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.

Micro-Thrombosis, Perfusion Defects, and Worsening Oxygenation in COVID-19 Patients: A Word of Caution on the Use of Convalescent Plasma

To the Editor: Joyner et al[1] recently provided a safety update on the use of convalescent plasma (CP) in a population of 20,000 patients with coronavirus disease-19 (COVID-19). The results on the safety aspects, elegantly presented by the authors, may seem encouraging from many perspectives. However, we would like to comment on an extremely important aspect when considering the use of CP.

Most of the attention on safety issues during administration of CP has been directed toward adverse effects unrelated to the clinical settings (ie, infection, transfusion-related acute lung injury, or transfusion associated circulatory overload) and "disease-specific" (eg, viral enhancement). However, clinicians should bear in mind that CP contains procoagulant factors and in common clinical practice plasma is administered in patients with coagulopathies or hemorrhage, or both. Thus, administering CP to patients with COVID-19 means introducing procoagulant factors into their bloodstream. This may be troublesome when considering that COVID-19 patients stand at the other side of hemostasis disorders and that their tendency to develop a prothrombotic disease has been reported.[2] This prothrombotic state causes perfusion abnormalities at the pulmonary level, contributing to the peculiar phenotype of respiratory failure in patients with COVID-19.[3]

In this context, it is worth noting the results of a recent study investigating the pulmonary abnormalities in COVID-19. Indeed, Patel et al[4] recently showed significant alterations in the pulmonary vasculature in patients with severe COVID-19. The authors presented a combination of physiologic data, findings of high-resolution imaging, and hematologic results; they showed an activation of both inflammatory and coagulation pathways playing a pivotal role in the development of respiratory failure and compromising oxygenation in patients with severe COVID-19. Of note, hypercoagulability and reduction in the fibrinolytic activity in the pulmonary vasculature resulted in pulmonary perfusion abnormalities.

Although Joyner et al[1] reported a low incidence of thromboembolic or thrombotic events at 7-day follow-up (n = 113; <1%), when considering the administration of CP to COVID-19 patients, clinicians should bear in mind that even small quantities of coagulation factors contained in the CP can enhance the coagulation cascade. Such an event might represent a serious harm for patients with severe COVID-19; indeed, enhancing microthrombosis and the consequential perfusion abnormalities at the pulmonary level might ultimately lead to worsening oxygenation and increased risk of clinical deterioration.

In consideration of this risk, it would be interesting to access data on the ratio between partial pressure of oxygen in arterial blood and the fraction of inspired oxygen (PaO2/FiO2) before and after CP administration. Meanwhile, we would like to express a word of caution on the use of CP in severe COVID-19 patients.

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In Reply — Micro-Thrombosis, Perfusion Defects, and Worsening Oxygenation in COVID-19 Patients: A Word of Caution on the Use of Convalescent Plasma

To the Editor: We would like to thank our colleagues for their letter in response to our manuscript. The

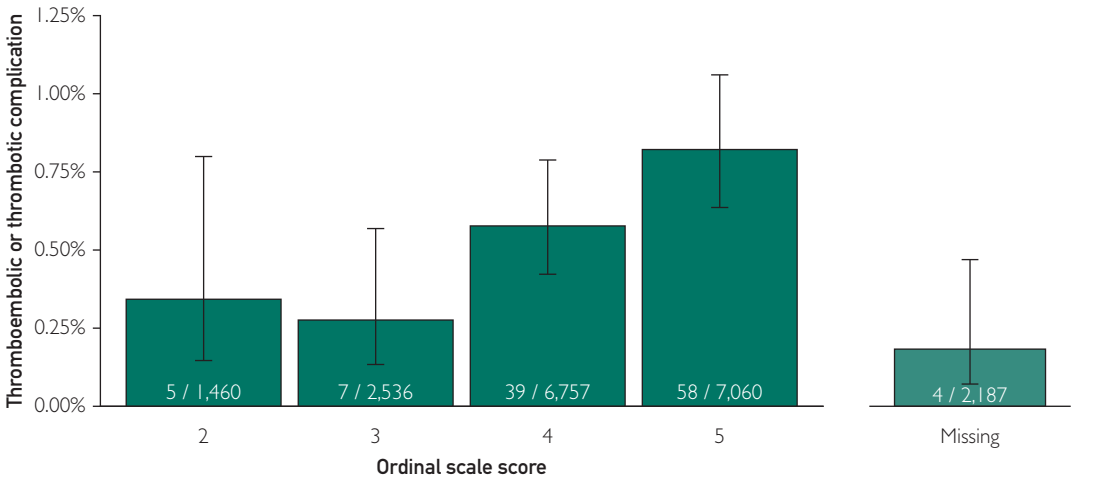

FIGURE. The rate of thrombotic and thromboembolic events stratified using a 6-level ordinal scale to assess the clinical course of COVID-19. Scores on the ordinal scale were defined as follows[6]: a score of 1 indicated not hospitalized; 2, hospitalized and not receiving supplemental oxygen; 3, hospitalized and receiving supplemental oxygen; 4, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or noninvasive ventilation; 5, hospitalized and receiving mechanical ventilation; and 6, death. Wilson confidence interval calculation for binomial proportions was used to estimate the 95% confidence intervals for each point estimate.

letter raises important theoretical concerns about the impact of procoagulant factors in plasma on the coagulation cascade in the context of patients with severe COVID-19.[1] Generally, we agree with the word of caution regarding the use of convalescent plasma in the context of patients with severe COVID-19 and evidence of dysregulated hemostasis, as observed among patients who required extracorporeal membrane oxygenation (ECMO) support.[2] Indeed, fresh frozen plasma contains physiologic ratios of both procoagulant and anticoagulant proteins.[3] Theoretically, if transfused to a patient that is prothrombotic, plasma can contribute to ongoing dysregulated hemostasis. Despite the theoretical concerns enumerated by our colleagues, some evidence suggests that transfusion of fresh frozen plasma in nonbleeding critically ill patients does not aggravate their inflammatory response, and it might stabilize endothelial condition.[4]

As noted in our original article,[5] the low rate (~0.5%) of thrombotic and thromboembolic events—113 events in 20,000 patients with COVID-19—is encouraging, particularly given the high prevalence of both COVID-19 associated—respiratory failure and hypoxemia in the observed patients. Herein, the rate of thrombotic and thromboembolic events was stratified using a 6-level ordinal scale to assess the clinical course of COVID-19,[6] with higher scores indicating worse condition at time of enrollment (Figure). The rate of thrombotic and thromboembolic events appears to increase with more advanced clinical course of COVID-19; however, the rate of events is objectively low among patients in the most severe category of COVID-19 (~0.8%).

In summary, we agree with the word of caution provided by our colleagues, particularly among patients with COVID-19 who have a dysregulated coagulation system promoting hypercoagulation. The coagulation profile of plasma and its likely effect on hemostatic balance should be a factor in clinical decisions about the therapeutic use of convalescent plasma. However, the low rate of thrombotic and thromboembolic events provides strong support of the safety profile of convalescent plasma, even among hospitalized patients with severe COVID-19.

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Coronary Artery Calcium Scores I

To The Editor: I applaud Drs Orringer and Maki[1] for their recent article in the August 2020 issue of *Mayo Clinic Proceedings*. It provides an excellent summary of the relevant literature for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in the current era of medicine. Overall, it provides a practical guide for clinicians that is based on the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol (2018 Guideline) but provides further guidance on incorporation of coronary artery calcium (CAC) scores to more accurately determine ASCVD risk for individual patients. Although guidelines are valuable, patient care should be individualized, and incorporating CAC for individualized risk stratification can be very valuable.

Although the article overall is very well written, the section on how to manage patients with CAC between 1 and 99 scores could be further elucidated. For patients with CAC scores of zero and those with CAC scores >100, there is fairly universal agreement on management (without statin and with statin therapy, respectively); however, the middle group of patients with CAC 1 to 99 scores is the quandary. As written, the article simply leaves patients in this group to clinician–patient discussion but without details on how to guide this discussion. I suggest taking the authors' algorithm one step further.

The CAC score can be used as an input for a revised or individualized 10-year ASCVD risk estimate, most notably by using The Multi-Ethnic Study of Atherosclerosis (MESA) calculator.[2] Similar to the rest of the authors' algorithm, by incorporating the CAC score into the MESA calculator, clinicians can determine a risk score that is individualized for each patient. Clinicians can use this revised and more accurate risk estimate in a similar manner to the pooled cohort calculator from the 2018 Guideline (eg, recommend statin if 10-year risk of ASCVD is >7.5%, suggest only therapeutic lifestyle changes if risk is <5%, with an acknowledgment that there is some benefit to statins, but the benefit is sufficiently small that treatment can be deferred). The management of patients who have revised 10-year risks between 5% and 7.5%, unfortunately, remains unclear, and this should be left to clinician–patient discussion, as originally stated in the article. But at least for patients with revised risk estimates <5% or >7.5%, the guidance for clinicians and to patients can be clearer. And even for the patients with risks between 5% and 7.5%, there is at least a quantifiable risk that can be used as part of shared decision making rather than simply using the CAC score, which is too abstract to help patients understand their conditions.

I express my gratitude to the authors and editors for their contribution to the medical literature, and I hope they find my additional personalization of the proposed algorithm as proper and valuable.

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