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LETTER TO THE EDITOR

The Coagulation Profile of Severe COVID-19

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To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is frequently associated with marked thrombo-embolic events.[1] In severe cases SARS-CoV- pneumonia necessitates ECMO—an invasive technique for gas exchange—while the failing lung is given time to recover. Unfortunately, mortality of respiratory failure in SARS-CoV-2 pneumonia remains unacceptably high.[2] We read with great interest the recent article by Corey et al. who studied the coagulation profile of critically ill COVID-19 patients.[3] The study findings addresses the ongoing controversy regarding the role of fibrinolytic shutdown in thrombosis in severe COVID-19,[4,5] and implicate the suppression of fibrinolysis in both micro- and macrovascular thrombosis in severe COVID-19. We salute the authors on this important investigation and would like to highlight several points.

First, the authors state that non-ECMO patients received heparin prophylaxis for venous thromboembolism, while ECMO patients received full heparinization titrated to a partial thromboplastin time goal (PTT) of 50 to 60 s. Thrombohemorrhagic events were especially common in ECMO patients (78% thrombosis, 78% hemorrhage; Supplemental Tables 2 Ref[3]) and were ascribed to the hypercoagulable state of severe COVID-19 infection and activation of coagulation by the ECMO circuit along with consumptive coagulopathy. Prolongation of prothrombin time / international normalized ratio (INR) and PTT are common in patients admitted with COVID-19 pneumonia and are prognostics of poorer outcomes.[6] Corey et al. reported prolonged PTT (49-50 s) for the non-ECMO patients, and the subgroup thereof with thrombosis had a PTT of 62.5 s and INR of 1.76 (Supplemental Tables 2 and 3 Ref[3]). In contrast, ECMO patients who received full heparinization had a PTT of 41 s and an INR of 1.06 (Supplemental Tables 2 Ref[3]). The subtherapeutic heparinization of the ECMO patients—according to the authors' own PTT-based goal—likely contributed to the high rate (78%) of thrombosis but is not addressed by the authors.

Second, in contrast to PTT, the readily available anti-Xa assay is not influenced by fluctuating levels of coagulation factors or fibrinogen. Recent studies demonstrated that in ECMO patients anti-Xa levels more precisely reflect the concentration and activity of heparin than PTT, and that an anti-Xa-based anticoagulation protocol for ECMO results in significantly fewer bleeding events and reduced mortality without an increase in thrombotic events.[7,8] The low anti-Xa activity in ECMO patients in the study [0.13 IU/ml (Supplemental Tables 2 Ref[3]); therapeutic range 0.3-0.7 IU/ml] confirms the subtherapeutic heparinization of the ECMO group. Inference from the study to adequately anticoagulated COVID-19 ECMO patients may, therefore, be limited. Given the prominent coagulation changes of COVID-19, we also believe that the authors' preference for a PTT-based anticoagulation protocol for the ECMO patients over an anti-Xa-based protocol warrants an explanation.

Lastly, in the *Clinical Characteristics* section of *RESULT* the authors stated that "The non-survivor group had *less* obesity, as well as *less* cardiovascular disease and chronic lung disease compared to the survivor group," while in *DISCUSSION* they stated that "…survivors and non-survivors had *similar* rates of cardiovascular disease, chronic lung injury, kidney disease, and diabetes." The reader is unable to assess comorbidities differences between survivors and non-survivors because statistical analysis (p values) is not provided (Table 1 and Supplemental Table 2 Ref[3]). The clinical characteristics of the cohort are, of course, important. The associations of comorbidities and poorer outcomes in COVID-19 are well established.[9] Inference from a small cohort (n=55) with unusual clinical characteristics to the general population of patients with severe COVID-19 may be limited.

While we appreciate the authors' objective to granularly portray the coagulation profile of critically ill COVID-19 patients, addressing these points would further strengthen their findings.

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