LETTER OPEN

Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence

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Dear Editor,

The evolving pandemic of coronavirus disease 19 (COVID-19), is arousing alarm to public health. According to epidemiological and observational investigations, coagulopathy was frequently seen in severe COVID-19 patients[1]. Some coagulation factors such as D-dimer, prothrombin time (PT), von Willebrand factor (VWF), platelet count, and fibrinogen were documented to be important predictors of critically ill patients with COVID-19 in many retrospective observational studies and were substantially discussed before (see Supplementary Notes), yet the causality from specific coagulation factors to the incidence of COVID-19 severity and the underlying mechanism remains elusive.

To investigate the causal relationships between coagulation factors and the incidence of COVID-19 severity, we systematically curated genome-wide significant SNPs associated with 12 coagulation factors from different genome-wide association study (GWAS) results (Supplementary Table 1-2). After correlated instruments removal and effect size harmonization, we performed Mendelian Randomization (MR) analyses based on two largest GWASs of COVID-19 severity to date (Fig. 1a). In this process, several MR methodologies including Inverse variance weighted (IVW), MR-Egger regression, and weighted median (WM) methods were leveraged to test the causal effect of each coagulation factor on the incidence of COVID-19 severity, and various sensitivity analyses were applied to assess the robustness of our findings. As shown in Fig. 1b and Supplementary Table 3, our results revealed that genetic predisposition to the antigen levels of VWF and the activity levels of its cleaving protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) were causally associated with the incidence of COVID-19 severity.

According to COVID-19 GWAS result from the Severe COVID-19 GWAS Group[2], among all investigated coagulation factors, we observed that VWF ($P_{IVW} = 0.005$) and ADAMTS13 ($P_{IVW} = 0.025$) both showed significant results but displayed opposite direction of causal effect on the incidence of COVID-19 severity. Specifically, genetically determined plasma VWF antigen level was positively associated with the incidence of severe COVID-19 ($P_{IVW} = 0.005$, odds ratio (OR) = 1.35, 95% confidence interval (CI): 1.09–1.68, false discovery rate (FDR) = 0.06 (<10%)) based on 17 instrumental single-nucleotide polymorphisms (SNPs) (Fig. 1c). Both MR-Egger ($P_{Egger} = 0.003$) and WM MR ($P_{WM} = 0.012$) also supported the causal association (Fig. 1c and Supplementary Table 3). After removing the instruments that are significantly associated with confounder traits, no additional pleiotropy was detected between VWF levels and COVID-19 severity by Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test ($P = 0.074$), Q_{Egger} ($P = 0.777$), and Q_{IVW} ($P = 0.515$). Besides, IVW MR revealed that plasma ADAMTS13 activity was inversely associated with the incidence of severe COVID-19 ($P_{IVW} = 0.025$, OR = 0.69, 95% CI: 0.50–0.96) based on four instrumental SNPs (Fig. 1d), and no pleiotropy was detected by MR-PRESSO global test ($P = 0.772$), Q_{Egger} ($P = 0.433$) or Q_{IVW} ($P = 0.630$). Interestingly, Given the VWF-cleaving function of ADAMTS13, this finding further supports the causal relationship between VWF levels and the incidence of COVID-19 severity. The statistical significance of ADAMTS13 disappeared after multiple testing correction (FDR = 0.15 (>10%)), which might be attributed to the relatively small number of valid instrumental variables.

In addition, based on COVID-19 severity GWAS data from the COVID-19 Host Genetics Initiative round 5[3], we observed that VWF is the only coagulation factor that exhibited genetic causal associations with the incidence of COVID-19 severity ($P_{IVW} = 0.029$, OR = 1.13, 95% CI: 1.01–1.25, Fig. 1e). WM MR also revealed the significant causal association ($P_{WM} = 0.046$, OR = 1.16, 95% CI: 1.00–1.35, Fig. 1e and Supplementary Table 3). Sensitivity analyses supported the robustness of the result, where no pleiotropy was detected by MR-PRESSO global test ($P = 0.104$), Q_{Egger} ($P = 0.245$), and Q_{IVW} ($P = 0.279$). However, no significant signal was observed from the results of ADAMTS13 MR analyses (Fig. 1f). Taken together, these results confirmed that elevated VWF antigen level is a potential causal factor for the incidence of COVID-19 severity.

A growing body of studies reported that hypercoagulation status was frequently seen in COVID-19 patients[1]. We also performed a literature review to summarize existing clinical epidemiological studies regarding VWF/ADAMTS13 and COVID-19 severity. The majority of curated studies showed that the elevation of VWF antigen levels and the reduced ADAMTS13 activities are associated with COVID-19 severity (Supplementary Table 4). Besides, a multi-omics analysis leveraged RNA-Seq and high-resolution mass spectrometry on 128 blood samples from COVID-19 positive and negative patients with diverse disease severities, and found VWF antigen level is significantly higher in COVID-19 patients when compared to normal controls[4]. We further confirmed that the VWF protein level is significantly higher in intensive care unit (ICU) COVID-19 patients compared to non-ICU patients based on their released peptide quantifications (Fig. 1g). These evidences largely support that the antigen level of blood-derived VWF is an associated biomarker for COVID-19 severity.

Using an independent COVID-19 cohort from UK Biobank (UKBB), we identified 1492 severe COVID-19 cases and 445,271 healthy controls (baseline demographic and clinical characteristics are summarized in Supplementary Table 5). We explored the predictive ability of polygenic risk score (PRS) that derived from the VWF-associated genetic variants (17 instrumental SNPs) in the prediction of severe COVID-19 risk together with several critical risk factors, including age, sex, body mass index (BMI), coronary artery disease (CAD), systolic blood pressure (SBP), type 2 diabetes mellitus (T2DM), and chronic obstructive pulmonary

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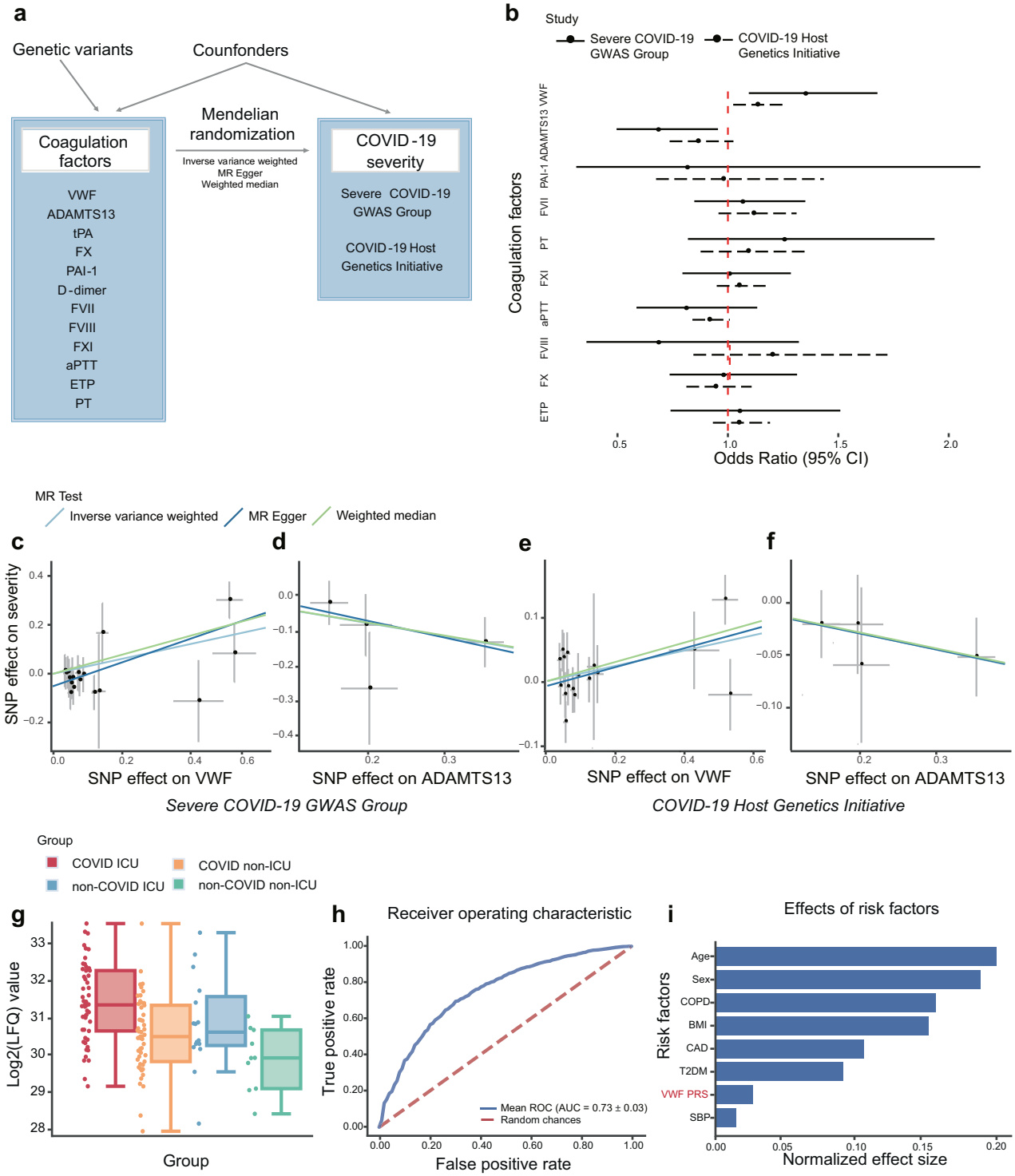

disease (COPD)[5]. By evaluating the association of the VWF PRS and COVID-19 severity risk using a logistic regression model adjusted for the top 10 principal components of genetic variations and other selected risk factors (age, sex, BMI, CAD, SBP, T2DM, and COPD), we found that PRS of VWF is an independent risk factor for distinguishing severe COVID-19 cases from healthy controls, which explains a 16% higher risk ($P = 0.011$, OR per SD increase = 1.16, 95% CI: 1.03–1.29).

Furthermore, to investigate the prediction performance of the overall COVID-19 severity model and the contribution of VWF PRS, we calculated the area under the receiver operating characteristic curve (AUC) by 10-fold cross-validation. We found that the model combining clinical risk factors and the VWF PRS received a mean AUC of 0.734 (±0.03) (Fig. 1h), and the VWF PRS moderately increased the mean AUC by 0.3% when compared with the model based on only clinical parameters. Since we

Fig. 1 Mendelian randomization analyses and validation between coagulation factors and COVID-19 severity. **a** Mendelian randomization analysis framework in this study. A directed acyclic graph illustrates Mendelian randomization assumptions. The solid lines depict the potential causal diagram. **b** Forest plot shows odds ratio (OR) and 95% confidence interval (CI) from the results of IVW MR. The solid lines indicate MR results based on COVID-19 GWAS data from the Severe COVID-19 GWAS Group and the dashed lines indicate MR results based on COVID-19 GWAS data from the COVID-19 Host Genetics Initiative. D-dimer and tPA are excluded in this plot for abnormal OR values. **c**–**f** Scatter plots of the estimated genetic associations on the COVID-19 severity against the genetic association estimates with the VWF and ADAMTS13. The MR results are based on COVID-19 GWAS from (**c**, **d**) the Severe COVID-19 GWAS Group; (**e**, **f**) the COVID-19 Host Genetics Initiative. The slopes of the lines are the estimated causal effects using different MR methods including inverse variance weighted, MR Egger regression, and weighted median. **g** Relative abundance measurements of VWF protein in different patient groups. The relative abundance of VWF protein was estimated based on the relative abundances of its unique peptides. Different colors indicate patient status: COVID-19 ICU (red), COVID-19 non-ICU (orange), non-COVID-19 ICU (blue), and non-COVID-19 non-ICU (green). This image was created using data from COVID-19 Multi-Omics Data Dashboard (https://covid-omics.app). **h** Predictive ability of VWF PRS and clinical risk factors against COVID-19 severity. Receiver operating characteristic (ROC) for logistic regression using clinical risk factors and PRS derived from VWF GWAS as independent variables, the area under the receiver operating characteristic curve (AUC) was the mean value for 10-fold cross-validation. **i** Barplot depicts the normalized effect size of each contributing variable, values of each bar are coefficients of logistic regression after normalizing raw values to the same scale via z-score normalization. *MR* Mendelian randomization, *VWF* von Willebrand factor, *ADAMTS13* a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, *tPA* tissue plasminogen activator, *PAI-1* plasminogen activator inhibitor-1, *FVII* Factor VII, *PT* prothrombin time, *FVIII* Factor VIII, *FXI* Factor XI, aPTT activated partial thromboplastin time, *FX* Factor X, *ETP* endogenous thrombin potential, *LFQ* label-free quantification, *ICU* intensive care unit, *BMI* body mass index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *PRS* polygenic risk score, *T2DM* type 2 diabetes mellitus

fitted the model with z-score normalized values, the coefficients of each contributing variable can be compared directly. We observed that age is the most important risk factor for COVID-19 severity, and male sex, high BMI, and history of COPD, CAD, and T2DM are also effective predictors (Fig. 1i), which is consistent with previous findings. Notably, VWF PRS showed a larger normalized effect size than SBP (Fig. 1i), emphasizing its predictive value during the prevention and personalized treatment of COVID-19.

In summary, together with the supporting evidence of recent retrospective cohort studies and independent validation based on UKBB data, our results suggest that the association between coagulation factor VWF and the incidence of COVID-19 severity is essentially causal, and the association between ADAMTS13 and the incidence of COVID-19 severity is likely to be causal, which illuminates one of the possible mechanisms underlying COVID-19 severity (Supplementary Notes). This study also highlights the importance of dynamically monitoring the plasma levels of VWF/ADAMTS13 after SARS-CoV-2 infection, and facilitates the development of a treatment strategy for controlling COVID-19 severity and associated thrombotic complication.

DATA AVAILABILITY

All supporting data are included in the Supplementary Information.

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ADDITIONAL INFORMATION

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Supplementary Materials for

Coagulation factors and the incidence of COVID-19 severity: Mendelian randomization analyses and supporting evidence

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Supplementary Methods

Instrumental variables for coagulation factors

As summarized in Supplementary Table 2, we searched PubMed and GWAS Catalog [1] for the coagulation factor-relevant GWASs in European ethnic participants to identify genetic variants that could be used as instrumental variables for two-sample mendelian randomization (MR) analysis. Single-nucleotide polymorphisms (SNPs) associated with specific coagulation factor at sub-threshold genome-wide significant level ($P < 5E-7$) were selected as instrumental variables. The identified coagulation factors with genetic instruments include (1) Factor VIII (FVIII), Factor XI (FXI), and activated partial thromboplastin time (aPTT) that involved in intrinsic pathways; (2) Factor X (FX) and endogenous thrombin potential (ETP) that involved in common pathways; (3) Factor VII (FVII) and prothrombin time (PT) that involved in extrinsic pathways; (4) von Willebrand factor (VWF) and a thrombospondin type 1 motif, member 13 (ADAMTS13) that involved in platelet adhesion; (5) D-dimer, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1) concentration that involved in the dissolution of fibrin clot. To ensure that MR results are more informative and horizontal pleiotropy can be assessed among instrumental variables, only coagulation factors with at least three genetic instruments were included in this study.

GWAS summary statistics for severe coronavirus disease 19 (COVID-19)

GWAS summary statistics for severe COVID-19 with respiratory failure were obtained from two sources, (1) the GWAS of severe COVID-19 with respiratory failure from the Severe COVID-19 GWAS Group (http://www.c19-genetics.eu), which was based on 1,610 patients and 2,205 healthy control participants in European ethnic groups, wherein age, sex, and top 10 genetic components were adjusted [2]; (2) the GWAS of COVID-19 with very severe respiratory from the COVID-19 Host Genetics Initiative (https://www.covid19hg.org, round 5, A2_ALL_leave_UKBB), which was based on 5,870 patients and 1,155,203 healthy control participants in mixed ethnic groups (mainly from European population) without UKBB cases [3].

UK Biobank (UKBB) COVID-19 data

The COVID-19 inspections result from the UKBB (up to 2021/3/1) was used, which included 446,763 unrelated (kinship coefficient > 0.0884, corresponding to 3rd-degree relationships) UKBB participants of European ancestry (mean age 70 years; 45.7% men). Specifically, we removed all participant without corresponding phenotype data, and then we directly included participants that do not relate to any other participants in our study, finally, we treated all participant pairs > KING kinship coefficient 0.0884 as candidate participants, we removed the individuals with the most relatedness to other participants in a stepwise manner, until there is no more relatedness among candidate participants, and included all remain participants to our study. All these participants were laboratory-confirmed COVID-19 patients. Baseline demographic and clinical characteristics of these participants are summarized in Supplementary Table 5.

The information of COVID-19 diagnosis was obtained from COVID-19 test results provided by Public Health England (PHE); death register provided by the National Health Service (NHS) Digital and NHS Central Register (NHSCR); hospital inpatient data provided by NHS Digital; and primary care data provided by TPP systems (https://www.tpp-uk.com/) and EMIS (https://www.emishealth.com/) systems. The selection criteria of UKBB participants included: ever reported as positive for SARS-CoV-2 by PHE; death from COVID-19 as the underlying cause

(International Classification of Diseases, Tenth Revision (ICD-10): U071); hospitalization for COVID-19 (ICD-10: U071) from Hospital Episode Statistics; or confirmed COVID-19 infection from primary care data (Clinical Terms Version 3 (CTV3): Y20d1, EMIS: EMISNQCO303 or SNOMED CT: 1240581000000100).

Individual genotypes that primarily called by two genotyping arrays known as UKBB Axiom array and UK BiLEVE Axiom array were imputed to ~92 million autosomal and X-chromosome variants using merged panel comprised of UK10K haplotype reference panel and 1000 Genomes Phase 3 reference panel by UKBB.

Mendelian randomization instruments construction

The MR framework used in this study was shown in Fig. 1a. To ensure valid instruments selection according to MR analysis criteria [4,5], we first harmonized instrumental SNPs for each exposure GWAS by (1) excluding SNPs associated with other potential confounders (body mass index, lipid, and metabolic diseases, etc.) of exposure-outcome associations by searching PhenoScanner [6]; (2) excluding SNPs located in the major histocompatibility complex (MHC) human leukocyte antigen (HLA) region from the list of instrumental SNPs due to potential horizontal pleiotropy with other confounder traits such as metabolic diseases and immune diseases [7-9]; (3) excluding rare SNPs (minor allele frequency < 0.01) from the list of instrumental SNPs; (4) standardizing the effect size (β) and standard error (SE) for each SNP by the following formula [10]:

$$\beta = \frac{z}{\sqrt{2f(1-f)(n+z^2)}}, \text{SE} = \frac{1}{\sqrt{2f(1-f)(n+z^2)}}$$

where $z = \beta/\text{SE}$ from the original summary data, f is the effect allele frequency, and n is the total sample size.

For SNPs that were not available in the GWAS data of COVID-19 severity, we used the LDlink tool [11] to find the most correlated proxies (r2 > 0.8), and the summary-level statistics for proxy SNPs were used instead. Based on SNPs reported to be associated with certain exposure by the above GWAS studies, we further applied the linkage disequilibrium (LD)-based clumping implemented in PLINK [12] (r^2 threshold = 0.01 and window size = 10Mb) to ensure the independence of selected SNPs. Individual-level genotype data from European population of 1000 Genomes project served as the reference panel in this study. The final SNPs used as instruments in this study are summarized in Supplementary Table 1. To evaluate the strength of each instrument variable, F-statistics of instrumental variables were calculated with the following equation.

$$\frac{R^2(\text{n} - 2)}{(1 - R^2)},$$

Where n is the sample size of the exposure and R^2 is the amount of variance of the exposure explained by the SNP that computed as described by a previous study [13]

MR statistical analysis

Several MR methodologies including Inverse variance weighted (IVW), MR-Egger regression, and weighted median (WM) methods were used to estimate the causal effects, wherein IVW was used in the main analysis [14,15]. We obtained Wald ratio estimates for each instrumental SNP on COVID-19 severity, and then combined Wald ratio estimates using inverse variance weighting with fixed effects. To identify potential horizontal pleiotropy, we searched PhenoScanner [6] to explore whether instrumental SNPs are associated with other potential cofounders of exposure-outcome associations. Moreover, we further performed several sensitivity analyses to assess the robustness of our findings by (1) we evaluated heterogeneity for causal estimates that calculated by MR-Egger regression and IVW among instrument SNPs based on

Cochran's Q statistic [16] and then used Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test [17] to detect global pleiotropy; (2) when the global test was significant ($P < 0.05$), we removed statistically significant outliers detected by MR-PRESSO outlier test ($P < 0.05$) and repeated MR analysis; (3) to avoid multiple comparisons problem, we applied Benjamini-Hochberg method to control False discovery rate (FDR significance threshold = 0.1), and the BH-adjusted *P*-values of IVW method were used in multiple comparisons correction. IVW, MR-Egger regression, WM methods were implemented in R package TwoSampleMR v0.5.4; MR-PRESSO global test and outlier test were implemented in R package MR-PRESSO.

Literature review

To gain more information regarding the two significant coagulation factors in MR analysis, we also performed a literature review to summarize existing clinical epidemiological studies regarding VWF/ADAMTS13 and COVID-19 severity. We used Google Scholar (up to 2020/10/1) to search terms: "COVID-19" or "SARS-CoV-2" or "2019-nCoV" or "Novel Coronavirus-Infected Pneumonia" or "2019 novel coronavirus" or "coronavirus 2019" and "severe" or "severity" and "VWF" or "Von Willebrand Factor" or "ADAMTS13" not only in the title and abstract, but also throughout the entire article.

Evaluation based on UKBB COVID-19 data

Severe COVID-19 cases from the UKBB cohort were defined as laboratory- or clinical-diagnosed COVID-19 patients with at least one of the following clinical features: (1) receiving care in the intensive care unit (ICU); (2) hospitalized inpatients; (3) depending on invasive ventilation using ventilator or ventilatory supports; (4) depending on noninvasive ventilation using other enabling machines and devices. Healthy controls were used for predicting the onset risk of severe COVID-19. We used PRSice-2 [18] to construct the PRS of VWF based on the effect sizes derived from the VWF GWASs and then investigated its association with the risk of critical illness in the COVID-19 patients from UKBB cohort. PRS based on significant instrumental SNPs of VWF were calculated by the following formula [18]:

$$\mathrm{PRS}_j = \sum_i \beta_i g_{ij}$$

where *j* indicates j^{th} individual and *i* indicates i^{th} variant, g is the number of risk alleles carried ($g \in \{0,1,2\}$), β is the harmonized effect size derived from the VWF GWASs.

We applied a multivariable logistic regression model to determine the association between the VWF PRS and the incidence of COVID-19 severity with adjustments for age, sex, body mass index (BMI), systolic blood pressure (SBP), top 10 principal components of genetic variations, history of coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), and chronic obstructive pulmonary disease (COPD). The significance of regression coefficients was determined by Wald statistics test under null hypothesis that the variable has no correlation with COVID-19 severity risk. To demonstrate the predictive power of PRS, we trained two logistic regression models with (1) clinical risk factors and (2) clinical risk factors + VWF PRS. Before fitting the models, we applied z-score normalization to transform raw values of variables into a same scale. Due to the nature of a probabilistic statistical method, logistic regression models tend to be biased towards the majority class. To compensate the class imbalance issue between cases and controls, the probability weight based on inversed case-control ratio was used in the model [19,20], that is, the minor class was given more weight and the major class was given less weight

(assigned 300:1 in this study). We used 10-fold cross-validation in the fitting process. Specifically, we randomly divided the entire sample into 10 equal-sized sub-samples, then iteratively fitted the model using the nine folds and validated the model using the remaining one fold. Furthermore, to evaluate the fit of the model, we took the mean value of an area under the receiver operating characteristic curve (AUC) measurement among the 10 iterations.

Supplementary Notes

Research background

The outbreak of COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with an unprecedented number of pneumonia cases from the late December 2019 put people on full alert [21]. Widespread comorbidities implicating several organs were frequently observed in COVID-19 patients, such as diseases in cardiovascular, neurological, and hematopoietic systems [22]. Of note, COVID-19-associated coagulopathy is a common complication among those patients developing severe systemic diseases and multiorgan failure [23-25], suggesting the importance of exploring clinical markers and the causal association between coagulopathy and COVID-19 [26].

Some coagulation parameters including D-dimer, prothrombin time (PT), von Willebrand factor (VWF), platelet count, and fibrinogen were previously documented to be important predictors of critically ill patients with COVID-19 [27-29]. A recent study revealed that specific coagulation biomarkers, such as VWF and factor VIII (FVIII) levels, are independent predictors of increased oxygen requirements in COVID-19 [30]. It has also been observed that hospitalized COVID-19 patients, especially those with severe respiratory or systemic symptoms, are at increased risk for thromboembolism [31,32] and aberrant bleeding manifestations [33,34]. Moreover, alveolar capillary microthrombi were 9 times as prevalent in patients who died from COVID-19 as those who died from H1N1 influenza [35]. These retrospective observational studies clearly demonstrated the remarkable relevance among coagulation factor levels, thrombotic complications and COVID-19 severity. Nevertheless, it remains unclear which coagulation factor(s) can faithfully indicate the severity of COVID-19 illness or whether genetic predisposition to coagulation factor levels is causally related to severity and mortality of COVID-19 as well as the underlying biological pathways.

Novelty and clinical implication of this study

Emerging evidence from observational studies showed that COVID-19 patients are prone to developing thrombotic diseases [36,37] which are significantly associated with COVID-19 severity, poor prognosis, and mortality risk [38,39]. However, whether exceptional plasma levels or activities of specific coagulation factors account for a higher risk of COVID-19 severity and aberrant thrombotic manifestation is elusive. In this study, we first explored the causal relationship between multiple coagulation factors and the incidence of COVID-19 severity using MR approaches. Together with the supporting evidence of recent retrospective cohort studies, our results revealed that the associations between VWF/ADAMTS13 and COVID-19 severity are essentially causal, suggesting the elevated VWF antigen and decreased ADAMTS13 activity are confident biomarkers that indicate progressive severity of COVID-19 and more aggressive critical care needed. In addition, genetic determents explain a considerable portion of the observed variance of plasma coagulation factor levels, including VWF levels [40]. By PRS analysis on UKBB COVID-19 cohort, we uncovered that VWF PRS is an independent contributor for COVID-19 severity prediction. When combined with age, sex, BMI, and several pre-existing disease statuses, the model achieved good predictive ability in distinguishing severe cases from healthy controls.

VWF, stored in Weibel-Palade bodies and platelet α-granules for secretion upon stimulation, is a large multimeric glycoprotein which plays an important role in platelet recruitment after injury by forming a bridge between platelet surface receptors and endothelium [41]. While, ADAMTS13 is

a plasma protein cleaving VWF and decreasing its activity that anchored on the endothelial surface and in circulation [42]. The dysfunction of VWF/ADAMTS13 dynamic equilibrium had been reported to be associated with thrombotic diseases [43-46] and cardiovascular diseases [47]. COVID-19 patients are prone to developing thrombotic diseases [36,37], reciprocally, the development of thrombotic diseases could account for poor prognosis and mortality of COVID-19 [38,39]. We suspected that SARS-COV-2 invades human lungs and causes injury or inflammation in the blood vessels, which then promoting a pro-coagulative state. As an important consideration for COVID-19, elevated VWF level and insufficient ADAMTS13 activity confer a higher risk of forming blood clots and ultimately develop venous thromboembolism. Thrombus can block normal blood flow and decrease oxygen supplement to alveoli, and this may explain partially why COVID-19 patients are at risk of respiratory failure. The patients with severe COVID-19 often have findings consistent with prominent endotheliopathy [35,48,49]. The incidence of endotheliopathy and platelet activation are ubiquitous in COVID-19-associated coagulopathy and might play key roles in the progression of disease. Evidence showed that endotheliopathy could lead to the clinical prothrombotic manifestations of COVID-19-associated coagulopathy by augmented VWF release, platelet activation, and hypercoagulability [29]. Mean level of VWF antigen in critical COVID-19 patients has been reported to range from 455 to more than 600% (normal range: 50-150%), mean level of ADAMTS13 activity in critical COVID-19 patients has been reported to range from 32.17 to 36% (normal range: 40-130%) [29,50-54]. Regarding clinical practice, the association between VWF/ADAMTS13 and COVID-19 severity requires further confirmation, an ideal way to explore this association could be measuring VWF/ADAMTS13 at multiple time points during the hospitalization of COVID-19 patients and evaluate its correlation with the disease status. According to our MR causal inference and PRS analysis in the UKBB COVID-19 cohort, we could advise individuals carry certain VWF/ADAMTS13 alleles to closely monitor their coagulation factors and take supportive care for coagulopathy prevention after SARS-CoV-2 infection. Also, existing drugs targeting VWF or its molecular interactions could be considered to control COVID-19 severity and associated thrombotic complication for specific cohorts. Several other coagulation factors such as D-dimer and PT were previously documented to be associated with COVID-19 severity in observational studies [27,28], however, we found no causal relationships through MR analyses. This phenomenon could be attributed to potential confounding factors in observational studies, where associations between coagulation factors and COVID-19 severity was not due to direct causality, but rather because both coagulation factors and COVID-19 severity are likely caused by other unrevealed confounders.

Potential confounding factor and limitations

ABO gene loci obtained the most prominent GWAS signal in plasma VWF levels [40] and strong associations with COVID-19 [2], implying ABO blood group may confound the establishment of causality between VWF/ADAMTS13 and COVID-19 severity. Recent epidemiological studies have investigated and observed tight association of ABO blood group with the COVID-19 susceptibility, severity, and mortality [55-58]. It was also reported that the *ABO* genotypes and ABO blood group are associated with ACE activity in hypertensive patients [59], and increased plasma ABO protein is causally associated with the risk of severe COVID-19 [60]. Among the associated variants of VWF levels within the *ABO* locus, SNPs rs10901252 and rs687621 can perfectly

discriminate B and O blood groups from A [61]. Individuals with blood group O have lower VWF plasma concentrations compared with individuals with blood group non-O [62]. The presence of blood group A and B antigens on VWF molecules may have clinically significant effects on VWF proteolysis and clearance [63]. In our analysis, we excluded SNP rs687621 due to potential horizontal pleiotropy with other traits (such as Interleukin 6 levels and coronary artery disease) and rs10901252 for high LD with other instrumental SNPs (such as rs8176743). We found that the causality between VWF levels and COVID-19 severity was established when taking away the genetic effect of these SNPs. However, whether the causal mechanisms of VWF levels on COVID-19 severity could be independent of ABO blood group still needs further investigation.

Our study is also subject to some data limitations. First, only genome-wide significant variants were available from existing GWAS results of VWF/ADAMTS13 and most of the investigated coagulator factors, which makes it impossible to perform bi-directional MR analysis, and such limited number of instrumental SNPs for particular coagulation factors could affect the accuracy of both MR and PRS estimations. Similar to recent PRS studies on CAD [64] and ischemic stroke [65], we observed that incorporation of genetic component significantly contributes to the prediction model but only slightly improves the overall performance. The significant association between VWF PRS and COVID-19 severity indicated that the information captured by VWF PRS is not fully explained by other risk factors. But the current PRS study on COVID-19 cohort is likely underpowered due to insufficient sample size, the borderline significance required a larger study to ascertain the accuracy. Second, each method we utilized in MR analysis has its own assumptions, IVW obtains the causal estimate by a weighted regression of instrumental variable (IV) associations with an outcome on IV associations with an exposure [66]. MR-Egger attempts to model the distribution of the estimates from invalid IVs under the InSIDE (Instrument Strength Independent of Direct Effect) assumption [67]. WM method is the median of a weighted empirical density function of the ratio estimates. WM method has been confirmed to have better finite-sample Type 1 error rates than the IVW method and improved power of causal effect detection than MR-Egger, but does not need InSIDE assumption [68]. The usages of these methods may receive inconsistent results. Third, genetic risk loci for coagulation factors may vary among different populations [69,70], but our study mainly focuses on people of European descent. Whether there are population-specific causal mechanisms needs further exploration. Also, we didn't investigate gender- or age-specific effects because of the lack of gender- or age-stratified GWAS data. Fourth, regarding the failure to replicate ADAMTS13 in the COVID-19 Host Genetics Initiative cohort, the major constraint could be relatively small number of valid instrumental variables on ADAMTS13, as well as some biases like improper severe case selection. It is worth noting that, the used GWAS from the COVID-19 Host Genetics Initiative is a multicenter meta-analysis compared to the result from the Severe COVID-19 GWAS Group, and it contains heterogeneous mixtures of sample populations and the between-study individual heterogeneity, which may obscure the inference of the causal effect [71,72]. On the other hand, small number of instruments might lead to insufficient statistical power [73], thus our conclusion for ADAMTS13 remains conservative due to data limitation and needs more powerful analysis. Last, the sample size of severe COVID-19 GWAS is still insufficient in current stage, and further research is warranted when abundant and non-European ethnic GWAS data is available in the future. We also expect that prospective controlled trial could be applied to ascertain the causal role of VWF/ADAMTS13 and investigate potential treatments for certain infected populations.

Supplementary Tables

Table S1. Selected instrument SNPs of coagulation factors in this study

Exposure	SNP	Effect allele	Beta[a]	Se[b]	*P* value	F-statistics	Study
VWF	rs55954186	A	0.04	0.01	8.715E-09	25.00	Sabater-Lleal M [61]
VWF	rs548630	A	-0.04	0.01	1.329E-12	36.00	
VWF	rs9390460	T	-0.08	0.01	6.316E-38	120.99	
VWF	rs7788962	A	-0.07	0.01	6.291E-08	21.78	
VWF	rs4276643	T	0.04	0.01	5.768E-27	93.44	
VWF	rs10985344	A	0.13	0.02	4.106E-09	32.11	
VWF	rs34434834	A	0.12	0.01	6.348E-12	42.97	
VWF	rs2238109	A	0.09	0.01	1.37E-82	277.76	
VWF	rs4981022	A	0.05	0.01	5.442E-37	136.10	
VWF	rs4904820	A	-0.05	0.01	8.301E-18	53.78	
VWF	rs6494314	T	-0.06	0.01	9.628E-08	36.00	
VWF	rs2277998	A	-0.05	0.01	2.024E-15	58.77	
VWF	rs5750823	T	-0.42	0.07	2.978E-11	40.11	
VWF	rs8176743	C	-0.51	0.04	1.59E-17	33.46	Williams [74]
VWF	rs12518614	A	-0.53	0.06	1.52E-09	184.78	
VWF	rs651007	C	-0.14	0.02	4.415E-36	69.06	
VWF	rs216321	T	0.04	0.01	1.7E-17	61.92	Tang W [75]
ADAMTS13	rs10456544	A	0.20	0.04	1.1E-08	29.39	de Vries PS [76]
ADAMTS13	rs4075970	G	0.15	0.02	6.8E-09	35.98	Ma Q [77]
ADAMTS13	rs28673647	G	0.35	0.02	1.2E-57	201.52	
ADAMTS13	rs3124762	C	0.20	0.03	8.9E-09	34.01	
PAI-1	rs2227631	A	0.08	0.01	7.80E-15	63.99	Huang J [78]
PAI-1	rs3847067	A	0.07	0.01	4.10E-10	36.00	
PAI-1	rs6486122	T	0.05	0.01	3.00E-08	25.00	
PAI-1	rs314376	G	0.05	0.01	2.40E-09	25.00	
PAI-1	rs11128603	A	0.07	0.02	2.90E-08	20.25	
ETP	rs35800856	A	1.11	0.12	6.13E-09	80.92	Rocanin-Arjo A [79]
ETP	rs17787912	G	-0.28	0.04	1.63E-11	53.72	
ETP	rs2856656	C	0.38	0.06	4.62E-22	37.17	
D-Dimer	rs12029080	G	0.053	0.011	6.00E-52	25.00	Smith NL [80]
D-Dimer	rs6687813	A	0.056	0.021	2.00E-14	7.37	
D-Dimer	rs13109457	A	0.034	0.011	3.00E-18	9.00	
tPA	rs9399599	T	0.06	0.01	2.90E-14	56.25	Huang J [81]
tPA	rs3136739	A	0.12	0.02	1.30E-09	36.00	
tPA	rs7301826	C	0.07	0.01	1.00E-09	56.25	
FVII	rs569557	G	0.65	0.01	6.4E-600	2738.58	de Vries PS [82]
FVII	rs867186	G	0.26	0.01	3.3E-64	360.97	

FVII	rs1260326	T	0.10	0.01	2.3E-30	143.99	
FVII	rs7935829	G	0.08	0.01	6.3E-18	80.99	
FVII	rs6532796	G	0.07	0.01	2.6E-13	64.00	
FVII	rs1149616	T	0.06	0.01	1.7E-10	32.11	
FVII	rs10761784	A	0.06	0.01	6.7E-10	42.25	
FVII	rs498475	G	0.05	0.01	1.5E-08	36.00	
PT	rs6027	T	0.19	0.02	5.90E-29	128.44	
PT	rs7901813	A	0.05	0.01	6.50E-10	38.10	
PT	rs4399232	T	-0.06	0.01	9.30E-13	51.29	
PT	rs491098	C	-0.32	0.01	2.80E-147	695.00	
PT	rs1801690	C	-0.13	0.02	3.30E-13	56.25	
PT	rs2069940	C	-0.15	0.01	5.20E-29	115.97	
FXI	rs710446	T	-0.40	0.01	2.07E-302	1380.31	Sennblad B [83]
FXI	rs4253417	T	-0.33	0.01	2.86E-193	878.25	
FXI	rs780094	T	0.07	0.01	3.56E-09	34.85	
aPTT	rs2239852	T	0.09	0.02	1.90E-08	35.99	Weng L [84]
aPTT	rs710446	C	-0.41	0.01	2.30E-197	870.07	
aPTT	rs9898	T	-0.36	0.01	1.20E-123	600.13	
aPTT	rs4253399	G	-0.16	0.01	1.40E-25	115.54	
aPTT	rs1801020	A	0.61	0.02	8.30E-260	1501.25	
aPTT	rs657152	A	-0.27	0.01	5.00E-75	351.49	
FVIII	rs548630	A	-0.05	0.01	5.14E-10	36.00	Sabater-Lleal M [61]
FVIII	rs9399599	A	-0.06	0.01	3.73E-13	49.00	
FVIII	rs7816579	A	0.07	0.01	5.32E-16	68.65	
FVIII	rs10102164	A	0.05	0.01	1.66E-07	23.90	
FVIII	rs35165583	G	-0.07	0.01	1.74E-10	41.75	
FVIII	rs7135039	T	0.08	0.01	3.00E-19	83.59	
FVIII	rs4981022	A	0.07	0.01	1.16E-17	64.00	
FVIII	rs137631	T	0.06	0.01	2.35E-07	24.10	
FVIII	rs698078	A	0.06	0.01	4.26E-07	27.42	
FVIII	rs7962217	C	0.13	0.02	6.30E-09	34.00	Tang W [75]
FVIII	rs12557310	C	-0.07	0.01	8.02E-10	37.51	
FX	rs547138	A	0.23	0.02	8.91E-20	82.98	Sun BB [85]
FX	rs141217364	A	-0.29	0.03	2.57E-19	80.64	
FX	rs3762056	T	-0.54	0.04	3.02E-34	149.12	

[a,b] Beta and Se are standardized for each SNP by the following formula [10]:

$\beta = \frac{z}{\sqrt{2f(1-f)(n+z^2)}}$, $se = \frac{1}{\sqrt{2f(1-f)(n+z^2)}}$

where z = β/se from the original summary data, f is the effect allele frequency, and n is the total sample size.

Abbreviations: **VWF**, von Willebrand factor; **ADAMTS13**, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **tPA**, tissue plasminogen activator; **PAI-1**, plasminogen activator inhibitor-1; **FVII**, Factor VII; **PT**, prothrombin time; **FVIII**, Factor VIII; **FXI**, Factor XI; **aPTT**, activated partial thromboplastin time; **FX**, Factor X; **ETP**, endogenous thrombin potential.

Table S2. Data sources for 12 investigated coagulation factors in this study

Pathway[a]	Phenotype	Sample Size	Study	PMID	Consortium/Study
Platelet adhesion to exposed collagen	VWF	42,256	Sabater-Lleal M [61]	30586737	CHARGE
		2,100	Williams [74]	23381943	TwinsUK
		18,556	Tang W [75]	25779970	CARe
	ADAMTS13	5,448	de Vries PS [76]	25934476	Rotterdam
		3,238	Ma Q [77]	29296746	GABC + TSS
Dissolution of fibrin clot	D-dimer	21,052	Smith NL [80]	21502573	CHARGE
	PAI-1	19,599	Huang J [78]	22990020	FHS + PROCARDIS +TwinsUK + MONICA/KORA + HealthABC + MARTHA + PREVEND
	tPA	19,599	Huang J [81]	24578379	CHARGE
Extrinsic pathway	FVII	27,495	de Vries PS [82]	30642921	CHARGE
	PT	30,972	Goldstein JA [86]	\	BioVU + MGI
Intrinsic pathway	FXI	16,169	Sennblad B [83]	28053049	ARIC + PROCARDIS + GHS-1 + GHS-2 + MARTHA
	aPTT	9,719	Weng L [84]	25552651	ARIC
	FVIII	29,573	Sabater-Lleal M [61]	30586737	CHARGE
		18,556	Tang W [75]	25779970	CARe
Common pathway	FX	3,301	Sun BB [85]	29875488	INTERVAL
	ETP	1,967	Rocanin-Arjo A [79]	24357727	MARTHA + 3C

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; **GABC**, Genes and Blood Clotting; **TSS**, Trinity Student Study; **FHS**, Framingham HeartStudy; **PROCARDIS**, Precocious Coronary Artery Disease Study; **MARTHA**, Marseille Thrombosis Association study; **PREVEND**, Prevention of Renal and Vascular End Stage; Disease study; **MGI**, Michigan Genomics Initiative; **ARIC**, Atherosclerosis Risk in Communities; **CARe**, Candidate Gene Association Resource; **INTERVAL**, International Network against VENous Thrombosis; **3C**, Three Cities Study.

VWF, von Willebrand factor; **ADAMTS13**, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **tPA**, tissue plasminogen activator; **PAI-1**, plasminogen activator inhibitor-1; **FVII**, Factor VII; **PT**, prothrombin time; **FVIII**, Factor VIII; **FXI**, Factor XI; **aPTT**, activated partial thromboplastin time; **FX**, Factor X; **ETP**, endogenous thrombin potential.

[a] Pathways are classified based on the Reactome database [87] by Harshfield EL [88].

Table S3. Summary statistics of the MR estimates of coagulation factors on COVID-19 severity

Exposure	nSNPs	IVW OR (95% CI)	P_{IVW}	Egger OR (95% CI)	P_{Egger}	Egger Intercept	Egger Intercept *P*	WM OR (95% CI)	P_{WM}	IVW OR (95% CI)	P_{IVW}	Egger OR (95% CI)	P_{Egger}	Egger Intercept	Egger Intercept *P*	WM OR (95% CI)	P_{WM}
		The Severe COVID-19 GWAS Group [2]								The COVID-19 Host Genetics Initiative [3]							
VWF	17	1.35 (1.09-1.68)	**0.005**	1.62 (1.24-2.13)	**0.003**	-0.05	0.513	1.47 (1.09-2.00)	**0.012**	1.13 (1.01-1.25)	**0.029**	1.16 (1.01-1.33)	0.055	-0.01	0.533	1.16 (1.00-1.35)	**0.046**
ADAMTS13	4	0.69 (0.50-0.96)	**0.025**	0.62 (0.25-1.53)	0.409	0.03	0.829	0.69 (0.48-0.99)	**0.044**	0.86 (0.73-1.03)	0.099	0.85 (0.54-1.36)	0.626	0.01	0.963	0.86 (0.72-1.03)	0.099
D-dimer	3	3.80 (0.52-27.90)	0.189	133.44 (0.01-2203234.91)	0.504	-0.17	0.597	3.66 (0.28-47.28)	0.320	0.88 (0.28-2.80)	0.831	41.73 (0.88-1981.36)	0.309	-0.18	0.295	1.27 (0.45-3.57)	0.654
PAI-1	5	0.82 (0.31-2.14)	0.685	0.06 (0.01-9.19)	0.348	0.18	0.370	0.58 (0.17-1.92)	0.371	0.97 (0.66-1.42)	0.883	0.82 (0.10-6.39)	0.859	0.01	0.876	0.93 (0.59-1.47)	0.761
tPA	3	1.46 (0.15-14.27)	0.743	1.51 (0.01-752.29)	0.918	-0.29	0.438	0.88 (0.14-5.75)	0.897	1.11 (0.68-1.84)	0.671	1.86 (0.12-28.98)	0.734	-0.04	0.773	1.35 (0.75-2.45)	0.316
FVII	8	1.07 (0.85-1.35)	0.569	0.95 (0.70-1.28)	0.742	0.04	0.253	1.04 (0.81-1.34)	0.769	1.11 (0.95-1.30)	0.202	1.02 (0.84-1.25)	0.814	0.03	0.260	1.08 (0.97-1.21)	0.167
PT	6	1.26 (0.82-1.94)	0.294	1.04 (0.51-2.11)	0.917	0.04	0.540	1.13 (0.69-1.83)	0.631	1.08 (0.86-1.36)	0.482	1.05 (0.70-1.59)	0.816	0.01	0.872	1.16 (0.90-1.48)	0.256
FXI	3	1.01 (0.79-1.29)	0.934	0.96 (0.59-1.58)	0.904	0.02	0.862	1.01 (0.78-1.29)	0.958	1.04 (0.94-1.16)	0.437	1.05 (0.82-1.33)	0.781	0.01	0.987	1.04 (0.94-1.16)	0.445
aPTT	6	0.81 (0.59-1.13)	0.223	1.08 (0.52-2.23)	0.849	-0.11	0.441	0.98 (0.80-1.20)	0.839	0.91 (0.83-1.00)	0.045	0.85 (0.69-1.05)	0.214	0.02	0.542	0.92 (0.85-1.00)	0.047
FVIII	11	0.69 (0.36-1.32)	0.262	0.68 (0.03-17.22)	0.819	0.01	0.992	0.95 (0.41-2.22)	0.913	1.20 (0.84-1.71)	0.328	1.09 (0.21-5.64)	0.917	0.01	0.916	1.12 (0.71-1.77)	0.633
FX	3	0.98 (0.74-1.31)	0.908	1.57 (0.70-3.50)	0.472	-0.16	0.439	0.93 (0.67-1.30)	0.676	0.94 (0.80-1.10)	0.416	1.04 (0.66-1.65)	0.896	-0.03	0.719	0.94 (0.79-1.11)	0.455
ETP	3	1.06 (0.74-1.51)	0.761	1.05 (0.40-2.75)	0.937	0.01	0.990	0.98 (0.73-1.31)	0.881	1.04 (0.92-1.18)	0.514	1.11 (0.88-1.40)	0.544	-0.04	0.647	1.05 (0.91-1.20)	0.516

Values in bold indicate statistically significant results.

Abbreviations: VWF, von Willebrand factor; **ADAMTS13**, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **tPA**, tissue plasminogen activator; **PAI-1**, plasminogen activator inhibitor-1; **FVII**, Factor VII; **PT**, prothrombin time; **FVIII**, Factor VIII; **FXI**, Factor XI; **aPTT**, activated partial thromboplastin time; **FX**, Factor X; **ETP**, endogenous thrombin potential.

Table S4. Supporting evidence for the associations between VWF/ADAMTS13 activities and COVID-19 severity

Study	PMID	Area	Sample size	Criteria for severity	Findings
Helms J [52]	32367170	French	150	Admitted to ICU	VWF antigen level was increased in patients with severe COVID-19 compared to healthy controls
Panigada M [89]	32302438	Italy	24	Admitted to ICU because of acute respiratory syndromes	VWF antigen level was considerably increased in ICU patients compared to healthy controls
Bazzan M [54]	32557383	United States	88	Death	Patients who died had significant lower levels of ADAMTS13 and higher levels of VWF compared to patients with non-fatal outcome
Krishnamachary B [90]	32909001	United States	53	Requires oxygen delivery by non-rebreather mask, non-invasive ventilation, or heated high flow nasal cannula at a minimum	Significantly elevated levels of VWF and decreased ADAMTS13 in large extracellular vesicles from patients with severe COVID-19 compared to healthy controls
Overmyer KA [91]	32743614	United States	128	Admitted to ICU	VWF level was increased in ICU patients versus in non-ICU patients
Adam EH [53]	32723615	Germany	4	Admitted to ICU	Elevated levels of VWF and decreased ADAMTS13 in ICU patients
Adrian AN [92]	medRxiv	Germany	85	The severity degree of COVID-19 was categorized according to the guidelines of the Robert Koch Institute, Germany	Elevated levels of VWF and decreased ADAMTS13/VWF ratio in severe patients
Goshua, G [29]	32619411	United States	68	Admitted to ICU	VWF antigen level was significantly elevated in ICU patients compared with non-ICU patients

Abbreviations: ICU, intensive care unit; **VWF**, von Willebrand factor; **ADAMTS13**, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

Table S5. Baseline demographic and clinical characteristics of UK Biobank COVID-19 cohort

Characteristics	Case (n = 1,492)	Controls (n = 445,271)	*P* value
Age	72 ± 8	70 ± 8	< 0.001
Male sex	900 (60)	203,326 (46)	< 0.001
Body mass index (kg/m^2)	30 ± 5	27 ± 5	< 0.001
Systolic blood pressure (mmHg)	142 ± 19	139 ± 19	< 0.001
Comorbidities			
Coronary artery disease	410 (27)	42,849 (9)	< 0.001
Type 2 diabetes	381 (26)	31,367 (7)	< 0.001
COPD	295 (18)	20,293 (5)	< 0.001

Values are n (%) or mean ± SD.

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