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Persistent endotheliopathy in the pathogenesis of long COVID syndrome - Reply to comment from von Meijenfeldt et al.

We are grateful for the comments and the interesting additional novel data presented by von Meijenfeldt et al.[1] These findings provide further evidence that sustained endotheliopathy and coagulopathy are both common in patients following acute COVID-19.[2–5] The longitudinal data presented provide additional insights into the duration of specific aspects of COVID-19–induced hemostatic dysfunction. Previous studies have reported elevated D-dimer levels in 25% of patients in the first few months after SARS-CoV-2 infection.[2,5] Notwithstanding differences in patient cohorts and study design, von Meijenfeldt et al. show that these elevated D-dimer levels after acute COVID appear to normalize by 4 months.[1] Given that convalescent COVID-19 patients commonly present with respiratory symptoms, this observation has important clinical implications with respect to the utility of D-dimer testing in pulmonary embolism testing algorithms.

Dysfunction of the VWF-ADAMTS13 axis has been consistently reported in patients with acute COVID-19[6-8] and postulated to play a role in the pathogenesis of the disseminated pulmonary microvascular thrombosis that constitutes a hallmark of the condition. Interestingly, recent studies have also reported that elevated plasma von Willebrand factor:antigen (VWF:Ag), VWF propeptide, and factor VIII:coagulant (FVIII:C) are also common in convalescent SARS-CoV-2 patients.[3,4] Based upon the data of von Meijenfeldt et al.,[1] it appears that increases in circulating VWF-FVIII levels persist for longer than elevated D-dimers following COVID-19. Nonetheless, VWF and FVIII levels (and thus by inference endothelial cell activation) have returned to normal by 12 months after acute COVID-19.[1] Consistent with the time course in plasma FVIII:C levels, endogenous thrombin potential remained significantly elevated at 8 months but had normalized by 12 months following hospital discharge. In contrast, however, plasminogen activator inhibitor type 1 levels remained significantly increased even after 12 months. Together with our previous findings,[4] the data of von Meijenfeldt et al[1] therefore demonstrate that (1) sustained endotheliopathy, coagulopathy and alterations in fibrinolysis are common in convalescent COVID-19 patients and (2) the time course for normalization varies between different aspects of hemostatic dysfunction. Further studies will be required to define the biological mechanisms underpinning these observations and their relative clinical importance. Importantly however, the ongoing hemostatic dysfunction seen in these patients occurs independently of any ongoing acute phase response.[2] This finding is consistent with the intriguing observation that persistent coagulation abnormalities are not only seen in patients who experienced severe COVID-19 (requiring hospital and/or intensive care unit admission), but rather are also present in some individuals who had mild COVID-19 managed exclusively as an outpatient.[2,4]

The key question posed by our collective data is whether persistent hemostatic dysfunction following COVID-19 is contributing to post-acute sequelae of SARS-CoV-2 infection (PASC or long COVID syndrome).[9] In our study, we observed weak associations between 6-min walk test distance and both VWF:Ag and VWF propeptide levels at a median of 68 days after acute COVID-19.[4] In contrast, using the subjective Sheehan disability scale to assess functional impairment, von Meijenfeldt et al. found no relationship with any hemostatic biomarkers at either 8 or 12 months after discharge.[1] The differences in these results may be attributable to a variety of potential confounders. In particular, both studies included a relatively small number of patients ($n = 50$ and $n = 44$, respectively), and long COVID symptomatology was assessed using a combination of objective and subjective protocols performed at varying time points following discharge. Moreover, there were also differences between the study cohorts with respect to initial COVID-19 severity; patient comorbidities including obesity; and differences in patient management during acute COVID-19 (including anticoagulant therapy intensity). Finally, accumulating recent data have highlighted significant phenotypic heterogeneity amongst patients with long COVID syndrome.[9,10] In this context, it is clear that much larger stratified prospective studies that include state-of-the-art imaging will be essential to defining any relationship and/or any potential causality between PASC and persistent hemostatic dysfunction. Given the huge morbidity associated with long COVID, coupled with the limited understanding of the underlying disease pathogenesis, such studies are required as a matter of urgency.

CONFLICT OF INTEREST

James S. O'Donnell has served on the speaker's bureau for Baxter, Bayer, Novo Nordisk, Sobi, Boehringer Ingelheim, Leo Pharma, Takeda, and Octapharma. He has also served on the advisory boards of Baxter, Sobi, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, Takeda, and Pfizer. He has also received

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AUTHOR CONTRIBUTIONS

All authors contributed to literature review, final draft writing and critical revision. All the authors have participated sufficiently in this work, take public responsibility for the content, and have made substantial contributions.

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