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.

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Letter to the Editors-in-Chief

In situ immune-mediated pulmonary artery thrombosis and Covid-19 pneumonitis

To the Editor:

Covid-19 appears to be a thrombogenic state and we read with interest the retrospective review of single-centre data presented by Whyte and colleagues [1]. Their findings demonstrated that in patients with Covid-19 and a clinical suspicion for pulmonary embolus (PE), more than one-third of computed tomography pulmonary angiogram (CTPA) studies were found positive for PE compared to the yield of inpatient CTPA prior to the pandemic at 12 to 17%. The authors state there remains debate as to whether PE seen in Covid-19 represents true 'thrombus embolisation' or localised 'immunothrombosis'. We also congratulate van Dam et al. on their case series of 23 patients [2] which suggested that PE in Covid-19 patients was more likely to be located in the peripheral opacitated lung segments, suggesting local clot formation.

We would like to share our experience which lends weight to the growing concept of in situ pulmonary artery thrombosis (PAT). We conducted an observational cohort study of 15 Covid-19 patients diagnosed with PAT following CTPA [3]. Overriding symptoms in 12 out of 15 patients (80%) were non-resolving fever and dyspnoea for at least 7 days prior to hospitalisation. 7 (47%) required continuous positive airway pressure and 2 (13%) were intubated. All patients had significantly raised D-dimer level (range 2188–60,700 ng/mL [normal 270-750 ng/mL]), lactate dehydrogenase, C-reactive protein, ferritin and prothrombin time. Distribution of thrombosis correlated with pattern of consolidation observed on CTPA in 9 (60%) patients, the majority being peripheral or subsegmental ($N = 14$, 93%) and only 1 central artery occlusion. None of the patients had clinical evidence of deep vein thrombosis.

The diagnosis of PAT in this population appeared to depend reliably on clinical history (protracted course of non-resolving respiratory symptoms, presence of pleuritic chest pain and haemoptysis), persistent oxygen requirements disproportionate to the severity of pneumonia, non-resolving type 1 respiratory failure (T1RF) despite mechanical ventilation, deranged prothrombin time and significantly raised D-dimer level.

In situ immune-mediated pulmonary thrombosis within the context of Covid-19 is a preferred nomenclature and this is clearly a contributory factor to the pathogenesis of T1RF which often requires respiratory support. The correlation of sites of thrombosis with areas of pulmonary consolidation or infiltration suggests a reciprocal association between clot development and underlying anatomically localised infective or inflammatory processes. Notably, the pattern of prothrombotic coagulopathy in Covid-19 departs from that seen in sepsis where thrombocytopenia is common and from disseminated intravascular coagulation where deranged clotting times are accompanied by a haemorrhagic tendency [4].

Although the procoagulant mechanisms of Covid-19 have not been fully characterised, an important factor may be enhanced expression of angiotensin 2 (Ang 2) as a result of viral-angiotensin converting enzyme 2 binding. Ang 2 is thought to have a pathological role in the development of cytokine release syndrome or 'storm' through dysregulation of the renin-angiotensin-aldosterone system, with IL-6 as the key pro-inflammatory and pro-thrombotic cytokine [5]. Inflammation induced alveolar injury and hypoxaemia can also trigger a vascular endothelial response that augments thrombus formation [6].

In conclusion, emerging evidence appears to endorse the hypothesis that PAT originates in situ, and the threshold for CTPA should be low in the face of clinical deterioration and/or ongoing oxygen requirement. As Whyte et al. observed, Wells' scoring which is validated for classic PE [7] as part of venous thromboembolic disease, importantly, does not seem to determine pre-test probability in Covid-19 patients. Conventional thromboprophylaxis dosing regimens may be inadequate; hence the emergence of multiple local hospital guidelines based on best practice and scientific rationale advocating dose adjustments according to weight, clinical severity of disease and variably the D-dimer level. However, at the time of writing, as the evidence base grows, there seems an urgency for an international consensus on enhanced prophylaxis in Covid-19 patients.

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Declaration of competing interest

No potential conflict of interest was reported by the authors.

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