Bleeding and Bleeding Risk in COVID-19

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Semin Thromb Hemost 2020;46:815–818.

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Coronavirus disease 2019 (COVID-19) is a new, emerging medical challenge worldwide, with those affected showing a variety of clinical presentations, ranging from asymptomatic or mild conditions to critical illness. Patients affected by the causative virus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—usually experience cough, fever, dyspnea, myalgia, less frequently gastrointestinal (GI) manifestations and, rarely, neurological complications. Coagulopathy is common among those afflicted and appears to be one of the most significant adverse prognostic signs.[1,2] Coagulopathy results from concomitant activation of coagulation and fibrinolytic systems, most likely due to a severe proinflammatory state (i.e., the so-called cytokine storm) and/or by viral sepsis that sometimes leads to consumption of coagulation factors and decreased platelet count, resulting in thrombohemorrhagic events.[3] In this process, plasmin breaks down fibrin present in plasma and the bronchoalveolar lavage fluid, as well as potentially other organs, and leading to excess D-dimer/fibrin (ogen) degradation product (FDP) formation. This may also lead to reduction in platelet count and increased risk for hemorrhage.[4] In a systematic review of 6,892 patients and meta-analysis of 3,496 patients, platelets were low in 22.9% and D-dimer was high in 34.8%; D-dimer was associated with a severe clinical course with an odds ratio (OR) of 4.03, and low platelets with an OR of 1.78.[5] Disseminated intravascular coagulation (DIC) in COVID-19 is accompanied by a significant decrease of fibrinogen, and a marked increase of FDP and D-dimer, which are characteristics of DIC with hyperfibrinolysis, whereas the DIC caused by infection is accompanied by plasminogen activator inhibitor-1 release and suppression of fibrinolysis. Administration of antiproteases may prove beneficial.[6] Elevated D-dimer, and FDP, often mildly prolonged prothrombin time and mildly decreased platelet counts were also reported as common findings by Tang et al, more common and more profound in severely affected patients.[2] Fibrinogen levels are sometimes lowered, but may instead be elevated, while activated partial thromboplastin time is sometimes prolonged, but may instead be shortened, with these potentially suggestive of acute phase events.[2,6] Although hypercoagulability and thrombotic events are common in COVID-19, bleeding may occur at any time during the course of disease. Several factors make patients with COVID-19 prone to bleeding, including thrombocytopenia, hyperfibrinolytic state, consumption of coagulation factors, and thromboprophylaxis administration of anticoagulants. A proposed cytokine storm, prolonged tissue hypoxia, and direct invasion of affected tissues are other possible causes.[2,7,8] Although thrombosis is relatively well studied in COVID-19, bleeding and bleeding risk appear to be the forgotten side of this story, most probably due to the less-fatal consequences; however, hemorrhagic diatheses represents a significant morbidity and potential cause of death in COVID-19 in at least in a subset of patients.[7,8]

Thrombocytopenia

In one early study, about one-third and about half of patients developed thrombocytopenia and increased D-dimer, respectively, while among severely affected patients the rates were around 60%.[1] In another recent large-scale retrospective study on 1,476 consecutive patients, approximately 20% had thrombocytopenia ($< 150 \times 10^9$/L).[9] Those who died had a progressive decrease in platelet count, and when the platelet count was lower the risk of death was higher. For example, the relative risk of death and the morality rate were 3.42 (95% confidence interval [CI]: 2.36–4.96), 9.99 (95% CI: 7.16–13.94), and 13.68 (95% CI: 9.89–18.92), and 17.5, 61.2, and 92.1%, for platelet counts of 100–150, 50–100, and 0–50×10^9/L, respectively. Of all patients with thrombocytopenia, approximately 25% were severely ill, with platelet count between 0 and 50×10^9/L.[9] These patients are at risk of bleeding, and most guidelines recommend platelet transfusion when their platelet count is between < 30–50×10^9/L, for bleeders or for those at high risk of bleeding, and $< 10 \times 10^9$/L, whether bleeding or not.[10,11] Therapeutic response of platelet replacement is lower in patients with DIC, high fever, or splenomegaly.[10] In the setting of COVID-19, currently lacking randomized clinical trials, there is no definite guidance on threshold for platelet transfusion.

published online June 8, 2020

Issue Theme Maintaining Hemostasis and Preventing Thrombosis in COVID-19—Part I; Guest Editors: Emmanuel J. Favaloro, PhD, FFSc (RCPA), and Giuseppi Lippi, MD.

DOI https://doi.org/10.1055/s-0040-1713434.
ISSN 0094-6176.

In a study of 61 severe intensive care unit (ICU)-treated and 93 severe non-ICU patients, 41% of the former had severe thrombocytopenia ($< 50 \times 10^9$/L), 96% of which had fatal consequences. Fatal consequences were observed in ICU-treated nonsurvivors with progressively worsening thrombocytopenia, but this was rarely observed in non-ICU severe cases or ICU-treated survivors. More than 55% of nonsurvivors had a platelet count less than $< 50 \times 10^9$/L, and approximately 20% of nonsurvivors had a platelet count less than $< 10 \times 10^9$/L in the very late stage of the disease, 2 to 3 days prior to death. Continuous renal replacement therapy (CRRT) significantly decreased the platelet count in more than 80% of CRRT-treated patients: in approximately 50%, platelet count was $< 10 \times 10^9$/L a few days after treatment onset; subsequently bleeding might occur in these patients. The overall survival rate was approximately 6% for patients treated with CRRT.[12] Among severely affected ICU-treated patients, those under low-molecular-weight heparin (LMWH) therapy had a lower platelet count than patients not on therapy. ICU-treated patients under LMWH therapy also had a lower survival rate than those without heparin. Heparin exposure was considered a risk factor for progression toward mortality in severe COVID-19 patients.[12] In fact the authors found that CRRT, heparin exposure, and significant platelet decrease were risk factors for the severely ill. Significant heparin-induced thrombocytopenia (HIT) was observed, both spontaneously and after heparin exposure, which might contribute to occurrence of severe thrombocytopenia. Spontaneous HIT may be due to endogenous release of heparin in viral infection.[12] Although the usefulness of heparin-involving anticoagulation therapy in patients with severe COVID-19 was mentioned by Tang et al, the risk of HIT should also be considered in these cases.[2,12] Critically ill patients with COVID-19 and CRRT have a high mortality rate, mostly due to HIT. Therefore, careful clinical and laboratory monitoring should be performed to identify those with a risk of HIT; in these cases, heparin-involved therapy should be avoided or discontinued, alternative anticoagulants such as direct oral anticoagulants (DOACs) are recommended.[12]

Bleeding and Bleeding Risk

Although respiratory failure (70%), multiorgan failure (MOF; 28%), cardiac failure (15%), hemorrhage (6%), and renal failure (4%) were reported as leading causes of death in COVID-19 in one study,[13] a valuable recent prospective study revealed that pulmonary embolism (PE) was the direct cause of death in four (~33%), and deep vein thrombosis was observed in seven (58%).[14] In an autopsy report of four patients, one (25%) had large intra-alveolar hemorrhages and intra-alveolar fibrin cluster formation.[15] Another study analyzing mortality revealed that 1 (~7%) out of 14 patients died due to GI bleeding.[16] It is worth noting, however, that the patient had lymphoma, thus comorbidities may represent a part of the risk profile.

Bleeding, when seen as the first presentation in COVID-19, may lead to misdiagnosis and inappropriate clinical and laboratory work-up for other viral infections like dengue.[17] Fatal GI bleeding and intracranial hemorrhage (ICH) are other reported forms of severe bleeding.[18,19] Although anorexia is the most common digestive finding (up to 50%) in adults, and diarrhea is most common in both adults and children (up to ~50%) with COVID-19, GI bleeding was observed with a frequency of 4 to 13.7%, primarily among severely affected patients, 40% of whom were stool polymerase chain reaction positive.[19,20] It seems that prolonged hypoxia causes cell necrosis and mucosal injury, leading to ulceration and GI hemorrhage.[12] Focal hemorrhage in the kidney also has been reported.[21] Rare cases of COVID-19 with ICH have been reported, but further studies are required to clarify this finding.[18] This phenomenon could be attributed to the proposed cytokine storm, and even without direct viral invasion within the intracranial space could result in breakdown of the blood–brain barrier.[7] A rare case of COVID-19 with immune thrombocytopenic purpura that developed a subarachnoid microhemorrhage, while the patient had a platelet count of 2×10^9/L, has been reported.[22] It seems that pathological immune conditions may be relatively frequent in this disease. Multiple cerebral infarctions were reported in COVID-19 associated with immunoglobulin A antiphospholipid antibodies, although lupus anticoagulant was not present in these patients, and persistence was not investigated.[23] Thus, the association may not in general hold true.

Thus, overall, the above findings demonstrate that hemorrhage and risk of hemorrhage are not necessarily an infrequent finding in COVID-19, albeit most probably associated to contributing factors.

Also, due to a high risk of thrombosis, thromboprophylaxis with LMWH is recommended by the International Society of Thrombosis and Hemostasis (ISTH) interim guidance for all hospitalized patients with COVID-19.[24] This recommendation is based on expert opinion and a few case series. However, others recommend more aggressive anticoagulant therapy with unfractionated heparin (UFH), potentially accompanied by antithrombin supplementation.[25,26] Others believe that administration of LMWH may increase the risk of bleeding in special situations, such as those otherwise requiring a more aggressive anticoagulation, such as PE that is missed because of primary lung injury by the virus.[26] In Japan, nafamostat mesylate—an inhibitor of plasmin, thrombin, and trypsin—is used for the management of DIC in COVID-19. Unlike heparin, nafamostat mesylate does not have hemorrhagic side effects, even at high doses. Due to its antifibrinolytic actions, the drug is useful for the management of DIC with increased fibrinolytic activity. Moreover, it seems that nafamostat mesylate also has antiviral activity and may potentially be effective in treating DIC in COVID-19, but its low anticoagulant activity may also be a disadvantage.[27] Another study shows that thrombosis- and bleeding-predicting tools are useful in the management of patients.[28] The study assessed the potential usefulness of Padua prediction score—to predict thrombosis risk—and the improved bleed risk assessment model—to predict risk of bleeding—in COVID-19 patients under thromboprophylaxis with UFH and LMWH. According to the bleeding predicting tool, nine (6.5%) patients had a high risk of bleeding (improved score ≥ 7), six of whom (~67%) experienced hemorrhagic events during the course of thromboprophylaxis, including

mild or microscopic hematuria (*n*: 3), GI bleeding (*n*: 1), epistaxis (*n*: 1), and severe hemothorax (*n*: 1).[28] More detailed thromboprophylaxis of patients with COVID-19 and venous thromboembolism is outside the scope of this work and is presented elsewhere.[28] Anticoagulant therapy is contraindicated for patients with active bleeding and for those with a low platelet count (according to ISTH guidance $< 25 \times 10^9$/L).[17] In COVID-19 patients under treatment with DOACs, the coadministration of antivirals significantly increased the plasma concentration of DOACs; the trough level of DOAC was 6.14 times higher during hospitalization than before admission.[29] To prevent bleeding in such patients, it was suggested that DOACs be withheld during COVID-19 infection.[30]

Although clinical presentations in symptomatic children are relatively similar to adults, in severe cases, septic shock with irreversible bleeding and coagulation dysfunction may occur.[31] Among the newborns of infected mothers, thrombocytopenia accompanied by abnormal liver function was observed in two (20%) and GI bleeding in four (40%). Of the first two patients, one developed refractory shock, MOF, and DIC, which led to death in spite of platelet, plasma, and red blood cell transfusions. Another neonate, with GI bleeding and DIC, responded to intravenous administration of gamma globulin.[32]

Conclusion

In conclusion, despite its prevalence, COVID-19 remains a barely understood disease with a high rate of heterogeneous and disparate clinical pictures. New presentations may be observed among affected patients, and health care providers should update their knowledge to prevent severe and fatal consequences arising from insufficient knowledge. Due to a high rate of coagulopathy among COVID-19 patients, the risk of bleeding should always be considered in every case, as bleeding, although rare, may be one of the first clinical presentations at the time of diagnosis.

Conflict of Interest
None declared.

Acknowledgment
We highly appreciate Daisy Morant's valuable work in improving the English language of the manuscript.

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