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.

anticoagulation may be inadequate because the thrombotic process is likely to have spiralled and more aggressive and multimodal therapeutic approaches may be required for a good outcome. In the post-COVID era, hypoxia should be considered as an additional risk factor in all patients who require hospitalization for cardiorespiratory illnesses; especially those who require respiratory support in critical care units. In these patients, hypoxia should also be considered as a mechanism for heparin resistance.

CONFLICTS OF INTEREST

None.

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Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis: Response from original authors Pola et al

Dear Editor,

We thank Dr Thachil for his interesting comment regarding our article.[1] Indeed, we agree that the precise contribution of various risk factors to the development of venous thromboembolism (VTE) in COVID-19 patients remains to be fully elucidated. In this context, it is possible that hypoxia, either prior or during hospitalization, might also have a role in the development of thrombosis. In our study, non–intensive care unit subjects with deep vein thrombosis (DVT) more frequently required oxygen supplementation (100.0% versus 83.7%) and high-flow nasal oxygen therapy or non-invasive ventilation (NIV; 60.0% versus 8.1%) compared to those who had no DVT.[2] Based on the considerations of Dr Thachil, we have reanalyzed the dataset of our study, finding that the need for oxygen supplementation at the moment of the admission to the hospital also was relatively more frequent among those subjects who were subsequently found to have DVT, compared to those who were not (70.0% versus 42.2%). However, it is also likely that the general clinical conditions of the patients that had severe respiratory insufficiency were more critical than those of the other patients, or that their immobilization lasted for a longer period of time, or that additional unappreciated concomitant factors were present, and this makes it difficult to

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determine whether hypoxia per se was an independent and clinically relevant risk factor for thrombosis. We believe that this issue deserves further investigation and that future studies on thrombosis in COVID-19 patients should be designed to assess the independent contribution of hypoxia to the development of thrombosis.

CONFLICTS OF INTEREST

The authors of this article (Angelo Porfidia, Angelo Santoliquido, Giulia Cammá, Enrica Porceddu and Roberto Pola) have no conflicts of interest to disclose.

KEYWORDS

COVID-19, hypoxia, respiratory insufficiency, risk factors, thrombosis

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Response to Maccio et al, "Multifactorial pathogenesis of COVID-19-related coagulopathy: Can defibrotide have a role in the early phases of coagulation disorders?"

We read with interest the letter by Maccio et al, which postulates a role for defibrotide (DF) in the treatment of coagulation disorders observed in COVID-19.[1] Their commentary effectively explores the contribution of macrophages toward the coagulopathy observed in COVID-19, while highlighting the similarities between COVID-19–associated vascular lesions and veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS) and commonly referred to as VOD/SOS. DF has indeed been shown to improve overall survival in patients with severe VOD/SOS[2] and may be beneficial in the treatment of COVID-19, but not exclusively because of the observed similarities to VOD/SOS.

In detailing the role of macrophages in COVID-19–related coagulopathy, the letter overlooks some other etiologies. While macrophages may drive endothelial dysfunction by production of reactive oxygen species (ROS) and pro-inflammatory cytokines, the endotheliopathy observed in COVID-19 may also be driven by direct infection of endothelial cells by SARS-CoV-2.[3]

Angiotensin converting enzyme 2 (ACE2) receptors mediate the entry of SARS-CoV-2 into the cell, via direct interaction between ACE2 and primed viral spike proteins. ACE2 is expressed abundantly on lung alveolar epithelial cells and enterocytes of the small intestine but is also present in arterial and venous endothelial cells, pericytes, and vascular smooth muscle cells across numerous organ systems.[4] Direct infection and apoptotic death of endothelial cells by SARS-CoV-2 has been demonstrated across vascular beds of several organs via post mortem histology.[3]

The p38 mitogen-activated protein kinase (MAPK) pathway may be a critical factor in COVID-19–related endotheliopathy. Similar to other respiratory RNA viruses, SARS-CoV-2 infection induces upregulation of p38 MAPK, perhaps enhancing viral replication.[5] More notably, however, the entry mechanism of SARS-CoV-2 disables a key homeostatic process employed by the cell to diminish p38 MAPK

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