The association between COVID-19 infection and blood constituents: A Mendelian Randomization analysis

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Dear Editor,

The recent retrospective study by Tong M et al. [1] suggested an association between coronavirus disease 2019 (COVID-19) and endothelial cell adhesion molecules, and how this may affect coagulation function. However, it is difficult to infer causal effects only from observational studies because of the possibility that any identified associations may be attributable to confounding. Here, we leverage data from large-scale genetic association studies to verify the authors'findings and identify genetic proxies for some blood constituents (blood cell volume, blood cell count, blood cholesterol, etc..), and apply these in Mendelian randomization (MR) analyses investigating their causality with COVID-19. MR analysis is widely used to explore potential causal relationships between genetic determinants and selected outcome, independent of factors that may disrupt observational studies, and not prone to confounding biases and reverse causality.

Summary genetic association estimates for Blood constituents were obtained from the ieu open GWAS project[2].Genetic association estimates for COVID-19 were obtained from release 5 (January 2021) of the COVID-19 Host Genetics Initiative Genome-Wide Association Study, which considered 36,590 cases and 1,668,938 controls from the general population[3]. The MR analyses were performed using the inverse-variance weighted method. All summary data used in this work are publicly available, and they were obtained with relevant participant consent and ethical approval.

The MR analyses (Table 1) showed that higher genetically proxied COVID-19 were associated with decreased eosinophil cell count (OR=0.946, CI 0.916-0.977) and LDL-c(low-density lipoprotein) (OR=0.810, CI 0.730-0.899). There was consistent evidence that COVID-19 is causally associated with total cholesterol (TC) (OR=0.843, CI 0.760-0.935), B-cell receptor-associated protein 29 (OR=1.284,CI 1.086-1.518), and killer cell immunoglobulin-like receptor 2DL5A (OR=1.259, CI 1.083-1.463). There was moderate evidence for associations of COVID-19 with mean cell hemoglobin concentration (OR=0.956, CI 0.920-0.992), packed cell volume (OR=0.678,CI 0.478-0.963), platelet distribution

(OR=0.968, CI 0.940-0.998), monocyte cell count (OR=0.950, CI 0.907-0.995), histo-blood group ABO system transferase (OR=3.688, CI 1.305-10.418) and Pplatelet and endothelial cell adhesion molecule 1 (OR=0.491, CI 0.255-0.945). There was no strong evidence supporting an association of genetically proxied mean cell hemoglobin, mean cell volume, platelet count, red blood cell count, white blood cell count, lymphocyte cell count, neutrophil cell count , albumin, fibrinogen or HDL-c (high-density lipoprotein cholesterol) with COVID-19.

Taken together, our findings support the hypothesis that COVID-19 would affect certain blood constituents, especially for the significant MR results($p<0.05$). Eosinophils are circulating and tissue-resident leukocytes that have potent functions, including immunoregulation and antiviral activity. The pathophysiology for eosinopenia in COVID-19 is likely multifactorial, involving inhibition of eosinophil egress from the bone marrow, blockade of eosinophilopoiesis, reduced expression of chemokine receptors/adhesion factors, and/or direct eosinophil apoptosis induced by type 1 IFNs released during the acute infection[4]. Zhang et al reported that more than half the patients admitted with COVID-19 (53%) had eosinopenia (defined as absolute eosinophil counts $<0.02 \times 10^9$ cells/L) on the day of hospital admission[5]. Similarly, Du et al noted that 81% of the patients had eosinopenia at the time of admission by reviewing the medical records of 85 fatal cases of COVID-19[6].

Cholesterol is critical for viral entry and replication, and dyslipidemia in COVID-19 is considered to result from complicated biological and pathological processes triggered by SARS-CoV-2.Typically, there is a selective uptake of cholesterol as viruses bind to the cellular membrane, which ultimately enables severe infection. Most publications indicated that free cholesterol (FC), HDL, and LDL cholesterol levels were significantly low in patients with a viral infection, compared to the controls[7]. These studies may reveal the internal correlation between SARS-CoV-2 virus and serum cholesterol. Also, the changing conditions in patients may be indicated by observing serum cholesterol levels. In addition, previous studies have noted the importance of B cell subset, and

these lymphocytes could serve as potential biomarkers and even active participants in the adaptive antiviral response mounted against SARS-CoV-2[8].

In conclusion, we leveraged large-scale genetic summary data to investigate the effects of COVID-19 risk on certain blood constituents. Our findings support causal effects of infectious SARS-CoV-2 on eosinophil cell count, LDL-c, TC, B-cell receptor-associated protein 29 and Killer cell immunoglobulin-like receptor 2DL5A. The findings may help shed light on the mechanisms underlying COVID-19, and may have clinical implications. Many potential mechanisms may be involved in these relationships, Further studies are warranted to elucidate the mechanisms involved.

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Table 1 Mendelian randomization (MR) estimates of COVID-19 on blood constituents

Sample ID	Outcome	Snps	OR(95%CI)	Pavl
ieu-a-271	Mean cell haemoglobin	16	1.004(0.874,1.153)	0.958
ieu-a-272	Mean cell haemoglobin concentration	16	0.956(0.920,0.992)	**0.018**
ieu-a-273	Mean cell volume	16	1.110(0.743,1.657)	0.609
ieu-a-274	Packed cell volume	15	0.678(0.478,0.963)	**0.030**
ukb-d-30080_irnt	Platelet count	38	0.993(0.966,1.021)	0.613
ukb-d-30110_irnt	Platelet distribution width	38	0.968(0.940,0.998)	**0.038**
ebi-a-GCST004601	Red blood cell count	38	0.985(0.955,1.016)	0.334
ieu-b-29	Basophil cell count	38	0.985(0.963,1.007)	0.180
ieu-b-30	White blood cell count	38	0.983(0.934,1.034)	0.505
ieu-b-31	Monocyte cell count	38	0.950(0.907,0.995)	0.030
ieu-b-32	Lymphocyte cell count	38	1.013(0.954,1.076)	0.671
ieu-b-33	Eosinophil cell count	38	0.946(0.916,0.977)	**6.66E-04**
ieu-b-34	Neutrophil cell count	38	0.984(0.945,1.025)	0.430
bbj-a-9	Albumin	21	0.979(0.943,1.017)	0.279

bbj-a-22	Fibrinogen	21	1.059(0.989,1.133)	0.099
ebi-a-GCST005058	HDL cholesterol(HDL-c)	30	0.996(0.898,1.104)	0.934
ebi-a-GCST005068	LDL cholesterol(LDL-c)	29	0.810(0.730,0.899)	**6.99E-05**
ebi-a-GCST005065	Cholesterol, total(TC)	29	0.843(0.760,0.935)	**1.18E-03**
prot-a-10	Histo-blood group ABO system transferase	38	3.688(1.305,10.418)	**0.014**
prot-a-233	B-cell receptor-associated protein 29	38	1.284(1.086,1.518)	**3.38E-03**
prot-a-1644	Killer cell immunoglobulin-like receptor 2DL5A	38	1.259(1.083,1.463)	**2.67E-03**
prot-b-79	Platelet and endothelial cell adhesion molecule 1	19	0.491(0.255,0.945)	**0.033**

Sample id: gwas data id in the OpenGWAS database; OR: odds ratio; CI: confidence interval.