Correspondence

Re The source of elevated plasma D-dimer levels in COVID-19 infection

Dear Sir,

Markedly elevated D-dimer levels are seen in severe COVID-19 infection and have been related to a poor prognosis. D-dimers are elevated alongside other acute inflammatory plasma markers such as fibrinogen, C-reactive protein (CRP) and serum ferritin. The elevation of plasma D-dimers has been taken to indicate there is a coagulopathy, and the assumption has been made that the increased fibrinolysis is secondary (due to thrombin generation), indeed an indication of disseminated intravascular coagulation (DIC). However frank DIC seems unlikely as these patients do not fulfil the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC and there is hardly consumption of coagulation factors and physiological anticoagulants; indeed fibrinogen levels are very elevated. 1-4

We propose an alternative hypothesis: we suggest that the origin of D-dimers is a direct consequence of the acute lung injury seen in COVID-19 pneumonia. For one, the hallmark of acute lung injury is intra-alveolar fibrin deposition. The levels of fibrin are controlled by alveolar epithelial cells which produce urokinase and regulate extravascular proteolysis by regulating expression of urokinase-type plasminogen activator (uPA), its receptor uPAR, and plasminogen activator inhibitor-1 (PAI-1) at post-transcriptional levels. Urokinase...

Keywords: Monoclonal Gammopathy of Undetermined Significance (MGUS), COVID 19, coronavirus

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COVID-19 infection has many clinical and histological similarities to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV), Gralinski et al. have shown in a mouse model of SARS-CoV a critical role for the urokinase pathway in regulating severe end-stage lung disease outcomes following SARS-CoV infection. They showed that the larger the dose of SARS the more severe was the clinical manifestation and greater the rise in lung urokinase expression. Lastly, another marker of COVID-19 pneumonia is the presence of many macrophages within the lung tissue. Macrophages are well known to generate plasmin and metalloproteinases (MMPs), but they have also been described to produce fibrinolysis by an alternative pathway—fibrin and fibrinogen bind to CD11b/CD16 (also known as Mac-1) and are internalised into lysosomes where cathepsin D can degrade fibrin and fibrinogen independently of plasmin.°

Based on the above evidence we suggest it is logical to consider that D-dimer levels, like those of other acute-phase proteins such as CRP, ferritin and fibrinogen, which are similarly very high in severe COVID-19 infections, represent the degree of lung inflammation present within the lungs in COVID-19 infection. Being related to the extent of lung inflammation would therefore explain why their plasma levels relate to clinical outcome.

Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

Prevalence of venous thromboembolism in critically ill patients with COVID-19

COVID-19, the disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in January 2020. It has become apparent that coagulopathy is a hallmark of the disease. Additionally, thrombotic complications, including venous thromboembolism (VTE), have been reported to occur in 27–69% of critically ill patients with SARS-CoV-2. As a result of these reports and other anecdotal evidence, many critically ill patients are receiving empiric therapeutic anti-coagulation. Yet, experts generally recommend against the use of therapeutic anti-coagulation prior to the development of VTE or another clinical indication.

In order to further our understanding of VTE in COVID-19, we evaluated its prevalence as diagnosed through usual care in patients admitted to our intensive care unit (ICU).

We also sought to determine the association between a diagnosis of VTE and clinical outcomes. We describe the clinical characteristics of our critically ill patients, frequency of VTE diagnosis, and potential clinical and laboratory predictors of a VTE diagnosis. Last, we performed a multivariate analysis to investigate the association between presence of a VTE diagnosis and mortality.

Patients and methods

We performed a retrospective cohort study of critically ill patients with laboratory-confirmed COVID-19 admitted to an academic medical centre in Colorado. We included adult patients (age ≥18 years old) who received ICU care. The Colorado Multiple Institutional Review Board approved the study.

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