-0.032	0.042	0.450
	Plateletcrit	-0.055	0.038	0.140
	Platelet count	-0.018	0.039	0.646
	Platelet distribution width	0.064	0.042	0.123

Abbreviations: covid-19, coronavirus disease 2019; MPV, mean platelet volume.

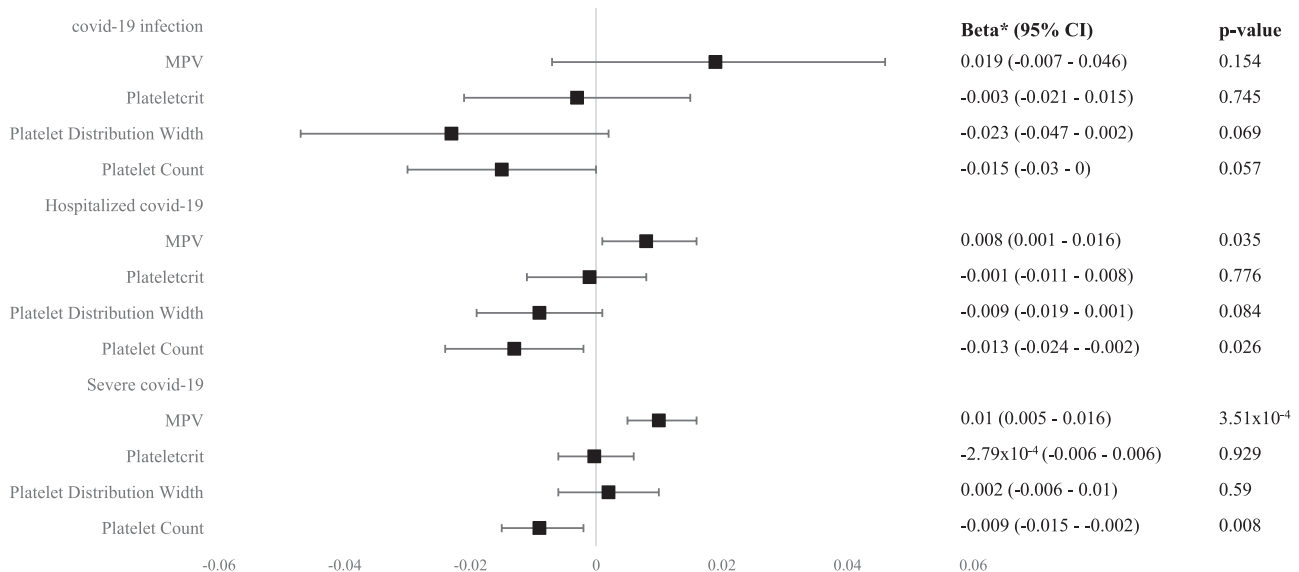
**TABLE 2** MR analysis of covid-19 infection (exposure) with four platelet trait outcomes.

Outcome	Method	Beta	95% CI	p	MR-Egger	Cochran's Q	MR-PRESSO
					intercept test	heterogeneity test	global test
					p	p	p
MPV	IVW	0.019	-0.007 to 0.046	0.154	0.546	0.022	0.063
	Weighted median	0.009	-0.012 to 0.029	0.4			
	MR-Egger	-0.001	-0.074 to 0.072	0.97			
	ConMix	0.007	-0.014 to 0.09	0.629			
Plateletcrit	IVW	-0.003	-0.021 to 0.015	0.745	0.872	0.536	0.629
	Weighted median	-0.007	-0.028 to 0.014	0.527			
	MR-Egger	0.001	-0.048 to 0.049	0.976			
	ConMix	-0.007	-0.028 to 0.055	0.414			
Platelet count	IVW	-0.015	-0.03 to 0	0.057	0.262	0.722	0.786
	Weighted median	-0.014	-0.033 to 0.004	0.132			
	MR-Egger	0.01	-0.036 to 0.055	0.679			
	ConMix	-0.014	-0.062 to 0	0.112			
Platelet distribution width	IVW <sup>a</sup>	-0.023	-0.047 to 0.002	0.069	NA	0.357	NA

Note: Beta is the beta per doubling in odds of covid-19 infection.

Abbreviations: CI, confidence interval; ConMix, contamination mixture; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume; MR, Mendelian randomization; MR-PRESSO, MR-pleiotropy residual sum and outlier; NA, not applicable.

<sup>a</sup>Only IVW was conducted because only two valid instruments were used in the analysis.



**FIGURE 1** Forest plot of Mendelian randomization IVW analyses of covid-19 exposure on platelet traits. \*Beta is the beta per doubling the odds of covid-19 exposure. CI, confidence interval; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume.

observed for MPV and platelet count on the majority of covid-19 outcomes, except that a weak and inconsistent association was observed for MPV with hospitalized covid-19.

To the best of our knowledge, no MR study evaluated the relationship of host genetic liability to covid-19 on MPV and platelet

count, whereas the association of covid-19 with reduced platelet count and increased MPV has been reported in observational studies. The current study observed null associations of SARS-CoV-2 infection with platelet traits. Meanwhile, covid-19 severity was causally associated with increased MPV and reduced platelet count.

**TABLE 3** MR analysis of hospitalized covid-19 (exposure) with four platelet trait outcomes

Outcome	Method	Beta	95% CI	p	MR-Egger	Cochran's Q	MR-PRESSO
					intercept test	heterogeneity test	global test
					p	p	p
MPV	IVW	0.008	0.001–0.016	0.035	0.529	0.043	0.062
	Weighted median	0.006	–0.001 to 0.014	0.111			
	MR-Egger	0.002	–0.017 to 0.022	0.814			
	ConMix	0.021	0–0.028	0.051			
Plateletcrit	IVW	–0.001	–0.011 to 0.008	0.776	0.904	0.958	0.963
	Weighted median	–0.002	–0.014 to 0.01	0.731			
	MR-Egger	–0.011	–0.168 to 0.146	0.89			
	ConMix	NA					
Platelet distribution width	IVW	–0.009	–0.019 to 0.001	0.084	0.457	0.17	0.222
	Weighted median	–0.015	–0.026 to –0.004	0.006			
	MR-Egger	–0.038	–0.116 to 0.04	0.339			
	ConMix	–0.014	–0.021 to –0.007	0.026			
Platelet count	IVW	–0.013	–0.024 to –0.002	0.026	0.858	0.261	0.346
	Weighted median	–0.014	–0.027 to –0.001	0.033			
	MR-Egger	–0.031	–0.237 to 0.174	0.764			
	ConMix	–0.014	–0.035 to 0	0.055			

Note: Beta is the beta per doubling in odds of hospitalized covid-19.

Abbreviations: CI, confidence interval; ConMix, contamination mixture; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume; MR, Mendelian randomization; MR-PRESSO, MR-pleiotropy residual sum and outlier; NA, not applicable.

Although the association observed for hospitalized covid-19 with MPV and platelet count was inconsistent between the IVW and sensitivity analyses, it was partially in line with the findings observed for severe covid-19. This could be due to the sharing of genetic instruments with severe covid-19 since 7 out of 11 instruments were also the instruments of severe covid-19 (Supporting Information: Table 1), which was in line with the original GWAS meta-analysis conducted by COVID-19 HGI that four out of nine genome-wide significant loci associated with covid-19 hospitalization were also significantly associated with severe covid-19. Nevertheless, these observations align with the previous meta-analyses that patients with severe covid-19 had a significantly lower platelet count<sup>10</sup> and higher MPV<sup>23</sup> compared to patients with non-severe covid-19. We further provide evidence that host genetic liability to severe covid-19 is causally associated with these two platelet traits. We observed no significant genetic correlation of severe covid-19 with platelet traits. It should be noted that genetic correlation represents the global correlation using all available genetic variants, and the LDSC is only powerful when there are many causal SNPs with small effect size sharing between traits.<sup>24</sup> Conversely, the MR approach focuses on the subset of the genetic variants associated with the trait.<sup>25</sup> Thus, the overall findings suggested that only a subset of genetic variants representing severe covid-19 were causally associated with the platelet traits.

No significant pleiotropy was detected in the current study. When we investigated the association of the instruments of severe covid with both MPV and platelet count, only a few nominal significant associations were observed, suggesting that the causal relationship of genetic liability of severe covid with MPV and platelet count could not be explained by the individual genetic instrument. Among the genetic instruments representing severe covid, rs111837807 was nominally associated with both MPV and platelet count, whereas rs2109069 and rs10860891 were nominally associated with MPV. The nearest gene of rs111837807 is coiled-coil alpha-helical rod 1, which interacts with mitotic spindle proteins and therefore may play a role in cell division.<sup>26</sup> At the same time, it is also a component of processing bodies, which regulate mRNA processing.<sup>27</sup> The nearest gene of rs2109069 is dipeptidyl peptidase 9, which is ubiquitously expressed intracellular prolyl peptidase. It was shown to regulate immune function. The nearest gene of rs10860891 is RP11-210L7.1, which is a long intergenic non-protein coding RNA. Notably, all these genes have no known role in thrombopoiesis. A future study investigating the relationship of the host genetic liability of severe covid with thrombopoiesis is warranted.

Most of the previous studies investigating the relationship of covid-19 with platelet traits were cross-sectional in nature. It is possible that higher MPV and reduced platelet count were indeed the

**TABLE 4** MR analysis of severe covid-19 (exposure) with four platelet trait outcomes

Outcome	Method	Beta	95% CI	p	MR-Egger intercept test p	Cochran's Q heterogeneity test p	MR-PRESSO global test p
MPV	IVW	0.01	0.005–0.016	$3.51 \times 10^{-4}$	0.896	0.056	0.075
	Weighted median	0.01	0.004–0.016	0.002			
	MR-Egger	0.011	–0.005 to 0.027	0.171			
	ConMix	0.014	0.007–0.021	0.005			
Plateletcrit	IVW	$-2.79 \times 10^{-4}$	–0.006 to 0.006	0.929	0.511	0.987	0.987
	Weighted median	–0.001	–0.009 to 0.006	0.772			
	MR-Egger	–0.01	–0.041 to 0.021	0.508			
	ConMix	NA					
Platelet distribution width	IVW	0.002	–0.006 to 0.01	0.59	0.329	0.003	0.006
	Weighted median	0.008	0–0.015	0.042			
	MR-Egger	0.012	–0.009 to 0.033	0.269			
	ConMix	0.014	–0.021 to –0.007 0.007–0.014	NA			
Platelet count	IVW	–0.009	–0.015 to –0.002	0.008	0.83	0.414	0.48
	Weighted median	–0.01	–0.019 to –0.002	0.014			
	MR-Egger	–0.005	–0.034 to 0.023	0.712			
	ConMix	–0.014	–0.021 to –0.007	0.043			

Note: Beta is the beta per doubling the odds of severe covid-19.

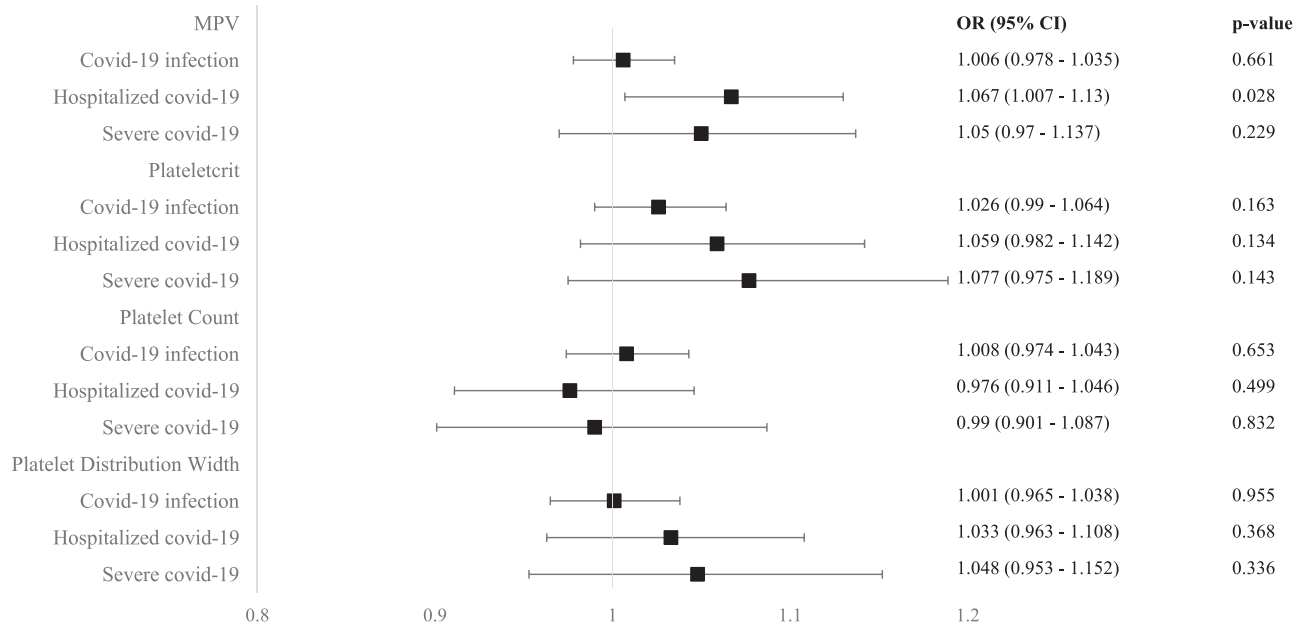
Abbreviations: CI, confidence interval; ConMix, contamination mixture; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume; MR, Mendelian randomization; MR-PRESSO, MR-pleiotropy residual sum and outlier; NA, not applicable.

Exposure	Outcome	OR	95% CI	p
MPV	Covid-19 infection	1.006	0.978–1.035	0.661
	Hospitalized covid-19	1.067	1.007–1.13	0.028
	Severe covid-19	1.05	0.97–1.137	0.229
Plateletcrit	Covid-19 infection	1.026	0.99–1.064	0.163
	Hospitalized covid-19	1.059	0.982–1.142	0.134
	Severe covid-19	1.077	0.975–1.189	0.143
Platelet count	Covid-19 infection	1.008	0.974–1.043	0.653
	Hospitalized covid-19	0.976	0.911–1.046	0.499
	Severe covid-19	0.99	0.901–1.087	0.832
Platelet distribution width	Covid-19 infection	1.001	0.965–1.038	0.955
	Hospitalized covid-19	1.033	0.963–1.108	0.368
	Severe covid-19	1.048	0.953–1.152	0.336

**TABLE 5** The reverse direction MR IVW analysis evaluates the association of platelet traits with covid-19 traits

Note: OR: Changes in odds of covid-19 event per SD increase in the platelet trait.

Abbreviations: CI, confidence interval; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume; MR, Mendelian randomization; OR, odds ratio.



**FIGURE 2** Forest plot of Mendelian randomization IVW analyses of platelet traits on covid-19 events. CI, confidence interval; covid-19, coronavirus disease 2019; IVW, inverse-variance weighted; MPV, mean platelet volume; OR, odds ratio.

risk factors for developing severe covid-19. We, therefore, conducted the MR analysis in the reverse direction. We found that majority of the platelet counts had null causal effects on COVID-19 outcomes. The only exception was that a weak association was observed for MPV with hospitalized covid-19 in the IVW analysis, but such association was inconsistent in other sensitivity analyses (Supporting Information: Table 4). Notably, the Cochran's Q test showed heterogeneity (heterogeneity  $p = 0.004$ ) while the MR-PRESSO global test was significant (Supporting Information: Table 4). Due to the presence of heterogeneity and pleiotropy, the inconsistent causal relationship of MPV with hospitalized covid-19 requires further investigation. Collectively, these findings suggest that host liability to severe covid-19 is causally associated with higher MPV and reduced platelet count but not the other way round, while such association was only observed in patients with severe covid-19 but not in those with non-severe covid-19.

Hypercoagulability is common in patients with covid-19. Severe inflammatory response and endothelial activation or damage<sup>28,29</sup> in SARS-CoV-2 infection lead to the cytokine storm<sup>30</sup> and increased thrombin generation,<sup>31</sup> which predispose to the subsequent thromboembolic events. Recently, a single-cell multiomics analysis further demonstrated that increased megakaryopoiesis with expanded megakaryocyte-committed progenitors and increased platelet activation was observed in symptomatic covid-19 patients but not in asymptomatic patients or healthy controls.<sup>32</sup> These findings show the effect of SARS-CoV-2 infection on host platelet activation. However, we should be clear that the current study was not able to evaluate the physiological changes due to the SARS-CoV-2 infection per se but instead emphasized the host genetics liability to covid-19 on platelet phenotypes. Whether platelet traits play a role in the

subsequent thromboembolic events among covid-19 patients warrants further investigation by multivariable MR analyses. When updated GWAS of covid-19 severity in a larger sample are available to provide genetic instruments explaining a higher proportion of variance, or when larger GWAS of thromboembolic events (including ischemic stroke and coronary heart disease) are released, multivariable MR analyses would have sufficient power to dissect the underlying mechanisms.

This study has important clinical implications. MPV reflects platelet size and is often associated with thrombocytopenia.<sup>33</sup> MPV also reflects platelet activity,<sup>34</sup> in which higher MPV is associated with increased platelet aggregation and hence the risk of adverse cardiac events.<sup>35</sup> Increased MPV with low platelet count is observed in multiple diseases, such as ischemic heart disease,<sup>36</sup> ischemic strokes,<sup>37</sup> and immune thrombocytopenic purpura,<sup>38</sup> while these conditions have been reported as complications of covid-19.<sup>39-41</sup> We showed that genetic liability to severe covid-19 is causally associated with the platelet traits that are linked to hypercoagulability. This may suggest that the increased risk of hypercoagulability-related clinical outcomes could be long-lasting even after recovery from covid-19, also known as long covid.

There are several strengths in the current study. The sample sizes of the datasets of both exposure and outcome were obtained from the largest GWAS or GWAS meta-analysis. The F-statistics of the genetic instruments are large (Supporting Information: Table 2), implying the presence of the weak instrument bias is unlikely. Since the GWAS of platelet traits was conducted in the UK Biobank population, we used the covid-19 dataset excluding the UK Biobank population to avoid sample overlapping and its related bias. Multiple sensitivity analyses were conducted to reduce the false-positive rate.

Nevertheless, there are limitations. First, the current study can detect genuine causal association with platelet traits if the beta estimate is larger than 0.052 per doubling the odds of hospitalized and severe covid-19, but the power for covid-19 infection on platelet outcomes is comparatively small due to the small variance explained by the genetic instruments (Supporting Information: Table 2). Second, the MR-Egger test was not statistically significant in all analyses. However, it is well documented that this test has the lowest power in detecting association. The significant associations observed in the more robust tests, weighted median, and ConMix tests, suggested that the findings were unlikely to be false-positive. Third, cautious interpretation is required on the host's genetic liability to covid-19 on platelet outcomes. The current study only provides evidence that patients who developed severe covid-19 after SARS-CoV-2 infection are causally associated with increased MPV and reduced platelet count due to shared host genetics. The platelet trait alteration in covid-19 patients is multifactorial, in which host genetics is only one of the factors affecting this.

In conclusion, host genetic liability to severe covid-19 was causally associated with increased MPV and reduced platelet count, while no significant association was observed for platelet traits on covid-19 outcomes. Further investigation on the role of platelet traits in hypercoagulability and thromboembolic events in covid-19 patients is warranted.

## AUTHOR CONTRIBUTIONS

Ching-Lung Cheung designed the study. Shun-Cheong Ho and Suhas Krishnamoorthy gathered data and conducted the analysis. Ching-Lung Cheung and Gloria H.-Y. Li revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available as shown in the Covid19 Host Genetics Initiative, <https://www.covid19hg.org/> and UKBiobank, [ftp://ftp.sanger.ac.uk/pub/project/humgen/summary\\_statistics/UKBB\\_blood\\_cell\\_traits/](ftp://ftp.sanger.ac.uk/pub/project/humgen/summary_statistics/UKBB_blood_cell_traits/). All data are freely available as stated in the manuscript.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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