Association Between Genetic Predictors for C-Reactive Protein and Venous Thromboembolism With Severe Adverse Coronavirus Disease 2019 Outcomes

Boya Guo, MPH[1]

Jessica Williams-Nguyen, PhD, MPH, MS[2]

Lu Wang, PhD[3]

Cameron B. Haas, PhD, MPH[1]

Christopher Kabrhel, MD, MPH[4,5]

Sara Lindström, PhD, MS[1,2]

OBJECTIVES: To assess if genetic predictors for C-reactive protein and risk of venous thromboembolism are associated with severe outcomes among individuals who tested positive for severe acute respiratory syndrome coronavirus 2.

DESIGN: Retrospective cohort study.

SETTING: U.K. Biobank.

PATIENTS OR SUBJECTS: U.K. Biobank participants with European ancestry who were recorded to have a positive polymerase chain reaction test result for severe acute respiratory syndrome coronavirus 2 between March 16, 2020, and August 14, 2020.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: We constructed separate genetic risk scores for C-reactive protein and venous thromboembolism consisting of 56 and 37 genetic variants that have been significantly associated with venous thromboembolism and C-reactive protein, respectively. Among 1,126 individuals who were diagnosed with coronavirus disease 2019, 48% had a coronavirus disease 2019–related hospitalization, 16% received critical care support, 10% had critical respiratory support, and 21% died from coronavirus disease 2019. Genetic predisposition to high C-reactive protein concentrations was marginally associated with a lower risk of death from coronavirus disease 2019 (odds ratio, 0.85; 95% CI, 0.73–1.00; $p = 0.05$). No other associations were significant.

CONCLUSIONS: Our results do not support associations between polygenic risk for elevated blood C-reactive protein concentrations or venous thromboembolism and severe coronavirus disease 2019 health outcomes. Thus, considering genetic predisposition associated with C-reactive protein concentrations or venous thromboembolism risk is not meaningful for predicting severe coronavirus disease 2019 health outcomes.

KEY WORDS: adverse health outcome; coronavirus disease 2019; C-reactive protein; genetic risk score; inflammation; venous thromboembolism

Coronavirus disease 2019 (COVID-19), caused by the novel pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can result in the need for hospitalization and critical care support, and ultimately death. The pathogenesis of severe COVID-19 is thought to involve initial evasion of the innate immune response followed by uncontrolled viral replication, delayed induction of adaptive immunity, and prolonged overactivation of the innate immune system (1, 2). This inflammatory process results in alveolar edema, hypoxia, and acute respiratory distress syndrome as well as coagulation abnormalities (3, 4). While estimates of venous thromboembolism (VTE)

in COVID-19 vary, a recent meta-analysis found that 18% of critically ill COVID-19 patients went on to develop clinically relevant VTE, potentially double the rate observed in critically ill influenza patients (5). Given the importance of inflammatory and coagulation processes in COVID-19 outcomes, we sought to determine whether individuals with a genetic predisposition for a dominant pro-inflammatory response (defined by elevated circulating concentrations of C-reactive protein [CRP]) or genetic predisposition for VTE are more likely to have severe COVID-19 outcomes and mortality.

MATERIALS AND METHODS

We used data from U.K. Biobank, a population-based cohort study with extensive phenotyping carried out across the United Kingdom from 2006 to 2010 (6). Within the 502,536 U.K. Biobank cohort, 1,713 participants had a positive polymerase chain reaction test result for SARS-CoV-2 between March 16, 2020, and August 14, 2020. We restricted our analysis to 1,126 participants of European ancestry due to the lack of validation of genetic risk scores (GRSs) used in participants of other ancestries (7, 8).

Severe COVID-19 outcomes were defined as: 1) hospitalization, 2) critical care (≥ 1 d of level 2 or 3 care), 3) critical respiratory support (≥ 1 d of basic or advanced respiratory support), and 4) death. An individual was considered to have a COVID-19–related hospitalization if admitted 2 weeks before their earliest positive test for SARS-CoV-2 or 4 weeks afterward. Critical care and basic and advanced respiratory support days were identified using the hospital inpatient admissions data. Mortality data came from the linkage to national death registries. A death that occurred 3 days before an individual's first positive test for SARS-CoV-2 or at any time afterward within the study period was counted as a mortality event.

For each individual, we calculated one GRS to estimate predisposition to high circulating CRP levels and another GRS for high VTE risk using the single-nucleotide polymorphisms (SNPs) at the genome-wide statistical significance ($p < 5 \times 10^{-8}$) (7, 8). GRS for each individual j was calculated as $GRS_j = \sum_{i=1}^{k} \beta_i G_{ij}$, where k is the number of SNPs ($n = 56$ for CRP and $n = 37$ for VTE), β_i is the log odds ratio for variant i, and G_{ij} is the number of risk alleles of variant i that

individual j is carrying. SNPs included in the GRS calculations were identified from prior genome-wide association studies (GWAS), and both CRP and VTE GRSs had previously been examined and validated (8, 9). Two variants (Chr: position: 3:47431869 and 17:5800169) identified in GWAS were not included in the CRP VTE calculation because they were not available in our data.

We also extracted information on blood type, body mass index (BMI) at time of enrollment, sex at recruitment, and age at first positive SARS-CoV-2 test result. To explore the association of each GRS with severe COVID-19 outcomes, we performed logistic regression analysis, adjusting for age, sex, and blood type and further adjusting for BMI and the first five genetic principal components (**Supplemental Table S1**, http://links.lww.com/CCX/A877). All analyses were performed using R 4.1.0 and SAS 9.3 (SAS Institute, Cary, NC). This study is a nonhuman contact study without any patient identifiers or specimens. The authors of this study have determined that this research does not involve human subjects and thus does not need to obtain an Institutional Review Board approval or a determination of exempt status.

RESULTS

Among 1,126 participants of European ancestry who tested positive for SARS-CoV-2, the mean age at diagnosis was 69 years (range, 50–83 yr). 46% were female, and average BMI at the time of enrollment was 28.6 (range, 16–61) (**Table 1**). Type A blood was slightly more common (49%) among those who later died from COVID-19 as compared with the whole sample (46%), as has been shown previously (10). Similarly, patients who were older (median: 75 vs 69 yr old) and males (67% vs 54%) were more likely to die of COVID-19 compared with the overall study cohort. Almost half (48%) had a COVID-19–related hospitalization, 16% received critical care support, and 10% had critical respiratory support.

Each SD increase in the GRS for elevated CRP concentrations was associated with 18% lower odds of death from COVID-19 (odds ratio [OR], 0.82; 95% CI, 0.71–0.95; $p = 0.01$) but not with any other of the severe COVID-19 outcomes examined (Supplemental Table S1, http://links.lww.com/CCX/A877). Adjusting for confounders slightly attenuated the association (OR, 0.85; 95% CI, 0.73–1.00; $p = 0.05$) (Supplemental Table

TABLE 1.
Characteristics of U.K. Biobank Participants of European Ancestry With Severe Acute Respiratory Syndrome Coronavirus 2 Positive Test Result During March 2020–August 2020[a]

Characteristics	All	Any Hospitalization[b]	Critical Care	Critical Respiratory Support	Death
n	1,126	536	180	115	232
Age at testing, mean (range)	69 (50–83)	72 (52–83)	71 (52–82)	69 (52–82)	75 (54–82)
Sex, n (%)					
Female	515 (46)	192 (36)	55 (31)	37 (32)	77 (33)
Male	611 (54)	344 (64)	125 (69)	78 (68)	155 (67)
Blood type, n (%)					
A	519 (46)	251 (47)	83 (46)	55 (48)	113 (49)
B	93 (8)	49 (9)	13 (7)	9 (8)	17 (7)
AB	34 (3)	16 (3)	8 (4)	6 (5)	7 (3)
O	479 (43)	219 (41)	75 (42)	44 (39)	95 (41)
Body mass index, mean (range)	28.6 (16.3–61.3)	29.1 (18.8–45.7)	29.3 (18.2–47.4)	29.6 (20.6–47.4)	29.3 (16.3–56.3)
C-reactive protein GRS, mean (range)[c]	-1.9×10^{-15} (−3.5 to 2.7)	−0.03 (−3.4 to 2.7)	0.1 (−2.1 to 2.3)	0.1 (−2.1 to 2.0)	−0.16 (−3.5 to 2.7)
Venous thromboembolism GRS, mean (range)[c]	-2.2×10^{-15} (−2.6 to 3.13)	0.02 (−2.2 to 3.14)	0.01 (−2.0 to 2.92)	0.03 (−1.7 to 2.9)	0.00 (−2.0 to 2.9)

GRS = genetic risk score.

[a]Numbers do not add up to the n due to missing values. Blood type was missing for one participant and body mass index was missing for 19 participants who tested positive for coronavirus disease 2019 (COVID-19).

[b]Date of hospital admission was missing for two participants. We are not able to determine if they were hospitalized during the proposed COVID-19 hospitalization period (2 wk before and 4 wk after the first positive test).

[c]C-reactive protein GRS and venous thromboembolism GRS were standardized to have a mean of 0 and a SD of 1.

S1, http://links.lww.com/CCX/A877). We also found that two individual SNPs (rs2064009 and rs13409371) included in the GRS of CRP showed marginal associations with a decreased risk of dying from COVID-19 (OR, 0.80; 95% CI, 0.65–0.98; $p = 0.04$ and OR, 0.80; 95% CI, 0.65–0.99; $p = 0.04$). Greater genetic risk for VTE was not associated with any severe COVID-19 outcomes, including death (OR, 1.00; 95% CI, 0.87–1.16; $p = 0.98$) (Supplemental Table S1, http://links.lww.com/CCX/A877).

DISCUSSION

In this study, we observed a marginal protective association between a GRS for circulating CRP concentrations and death due to COVID-19. In contrast, we did not find evidence for an association between CRP GRS and other severe outcomes. Although literature exists on the effect of CRP concentrations on all-cause mortality on a range of chronic diseases, to our knowledge, there are few studies on the association of genetically predicted CRP with infectious disease-related outcomes or severity. CRP, a biomarker of a dominant pro-inflammatory response, could hypothetically be involved in early innate immune activation and thereby influences the course of COVID-19. However, our study does not find evidence for a relationship between CRP GRS and severe COVID-19 outcomes. It is possible that our CRP GRS was not a good proxy of systemic inflammation in COVID-19 and the marginal protective association was driven by one or two SNPs.

The lack of association between genetic risk for VTE and severe COVID-19 outcomes, including death, is notable since the prevalence of VTE is approximately 30% in critically ill COVID-19 patients and is known

to double the mortality risk (11). The VTE GRS used was created based on VTE events occurring before the global emergence in 2019 and thereby captures genetic risk for non-COVID-19–related VTE events and may not be a good indicator of COVID-19–related VTE etiology. Our results may suggest that the mechanistic processes implicated in non-COVID-19 VTE events, such as the involvement of platelets, are less important in the etiology of COVID-19–associated VTE. However, we acknowledge that the contribution of thrombotic complications to mortality and other severe outcomes in our study population is unknown or small, and this may have limited our ability to detect an association.

These data should also be considered in the context of SARS-CoV-2 testing capacity over the course of the pandemic. It should be acknowledged that early in the COVID-19 outbreak, SARS-CoV-2 tests were limited throughout the United Kingdom, and only those with serious illness and high clinical suspicion were tested and hospitalized. These patients likely reflect more severe and high-risk COVID-19 cases. We, therefore, may have missed some people with mild or moderate and undetected SARS-CoV-2 infection, particularly during the initial wave and when a presentation was atypical. In addition, although testing capacity has since increased, hospitalization may not have been a good proxy for severe disease during the study timeframe. Finally, this study focused on middle-aged and elderly participants of European ancestry, and therefore results may not be generalizable. Despite these limitations, this analysis also has important strengths, including a large, well-characterized national cohort and validated GRS for circulating CRP concentrations and for VTE events that capture information about variants across the genome.

CONCLUSIONS

Overall, these data do not support a robust association between GRS for incident VTE events or elevated blood CRP and severe COVID-19 outcomes, including hospitalization and death. We found a marginal association between the CRP GRS and mortality due to COVID-19 that could warrant replication.

1 Department of Epidemiology, University of Washington, Seattle, WA.

2 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA.

3 Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA.

4 Center for Vascular Emergencies, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

5 Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

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