COVID-19 associated thromboembolism: causing the respiratory failure

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ABSTRACT
Coronavirus disease 2019 (COVID-19) has recently emerged in China and caused a global pandemic. WHO announced that COVID-19 could be characterised as a pandemic due to unprecedented swift global spread and severity of the outbreak. When infected with the virus, patients usually have a fever, dry cough, dyspnoea, myalgia, headache and sometimes diarrhoea. Updates on molecular characteristics of SARS-CoV-2, treatment and epidemiological control are more important to help optimise the disease control measures. Thrombotic complication is an essential issue in patients infected with COVID-19. Concomitant venous thromboembolism (VTE) seems to be a potential cause of unexplained deaths in COVID-19 cases. Thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation are the clinical findings related to such condition. In China, anticoagulant therapy in severe COVID-19 was suggested for improving outcome. Studies showed the urgency for VTE diagnostic strategies. Aetiology may be multifactorial, and therefore, we review the available literature relevant to acute venous thromboembolism associated with novel coronavirus infection.

INTRODUCTION
Since December 2019, the third zoonotic coronavirus breakout causes human to human transmission resulting in novel severe acute respiratory syndrome coronavirus 2. Started from Wuhan, China, this pathogen has become the centre of global attention, due to the rapid spread worldwide (Gorbalenya et al., 2020). Cardiovascular disease, hypertension and diabetes mellitus are the most common underlying diseases in adult patients, with males more severely affected than females (Lai et al., 2020; Giannis et al., 2020). This novel virus is related to the SARS virus and has the potential to develop the severe respiratory syndrome. Initially, the Spike protein(S-protein) of SARS-CoV-2 binds with angiotensin-converting enzyme 2 (ACE2). Furin-like cleavage site in the S-protein causes enhancing viral fusion with host cell membranes. This COVID-19 has a pro-inflammatory and hypercoagulable state with a marked increase in Lactate Dehydrogenase, Ferritin, C-reactive protein, D-Dimer, and Interleukin levels (Han et al., 2020). A thrombotic complication is an essential concern in COVID-19 patients with elevated D-dimer. Acute infections are even associated with a transiently increased risk of venous thromboembolic condition (Danzi et al., 2020). Association between influenza asso-
ciated pneumonia and thromboembolic events was previously well documented (Ishiguro et al., 2019). The potential relationship between COVID-19 and venous thromboembolic disease should exist in detail, which may aid better treatment during the current pandemic.

**Platelets and complement activation**

Viral infections stimulate the tissue factor (TF) expression on macrophages and enhance the production of interleukins. This inflammatory response causes an imbalance between procoagulant and anticoagulant homeostatic mechanisms, including endothelial dysfunction, toll-like receptor activation, and tissue-factor pathway activation (Key et al., 1990). Once the antigens are well recognised, the white blood cells interact with activated platelets to form a clot. These platelets act as inflammatory mediators and sensors of infectious agents. This activation of the coagulation pathway produces thrombin, and it is resumed as thrombo-inflammation. This coagulation mechanism activation in SARS-Cov-2 infection depends on the intensity of the individual inflammatory reaction (Gris et al., 2020). Histologic and immunohistochemistry studies in COVID-19 patients showed microvascular injury and thrombosis with stimulation of the alternative pathway (AP) and lectin pathway (LP) of complement. These activated pathways induce membrane attack complex-mediated microvascular endothelial cell injury and further activation of the clotting pathway, resulting in fibrin deposition (Gralinski et al., 2018).

**Antioxidant mechanism deprivation**

Production of reactive oxygen species (ROS) in high levels is related to oxidative stress causing cellular damage. Besides, viral infection alters antioxidant mechanism and results in unbalanced oxidative-antioxidant status with oxidative cell damage. Such deprived antioxidant condition involves in the pathogenesis of SARS-CoV infection, progression and finally, the severe respiratory disease (Delgado-Roche and Mesta, 2020). Besides, coronavirus infection when binding to ACE2 on multi-target tissues including lung, kidney, intestine and brain causes increased levels of angiotensin II. This raised angiotensin II also produces ROS interfering with the vasodilatory process with activation of the complement pathway resulting in thrombosis (Magro et al., 2020). Molecular study findings reported that the ROS are involved in the production of transcription factor NF-κB for apoptosis following the oxidative stress. This transcription factor NF-κB in the pro-inflammatory genes promoter region causes the increased levels of transforming growth factor-β (TGF-β), tumour necrosis factor-α (TNF-α) with IL-1α, IL-6 and IL-8 in patients with SARS viral infection (Lin et al., 2006). In severe COVID-19 cases, hypoxia was found, and thrombus formation will be increased under conditions of hypoxia. Further, a hypoxia-inducible transcription factor-dependent signalling pathway will be activated (Gupta et al., 2019).

**Rate of thromboembolic complications**

In severe cases of COVID-19, occlusion and micro thrombosis formation in small pulmonary vessels were reported (Luo et al., 2020). Increased D-dimer levels were observed in non-survivors. A case report from Milan hospital, Italy showed that out of 388 patients, Thromboembolic events occurred in 21%, and VTE was confirmed in 36% (Lodigiani et al., 2020). Another case series of three patients admitted to Northwell Plainview Hospital in Plainview, New York, with COVID-19 was documented with arterial vascular complications (Griffin et al., 2020). From a total of 184 patients, VTE was confirmed in 27% in another observational study. Further case reports on the thromboembolic disease in patients with COVID-19 was observed (Oudkerk et al., 2020; Zhang et al., 2020). However, the prevalence of VTE while screening was 25%, in a Chinese study (Cui et al., 2020).

**Treatment**

In some studies, the administration of low-molecular-weight heparin was recommended for positive effects in the early stage of infection (Tang et al., 2020). Casey et al. (2020), analysed a 42-year-old male covid-19 patient from China. This case study reported segmental PE’s without VTE risk factor in a SARS-CoV-2 infected patient. This study showed and created awareness of the possible association between COVID-19 and PE in a medical emergency. Use of Computerised Tomography Angiography (CTA) was equally recommended (Casey et al., 2020). Buja et al. (2020), collected the pathological findings from autopsy reports of 23 COVID-19 patients and determined that SARS-COV-2 patients have a hypercoagulable state with increased risk for pulmonary thrombotic microangiopathy. They also have a risk of developing deep vein thrombosis and pulmonary thromboembolism. This study support evaluation and management for coagulopathy early in the course of the disease (Buja et al., 2020).

According to guidelines prepared by Bikdeli et al. (2020), for patient care and treatment associated with thrombosis and antithrombotic therapy, COVID-19 may affect patients by venous and arterial thrombosis through excessive inflammation with
platelet activation. Those patients with the thrombotic disease even receiving antithrombotic therapy may develop COVID-19 as a thrombotic disease may be one of precedent factor or incident complications in COVID-19 patients. Patients with these high risk should treat with antithrombotic agents either as preventive or therapeutic (Bikdeli et al., 2020). The Critical Guiding Principles by medical experts from vascular surgery and vascular medicine, University of Michigan Health System (USA), stated that all patients with COVID-19 or suspected COVID-19 should be treated with thromboprophylaxis. Duplex ultrasonography is needed during high bleeding risk, and when pulmonary embolism (PE) is high. Most patients with venous thromboembolism (VTE) either confirmed or suspected, should receive therapeutic doses of anticoagulants, even at low risk of bleeding. Even in acute respiratory disease syndrome (ARDS) cases, low dose non-nomogram heparin infusion may reduce the risk of significant bleeding (Obi et al., 2020).

CONCLUSION

COVID-19 can be associated with thromboembolism with induced inflammatory changes. COVID-19 infected patients across the globe are gradually increasing, and uncertainty regarding the management of COVID-19 and its complications arise in the course of this viral infection. Respiratory failure is the major complication occurs with coagulopathy symptoms with the prominent elevation of D-dimer and fibrin/fibrinogen degradation products. At the same time, abnormalities in prothrombin time, platelet counts are relatively uncommon in initial presentations. Coagulation test screening with D-dimer and fibrinogen levels are suggested.

Conflict of Interest

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