Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

Blood Hyperviscosity

A Novel Link Between Hyperinflammation and Hypercoagulability in COVID-19*

Aldo Bonaventura, MD, PhD,[a] Nicola Potere, MD[b]

Originally regarded to as a mere respiratory illness, coronavirus disease-2019 (COVID-19) is characterized by dysregulated immune response and abnormal cytokine release affecting multiple organs including blood and the vasculature.[1] As part of an evolutionarily conserved, first-line defense mechanism known as immunothrombosis,[2] the innate immune system interacts with platelets and the endothelium and triggers the coagulation system, thus enabling confinement of invading pathogens. However, excessive immunothrombosis in response to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) may result in pathological thrombosis (macro- and microvascular), which accounts for substantial organ injury and mortality.[3,4] Despite current thromboprophylaxis approaches, a not negligible portion of patients experiences thrombotic events, thereby implicating the existence of knowledge and therapeutic gaps.[5] Researchers worldwide have attempted to identify early disease predictors, largely focusing on circulating biomarkers. Nevertheless, very few studies to date have investigated the changes induced by COVID-19 on blood rheology.[6-8] One of the main hemorheological properties is whole blood viscosity (WBV). Major determinants of WBV are hematocrit, plasma viscosity, and erythrocyte aggregation and deformability. As WBV is influenced by shear rate, high- and low-shear BV refer as to areas of the blood vessel at high- and low-shear flow, respectively. The former is generally characterized by laminar blood flow and contributes to erythrocyte aggregation and microvascular ischemia, whereas the latter is generally characterized by turbulent blood flow inducing endothelial damage to the vessel wall.[9]

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In this issue of the *Journal of the American College of Cardiology*, Choi et al[10] have provided several elements of innovation by exploring the prognostic value of estimated BV (eBV) to predict mortality in patients hospitalized for COVID-19. In this multicenter, retrospective cohort study, eBV (calculated according to Walburn-Schneck model) was measured in 5,621 hospitalized patients with COVID-19 and found to positively correlate with in-hospital mortality. This association, which was stronger for estimated high-shear BV (eHSBV) than for estimated low-shear BV (eLSBV), was overall consistent across major patient subgroups (including age, sex, comorbidities, disease severity upon admission, concomitant antithrombotic therapies, and proinflammatory markers).[10] Patients with higher eHSBV and eLSBV exhibited reduced survival rates. In particular, when compared with patients with eHSBV within the lowest quartile, those with highest eHSBV values exhibited a 50-fold higher risk of death (adjusted HR: 1.53; 95% CI: 1.27-1.84). Consistently, COVID-19 patients with highest values of eLSBV were at higher risk of death (aHR: 1.36; 95% CI: 1.14-1.64).[10]

Hyperinflammation may promote hyperviscosity through multiple mechanisms, including enhanced concentration of large proinflammatory and procoagulant proteins (eg, acute-phase proteins, such as

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From the [a]Medicina Generale 1, Medical Center, Ospedale di Circolo e Fondazione Macchi, ASST Sette Laghi, Varese, Italy; and the [b]Department of Innovative Technologies in Medicine and Dentistry, School of Medicine and Health Sciences, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy.

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fibrinogen).[11,12] Indeed, they increase plasma viscosity, a component of WBV, and may electrostatically interfere with physiological viscoelastic properties of erythrocytes, which also affect WBV. In line with previous observations, C-reactive protein and interleukin-6 were associated with poor survival in this study.[10] However, eHSBV retained its predictive value even after adjustment for proinflammatory biomarkers, thereby suggesting that hyperviscosity, although mechanistically related to hyperinflammation, may represent an additional, yet at least in part independent, predictor of adverse outcomes in hospitalized COVID-19 patients. This notion was further supported by the strong correlation observed between eBV and mortality in the stratum of patients with no concomitant cardiovascular or metabolic diseases,[10] in whom risk stratification may be particularly challenging. While still requiring adequate—both external and prospective—validation, eBV is likely to represent an attractive biomarker, as it was shown to be an early and robust predictor of mortality, and it is widely available and relatively inexpensive. In light of the translational potential associated with eBV, further investigation is eagerly warranted to confirm and expand the present findings, in order to advance eBV into the clinical scenario. It is, however, worth considering that eBV represents an indirect approximation of BV, which may not reflect BV as directly measured by viscometers. Hence, further research should be addressed to implement hemorheological models, and to establish the precise relationship between estimated and direct BV measurement. The study by Choi et al[10] also showed no association between WBW and in-hospital mortality in participants of Asian ethnicity, which opens to the possibility that genetic factors may influence COVID-19-related outcomes through differential hemorheological responses to SARS-CoV-2.

The impact of distinct SARS-CoV-2 variants and vaccines on blood viscosity still remains to be elucidated. In a small study, eBV increased after vaccination in both patients with and without previous COVID-19, but especially among those with prior symptomatic disease; however, it should be acknowledged that no clear information about the model used for estimation is provided.[13] Although preliminary, these observations suggest that screening for previous COVID-19 before vaccination might potentially have a role in preventing vaccine-related thrombotic complications. Moreover, different therapeutic strategies targeting hyperinflammation (eg, glucocorticoids, interleukin-6 receptor blockers, Janus kinase inhibitors, interleukin-1 inhibitors) or hypercoagulability (eg, anticoagulants, statins, antiplatelet agents) in hospitalized patients with COVID-19 may exert peculiar effects on BV, which have not been unraveled yet. Following the introduction of novel antiviral agents for COVID-19 to be administered especially in the community setting, refining risk stratification strategies to identify subjects with COVID-19 at elevated risk for disease progression is of utmost importance. The assessment of the prognostic role of eBV in the larger population of COVID-19 outpatients shall therefore be desirable. While it has been reported that hyperviscosity may increase the risk of developing thrombotic events in critically ill patients with COVID-19,[7] a clear, direct link between the proposed mechanism (ie, hyperviscosity) and the putative ensuing clinical event (ie, thrombosis) is still lacking. Yet, it is not possible to exclude that hyperviscosity may contribute to increase in-hospital mortality through multiple mechanisms other than hypercoagulability. Accumulating evidence indicates that COVID-19 can become a chronic disease, "long COVID," in some patients, and the increased thrombotic risk may persist long after the acute phase.[14,15] Hence, a potential extension of the present findings, currently restricted to the hospitalization period, may involve exploring the postdischarge period. This would allow to identify patients at risk for postdischarge thrombosis who might therefore benefit from extended-duration thromboprophylaxis. Despite the limitations inherent to the present study, including the retrospective design, the approximate nature of the estimation of BV, and the limited discriminative power of eBV for clinical decision making when used on top of available clinical data, the study by Choi et al[10] identified blood viscosity as a trackable biomarker that may play a previously neglected role in the pathogenesis of COVID-19. BV may also represent a novel therapeutic target in COVID-19, which certainly deserves additional attention, and it could generate relevant therapeutic implications for, but not limited to, COVID-19.

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ADDRESS FOR CORRESPONDENCE: Dr Aldo Bonaventura, Medicina Generale 1, Medical Center, Ospedale di Circolo e Fondazione Macchi, ASST Sette Laghi, Via Guicciardini 9, 21100 Varese, Italy. E-mail: aldo.bonaventura@asst-settelaghi.it. Twitter: @aldobonaventura.

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