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RESEARCH LETTER

Inherited Thrombophilias Are Associated With a Higher Risk of COVID-19–Associated Venous Thromboembolism: A Prospective Population-Based Cohort Study

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The risk of venous thromboembolism (VTE) is markedly increased in patients with COVID-19 (COVID-19 VTE) and is associated with higher COVID-19 mortality.[1] Whether the presence of inherited thrombophilias is associated with a higher risk of COVID-19 VTE remains a key outstanding issue, because the identification of risk factors that predispose to COVID-19 VTE is likely to be important in determining thrombotic risk and defining optimal antithrombotic regimens. Common inherited thrombophilias, including Factor V Leiden (FVL) and prothrombin mutation, have an estimated prevalence of 30% and are associated with a higher risk of VTE in the general population.[2]

Using data from the UK Biobank, we report on the association between inherited thrombophilias, COVID-19 VTE, and COVID-19 mortality. Participants included in the analysis were 45 to 69 years old when they were prospectively enrolled in the UK Biobank between 2006 and 2010 and subsequently tested positive for COVID-19 between January 2020 and May 2021. The study population was characterized by demographic information, body mass index, smoking status, medical comorbidities on enrollment to the UK Biobank, and the presence of defined genetic thrombophilias. To account for potential population genetic variation, we performed principal component analysis and estimated the top 10 principal components from highest to lowest variance. Participants were excluded if demographic, health, or genetic data were incomplete.

The study cohort was analyzed for 6 single-nucleotide polymorphisms (SNPs) resulting in inherited thrombophilia, including FVL (rs6025) and prothrombin mutation (rs1799963), in addition to variants in fibrinogen gamma gene (rs2066865), coagulation factor XI (rs4253416), and ABO blood group (rs2519093 and rs8176645). In addition, the utility of 2 polygenic risk scores (PRS) were examined that have been used to predict VTE risk in non–COVID-19 populations. The venous thromboembolism PRS (PRS-VTE) uses 297 variants, excluding SNPs defining FVL and prothrombin mutation, and identifies 5% of the population with a risk profile similar to carriers of FVL and prothrombin mutation.[3] A second PRS (PRS-ABO) uses tag SNPs for ABO blood groups to assign a score associated with VTE risk.[4]

COVID-19 VTE was defined using *International Classification of Diseases, 10th Revision* coding for VTE (ie, *International Classification of Diseases, 10th Revision* codes I260, I269, I801, I802, and I822) after a COVID-19 diagnosis. COVID-19 mortality was defined using *International Classification of Diseases, 10th Revision* codes for COVID-19 on the death certificate.

Logistic regression was used to evaluate whether the SNPs or PRS were associated with COVID-19 VTE or COVID-19 mortality. Multivariable analysis was performed using the variables of age, sex, body mass index, smoking

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Nonstandard Abbreviations and Acronyms

FVL	Factor V Leiden
PRS	polygenic risk score
SNP	single-nucleotide polymorphism
VTE	venous thromboembolism

status, hypertension, ischemic heart disease, cardiac failure, diabetes, dialysis-dependent renal failure, malignancy, and the top 10 principal components. We report adjusted odds ratio (OR) with 95% CIs for the outcomes. Analysis was performed in R version 4.0.3. The data supporting this study are available from the corresponding author on reasonable request. The UK Biobank received ethical approval (11/NW/0382), and all participants gave informed consent.

Overall, 13712 individuals with COVID-19 were included with a median age of 54 years, median body mass index of 27.6, and 52.5% were female. COVID-19 VTE was identified in 197 cases (1.4%), and there were 890 deaths from COVID-19 (6.5%; Table). The median follow-up time was 146 days (interquartile range, 115–198) and the median time to COVID-19 VTE diagnosis was 12 days (interquartile range, 6–27). The presence of rs6025, synonymous with the FVL mutation, was associated with an approximate 1.8-fold odds of COVID-19 VTE (OR, 1.80 [95% CI ,1.03–2.92]; Table). Moreover, both rs2066865 (OR, 1.35 [95% CI, 1.07–1.68]) and the PRS-VTE (OR, 1.26 [95% CI, 1.08–1.47]) were also associated with a higher risk of COVID-19 VTE (Table). In contrast, neither the PRS-ABO nor the presence of rs4253416, rs2519092, rs8176645, or rs1799963 was associated with COVID-19 VTE (Table).

Consistent with previous reports,[1] we observed that COVID-19 VTE was associated with higher COVID-19 mortality (OR, 2.77 [95% CI, 1.91–3.95]; Table**),** but no association was observed between either the SNPs or PRS with COVID-19 mortality.

These findings demonstrate for the first time that the thrombophilic SNPs, rs6025 and rs2066865, in addition to the PRS-VTE, are associated with a higher risk of COVID-19 VTE. Limitations of this study include the predominance of European ancestry in the study population and the absence of a general population control cohort. Moreover, timely access to genetic testing remains an outstanding issue. Although prospective validation of these findings is required to determine the utility of routine thrombophilia testing in COVID-19, significant interest remains regarding the optimal antithrombotic regimen for the prevention of COVID-19 thrombotic complications. To date, studies evaluating the benefit of anticoagulation in patients with COVID-19 have been conflicting, and these regimens have consistently been associated with higher bleeding complications.[5] Therefore, the identification of novel risk factors, such as genetic thrombophilias, may stratify patients with a higher risk of COVID-19 VTE, and ultimately help identify patients with COVID-19 who are more likely to benefit from higher-dose antithrombotic regimens.

ARTICLE INFORMATION

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Table. Association of Genetic Thrombophilia With Venous Thromboembolism and Mortality in Individuals With COVID-19

Predictor	COVID-19 VTE (n=197)	COVID-19 without VTE (n=13515)	Odds ratio* (95% CI) for COVID-19 VTE	Odds ratio* (95% CI) for COVID-19 mortality
rs6025	16 (8.1)	614 (4.5)	1.80 (1.03–2.92)	1.23 (0.89–1.68)
rs1799963	7 (3.6)	529 (3.9)	1.04 (0.36–2.33)	1.06 (0.64–1.68)
rs2519093	69 (35)	4788 (35.4)	0.94 (0.68–1.31)	1.18 (1.00–1.40)
rs8176645	106 (53.8)	7640 (56.5)	0.83 (0.56–1.21)	1.05 (0.86–1.27)
rs2066865	98 (49.7)	5669 (41.9)	1.35 (1.07–1.68)	0.99 (0.88–1.12)
rs4253416	163 (82.7)	11059 (81.8)	1.06 (0.86–1.30)	0.96 (0.87–1.07)
Polygenic risk score-VTE	–	–	1.26 (1.08–1.47)	1.01 (0.93–1.10)
Polygenic risk score-ABO	–	–	0.97 (0.76–1.23)	1.10 (0.98–1.25)
COVID-19 VTE	–	–	–	2.77 (1.91–3.95)

*Odds ratio with 95% CIs computed based on logistic regression, and adjusted for sex, age, body mass index, smoking status, medical comorbidities (hypertension, ischemic heart disease, cardiac failure, diabetes, dialysis-dependent renal failure, and malignancy), and top 10 genetic principal components. Effect sizes are per standard deviation of the thrombophilia predictor used.

COVID-19 VTE indicates COVID-19–associated venous thromboembolism; and VTE, venous thromboembolism.

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Disclosures

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