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Pulmonary Intravascular Coagulopathy Infectious Origin in the Alveolar Cavity.

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We thank Brondani et al[1], Reines et al[2], and Suri[3] for their letters on our perspective on the novel SARS-CoC-2 coronavirus with diffuse alveolar centred inflammation triggering immunothrombosis in the lung microvasculature [4]. Brondani et al [1] posit the role of SARS-CoV2 infection of ACE2 expressing endothelial cells in driving this immunothrombosis, as well as other systemic COVID-19 manifestations including cardiac, neurological and occasional cutaneous features. It is worth noting that other lung viral infections including SARS resulted in a similarly high degree of pulmonary intravascular coagulopathy (PIC). Since compelling evidence of cardiac endothelial damage is lacking, we favour the PIC model particularly as thrombosis is predominantly observed within the lungs. Nevertheless, ACE2 expression on endothelial cells, detection of SARS-CoV2 in endothelium by the electron microscope, juxtaposition of infected alveoli and reported circulatory viral RNAaemia support the importance of endothelium in PIC. Brondani et al further highlight the pivotal role of endothelium in experimental murine influenza, and that use of a sphingosine-1-phosphate ($S1P_1$) agonist improved survival. However we can point to other influenza murine models where similar therapies worsened survival[6]. We also note the comments on NETosis and pulmonary vasculature megakaryocytes as potential contributors to pulmonary thrombosis. These may indeed be important factors, but do not detract from our central PIC concept driven by initial ACE2+ expressing type pneumocyte SARS-CoV2 infection.

Reines et al [2] argue for a new conceptual framework to understand COVID-19 disease and believe that the use of the terminology of "diffuse" is incorrect. We used this term to reflect the extensive and widespread lung involvement typically seen in severe COVID-19 cases. Given the larger surface area of the lungs, together with the close juxtaposition of endothelium to pneumocytes, then a vast territory for triggering immunothrombosis exists. We acknowledge that other pathological factors including type 2 pneumocyte and surfactant

biology may contribute to the disease pathophysiology, but that was beyond the remit of our viewpoint which was to highlight how a PIC with consequent secondary pulmonary hypertension accounts for mortality in certain groups. As indicated in our article and previous publications[7], it seems highly likely that multiple mechanisms contribute to the PIC which clearly diverges from the classical MAS pattern typically observed in Rheumatology practice.

Dr Suri [3] pointed out that critical covid-19 patients may be actually developing a catastrophic antiphospholipid antibody syndrome (CAPS) and that antiphospholipid antibodies (APA) should be checked towards improving the management of these patients. In a cohort of 56 patients, 25 cases (45%) were reported to be positive for lupus anticoagulant[8]. Crucially however, it is not known at this stage whether these APA are transient or persistent in nature, nor whether they play any pathological role in the development of thrombi within the lung microvasculature. Pending the results of further studies to address these key questions, we consider it premature to implicate CAPS in the aetiology underpinning PIC in severe COVID-19.

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