

Gastrointestinal and thromboembolic manifestations in COVID-19 Patients: An imaging review

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Abstract

While coronavirus disease 2019 (COVID-19) predominantly involves the respiratory system, it is increasingly recognized that the infection is not restricted to pulmonary system only but other organs are also affected to varying degrees of severity. Gastrointestinal, neurological and cardiac manifestations are reported in addition to dysfunction of hepatic, renal, hematological systems. The wide range of clinical presentations involving multiple organ systems necessitate investigating the causal and association factors of COVID-19 infection. Prompt recognition of the symptoms is necessary for selection of appropriate diagnostic methods and confirmatory tests to reduce delay in initiating the therapy. This manuscript aims to review the spectrum of clinical and imaging aspects of gastrointestinal and thrombo embolic manifestations of COVID-19.

Keywords: coronavirus; COVID-19; SARS-CoV-2; gastrointestinal manifestations; thromboembolism

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Key message

A broad spectrum of clinical presentations of COVID-19 patients is due to involvement of gastrointestinal system, central nervous system, hepato-renal and musculoskeletal systems in addition to the more extensively known pulmonary infection by the virus. The radiological imaging features indicate the etiopathogenesis of COVID-19 infection. Abdominal cross sectional imaging of intensive care patients often reveals bowel ischemia, gall bladder pathology and vascular occlusions. Pulmonary embolism is another fatal hypercoagulable condition requiring immediate recognition. In addition, cardiac arrhythmia, myocarditis, acute coronary syndromes, hepatocellular injury, hyperglycemia and ketosis are also reported. Isolated non pulmonary clinical presentation should be considered in the diagnostic work up of these patients. Abdominal imaging for

other indications should include the lower chest also to look for evidence of COVID-19 infection.

Introduction

The Ministry of Health and Family Welfare, Government of India confirmed a total of 849,553 cases, 534,620 recoveries and 22,674 deaths in the country due to corona virus disease 2019 (COVID-19) pandemic at the time of submission of this manuscript. The corona virus 2 (novel corona virus-2019; COVID-19; SARS-CoV-2) is a genetic consequence of the original SARS-CoV which spread to 29 countries in the years 2002—2004 with an epidemic leaving more than 700 dead [1, 2]. The highly contagious COVID-19 virus was first reported in China spreading rapidly to more than 160 countries. It is increasingly recognised that the respiratory system is not the only target to the virus, but it is a multi system disease because of its affinity for angiotensin converting enzyme 2 (ACE2) receptors resulting in cytokine-mediated immune response and inflammation. The receptors are present in the gastrointestinal system, hepatocytes, vascular endothelial cells, gall bladder, brain, heart and kidneys increasing their vulnerability to infection. Single cell RNA-sequencing demonstrated the organs at risk, such as lung, heart, esophagus, kidney, bladder, and ileum [3]. Decreased immune status because of underlying comorbid factors such as chronic pulmonary disease, diabetes, hypertension, altered renal function triggers the disease manifesting in non pulmonary symptoms of COVID-19 [4, 5].

Extra pulmonary symptoms include headaches, syncope, seizures, confusion, fatigue, myalgia, diarrhea, vomiting, chest pain, acute cardiovascular events, abdominal pain, elevated liver enzymes and acute kidney injury [6]. Hematological involvement manifests as thromboembolic phenomena. These COVID-19 clinical presentations with variable radiologic findings need a broad range of radiologic imaging strategies and this article attempts to present an overview of the atypical imaging spectrum in gastrointestinal and thrombo embolic manifestations of COVID-19.

Gastrointestinal manifestations & imaging

Some patients with COVID-19 infection may experience gastrointestinal symptoms such as abdominal pain, vomiting and diarrhea and a

few showing severe acute respiratory syndrome coronavirus (SARS-CoV-2) RNA in the fecal matter. Systematic review and meta-analysis of the current research demonstrated that digestive tract is definitely involved in a significant percentage of patients with COVID-19. Of the 2256 studies from USA, South Korea, Singapore and China, initially generated in the literature search, 37 studies were eligible for inclusion in the meta-analysis. The prevalence rates of diarrhea, nausea/vomiting, and abdominal discomfort/pain were ranging from 6.6 to 9 % with almost similar prevalence in children. SARS-CoV-2 RNA was detected in feces by reverse-transcriptase polymerase-chain-reaction (RT-PCR) in 30 % of these patients though positive RT-PCR in the stool specimen was detected in some asymptomatic patients. The meta-analysis revealed higher prevalence of gastrointestinal (GI) symptoms in patients with severe disease than in those with less severe disease indicating the need for closer monitoring [7, 8].

GI tract involvement as a potential route of transmission is explained by the expression of large amount of ACE2 surface expression in the enterocytes of small and large intestines and the receptor-binding domain on COVID-2 binding to ACE2 with strong affinity [9-11]. Fever, cough and breathlessness are the most recognised and expected symptoms of COVID-19 patients. Those presenting with atypical symptoms may go untested since they do not have the well known respiratory symptoms. It has been also reported that patients undergoing imaging for some other reason may demonstrate lung changes on CT scanning as the first indicators of COVID-19, preceding the illness. Timely recognition of imaging features and treatment of patients with atypical clinical presentations prevents the spread [12, 13]. There is very little published literature on abdominal imaging in COVID-19. In a single centre study of largest number of 224 patients who tested positive for severe COVID-19 disease, abdominal imaging studies were performed (Ultrasound=44, CT=42, MRI=1, radiography=137). Most of these patients who had cross sectional imaging presented with abdominal pain (33%) and sepsis (29%). Also, Nausea / Vomiting, diarrhea, GI bleed, suspected intestinal ischemia were observed as presenting features. Right upper quadrant ultrasound was most commonly performed and majority were admitted in ICU (84%). Elevated LFT, acute kidney injury and source of infection as evidenced by

laboratory findings were considered indications for ultrasonography in these patients. Source of infection was noted in 29 % [14].

In this study frank bowel infarction and ischemic mucosal necrosis were observed at laparotomy in two patients each (Table 1).

Table 1: CT (plain and contrast enhanced) features of abdomen in COVID-19 in 42 patients.

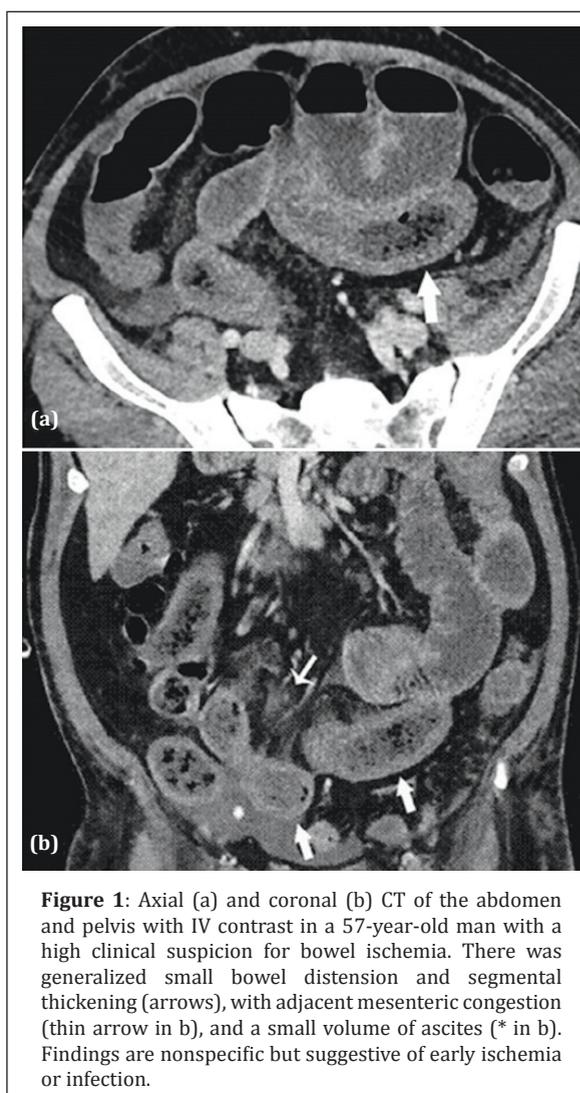
Bowel wall thickening	12
Colon / rectal thickening	7
Small bowel wall thickening	5
Pneumatosis or portal venous gas	4
Pneumatosis cystoides intestinalis	1
Perforation of small bowel	1

Direct viral infection, small vessel thrombosis, or nonocclusive mesenteric ischemia are possible explanations for the bowel involvement. Systemic coagulopathy is common in critically ill patients which supports the mechanism of complement associated microvascular injury and fibrin thrombi causing ischemic necrosis of the bowel. It has been reported that vascular endothelium may be directly affected by inflammation [15]. Submucosal edema, pneumatosis and arterioles with fibrin thrombi beneath the damaged mucosa were noted at histopathology [16]. Four patients, all in the ICU were detected to have cholestasis on ultrasonography which revealed negative bacterial culture. Interestingly radiograph or ultrasound in this study recognized three of the four patients with pneumatosis or portal venous gas though sensitivity on radiography or ultrasonography is low. The study did not identify portal venous thrombosis despite the hypercoagulable state of these patients (Figures 1-5).

Pulmonary embolism

Recent literature indicates significant prevalence of pulmonary embolism in COVID-19 patients compromising the pulmonary function which is already diminished significantly. Many of these patients are severely ill and have acute kidney injury and multi-organ failure. Clinical reports and recent European cohort studies are published on pulmonary embolism correlating the increased serum proteins such as D-dimer and increased mortality. D-dimer values showed a statistically significant difference

between CT pulmonary angiography (CTPA) positive and CTPA negative subgroups indicating the severity of pulmonary obstruction. In a cohort study, CTPA is indicated for the patients who are in respiratory distress, tachycardia, elevated D-Dimer, lower extremity swelling, hypoxia, chest pain and unspecified indications. The sensitivity and specificity of CTPA positive result depend on the threshold value of the D-dimer, a clear indicator of hypercoagulable state. Other laboratory values of platelet counts, serum ferritin, C-reactive protein, fibrinogen did not correlate with CTPA results statistically [17-20]. Recent studies confirmed the association of COVID-19 and pulmonary embolism, with a high prevalence of peripheral venous thrombosis in 56% and pulmonary embolism in 23% of ICU patients, in spite of prophylaxis and therapeutic anticoagulation compared with normal population. A large single



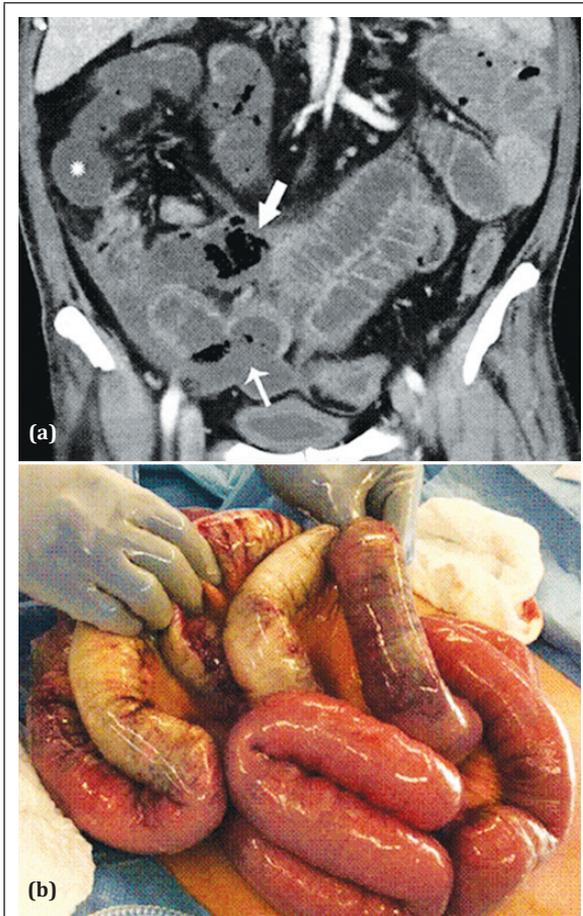


Figure 2: Coronal (a) CT of the abdomen and pelvis with IV contrast in a 47-year-old man with abdominal tenderness demonstrates typical findings of mesenteric ischemia and infarction, including pneumatosis intestinalis (arrow) and non-enhancing bowel (*). Frank discontinuity of a thickened loop of small bowel in the pelvis (thin arrow) is in keeping with perforation. These findings were confirmed at laparotomy (b), with the additional observation of atypical yellow discoloration of bowel.

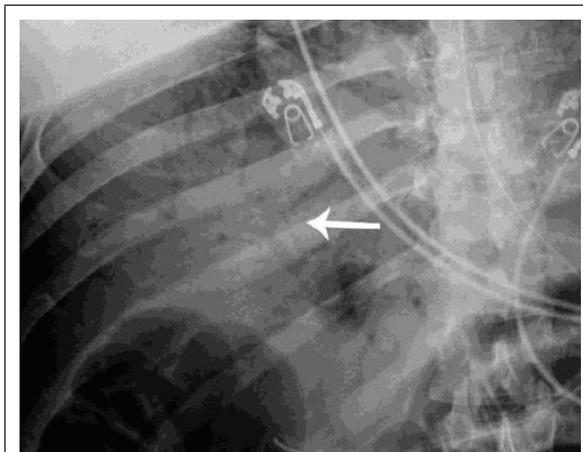


Figure 3: Abdominal radiograph in a 52-year-old man demonstrates portal venous gas suggestive of bowel infarction.

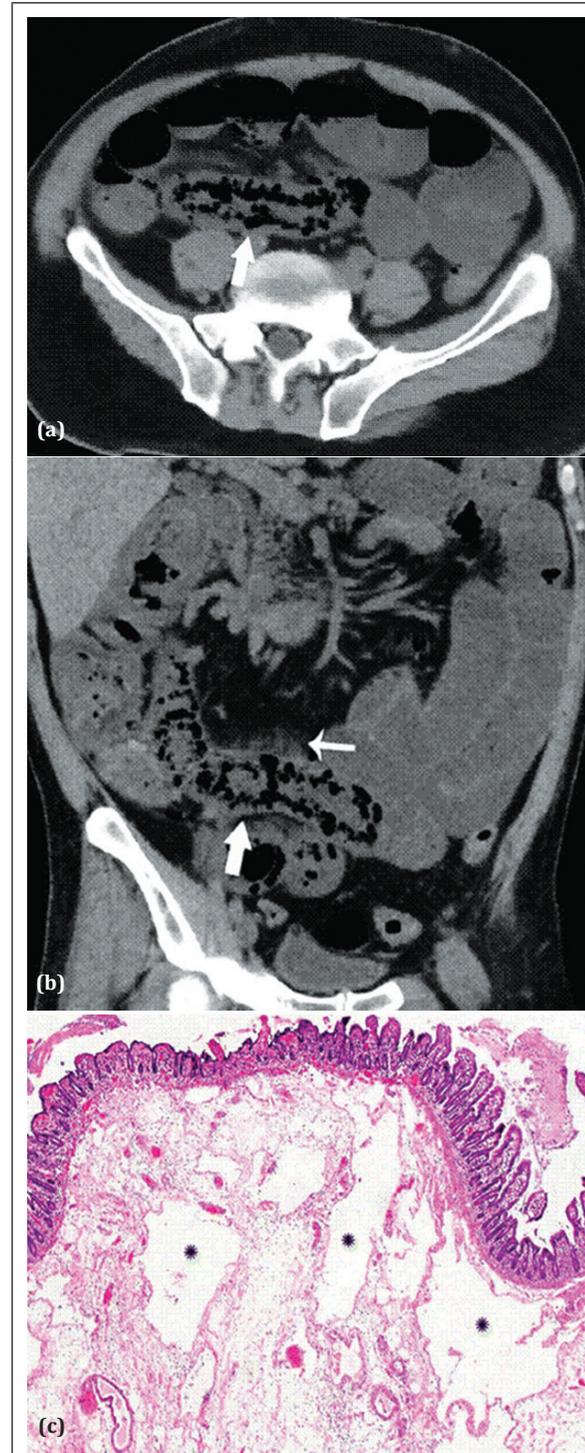


Figure 4: Non-contrast axial (a) and coronal (b) CT performed in a 54-year-old man demonstrates pneumatosis cystoides intestinalis (arrows) in a long segment of ileum. Adjacent mesenteric congestion is also noted (thin arrow). Laparotomy demonstrated no frank bowel necrosis. Low power photomicrograph (H and E, 40x) of the ileum (c) shows ischemic degenerative changes of the mucosa with villous blunting (left) and withered crypts. There is marked submucosal edema with large empty spaces consistent with pneumatosis (*).

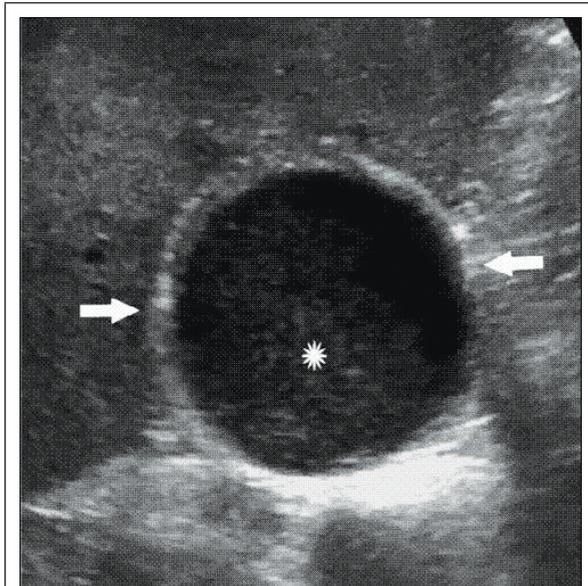


Figure 5: Abdominal ultrasound in an 83-year-old man with elevated liver enzymes and sepsis demonstrated a distended gallbladder (arrows) containing sludge (*), suggestive of cholestasis.

centre study concluded that 37.1% of COVID positive patients were diagnosed pulmonary embolism on CTPA and D-dimer can be used to stratify patients regarding PE risk and severity [21-24]. On CTPA, it is difficult to distinguish thrombus from embolism and whether the central CTPA intravascular defects migrate distally into subsegmental vessels (Figures 6-9). Thrombosis secondary to vascular injury and hypercoagulable state is a proposed mechanism in these patients. The higher rate of DVT (53%) compared to 29% in the pre-COVID cohort, suggests a thromboembolic component for the intravascular defects on CTPA. Vascular enlargement within the areas of lung opacity are reported as a feature of COVID-19 on high resolution CT examinations of chest. This may be appreciated in milder and earlier presentations of pulmonary COVID-19 when HRCT is performed as a routine diagnostic test [25, 26]. A subsegmental vessel greater than 3 mm in diameter is considered as definite vascular enlargement. The enlargement may be related to regional hyperemia and inflammation. In addition, reverse halo sign is noted as a combination of consolidation and ground-glass opacity [27-29].

Mastora obstruction scoring system helps grading the degree of obstruction of pulmonary vessels (Grade 1 to 5 : 25% - 100%) main pulmonary artery (MPA), right pulmonary artery (RPA), left pulmonary

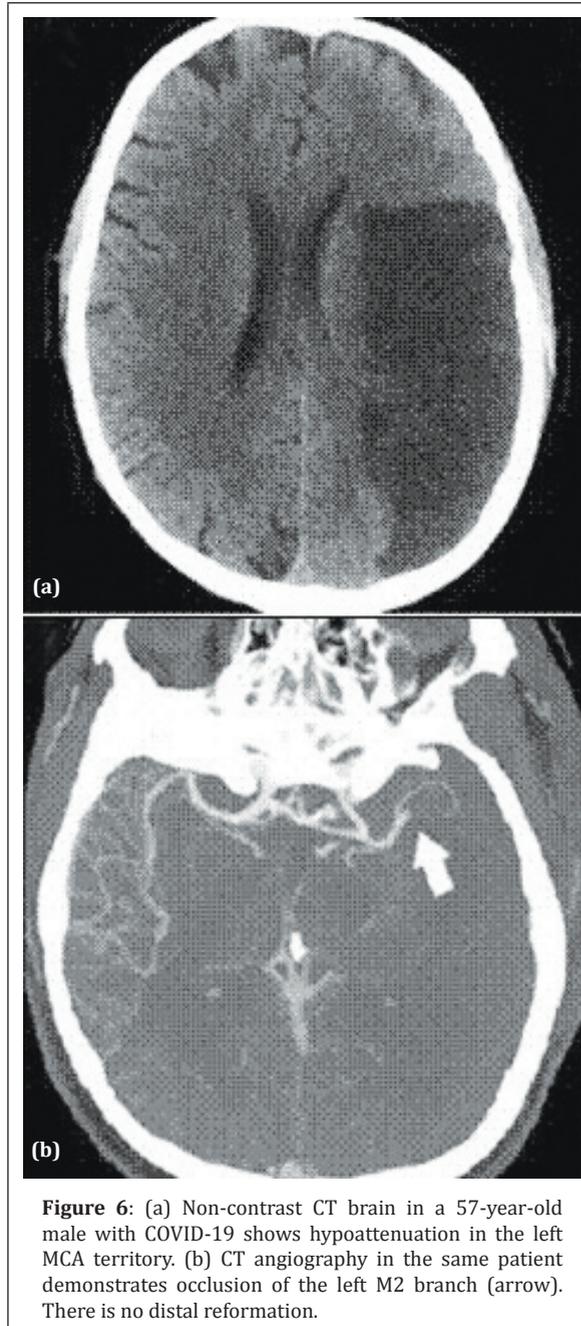


Figure 6: (a) Non-contrast CT brain in a 57-year-old male with COVID-19 shows hypoattenuation in the left MCA territory. (b) CT angiography in the same patient demonstrates occlusion of the left M2 branch (arrow). There is no distal reformation.

artery (LPA), both interlobar arteries, lobar, and segmental pulmonary arteries. Positive correlation between the obstruction scores (ObstGenRatio and ObstTotRatio) and D-dimer levels was noted in severe pulmonary embolism [30]. It should be noted though CT pulmonary angiography (CTPA) is the mainstay to diagnose pulmonary embolism there is a potential risk of nephrotoxicity due to contrast administration particularly in the acutely-ill and multi-organ failure patients with possible acute kidney injury.



Figure 7: A COVID+ patient with bilateral pulmonary emboli had D dimer of > 10,000 four days after admission. (a) Axial CTPA image shows bilateral pulmonary emboli in the left main pulmonary artery and right upper lobe proximal segmental vessels. (b) On an image in the lower thorax, the right ventricle is larger than the left ventricle indicating right heart strain. (c) Bilateral parenchymal consolidative and ground glass opacities are present with a peripheral orientation in the right upper lobe and left lower lobe superior segments. Central and peripheral ground glass in the left upper lobe is present. ObstTotRatio was 0.568.

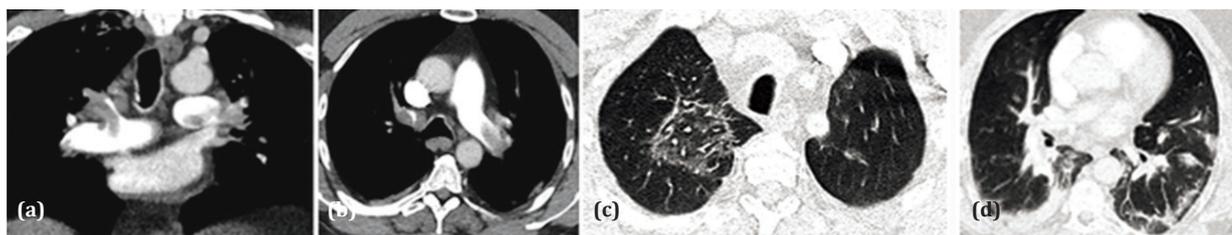


Figure 8: A COVID+ patient with bilateral pulmonary emboli had D dimer of > 10,000. (a) Coronal CTPA image identifies bilateral pulmonary emboli that involve the left main pulmonary artery, distal right main pulmonary artery, right upper lobe pulmonary artery, and proximal segmental vessels. (b) On an axial CTPA image, there is an embolus present in the left main and right upper lobe pulmonary arteries extending into the bilateral anterior segmental arteries. Dilated vessels are present centrally. The ObstTotRatio was 0.674. (c) A ground glass opacity is present in the right upper lobe centrally with a reversed halo appearance, peripheral dense area, and central ground glass opacity attributed to lung involvement from COVID-19. (d) Axial image through the lung base demonstrate basilar consolidation compatible with COVID-19.



Figure 9: Venous thromboembolic disease in COVID-19. (a) Doppler ultrasound of the left lower extremity in a 57-year-old male with COVID-19 demonstrates non-occlusive thrombus in the popliteal vein (arrow). (b) CT pelvis in a 33-year-old male demonstrates non-occlusive thrombus in the right common femoral vein (arrow). (c) CT chest Angiography in a 69-year-old male demonstrates saddle pulmonary embolus (arrow).

Conclusion

COVID-19 is a progressive multisystem disease manifesting widely in different organs. Mechanism of dissemination of the virus into extrapulmonary systems causing multiorgan injury is not yet clear. Although widespread expression of ACE2, receptor

for SARS-CoV-2 is established, the causal effect needs further studies. Understanding of the imaging features in relevant extrapulmonary organ systems is essential for diagnosis, treatment and prevention of complications.

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Conflicts of interest

Authors declare no conflicts of interest.

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