

RadioGraphics Update:

Venous Thrombosis and Hypercoagulability in the Abdomen and Pelvis—Findings in COVID-19

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Abbreviation: COVID-19 = coronavirus disease 2019

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Introduction

First described in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) is a viral illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1,2). According to the World Health Organization, over 5 488 825 cases and 349 095 deaths have been reported worldwide as of May 27, 2020 (3). Clinically, the disease typically manifests as a pneumonia characterized by fever, cough, dyspnea, myalgia, and fatigue (1).

To date, most radiologic literature has focused on the distinctive chest CT abnormalities caused by COVID-19, including peripheral basal-predominant areas of ground-glass opacification or consolidation, often in a bilateral distribution (4). However, emerging research has demonstrated that the inflammation and hypoxemia caused by COVID-19 can result in deranged coagulation parameters and a markedly increased risk of thromboembolic complications, which may be associated with significant morbidity and mortality (5,6). It is thought that viral spreading beyond the respiratory system to other organ systems in the 2nd week of the disease course (correlating with clinical worsening) leads to increased immune-mediated injury and hypercoagulability (7). In this updated review, we expand on the information presented in our 2020 article (8) and focus on the development of thrombosis and thrombus-related complications in COVID-19.

Thrombus and Thrombus-related Complications in COVID-19

Several recent studies have explored the link between COVID-19 and hypercoagulability, with early investigations suggesting that the most common laboratory test result abnormalities include elevated D-dimer levels and mild thrombocytopenia (2). Less commonly, test results may indicate prolonged international normalized ratio (INR), thrombin time, and prothrombin time (PT) or a shortened activated partial thromboplastin time (aPTT) (2). In contradistinction, some studies have shown prolonged aPTT in patients with confirmed COVID-19, often in conjunction with the presence of lupus anticoagulant antibodies. Despite the prolonged aPTT, these patients do not exhibit symptoms of bleeding diathesis, and the use of anticoagulation therapy should not be discouraged (9). Elevated levels of D-dimer and fibrin degradation products and PT prolongation have been significantly correlated with increased mortality (10).

Some investigators have also reported a significant association between COVID-19 and abdominopelvic organ dysfunction, includ-

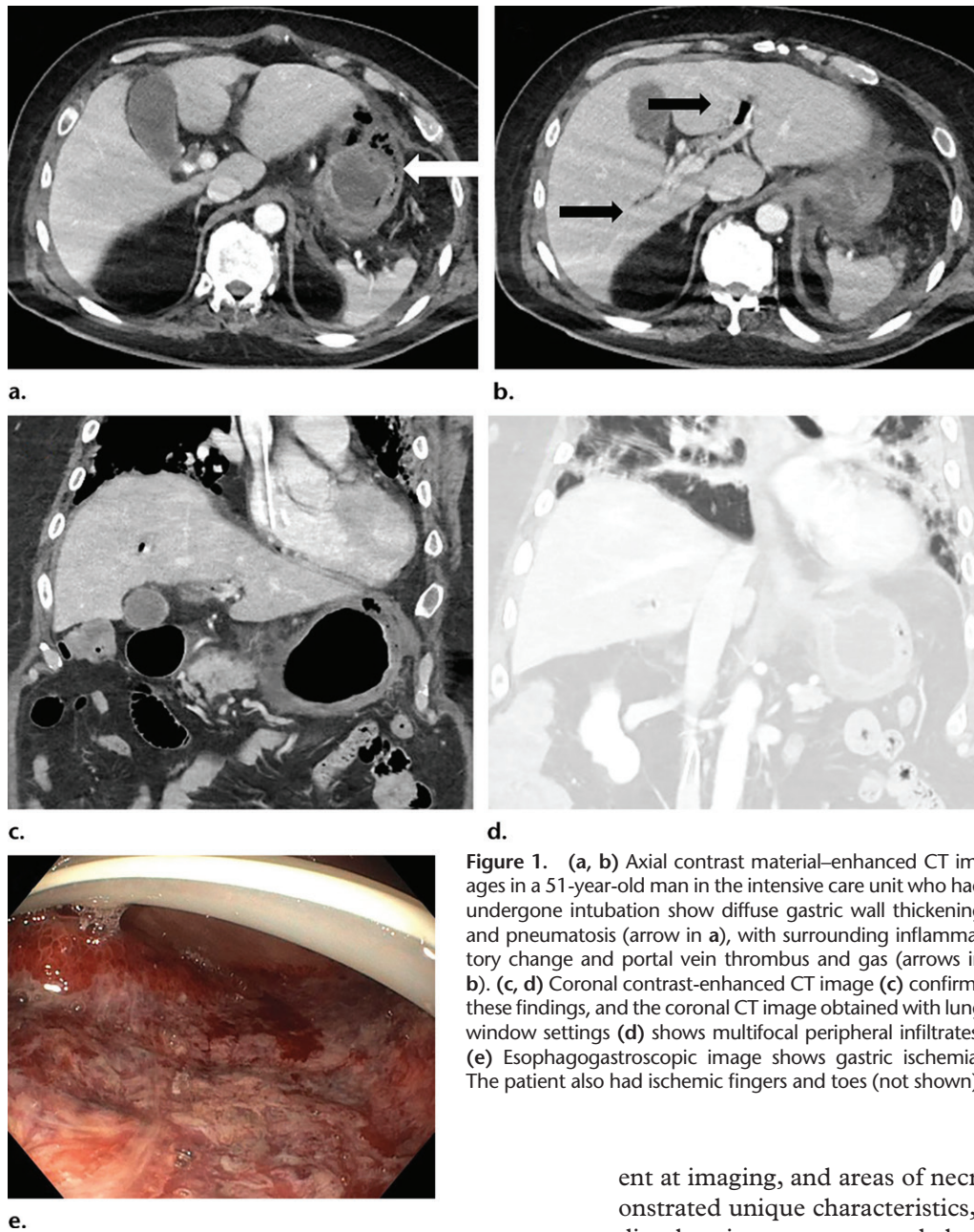


Figure 1. (a, b) Axial contrast material–enhanced CT images in a 51-year-old man in the intensive care unit who had undergone intubation show diffuse gastric wall thickening and pneumatosis (arrow in a), with surrounding inflammatory change and portal vein thrombus and gas (arrows in b). (c, d) Coronal contrast-enhanced CT image (c) confirms these findings, and the coronal CT image obtained with lung window settings (d) shows multifocal peripheral infiltrates. (e) Esophagogastrosopic image shows gastric ischemia. The patient also had ischemic fingers and toes (not shown).

ing abnormal liver function test results, pancreatic injury, and bowel necrosis (11–13). The pathogenic mechanisms by which COVID-19 incites thrombosis and generalized organ damage are still emerging, but it has been observed that SARS-CoV-2 enters alveolar epithelial cells in the lung by binding to the angiotensin-converting enzyme 2 (ACE2) receptor (14). These receptors are expressed at high levels in biliary epithelial cells (14) and pancreatic islet cells (12) and have been detected in gastrointestinal epithelial cells (15), suggesting that receptor expression may enhance cytotoxic effects by facilitating local viral infection and replication.

In cases demonstrating bowel ischemia or necrosis, the main mesenteric vasculature was pat-

ent at imaging, and areas of necrosis have demonstrated unique characteristics, including yellow discoloration at surgery and clear demarcation of the borders of ischemia without anatomic transition zones, varying between circumferential and patchy antimesenteric involvement (13,16).

It has been suggested by some groups that this phenomenon may occur as a result of microvascular thrombosis and associated inflammation (13,16). In one study, several bowel pathologic specimens demonstrated fibrin thrombi in submucosal arterioles, as well as arteriole damage with perivascular neutrophils (16). At imaging, bowel wall abnormalities, including wall thickening and altered enhancement, can be visualized, and on 20% of CT images in patients in the intensive care unit, changes of late ischemia, including pneumatosis and portal venous gas, have been described (Figs 1, 2) (15).

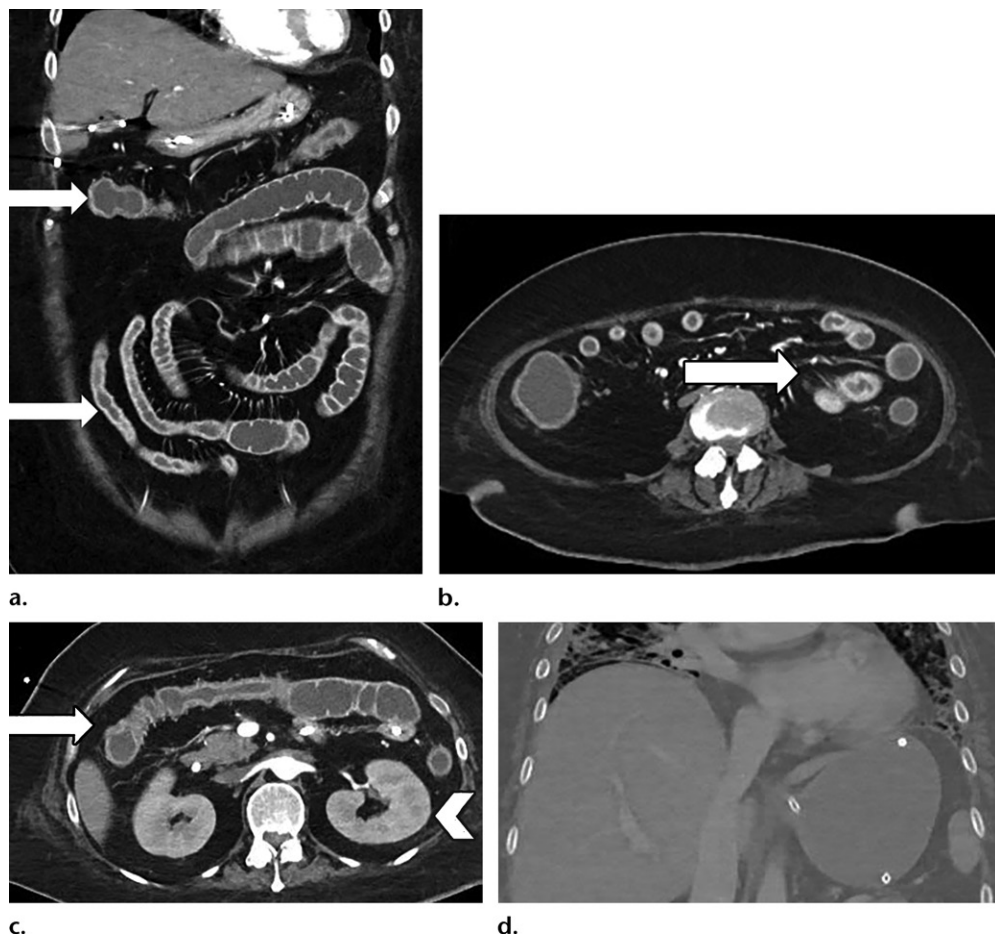


Figure 2. Cough and shortness of breath in a 46-year-old woman with diabetes mellitus who was initially diagnosed with COVID-19. The patient's condition clinically deteriorated, and the use of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and pressor support was required. The clinical course was complicated by acute toxic metabolic encephalopathy, pneumonia, acute respiratory distress syndrome, cardiogenic shock, acute kidney injury, and secondary adrenal insufficiency. Coronal (**a**) and axial (**b**, **c**) contrast-enhanced CT images show multifocal small and large bowel wall thickening (arrows) creating a ribbonlike appearance, likely related to small vessel ischemia. Note the altered enhancement of the kidneys (arrowhead in **c**) in the setting of acute kidney injury and multifocal peripheral airspace opacities at the lung bases on the coronal CT image (**d**).

In a recent study, lungs obtained at autopsy in patients who died from COVID-19 demonstrated distinctive vascular features, including severe endothelial injury associated with intracellular virus and disrupted cell membranes, as well as extensive thrombosis, microangiopathy, alveolar capillary microthrombi, and more new vessel growth or angiogenesis compared with those lungs obtained at autopsy from patients who died from influenza (17).

Other authors have postulated that lung injury and impaired gas exchange may increase production of proinflammatory cytokines, and contributing viral infection may also result in direct damage to the vascular endothelium (18). Some data suggest that the hypoxia induced by COVID-19 pneumonia may result in hypoxia-reperfusion and resultant cell death. The concomitant rise in circulating reactive oxygen species and oxidation products can contribute to the further release of

inflammatory markers. This is among the proposed mechanisms of liver injury in patients with COVID-19 (14).

Furthermore, several authors have proposed that the abrupt onset of multisystem organ failure in some patients with COVID-19 may be attributable to severe systemic inflammation caused by the upregulation of both cellular and natural immunity (14,19). SARS-CoV-2 infection triggers activation of T lymphocytes and inflammatory signaling pathways that ultimately result in the release of multiple proinflammatory markers, including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-2, IL-6, IL-7, IL-10, and tumor necrosis factor- α (TNF- α), among others. This cytokine cascade can ultimately yield extensive cell damage, necrosis, and injury to multiple organs (14,19) and may partially explain the disparate multisystem symptoms in patients

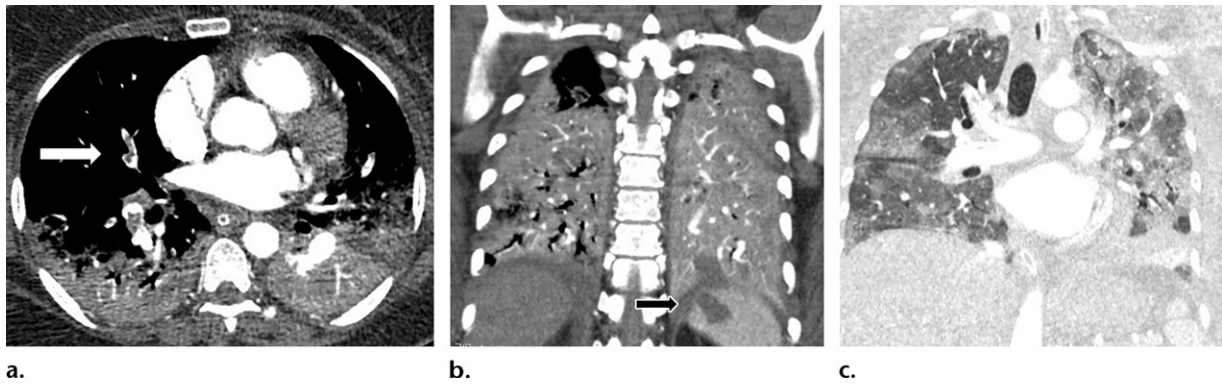


Figure 3. (a, b) Axial CT pulmonary angiogram (a) shows multiple right-sided pulmonary emboli (arrow in a), as well as a splenic infarct (arrow in b) on the coronal angiogram (b). (c) Coronal CT pulmonary angiogram (lung window) shows multifocal and bilateral ground-glass opacities and consolidation in a patient with known COVID-19. (Case courtesy of Mario Santamarina, MD, Viña del Mar, Chile.)

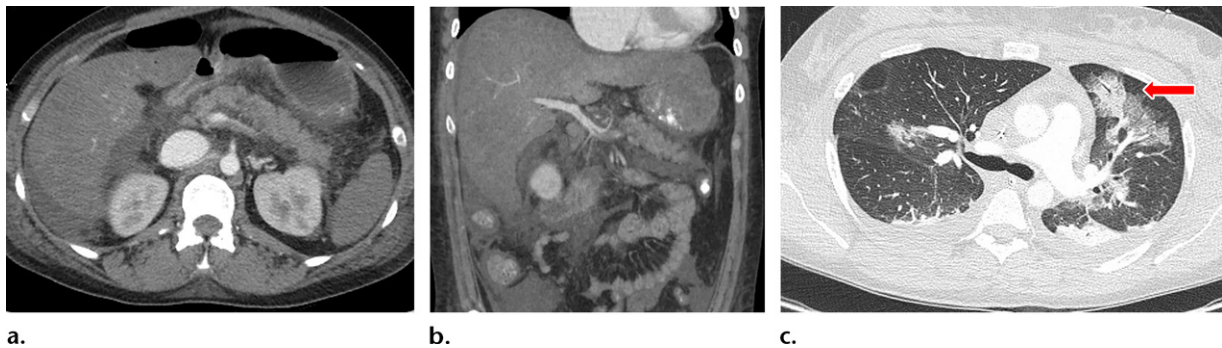


Figure 4. Severe pancreatitis and hypoxia in a 32-year-old woman. (a, b) Axial (a) and coronal (b) contrast-enhanced CT images of the abdomen and pelvis show severe acute interstitial pancreatitis. (c) Axial CT image of the lung shows multifocal peripheral areas of ground-glass opacity and consolidation (arrow), findings concerning for organizing or viral pneumonia. Test results for COVID-19 were negative. However, the patient was clinically still presumed to be a patient under investigation, as ischemic pancreatitis had been described, possibly related to microthrombi.

with confirmed viral infection, including hepatic, pancreatic, and gastrointestinal ischemia. Preliminary data suggest that in patients with COVID-19 with coagulopathy, treatment with low-molecular-weight heparin may decrease mortality (20).

In a recent study by Cui et al (21), which encompassed 81 patients who were critically ill, the incidence of venous thromboembolism (VTE) was 25%, with a mortality rate of 40% in that subset of patients. In a study by Klok et al (5), 184 patients with confirmed COVID-19 pneumonia who were admitted to intensive care units across three hospitals in the Netherlands were evaluated, and thrombotic complications were found in 31% (VTE in 27%, arterial thrombotic events in 3.7%), the most common of which was pulmonary embolism (Fig 3). Similar results were reported by Leonard-Lorant et al (22), who demonstrated a positivity rate of 30% for thrombotic complications (32 of 106 patients) in patients with COVID-19 who underwent CT pulmonary angiography. As noted previously, other groups have described

bowel ischemia (Figs 1, 2), pancreatitis (Fig 4), portal vein thrombus, ischemic-type liver injury, or other visceral infarct (Figs 1, 3).

Conclusion

The results from the previously described studies indicate that in patients with suspected or confirmed COVID-19, radiologists should maintain a high index of suspicion for thromboembolic complications. Imaging features of thrombosis due to COVID-19 are nonspecific and similar in appearance to those seen in other pathologic conditions. However, radiologists' familiarity with its prevalence and pathogenesis in this subset of patients may lead to increased detection and more favorable outcomes. Further, given that fairly aggressive anticoagulation regimens are being adopted for these patients, bleeding complications can also be visualized at imaging. Finally, the presence of unexpected VTE at imaging performed for unrelated indications could herald the need for further workup for COVID-19, particularly in regions with high rates of endemic infection.

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