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Review

Thromboembolic complications of COVID-19: the combined effect of a pro-coagulant pattern and an endothelial thrombo-inflammatory syndrome

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Coronavirus disease 2019 (COVID-19) is a newly emerging human infectious disease that has quickly become a worldwide threat to health, mainly causing severe acute respiratory syndrome. In addition to the widely described respiratory syndrome, COVID-19 may cause life-threatening complications directly or indirectly related to this infection. Among these, thrombotic complications have emerged as an important issue in patients with COVID-19 infection, particularly in patients in intensive care units. Thrombotic complications due to COVID-19 are likely to occur due to a pro-coagulant pattern encountered in some of these patients or to a progressive endothelial thrombo-inflammatory syndrome causing microvascular disease. In the present authors' experience, from five different hospitals in Italy and the UK, imaging has proved its utility in identifying these COVID-19-related thrombotic complications, with translational clinical relevance. The aim of this review is to illustrate thromboembolic complications directly or indirectly related to COVID-19 disease. Specifically, this review will show...
Background

Coronavirus disease 2019 (COVID-19) is a newly emerging human infectious disease that has quickly spread worldwide, mainly causing a severe acute respiratory syndrome. In addition to lung disease, COVID-19 may cause a wide spectrum of non-respiratory COVID-19 disease due to involvement of organs by the virus or to complications directly or indirectly related to this infection. Among these, thrombotic complications due to abnormal coagulation status have emerged as an important issue in patients with COVID-19 infection, and may occur in up to 31% of intensive care unit (ICU) COVID-19 patients. Bikdeli et al. suggested some possible causative mechanisms for COVID-19-associated thrombotic disease, including direct effects of COVID-19 through severe illness and hypoxia or severe inflammatory response, or an indirect effect of infection related to investigational therapies used for treating COVID-19, which may have adverse drug–drug interactions with antiplatelet agents and anticoagulants.

Interestingly, some COVID-19 patients have haemostatic abnormalities, including mild thrombocytopenia, increased D-dimer levels, increased clot strength, and hyperfibrinogenaemia, which all indicate a pro-coagulant pattern. Increased levels of D-dimer and fibrin degradation products and prothrombin time prolongation are associated with a higher risk of death in these patients. In addition, anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer.

The pro-coagulant pattern identified in many patients with COVID-19 explains the relatively high rate of thrombotic complications, including pulmonary embolism, deep-vein thrombosis of leg, catheter-related upper extremity thrombosis, renal infarct, and ischaemic stroke, which have also been identified in patients without known prior hypercoagulable conditions and no prior history of atrial fibrillation.

Thrombotic complications due to COVID-19 have also been suggested to occur due to a progressive endothelial thrombo-inflammatory syndrome causing microvascular disease. Some theories have suggested that this endothelial thrombo-inflammatory syndrome may be related to the presence of ACE2, which is the target receptor of COVID-19, in the endothelial cells of many small vessels or to complement–mediated microvascular injury. Varga et al. also recently demonstrated at histopathology endothelial cell involvement across the vascular beds of different organs in a series of patients with COVID-19, including glomerular capillary loops of the kidney, vessels feeding the small bowel in three patients causing mesenteric ischaemia, and lymphocytic endothelitis in the lung, heart, kidney, and liver causing multi-organ failure in one patient. In one of the three reported patients with small bowel mesenteric ischaemia, computed tomography (CT) demonstrated pneumatosis intestinalis of the jejunum and air within the portal vein as signs of mesenteric ischaemia. COVID-19 endothelitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19.

Although evidence regarding the mechanism of thromboembolic complications of COVID-19 is accumulating rapidly, there are few imaging presentation reports of these complications in COVID-19. In the authors’ experience from four different COVID hospitals in Italy, including three centres in the Lombardy region and one in Sicily, and a hospital in the UK, imaging has proved its utility in identifying these COVID-19–related thrombotic complications, with translational clinical relevance.

The aim of this review is to illustrate the direct or indirect thromboembolic effects of COVID-19 disease, including those caused by pro-coagulation thrombosis and endothelial thrombo-inflammatory syndromes.

Pulmonary embolism

Pulmonary embolism has been demonstrated radiologically in up to 30% of patients with COVID-19 on pulmonary CT angiography, and in 14% patients with proven COVID-19 pneumonia admitted to the ICU. Pulmonary emboli detected in COVID-19 patients are located in main pulmonary artery in 22% of the cases, lobar artery in 34%, segmental artery in 28%, and subsegmental artery in 16% (Figs 1 and 2). COVID-19 patients with pulmonary embolism have higher D-dimer levels than those without pulmonary emboli and are more likely to be admitted to the ICU. In case of elevated D-dimer levels on hospital admission or sudden clinical worsening, CT pulmonary angiography should be considered, as pulmonary embolism is a life-threatening, but potentially curable, condition. Interestingly, in patients with COVID-19 infection, D-dimer >2,660 ng/mL had a sensitivity of 100% and a specificity of 67% for predicting the diagnosis of pulmonary embolism. Therefore, in patients that are likely to be admitted to the ICU, CT pulmonary angiography should be performed in addition to unenhanced chest CT on hospital admission, particularly if D-dimer levels are elevated. Indeed, once these patients with severe acute respiratory distress syndrome (ARDS) are admitted to the ICU, CT pulmonary angiography for pulmonary embolism may not be feasible or particularly difficult to perform due to critical illness and prone position. Pulmonary embolism
may cause acute right-sided heart failure leading to increased central venous pressure and potentially passive hepatic congestion with hepatomegaly and nutmeg liver aspect on contrast-enhanced CT (Fig 3).\textsuperscript{19–22} Lung infarction as a complication of pulmonary embolisms is rare due to the double arterial circulation of the lung, but it has been described in COVID-19 patients (Fig 4); if present, it appears on CT as ground-glass opacities in the early phases in unobstructed lung zones representing pulmonary haemorrhage and peripheral wedge-shaped pulmonary consolidation and may rarely show a reverse halo sign or excavation.\textsuperscript{24–26} Therefore, lung infarction from pulmonary embolism needs to be differentiated from ground-glass opacities or consolidations related to COVID-19, also

![Figure 1](image1.png)

**Figure 1** Embolisms of the saddle and main pulmonary arteries in two patients with COVID-19. (a) CT pulmonary angiogram of a 72-year-old woman with D-dimer level >20,000 ng/ml on admission to the emergency department reveals a thrombus (arrow) in the main pulmonary artery at the saddle extending across the origin of both the right and left pulmonary arteries. (b,c) A 72-year-old woman with D-dimer level >2,000 ng/ml: (b) CT pulmonary angiogram on admission shows a pulmonary thrombus (arrow) in the right main pulmonary artery, sub-segmental thrombi in the left, bilateral pleural effusion with atelectasis. (c) CT pulmonary angiogram at 1-week follow-up for clinical worsening shows pulmonary thrombus (arrow) in the left main pulmonary artery, bilateral pleural effusion with atelectasis, and a small clot is also visible in the right pulmonary artery (arrowhead).

![Figure 2](image2.png)

**Figure 2** Embolisms in the lobar, segmental, and subsegmental pulmonary arteries in three COVID-19 patients. (a) CT pulmonary angiogram of a 74-year-old man with D-Dimer level >800 ng/ml on admission reveals thrombus (arrow) in the right lobar pulmonary artery for the inferior lobe. (b,c) A 63-year-old man on day 23 after admission and D-dimer level of 15,862 ng/ml. CT pulmonary angiogram reveals pulmonary thrombus (arrow) in the right segmental pulmonary artery for the basal pyramid, bilateral pleural effusion with atelectasis, consolidations in the posterior segments of the inferior lobes (gravitational segments), and ground-glass opacities in the anterior segments (anti-gravitational segments), consistent with acute respiratory distress syndrome. (d,e) A 79-year-old man on day 1 after admission and D-dimer level of 54,158 ng/ml with pulmonary thrombus (arrow) in the subsegmental pulmonary artery for the postero-basal segment of the left inferior lobe, bilateral pleural effusion with consolidations and pneumothorax on the right side.
considering that these consolidations may show a reverse halo in about 4% of patients, or from cavitation due to pulmonary septic embolism (Fig 5) and from ground-glass opacities related to small vessel thrombosis considering that alveolar capillary microthrombi and pulmonary vascular microangiopathy have been described on autopsy series of COVID-19 patients. The wedge-shaped appearance of the consolidation and the identification of associated pulmonary embolism may be helpful for the differential diagnosis.

Ischaemic stroke

Neurological symptoms manifest in up to 36% of COVID-19 patients, and are more common in patients with severe infection. In a series of 214 COVID-19 patients, acute cerebrovascular disease, which includes ischaemic stroke and cerebral haemorrhage, was demonstrated in 2.8% (6/214) of the patients on head CT. In most cases (83%, 5/6), it was an ischaemic stroke (Fig 6) and occurred in critically ill patients with increased D-dimer levels. These data are...
confirmed by the study of Klok et al.\textsuperscript{5} that reported ischaemic stroke in approximately 2\% (3/184) of ICU patients with proven COVID-19 pneumonia. Recently, Kandemirli et al.\textsuperscript{30} showed that 44\% of ICU COVID-19 patients with neurological symptoms who underwent brain magnetic resonance imaging (MRI) had abnormal findings.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{A 45-year-old man with ischaemic stroke, pulmonary embolism, and COVID-19 infection. (a) CT of the head shows bilateral loss of grey–white matter differentiation, cortical hypodensity with associated parenchymal swelling with resultant mass effect, and compression on the lateral ventricles, findings consistent with ischaemic stroke. (b) CT pulmonary angiogram in the same patient reveals right pulmonary embolism (arrowhead).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{A 51-year-old woman with COVID-19. The patient was admitted after a few weeks of cough and dyspnoea and then subsequently developed ARDS. In addition to lung involvement, the patient developed unilateral foot necrosis with clinical features of peripheral ischaemia. (a) Contrast-enhanced CT in the axial and (b) reconstructed sagittal images showed a medium-density structure resembling a collection with hyperattenuating rims in the adductor hallucis muscle (arrow), slightly decreased small artery opacification, with patent major arteries, gas locules (white arrowhead) around the first distal phalange without osseous destruction. (c) MRI performed 1 day after CT showed on the axial T1-weighted and (d) sagittal T2-weighted spectral presaturation with inversion recovery (SPIR) sequence thickened and oedematous but intact muscular fibres of the adductor hallucis muscle.}
\end{figure}
such as increased cortical diffusion-weighted signal with corresponding low ADC values, subtle leptomeningeal enhancement, and punctate cortical blooming artefact. Although the mechanisms and phenotype of ischaemic stroke in COVID-19 patients are not yet understood, it is usually caused by large-vessel occlusion due to a pro-thrombotic state.

**Acral ischaemia and endothelial thrombo-inflammatory syndrome**

Microvascular injury related to progressive endothelial thrombo-inflammatory syndrome may explain skin manifestations of COVID-19 disease, which include perniosis-like skin lesions, purpuric skin rash, or acro-ischaemia presentations (i.e., finger/toe cyanosis, red-purple papules and dry gangrene). In these patients, CT and MRI can reliably diagnose the location and severity of arterial stenosis or occlusion and may demonstrate collections, abscesses, and oedematous muscular fibres (Fig 7).

**Other thromboembolic events**

COVID-19 has been also associated with cardiac, renal, and gastrointestinal thromboembolic complications. Bhayana et al. described abdominal bowel wall abnormalities, such as large or small bowel thickening, pneumatosis, or portal vein gas or perforation (Fig 8), in approximately 42% of COVID-19 patients who underwent abdominal CT, and bowel ischaemia or necrosis was demonstrated in some of the patients who underwent surgery. In addition, acute infarct in abdominal solid organs was demonstrated in 4.8% of patients. Cardiac manifestations due to COVID-19 are usually delayed from the onset of symptoms, and include acute ischaemic stroke, myocardial injury, and cardiogenic shock. Other thromboembolic complications in COVID-19 include catheter-related deep vein thrombosis and disseminated intravascular coagulation.

**Conclusions**

To conclude, the rate of thromboembolic complications in COVID-19 patients is relatively high. The likely mechanism includes a pro-coagulant pattern and an endothelial thrombo-inflammatory syndrome, which may result in multisystemic thrombotic disease. Therefore, in addition to the widely described role of imaging for assessment of COVID-19 pneumonia, CT may be useful for identification of thromboembolic complications, such as pulmonary embolism, ischaemic stroke, mesenteric ischaemia, and acro-ischaemia. Specifically, in patients with elevated D-dimer levels and those likely to be admitted to the ICU, pulmonary CT angiography should be considered for suspicion of pulmonary embolism in addition to chest CT.

**Conflict of interest**

The authors declare no conflict of interest.

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