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Patients with Congenital Bleeding Disorders Appear to be Less Severely Affected by SARS-CoV-2: Is Inherited Hypocoagulability Overcoming Acquired Hypercoagulability of Coronavirus Disease 2019 (COVID-19)?

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Semin Thromb Hemost

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the gravest current challenge worldwide, with approximately 5 million infected patients, more than 300,000 deaths, and an overall mortality rate of approximately 7% at the time of writing.[1] Although the underlying disease, coronavirus disease 2019 (COVID-19), is the major medical challenge for the general population, it is more threatening for patients with underlying risk factors such as diabetes, cardiovascular disorders, hypertension, obesity, cancer, and chronic renal and hepatic failures.[2] Coagulopathy is a major pathophysiological characteristic of COVID-19, and the virus can affect all patients including those with congenital bleeding disorders (CBDs). However, due to a paucity of data, it is not clear whether these patients are more or less prone to the severe form of the disease. In this context, we report our observations of COVID-19 patients with CBDs. For this purpose, we collected laboratory and clinical data of patients with identified CBDs receiving a diagnosis of COVID-19 with reverse transcriptase–polymerase chain reaction (RT-PCR) and/or a computed tomography (CT) scan. The latter is now an accepted surrogate marker of COVID-19, in particular ground-glass opacities, when aligned to other clinical features of COVID-19,[3,4] considering also the potential for false-negative RT-PCR. Clinical presentations and laboratory phenotypes for our patient cohort were collected through patient interviews and medical files. Nine patients could be identified, who were noted to be suffering from hemophilia A (HA) ($n = 5$ [~55.5%]), von Willebrand disease (VWD) ($n = 2$ [22.2%]), hemophilia B (HB) ($n = 1$ [11.1%]), and factor XIII (FXIII) deficiency ($n = 1$ [11.1%]). All but one of these patients ($n = 8$ [~89%]) were male, with a mean age of 48.2 years (range: 26–59 years), and most were symptomatic with COVID-19 at the time of SARS-CoV-2 infection ($n = 7$ [~78%]). Of interest, two were asymptomatic for COVID-19: one was a hospital employee identified to have SARS-CoV-2 following routine employee screening and another was randomly referred to undergo testing. Among the nine patients, two (~22%) experienced bleeding and one (~11%) experienced thrombosis. Both patients with bleeding events had contributing risk factors: one with lymphoma and another with factor VIII inhibitor. Thrombosis was observed in a young patient with type 1 VWD, the only hospitalized patient, who was treated in the intensive care unit for 2 days. It is worth noting that this was the patient who was RT-PCR-negative for SARS-CoV-2 and was hence hospitalized based on CT findings and clinical presentation. Although molecular studies failed to confirm an active infection by SARS-CoV-2 at admission, we believe this may have been a false-negative finding, and further

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Table 1 Demographic, laboratory, and clinical characteristics of patients with congenital bleeding disorders

Disorder	Severity	Age (year)	Sex	COVID-19 diagnosis	Severity of COVID-19	Presentations	D-dimer	Routine coagulation tests	Platelet count ($x10^9$/L)	Thrombosis during COVID-19
HB	< 1%	50	M	RT-PCR CT scan	Mild[a]	Diarrhea	NA	PT: N APTT: P	221	No
HA[b]	< 5%	59	M	CT scan RT-PCR	Mild	Runny nose Sore throat Diarrhea Shortness of breath	NA	NA	NA	No
HA[c]	< 1%	52	M	CT scan RT-PCR	Mild	Cough Shortness of breath Anorexia	NA	NA	NA	No
HA	< 1%	47	M	RT-PCR CT scan	Asymptomatic	Asymptomatic	NA	PT: N APTT: P	125	No
HA	> 30%	38	M	RT-PCR	Asymptomatic	Asymptomatic	NA	NA	NA	No
VWD	Type 1	26	F	CT scan	ICU (2 d)	Cough Fever	NA	PT: N APTT: N	171	Yes
FXIIID	Severe[d]	59	M	CT scan	Mild	Cough	NA	NA	NA	No
HA	< 1%	49	M	RT-PCR	Mild	Cough Diarrhea	N	PT: N APTT: P	NA	No
VWD	Type 3	54	M	RT-PCR CT scan	Mild	Shortness of breath	N	NA	315	No

Abbreviations: APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CT, computed tomography; F, female; FXIIID, FXIII deficiency; HA, hemophilia A; HB, hemophilia B; ICU, intensive care unit; M, male; N, normal; NA: Not available; P, prolonged; PT, prothrombin time; RT-PCR, reverse transcriptase–polymerase chain reaction; VWD, von Willebrand disease.
[a]All nonhospitalized patients considered mild, except asymptomatic ones.
[b]Patient was also affected by lymphoma.
[c]Patient had FVIII inhibitor.
[d]Abnormal clot solubility test.

repeat testing was not performed. D-dimer was only available for two patients, with these yielding normal results, and prothrombin time (PT) also was normal in all cases with available data ($n = 4$). Platelet count was also available in four cases; only one of these experienced mild thrombocytopenia (►**Table 1**).

COVID-19 is a relatively severe infectious disease, with a cumulative mortality rate of approximately 7%,[1] but we did not have any mortality in our cohort. The disease is more severe and profound in patients with underlying risk factors, whereas the effect of the disease on patients with CBDs is currently largely unknown. Only one case with severe HA and mild COVID-19-related symptoms has been reported up to now.[5] Since hypercoagulability is a common feature of COVID-19, the effect of a disorder with such a feature on patients with congenital hypocoagulability is illuminating. In this study, we tried to collect data for all SARS-CoV-2 infected patients with CBDs, but we are certain that some infected patients with CBD, even symptomatic ones, were missed in our search. During our study, no death was observed among patients with CBDs and COVID-19 despite a mean age of approximately 50 years. Only one patient needing hospitalization experienced a thrombotic event; this was a case of mild type 1 VWD. Although thrombosis is a (rare) presentation in VWD, it is a multifactorial phenomenon, with the majority of affected individuals being type 1 VWD.[6] Apart from this one patient, no other thrombotic event and no hospitalization were observed in our patient cohort. Two patients with further risk factors experienced bleeding, with one patient's bleeding similar to his usual pattern. Gastrointestinal bleeding, the most common hemorrhagic manifestation in COVID-19, has been reported with a frequency of 4 to 13.7%, mostly in severely affected patients.[7] In this study, only two patients with contributing risk factors experienced bleeding during COVID-19 infection, even including those with severe factor deficiencies. An interesting evidence that emerged from this study is the absence of thrombotic events in seven patients with moderate-to-severe factor deficiencies. This is an important finding, which might result in lower overall rates of morbidity and mortality among patients with CBDs. It should be noted that none of the patients in our cohort were receiving regular prophylaxis prior to the pandemic, except the severely affected HB and FXIII deficient patients. Patient with severe FXIII deficiency and history of intracranial hemorrhage abandoned to receive his prophylaxis. As FXIII acts in the final stage of the coagulation cascade, such patients are not considered to be in a general hypocoagulable state.[8]

In a published study on 12 autopsies, 4 deaths were directly attributed to pulmonary embolism, and deep vein thrombosis was observed in more than 50% of cases.[9] Although prolonged PT is a common finding in COVID-19, none of four patients with available data in our study had prolonged PT times, which could be reflective of reduced comparative disturbance of the coagulation system. While concomitant activation of coagulation and fibrinolytic

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systems, and subsequent prolongation of PT, as well as increased D-dimer and fibrin/fibrinogen degradation products, are common findings and risk factors presaging a poor outcome in COVID-19,[10] they were absent in this cohort where tested, and we observed a more favorable outcome. Moreover, thrombocytopenia, another common adverse feature of COVID-19,[11] which can be attributed to concomitant activation of the coagulation factors and fibrinolytic system, was observed in only one of four patients. Viral associated depletion of platelets may represent another characteristic of patients with COVID-19, which can thus lead to potential platelet consumption.[12,13]

It should be mentioned that one major limitation of our study is the absence of all coagulation parameters in most patients. Since being male is a risk factor for mortality, one might expect that patients with hemophilia would potentially be at a greater risk of more severe forms of COVID-19, but this was not the experience in our cohort. Our findings thus support our proposal that patients with CBDs, at least moderately to severely affected individuals, are less susceptible to hypercoagulability-related severe presentations in COVID-19, for example, as reported following autopsy.[9] Indeed, hypercoagulability may not be a big challenge for patients with congenital hypocoagulability compared with the general population. There are some exceptions among patients with CBDs who have a relatively higher tendency to thrombosis.[14]

Our findings are important in several aspects: a D-dimer higher than 1 µg/mL, a clear adverse prognostic factor related to a higher rate of morbidity and mortality,[10] is less likely to occur in patients with severe hypocoagulability states, particularly in severe FXIII deficiency.[8] In addition, thrombocytopenia is shown to be accompanied by a higher rate of mortality attributed in part to intravascular coagulopathies and a state of hyperfibrinolysis, which, again, is less probable in CBD states. In addition, thrombosis is considered one of the most common causes of death in COVID-19. The rate of thrombosis is substantially lower in most patients with CBDs, with exception of those with some conditions such as congenital fibrinogen disorders and dysprothrombinemia.[11] Therefore, this significant adverse effect is less common in congenital hypocoagulability states. It was suggested that instead of pulmonary embolism, in situ pulmonary thrombosis can be considered as one of the main causes of death in COVID-19.[15] This phenomenon could be attributed to direct virus invasion of lung endothelial cells and local activation of hemostasis triggered by the sustained underlying proinflammatory state. It is postulated that subsequent release of a large amount of von Willebrand factor swamps ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), resulting in platelet aggregates and pulmonary thrombosis,[15] a phenomenon that is less likely in some CBDs, especially type 3 VWD and Bernard–Soulier's syndrome, thus making them less susceptible to any such related fatal event.[16]

In conclusion, it appears that a severe hypocoagulability state may be protective against COVID-19 hypercoagulability-related adverse effects, an important consideration otherwise making anticoagulation mandatory for all patients hospitalized with COVID-19. Some authors suggest mild anticoagulant therapy, whereas others prefer more aggressive therapeutic strategies.[7] Nevertheless, although our data are important, these observations are only confined to a limited number of patients with CBDs; however, they warrant further, more extended studies, including our ongoing study on a large number of patients with CBDs, which should then resolve some of the ambiguities this report presents.

Conflict of Interest
None.

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