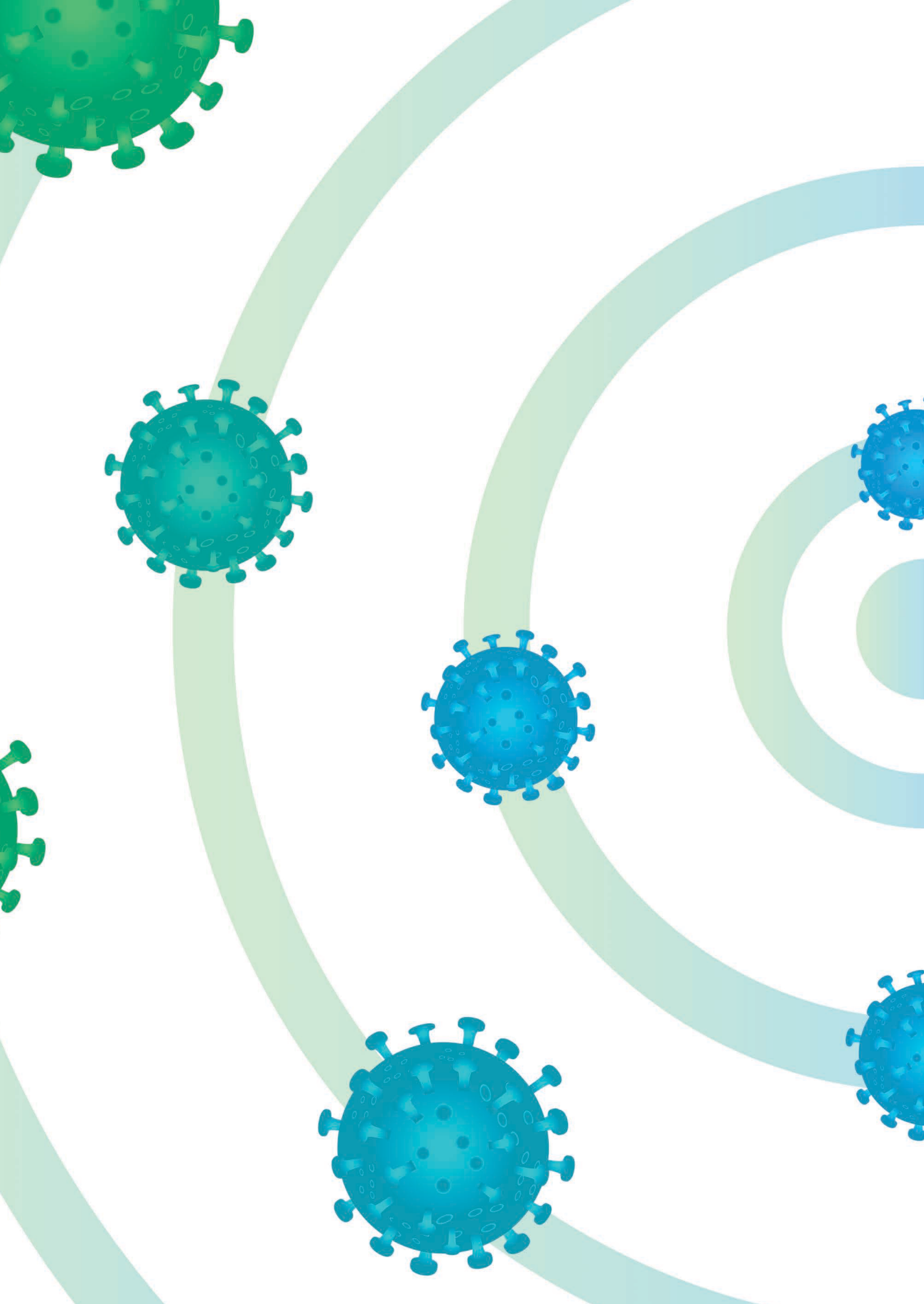
PART II

Coagulation and venous thrombotic events as adverse events following SARS-CoV-2 infection and SARS-CoV-2 vaccination



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CHAPTER 5

High thrombin potential prior to infection and severe COVID-19

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Under review

ABSTRACT

Introduction

Disease severity in infections varies, with severe SARS-CoV-2 infections often involving thrombosis.

Aim

To investigate whether high thrombin generation (TG) potential prior to infection is linked to SARS-CoV-2 infection or severe COVID-19.

Methods

This study was part of a randomized-controlled trial evaluating the BCG vaccine's effect on COVID-19 in individuals aged ≥60 with chronic comorbidities. Participants had no COVID-19 in the first 14 days after inclusion and did not use anticoagulants. Baseline blood samples were collected, and participants were followed for six months. TG peak height was the primary measure. An exploratory analysis of 159 proteins, including coagulation-related markers, was conducted using Quantitative Protein Mass Spectrometry (QPMS). Cox regression assessed associations with SARS-CoV-2 infection and severe COVID-19 (defined as requiring medication, hospitalization, ICU admission, or death), adjusting for age, sex, BMI, frailty, and comorbidities.

Results

Among 1,119 participants, 47 contracted SARS-CoV-2, with 10 developing severe disease. TG peak height was not associated with infection risk (adjusted Hazard ratio (aHR) 0.8; 95% CI: 0.4–1.7) but showed a potential link with severe COVID-19 (aHR 3.2; 95% CI: 0.4–28). Other TG parameters, excluding endogenous thrombin potential and start tail time, also indicated associations with severity. Several coagulation and immune-related proteins were linked to severe disease, though findings were limited by multiple testing.

Discussion

In older adults with comorbidities, higher TG potential was not linked to infection risk but may be associated with more severe COVID-19. These results could aid for further exploration of intrinsic risk factors and protective strategies for severe COVID-19 infections.

INTRODUCTION

COVID-19 has presented substantial clinical challenges, in a large part due to its highly heterogenous clinical presentation, which can range from asymptomatic or mild to severe disease or death.(1) A better understanding of the determinants associated with a severe course of COVID-19 may help to target treatment and preventive strategies.(2-11) Many of the severely ill COVID-19 patients suffer from venous thrombotic events.(12) Markers of increased coagulation (hypercoagulability), such as D-dimer, fibrinogen, factor VIII, von Willebrand factor, and thrombin generation (TG), have been associated with an increased risk of organ failure and mortality in patients with Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infections.(7, 13-15) Severity of other infectious diseases, such as influenza, is also associated with dysregulation of coagulation.(16, 17) In addition, severity of sepsis can be predicted using coagulation parameters.(18, 19) The inflammatory and coagulation system are connected in multiple ways.(20) While coagulation markers have been associated with an increased risk of organ failure and mortality in individuals during a SARS-CoV-2 infection, it is currently unknown whether hypercoagulability prior to COVID-19 is associated with an increased risk of a SARS-CoV-2 infection or a more severe course of the disease, resembling an intrinsic susceptibility to severe infection.

Between September and December 2020, during the second wave of the COVID-19 pandemic prior to the approval of COVID-19 vaccines, a large double-blind placebo-controlled randomized controlled trial was conducted to assess the risk of COVID-19 associated with the Bacillus Calmette-Guérin (BCG) vaccine in individuals aged over 60 with comorbidities. Over 6000 individuals of 60 years of age were randomized 1:1 to receive either BCG or placebo. In a subset of the participants venous blood was drawn prior to randomization. At 6 months follow-up, no association was found between the BCG vaccine and the risk of COVID-19 infection, while no conclusions could be drawn regarding the effects of BCG on severity and mortality caused by the infection due to lack of power.(21) In a secondary analysis of these trial data we aimed to assess whether hypercoagulability, i.e., an increased TG potential, is associated with an increased risk of a SARS-CoV-2 infection or with a severe course of COVID-19.

METHODS

Trial design and selection of participants

This study was embedded in the BCG-PRIME study, a large placebo-controlled double-blind randomized controlled trial aimed to assess the risk of a SARS-CoV-2 infection or a severe course of COVID-19 associated with the BCG vaccine.(21) Between September and December 2020, participants were recruited from 20 hospitals in the Netherland or via self-report. Inclusion criteria were age 60 years or older, having one or more comorbidities, no contraindications to BCG vaccination, and no documented SARS-CoV-2 infection. Venous blood was drawn prior to BCG or placebo vaccination (1:1) in participants included in four of the 20 participating hospitals.

The primary trial was approved by the Utrecht Institutional Review Board (protocol NL74730.041.20) and registered in the European Clinical Trials Database (2020-003470-47). The current study was approved by the local Scientific Committee of the Department of Clinical Epidemiology of the Leiden University Medical Center (LUMC) (Protocol number A204).

For the current analysis, we included participants who donated a blood sample, excluding participants using anticoagulants (vitamin K antagonists, heparin or direct oral anticoagulants). Furthermore, we excluded participants with missing information on thrombin generation or details about comorbidities or with outliers for TG parameters (defined as five times the SD). Follow-up started two weeks after baseline, excluding participants with a positive SARS-CoV-2 test within the first two weeks that potentially influenced the baseline measurement of TG.

Follow-up consisted of questionnaires in a smartphone app (Research Follow App, Your Research, Huizen, the Netherlands) with bi-weekly reminders or by bi-weekly telephone consultations for a duration of six months. In addition to the questionnaires, information on the participants was retrieved from their general practitioner and hospital regarding SARS-CoV-2 infection, hospital visits, hospital admission, Intensive Care Unit (ICU) admission, or death.

Laboratory measurements

TG was assessed using the Calibrated Automated Thrombogram® (Diagnostica Stago, Asinères, France), according to the manufacturer's specifications.(22) In brief, coagulation was activated using a low amount of tissue factor and phospholipids, followed by continuous measurement of thrombin formation. The TG parameters measured were the endogenous thrombin potential (ETP), thrombin peak, time to peak, lag time, velocity index, and start tail time. We used peak height as the primary outcome of the TG assessment, as this is the most strongly associated with venous thrombosis in literature.(23, 24)

To explore possible pathophysiologic mechanisms, we analyzed 159 proteins with Quantitative Protein Mass Spectrometry (QPMS). These proteins are from a diverse range of physiological pathways, including 21 coagulation-related proteins, 18 complement pathway proteins and 14 apolipoproteins. The technical procedure of the QPMS and selection of these proteins is described by Van der Vliet et al.(25) In brief, using pre-synthesized $^{13}C^{15}N$ stable isotope labeled (SIL) peptides, quantification of several plasma proteins is possible in one measurement using liquid chromatography by a reversed-Phase UHPLC column (EclipsePlusC18 RRHD 150 x 2.1 m, 1.8 µm particles; Agilent Technologies, Santa Clara, USA) in combination with mass spectrometry analysis on a triple-quadrupole mass spectrometer (Agilent 6495C; Agilent Technologies, Santa Clara, CA, USA).(26) In each run the assay was calibrated using a pooled citrate sample of ten healthy individuals. We measured the proteins in all participants who developed COVID-19 during follow-up and 90 randomly selected participants (frequency matched by hospital of recruitment) without COVID-19 during follow-up for exploratory analyses into proteins or protein pathways associated with the development of severe COVID-19.

Outcomes

Two outcomes were defined. The first outcome was development of an infection with SARS-CoV-2 during follow-up. The second outcome was development of severe COVID-19, defined as requiring contact with a physician and need for medication, requiring hospital admission or admission to ICU, or COVID-19 resulting in dead. Both outcomes were adjusted for potential confounders, i.e., age, sex, BMI, clinical frailty score, and comorbidities (hypertension, cardiovascular disease, stroke, diabetes, chronic obstructive pulmonary disease, asthma, other pulmonary disease, chronic kidney disease and malignancy).

Statistical analysis

Baseline characteristics of participants are reported with proportions, means (with standard deviations (SD)) or medians (with interquartile ranges (IQR)). In addition, we compared included and excluded participants who were patients in the four participating hospitals.

All TG parameters and proteins were continuous variables. Because of inter-center differences in the blood sampling techniques, we normalized these continuous variables within each center. Incidence rates of infection were determined for quartiles of the TG parameters. We calculated hazard ratios for infection with SARS-CoV-2 with Cox-regression for each quartile with the first quartile as the reference, adjusted for confounders. As a sensitivity analysis we repeated this analysis after exclusion of participants who received a SARS-CoV-2 vaccination during follow-up. To study the association between TG parameters and the risk of a severe course of COVID-19, we calculated hazard ratios for severe disease with Cox-regression for tertiles of the TG parameters with the first tertile as the reference, adjusted for confounders.

In the exploratory analyses of the proteins measured with QPMS, we calculated hazard ratios with Cox-regression comparing above with below median values of these proteins for both outcomes. As this is an exploratory analysis with a large number of proteins, we only adjusted for confounders age and sex. We corrected for multiple testing in correlated data with the eigenvalues of a correlation matrix by an adapted Benjamini-Hochberg procedure with a false discovery rate of 25%.(27, 28) In addition we performed a hierarchical cluster analysis on the normalized protein levels with a Ward-linkage method, to find clusters of patients and compare them with patient characteristics and clinical outcomes.

RESULTS

In total, 6112 participants were randomized in the BCG-PRIME study, of whom 2221 participants were included in the four centers where blood samples were taken. Of these 2221 participants, 406 did not provide consent for a blood draw, four participants were excluded because of missing baseline characteristics, 668 participants were excluded because of use of anticoagulants at the time of the blood draw, five participants were excluded because of SARS-CoV-2 infection within two weeks after the blood draw, and 19 were excluded because of outliers in TG. This resulted in 1119 participants eligible for analysis. Baseline characteristics of these participants are shown in Table 1. Comparison of excluded and included participants from the four participating hospitals (supplementary Table 1) showed no differences in outcomes, and only trivial differences in frequency of some comorbidities.

Table 1: Baseline characteristics of participants

N	1119
Sex, women (%)	473 (42)
Age, mean (SD)	69.3 (5.9)
BMI, mean (SD)	26.6 (4.1)
Frailty scale, median (IQR)	2.0 (1, 3)
Comorbidities, median (IQR)	2.0 (1, 2)
Hypertension (%)	602 (54)
Cardiovascular disease or stroke (%)	548 (49)
Diabetes Mellitus (%)	221 (20)
COPD (%)	122 (11)
Asthma (%)	159 (14)
Other pulmonary disease (%)	57 (5)
Chronic kidney disease (%)	46 (4)
Malignancy (%)	75 (7)
Vaccinated during follow-up (%)	390 (35)

COPD: chronic obstructive pulmonary disease. SD: standard deviation. IQR interquartile range

The participants were followed for a median of 170 days (range: 3 – 209 days), with a total of 508 patient-years; 47 (4%) participants tested positive for SARS-CoV-2 and ten participants (0.9%) developed severe COVID-19 during follow-up. Of these ten participants, two received antibiotics from a physician, three were hospitalized, three were admitted to the ICU, and two participants died with COVID-19 registered as the primary cause of death (see supplemental table 2 for baseline characteristics for participants who had severe or non-severe COVID-19). During follow-up 390 (35%) participants received a SARS-CoV-2 vaccine, but none of the participants who tested positive for SARS-CoV-2 received the vaccine prior to their infection.

Peak height of TG was not associated with the risk of a SARS-CoV-2 infection (risk of individuals with a peak height quartile 4 vs quartile 1: adjusted hazard ratio (aHR) 0.8; 95% CI 0.4, 1.7, see table 2 and figure 1). Similarly, velocity index was not associated with the risk of a SARS-CoV-2 infection. However, the fourth quartile of lag time, time to peak and start tail time, were associated with increased risk of a SARS-CoV-2 infection (with HR ranging between 1.4 and 1.8. Compared with the first quartile of ETP, all other quartiles of ETP had higher incidences of SARS-CoV-2 infections (aHR Q4 vs Q1 ETP: 1.9; 95%CI 0.7, 5.6). In an analysis restricted to participants who did not receive a SARS-CoV-2 vaccination during follow-up (N=729), TG showed similar associations with the risk of a SARS-CoV-2 infection (supplemental table 3).

Peak height appeared associated with an increased risk of a severe course of the disease (aHR tertile 3 vs tertile 1: 3.2; 95%CI: 0.4 – 29; see table 3 and figure 2). Out of the 10 people with severe COVID-19, one had a peak height within tertile 1, five in tertile 2, and four in tertile 3 (see supplementary table 4). Like peak height, other TG parameters indicating hypercoagulability were associated with an increased risk of severe COVID-19, except for ETP and the start tail time (table 3). However, all effect estimates had wide confidence intervals. Distributions of TG parameters, stratified by outcome, showed small differences towards hypercoagulability in those with a severe outcome (mean Z-score Peak height no COVID-19: 0.04, SD 1,0; non-severe COVID-19: -0.1, SD 1.0; severe COVID-19: 0.3, SD 0.6, see figure 3).

To explore the relation between coagulation and development of COVID-19 in greater depth, we measured 159 proteins using QPMS. One protein had concentrations that fell below the assay's detection limit, leaving 158 proteins for analyses. After adjustment for confounding and multiple testing protein levels were not associated with SARS-CoV-2 infection (see supplementary table 5 and supplementary figure 1). Ten proteins were associated with SARS-CoV-2 infection, with a p-value <0.05 (unadjusted for multiple testing) (i.e., Hemopexin, Fibulin-1, Peroxiredoxin-2, Immunoglobulin G Fc-Binding Protein, Phospholipid transfer protein, Complement Factor B, Adhesion G protein-coupled receptor F5, Mannan binding lectin serine protease 1, Carbonic anhydrase 1 and Antithrombin).

Table 2: Association between trombin generation parameters at baseline and the development of COVID-19.

	HR (95% CI)				**aHR (95% CI)**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Peak height (nmol)	Ref	0.8 (0.4; 1.9)	0.7 (0.3, 1.6)	0.9 (0.4, 1.9)	Ref	0.9 (0.4, 1.9)	0.7 (0.3, 1.5)	0.8 (0.4, 1.7)
Lag time (minutes)	Ref	0.5 (0.2, 1.3)	0.6 (0.2, 1.4)	1.5 (0.7, 2.9)	Ref	0.5 (0.2, 1.4)	0.6 (0.3, 1.5)	1.4 (0.7, 3.0)
Time to peak (minutes)	Ref	0.7 (0.3, 1.6)	0.6 (0.2, 1.85)	1.8 (0.9, 3.7)	Ref	0.7 (0.3, 1.6)	0.6 (0.2, 1.4)	1.8 (0.9, 3.7)
ETP (nmol x minutes)	Ref	3.2 (1.2, 8.7)	2.5 (0.9, 6.9)	2.3 (0.8, 6.4)	Ref	3.5 (1.3, 9.5)	2.4 (0.9, 6.8)	1.9 (0.7, 5.6)
Velocity index (minutes)	Ref	0.6 (0.3, 1.3)	0.5 (0.2, 1.1)	0.8 (0.4, 1.6)	Ref	0.6 (0.3, 1.3)	0.4 (0.2, 1.0)	0.7 (0.3, 1.5)
Start tail time (minutes)	Ref	0.5 (0.2, 1.2)	0.3 (0.1, 0.9)	1.7 (0.9, 3.4)	Ref	0.5 (0.2, 1.1)	0.3 (0.1, 0.8)	1.6 (0.8, 3.2)

Q: quartile. CI: confidence interval, ETP: endogenous thrombin potential, aHR: adjusted for sex, age, Body Mass Index (BMI), frailty score and comorbidities. Ref: reference

None of the proteins were significantly associated with a severe course of COVID-19, after adjustment of confounding and multiple testing (see supplementary table 4, supplemental figures 2 and 3). However, 18 proteins were associated with a severe course of SARS-CoV-2 infection with a p-value <0.05 (unadjusted for multiple testing) (i.e., Angiotensinogen, Kallistatin, Retinol Binding protein 4, Complement Component 7, Complement Component C5, Zinc-Alpha-2-Glycoprotein, Beta-2-Glycoprotein 1, Vitamin K dependent proteins 1, Z and C, Alpha-1-microglobulin, Serum Amyloid A4, Antithrombin III, Coagulation factor IX, Glycosylphosphatidylinositol-phospholipase D, Pigment Epithelium-Derived Factor, Alpha-1-acid glycoprotein and IgGFc-binding protein).

In the hierarchical cluster analysis, no clear clustering was seen of individuals who had a COVID-19 infection during follow-up (see supplemental figure 4). In the cluster analysis selecting only the 47 participants that developed COVID-19 during follow-up also no clear clustering was observed of participants who had a severe course of the disease (see supplementary figure 5).

Tabel 3: Association between trombin generation parameters at baseline and the development of severe COVID-19

	HR (95% CI)			aHR (95% CI)		
	T1	**T2**	**T3**	**T1**	**T2**	**T3**
Peak height (nmol)	Ref	4.8 (0.6, 41)	3.8 (0.4, 34)	Ref	4.6 (0.5, 40)	3.2 (0.4, 29)
Lag time (minutes)	Ref	0.7 (0.2, 3.3)	0.8 (0.2, 3.6)	Ref	0.7 (0.2, 3.3)	0.9 (0.2, 4.2)
Time to peak (minutes)	Ref	0.2 (0.02, 1.4)	0.5 (0.1, 2.1)	Ref	0.2 (0.02, 1.6)	0.6 (0.1, 2.3)
ETP (nmol x minutes)	Ref	1.9 (0.3, 10.4)	1.9 (0.3, 10.4)	Ref	1.8 (0.3, 10.2)	1.4 (0.2, 8.0)
Velocity index (minutes)	Ref	4.8 (0.6, 41)	3.8 (0.4, 34)	Ref	4.5 (0.5, 39)	3.3 (0.4, 30)
Start tail time (minutes)	Ref	(0.1, 2.0)	0.6 (0.2, 2.7)	Ref	0.4 (0.1, 2.2)	0.7 (0.2, 2.8)

T: tertile. CI: confidence interval. ETP: endogenous thrombin potential. Severe COVID-19: requiring contact with a physician and need for medication, requiring hospital admission or admission to ICU or COVID-19 resulting in dead. Ref: reference HR: Hazard ratio adjusted for sex, age, BMI, frailty score and comorbidities (except for pulmonary diseases and chronic kidney disease, because of non-positivity)

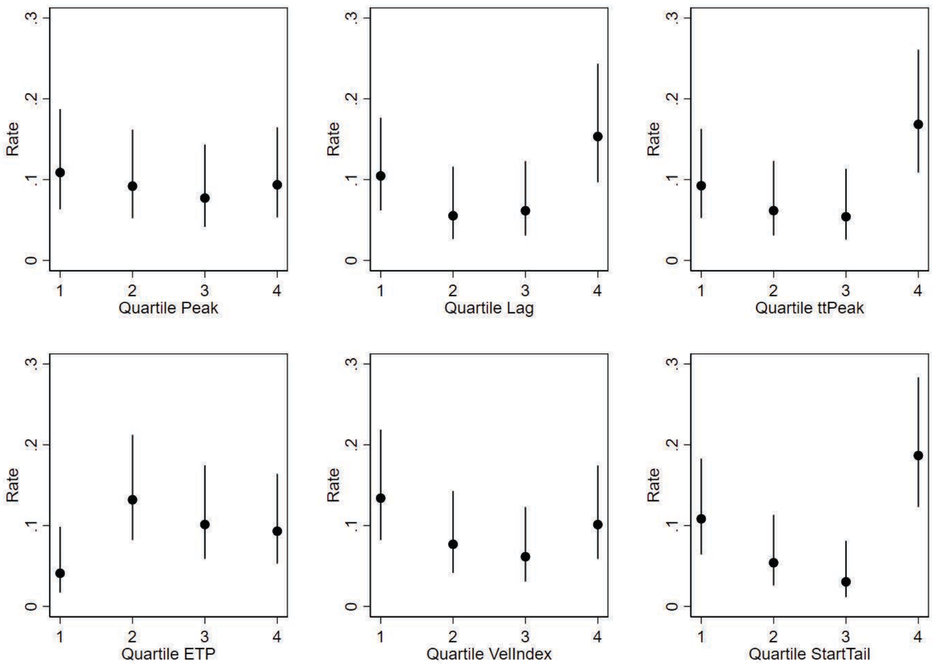

Figure 1: Incidence rate (per person year) and 95% confidence interval of development of an infection with SARS-CoV-2, by quartile of thrombin generation parameter at baseline. The confidence intervals are calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. ETP: endogenous thrombin potential. ttPeak: time to peak. VelIndex: Velocity index.

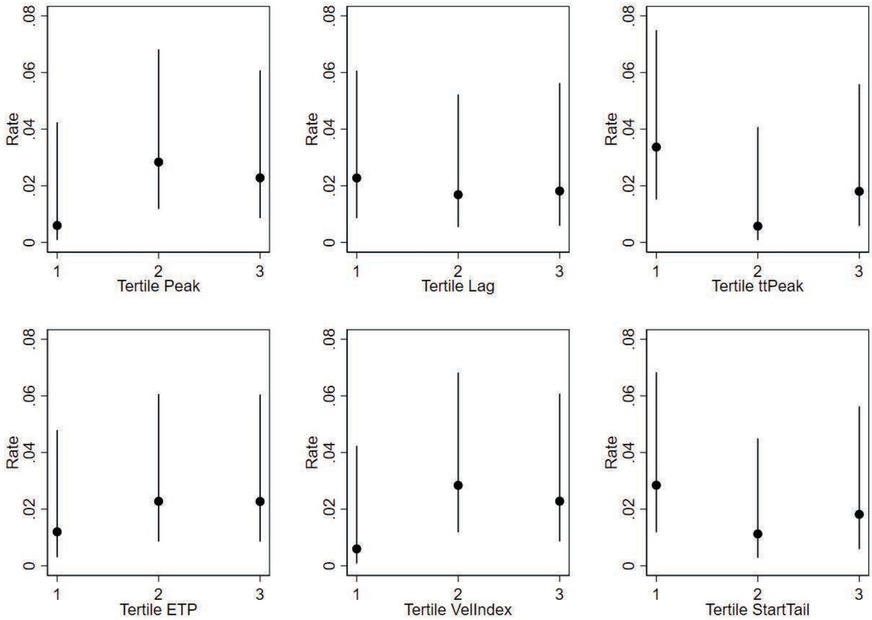

Figure 2: Incidence rate (per person year) and 95% confidence interval of development of severe COVID-19, by tertile of thrombin generation parameter at baseline. The confidence intervals are calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. ETP: endogenous thrombin potential. ttPeak: time to peak. VelIndex: Velocity index.

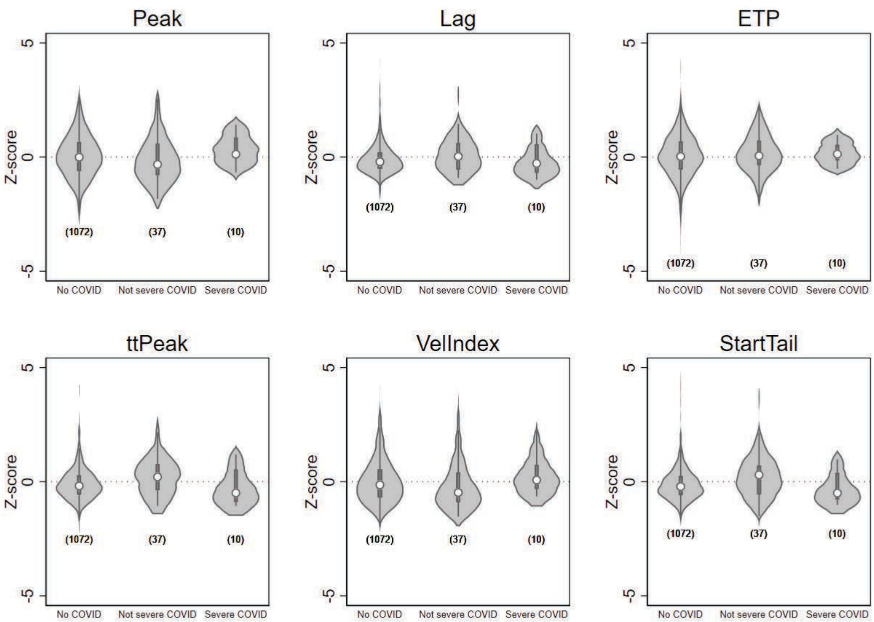

Figure 3: Plots of levels of thrombin generation parameters in participants without COVID-19 (1072), with non-severe COVID-19 (37) and severe COVID-19 (10). Values are normalized Z-values by center. ETP: endogenous thrombin potential. ttPeak: time to peak. VelIndex: Velocity index.

DISCUSSION

In a large cohort of older adults with comorbidities, we found that a high TG potential (expressed as a high peak height) prior to infection was not associated with a subsequent SARS-CoV-2 infection, but the data suggest an association with a severe course of the disease. In a quantitative protein assay, multiple proteins showed associations with SARS-CoV-2 infection, exhibiting diverse roles in coagulation, oxidative stress protection, immune system function, and inflammatory responses.

It is known that severe COVID-19 is often complicated by hypercoagulability.(7, 12-15) This may be a consequence of the severe infection, caused by hyperinflammation, hypoxia, immobilization, microvascular injury, or disseminated intravascular coagulation.(29, 30) However, our results show that also an intrinsic pre-existing hypercoagulant potential of the coagulation system may be associated with an increased risk of a more severe course of COVID-19.

In the exploratory analyses, after adjustment for confounding and multiple testing, none of the proteins measured with QPMS were associated with infection with SARS-CoV-2 or severe COVID-19. Some of the proteins with associations in this exploratory analyses (without adjustment for multiple testing) could be influenced by hemolysis caused by the differend blood collection (Hemopexin, Peroxiredoxin-2 and Carbonic anhydrase 1).(31) Other proteins associated with SARS-CoV-2 infection had diverse roles, e.g. in coagulation, oxidative stress protection, the immunesystem or inflammatory responses.(32-34) Regarding severe COVID-19, analyses unadjusted for multiple testing identified several proteins with functions related to inflammation, oxidative stress regulation, and coagulation.(35-38) The protein Angiotensinogen is part of the renin-angiotensin-aldosterone system, what is known to play a key part in COVID-19 disease progression, especially in patients with cardiovascular comorbidities.(39, 40) Complement component 7, together with components 5, 6, 8 and 9, is involved in lysis of pathogens by forming the Membrane Attack Complex and is involved in the pathogenesis of severe COVID-19.(34, 41) Zinc-alpha-2-glycoprotein is associated with severe COVID-19 via immunoregulatory pathways.(42-44) Alpha-1-acid glycoprotein plays significant roles in inflammation, immune response and is upregulated in severe COVID-19 in prior research.(45) The protein Retinol-binding protein 4 is known to be associated with severe COVID-19 via antiviral pathways.(46) Several antiphospholipid antibodies were associated with COVID-19 in prior research, suggesting the interplay between immunoinflammatory pathways and coagulation.(47) Although Serum Amyloid A4 itself is not described being associated with severe COVID-19, levels of other Serum Amyloid A proteins are known to be linked with severity of disease.(48)

To our knowledge this is the first study to measure TG in individuals prior to SARS-CoV-2 infection. There are studies in which TG was measured during COVID-19, where TG parameters were associated with severe COVID-19 or deterioration.(4, 5) In contrast, several studies in hospitalized COVID-19 patients did not find a prognostic value of TG for severity of disease.(49, 50) However, comparison with our results is difficult, because of the different timing of measurement of the exposure, i.e., before or during COVID-19 infection, and in many prior studies patients used antitrombotic therapies during measurement of TG.

The strengths of this study include the large cohort of individuals with TG measurements performed before infection with SARS-CoV-2 and the detailed and extensive data collection, which allowed for adjustment for several potential confounders. Furthermore, the inclusion of participants in the study and the subsequent follow-up took place during the first half of the pandemic, during which period only one SARS-CoV-2 variant was present, which limited possible effect modification by variants.

Our study also has some limitations. The results are only applicable to older adults with comorbidities, without use of anticoagulants. However, older adults with comorbidities are most vulnerable and at risk of developing severe COVID-19, making them the most relevant population in this context. Our study was embedded in a randomized-controlled trial. Therefore a sample size calculation was not performed specifically for our research question. Particularly in the subgroup analysis of patients with severe COVID-19, sample size was small, resulting in wide confidence intervals and limited certainty in the results of this analysis. We considered several possible confounders in our analyses, i.e., age, sex, BMI, clinical frailty score, and comorbidities. However, for comorbidities and frailty, the direction of the association with TG is not clear, these could either be a cause or a consequence of an elevated TG. Infection with SARS-CoV-2 was based on self-reported test results. Even though all positive tests were confirmed by data from medical records, some infections could have been missed. We used a broad definition for severe COVID-19. This may have result in heterogeneity in severity in the patients classified as severe COVID-19. The measurements of TG were influenced by variations in blood collection methods, sample preparation and storage across the four hospitals.(51) However, all laboratory measurements were performed in one center using standardized procedures, and the data were normalized by hospital during analysis.

In conclusion, our results indicate that hypercoagulability, reflected by an increased peak TG, is not associated with an increased risk of a SARS-CoV-2 infection. However, when infected, pre-existant hypercoagulability may be associated with a more severe course of COVID-19. Several proteins related to the inflammation and coagulation were also associated with infection and COVID-19 severity. These results could aid further exploration of intrinsic risk factors for severe courses of an infectious disease.

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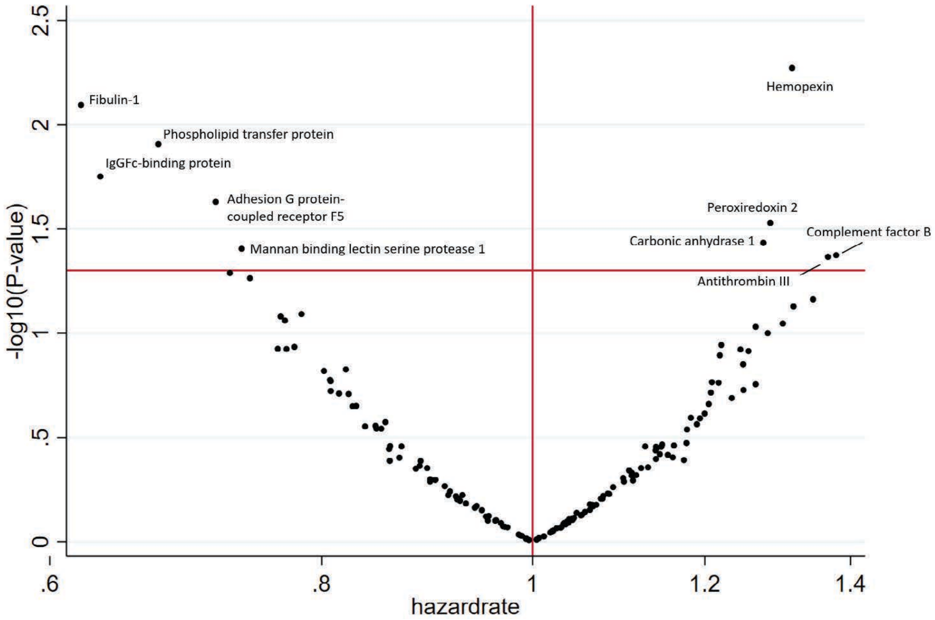
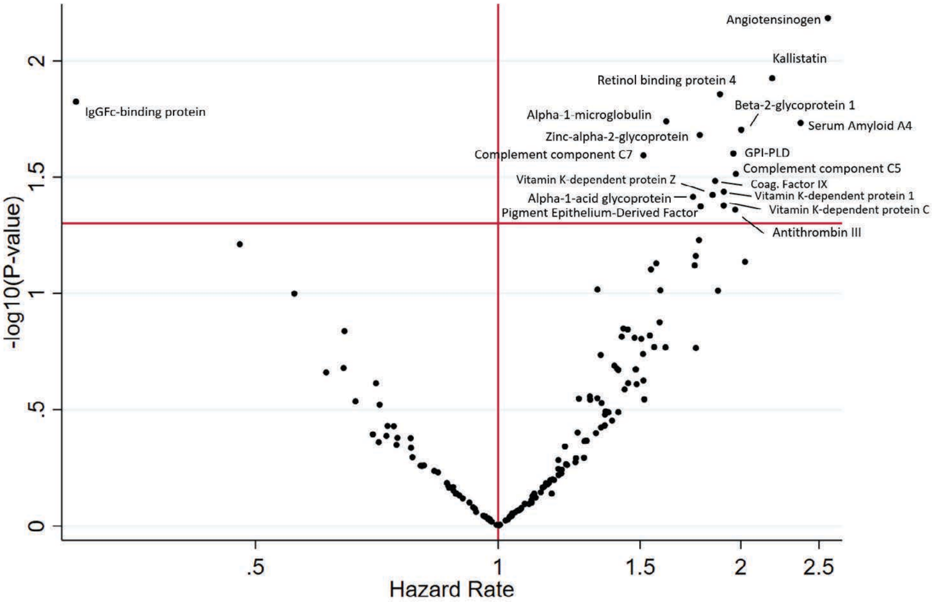
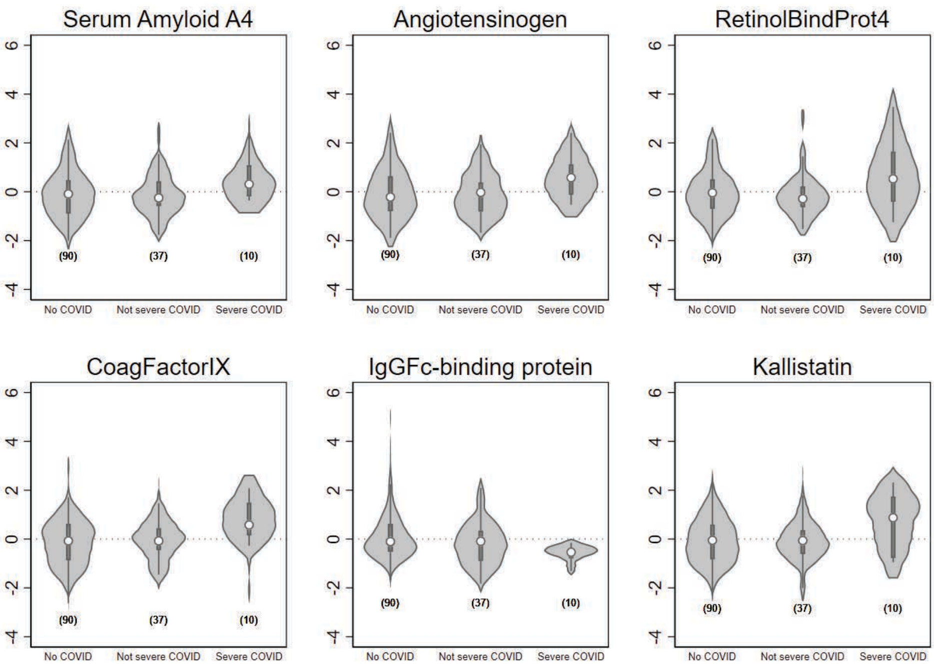
SUPPLEMENTALS



SFigure 1: Vulcanoplot of assocations of 158 proteins with development of subsequent SARS-CoV-2 infection, adjusted for age and sex. (Horizontal red line: unadjusted for multiple testing; p=0.05). After adjustment for multiple testing, non of the proteins remained statistically significant.



SFigure 2: Vulcanoplot of assocations between 158 proteins with development of subsequent severe COVID-19 (horizontal red line: p=0.05, unadjusted for multiple testing). After adjustment for multiple testing, non of the proteins remained statistically significant. GPI-PDL: Glycosylphosphatidylinositol-phospholipase D



SFigure 3: Plots of levels of six proteins in participants without COVID-19 (90), with non-severe COVID-19 (37) and severe COVID-19 (10). Values are normalized Z-values by center.

See other supplementals: