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.

pulmonary embolism than patients with HPAC. Clinicians using HPAC are less likely to consider CT chest scans for a diagnosis of pulmonary embolism because the patient was already on HPAC. The authors may clarify this issue by reporting the number of CT scans performed for both groups. The practice of anticoagulation is highly variable and dynamic. We documented this practice and this practice's impact on clinical outcome.[2] Tacquard et al[1] divided data into five time points and captured only the first or last timeframe to define groups (UPAC or HPAC). They did not include data from the middle timeframes in their study, which might have affected results. Moreover, cumulative doses would likely be higher for the UPAC group because they started earlier, while cumulative doses for HPAC would be lower because they started later. Therefore, thrombotic complications may not be accurate and possibly overestimated in UPAC group.

Bleeding complications may have been under estimated because the follow-up time to detect bleeding complications was truly short; for 38% of the sample, bleeding complications dates were not available. The number and nature of bleeding complications, if available, can improve our understanding of the issue.

In fact, high thrombotic complications in the UPAC group in their study may be a result of higher severity of illness, prolonged mechanical ventilation (extended use of sedatives and muscular paralytics), higher usage of continuous renal replacement therapy, and extracorporeal membrane oxygenation. Adjustment for all confounding factors by appropriate statistical modeling would allow a true estimate of thrombotic complications.

Global improvement in the provision of ICU beds, ventilators, and society guidelines occurred at approximately the last week of March 2020. Subsequently patients might have received better care in terms of location and trained staff. This could improve the occurrence of thrombotic complications in the HPAC group. We have observed that continuous renal replacement therapy circuits clot more often when care is provided outside the ICU by staff who are not trained for critical care.

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Response

To the Editor:

We thank Nadeem et al for taking interest in our study that reports the benefit of high-dose prophylactic anticoagulation (HPA) on thrombotic complications in critically ill patients with COVID-19.[1]

Nadeem et al hypothesized that patients treated with standard thromboprophylaxis were more severe and had more chest scans, thus more thrombotic complications. This possibility calls for several comments: (1) To evaluate the effect of cumulative individual exposure specifically to HPA on thrombotic complications, we used an original method based on a dedicated time-varying exposure model. Cumulative individual exposure was used as a surrogate for "time within the therapeutic range" and allowed a more appropriate evaluation of the anticoagulation regimen, exposed to frequent changes of doses in ICU. (2) According to the Groupe d'Intérêt en Hémostase Périopératoire guidance document,[2] the anticoagulant dose increased with the severity of COVID-19 pneumonia. (3) The benefit of HPA on thrombotic complications remained significant after adjustment for severity markers that included SOFA score, Pao_2/Fio_2 ratio, renal replacement therapy, and extracorporeal membrane oxygenation status. In our study, renal replacement therapy was performed in the ICU with trained staff, and renal replacement therapy filter clotting was recorded as an event only when it appeared unusual to experienced physicians.

We agree with Nadeem et al that we may have underestimated the complications of bleeding, and this point is addressed in the discussion.

The current challenge is to identify accurately the patients who are at particularly high thrombotic risk who could benefit from HPA and then determine when

the period of high thrombotic risk ends to prevent bleeding events by switching to standard thromboprophylaxis. Biomarkers may play a crucial role to monitor this biphasic progression; during the initial inflammatory phase, when thrombotic complications are reported, prothrombotic and inflammatory markers (which include D-dimers, fibrin monomers, fibrinogen, CRP, and IL-6) reach very high levels.[2,3] After a few days in the ICU, they gradually decrease, along with the inflammatory syndrome and with a potential increase in bleeding risk. To identify this shift between thrombotic risk and hemorrhagic risk, we need to monitor a set of biomarkers that reflect the evolution of thromboinflammation. Patient profile, disease progression, and biomarkers could be combined to modulate thromboprophylaxis strategy to capture the complex interaction between thrombotic and bleeding risks.

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