



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Body Imaging

Review of COVID-19, part 1: Abdominal manifestations in adults and multisystem inflammatory syndrome in children

Devaraju Kanmaniraja^{a,*}, Jessica Kurian^a, Justin Holder^a, Molly Somberg Gunther^a, Victoria Chernyak^b, Kevin Hsu^a, Jimmy Lee^a, Andrew McClelland^a, Shira E. Slasky^a, Jenna Le^a, Zina J. Ricci^a

^a Department of Radiology, Montefiore Medical Center/Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, United States of America

^b Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States of America



ARTICLE INFO

Keywords:

Abdominal imaging

COVID-19

Multisystem inflammatory syndrome

ABSTRACT

The coronavirus disease 2019 (COVID -19) pandemic caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected almost every country in the world, resulting in severe morbidity, mortality and economic hardship, and altering the landscape of healthcare forever. Although primarily a pulmonary illness, it can affect multiple organ systems throughout the body, sometimes with devastating complications and long-term sequelae. As we move into the second year of this pandemic, a better understanding of the pathophysiology of the virus and the varied imaging findings of COVID-19 in the involved organs is crucial to better manage this complex multi-organ disease and to help improve overall survival. This manuscript provides a comprehensive overview of the pathophysiology of the virus along with a detailed and systematic imaging review of the extra-thoracic manifestation of COVID-19 with the exception of unique cardiothoracic features associated with multisystem inflammatory syndrome in children (MIS-C). In Part I, extra-thoracic manifestations of COVID-19 in the abdomen in adults and features of MIS-C will be reviewed. In Part II, manifestations of COVID-19 in the musculoskeletal, central nervous and vascular systems will be reviewed.

1. Abdominal findings of COVID19 in adults

The coronavirus 2019 disease (COVID-19), which originated in Wuhan, China, has quickly become a global pandemic, bringing normal life to a standstill in almost all countries around the world. The severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel virus preceded by two other recent coronavirus infections, the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), but it has more far-reaching and devastating consequences. As of March 2021, the COVID-19 pandemic has resulted in over 29 million cases in the United States and over 121 million cases globally. As of April 2021, it is responsible for the deaths of over half a million people in the United States and more than 2 ½ million worldwide [1]. As the disease has evolved over the past year, so has our understanding of the virus, including its pathophysiology, clinical presentation and imaging

manifestations. Although COVID-19 is predominately a pulmonary illness, it is now established to have widespread extra-pulmonary involvement affecting multiple organ systems. The SARS-CoV-2 has a highly virulent spike protein which binds efficiently to the angiotensin converting enzyme 2 (ACE2) receptors which are expressed in many organs, including the airways, lung parenchyma, several organs in the abdomen, particularly the kidneys and GI system, central nervous system and the smooth and skeletal muscles of the body [2]. The virus initially induces a specific adaptive immune response, and when this response is ineffective, it results in uncontrolled inflammation, which ultimately results in tissue injury [2].

This article provides a comprehensive review of the pathophysiology and imaging findings of the extra-thoracic manifestations of COVID-19 with the exception of unique cardiothoracic features associated with multisystem inflammatory syndrome in children (MIS-C). In Part I, extra-thoracic manifestations of COVID-19 in the abdomen in adults and

* Corresponding author.

E-mail addresses: dkanmani@montefiore.org (D. Kanmaniraja), jkurian@montefiore.org (J. Kurian), jholder@montefiore.org (J. Holder), msomberggu@montefiore.org (M.S. Gunther), khsu@montefiore.org (K. Hsu), jimmylee@montefiore.org (J. Lee), amcclell@montefiore.org (A. McClelland), jle@montefiore.org (J. Le), zricci@montefiore.org (Z.J. Ricci).

<https://doi.org/10.1016/j.clinimag.2021.06.025>

Received 9 April 2021; Received in revised form 23 May 2021; Accepted 17 June 2021

Available online 24 June 2021

0899-7071/© 2021 Elsevier Inc. All rights reserved.

Table 1
Summary of abdominal imaging findings in COVID-19 in adults.

Organ	Imaging findings
Liver	<ul style="list-style-type: none"> • Hepatomegaly • Increased or coarsened echogenicity on US • Hypoattenuation on non-contrast or contrast enhanced CT • Periportal edema and heterogeneous enhancement on CT • Loss of signal on opposed-phase sequences on MRI • Portal vein thrombus
Pancreas	<ul style="list-style-type: none"> • Features of acute interstitial pancreatitis
Biliary Tree	<ul style="list-style-type: none"> • Biliary ductal dilatation
Kidney	<ul style="list-style-type: none"> • Increased or heterogeneous parenchymal echogenicity on US • Loss of corticomedullary differentiation on US • Preserved cortical thickness • Perinephric fat stranding and thickening of Gerota's fascia on CT • Wedge shaped perfusion defects on CT or MRI • Thrombus in the renal artery or vein
Gallbladder	<ul style="list-style-type: none"> • Distension • Mural edema • Sludge • Acalculous cholecystitis
Urinary Bladder	<ul style="list-style-type: none"> • Bladder wall thickening • Mural hyperenhancement • Perivesicular stranding
Bowel	<ul style="list-style-type: none"> • Mural thickening • Ileus • Fluid-filled colon • Pneumatosis intestinalis • Portal vein gas • Pneumoperitoneum • Acute mesenteric ischemia • Vascular occlusion (superior mesenteric artery, superior mesenteric vein, or portal vein) • Mesenteric fat stranding, ascites • Active gastrointestinal bleeding (duodenal or gastric ulcer) on CTA • <i>Clostridium difficile</i> colitis • Ischemic colitis
Spleen	<ul style="list-style-type: none"> • Wedge shaped perfusion defects on CT or MRI • Thrombus in the splenic artery or vein

Table 2
Summary of imaging findings in Multisystem Inflammatory Syndrome in Children.

Region	Imaging findings
Cardiothoracic	<ul style="list-style-type: none"> • Bilateral symmetric diffuse airspace opacities with lower lobe predominance on CXR • Diffuse ground glass opacity, septal thickening, and mild hilar lymphadenopathy on CT • Bilateral pleural effusions • Cardiomegaly • Pericardial effusion • Myocarditis pattern on cardiac MRI
Abdominal	<ul style="list-style-type: none"> • Mesenteric lymphadenopathy, most common in right lower quadrant • Mesenteric edema • Ascites • Bowel wall thickening • Ileus • Hepatosplenomegaly • Gallbladder wall thickening

the varying features of multisystem inflammatory syndrome in children will be reviewed, with imaging findings summarized in [Tables 1 and 2](#). In Part II, manifestations of COVID-19 in the musculoskeletal system, the central nervous system and central and peripheral vascular systems will be reviewed.

2. Abdominal findings of COVID-19 in adults

2.1. Hepatobiliary derangement

Varying derangements of the liver, biliary system, gallbladder, portal vein and pancreas may occur in COVID-19 with hepatic parenchymal injury and biliary stasis reported with highest frequency. The mechanism of involvement of these structures appears to be multifactorial. The most direct form of injury results from SARS CoV-2 entry into host cells by binding to ACE2 receptors detected in several locations in the hepatobiliary system, including biliary epithelial cells (cholangiocytes), gallbladder endothelial cells and both pancreatic islet cells and exocrine glands [3–6].

2.1.1. Hepatic injury

Direct SARS CoV-2 entry into cholangiocytes may cause liver damage by disrupting bile acid transportation or by triggering acid accumulation resulting in liver injury [7]. Systemic inflammation, hypoxia inducing hepatitis and adverse drug reactions may incite liver injury [8]. Several drugs commonly used to treat COVID-19 patients, including acetaminophen, lopinavir and ritonavir can be hepatotoxic [9]. One study excluding COVID-19 patients receiving hepatotoxic drugs, still found patients with liver injury. Therefore, liver damage in COVID-19 patients is likely not entirely drug-induced but may also be due to acute infection [8,9]. Furthermore, since patients with chronic liver disease such as cirrhosis, autoimmune liver disease and prior liver transplantation are more susceptible to COVID-19 infection [9], underlying conditions may also contribute to liver injury.

The most frequent hepatic derangement is abnormal liver function tests reported in 16–53% of patients [10,11] and including raised levels of alanine aminotransferase, aspartate aminotransferase, and γ -glutamyl transferase with mild elevation of bilirubin. The majority of cases are mild and self-limited, with severe liver damage rare [7]. Liver injury is most prevalent in the second week of COVID-19 infection, and has a higher incidence in those with gastrointestinal symptoms and more severe infection [9]. Based on a meta-analysis of hepatic autopsy findings of deceased COVID-19 patients in 7 countries, hepatic steatosis (55%), hepatic sinus congestion (35%) and vascular thrombosis (29%) were the most common [10]. In a retrospective study of abdominal imaging findings of 37 COVID-19 patients, 27% who underwent ultrasound had increased hepatic echogenicity considered to represent fatty liver with elevated liver enzymes being the most frequent indication for ultrasound [4]. It should be noted that since obesity is a major risk factor for severe COVID-19 infection, it might contribute to the frequency of steatosis identified on imaging. In another retrospective abdominal sonographic study of 30 ICU patients with COVID-19, the most common finding was hepatomegaly (56%), with most cases having increased hepatic echogenicity and elevated liver function tests [12]. In the only retrospective case-control study of 204 COVID-19 patients who underwent non-contrast chest CT scan, steatosis was found in 31.9% of cases and only 7.1% of controls [13]. Steatosis was based on a single ROI measurement in the right lobe with an attenuation value ≤ 40 HU. However, underlying risk factors for steatosis such as diabetes, obesity, hypertension and abnormal lipid profile, were not available to exclude preexisting conditions leading to steatosis. Finally, unlike in the spleen and kidney where infarcts are reported in COVID-19, hepatic infarction is not a distinct feature. This is likely due to the liver's unique dual blood supply.

On imaging the liver may be enlarged. On ultrasound, the liver of patients with abnormal liver function tests may be coarsened and/or increased in echogenicity ([Figs. 1, 2](#)). On CT scan, the liver may be hypoattenuated on non-contrast or contrast-enhanced exam due to steatosis ([Fig. 3](#)). Periportal edema and heterogeneity of hepatic enhancement may be seen on contrast-enhanced CT or MRI due to parenchymal inflammation. On MRI, loss of signal on opposed-phase sequences ([Fig. 4](#)) may be seen due to steatosis and periportal edema may be conspicuous on T2-weighted images or on contrast-enhanced

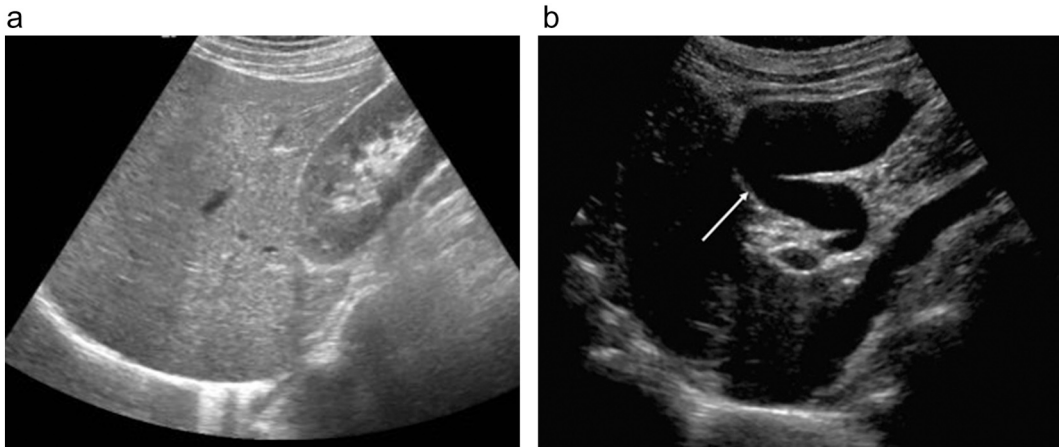


Fig. 1. 40-year-old man with COVID-19 pneumonia and no known liver disease with increasing liver function tests. (1a) Sagittal gray-scale ultrasound image demonstrates increased liver echogenicity, consistent with steatosis without hepatomegaly. (1b) Sagittal gray-scale ultrasound image shows a normal gallbladder (arrow) and no biliary dilatation (not shown).

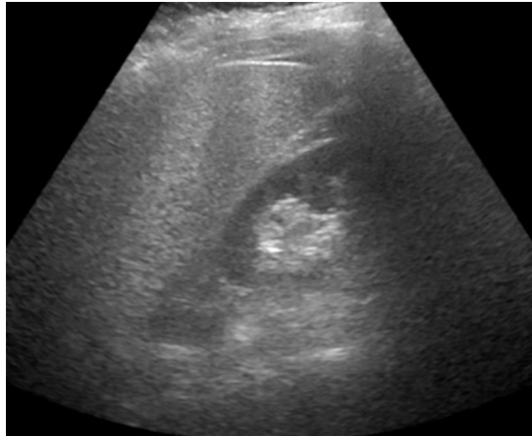


Fig. 2. 68-year-old woman with COVID pneumonia and newly elevated liver function tests. Sagittal gray-scale ultrasound image shows increased hepatic echogenicity with poor acoustic penetration and contrasting hypoechogenicic appearance of the right kidney compatible with steatosis, without hepatomegaly. Gallbladder (not shown) is normal.

images [7,8,14]. Periportal lymphadenopathy, typical of chronic liver disease, is not reported in COVID-19 [8]. In patients with severe COVID-19 infection, ancillary manifestations of hepatic inflammation and injury, such as parenchymal attenuation changes and abscesses may be seen (Fig. 5).

2.1.2. Portal vein thrombosis

Portal vein thrombosis is not common in COVID-19 with only few reported cases [15–19]. Its mechanism is likely multifactorial. Since ACE2 receptors are present on vascular endothelial cells, direct viral entry can incite coagulopathy [4]. The vascular endothelium can be damaged by inflammatory cytokines, although sepsis-induced coagulopathy and endothelial dysfunction may play a role, especially in patients who are critically ill [3,4]. Adult respiratory distress syndrome (ARDS) and hypoxia can also trigger a generalized thrombotic state by increased blood viscosity and a transcription-factor signaling pathway [3]. Many of those who have severe disease are afflicted with comorbidities such as obesity and malignancy, and critically ill patients are often immobile, all of which may increase thrombotic risk [3]. Microthrombosis within hepatic parenchyma has also been described, with autopsy results revealing thrombosis within the central veins and hepatic sinusoids [7].

On ultrasound, portal vein thrombosis appears as echogenic material within the vein, although it may be anechoic and undetectable in the

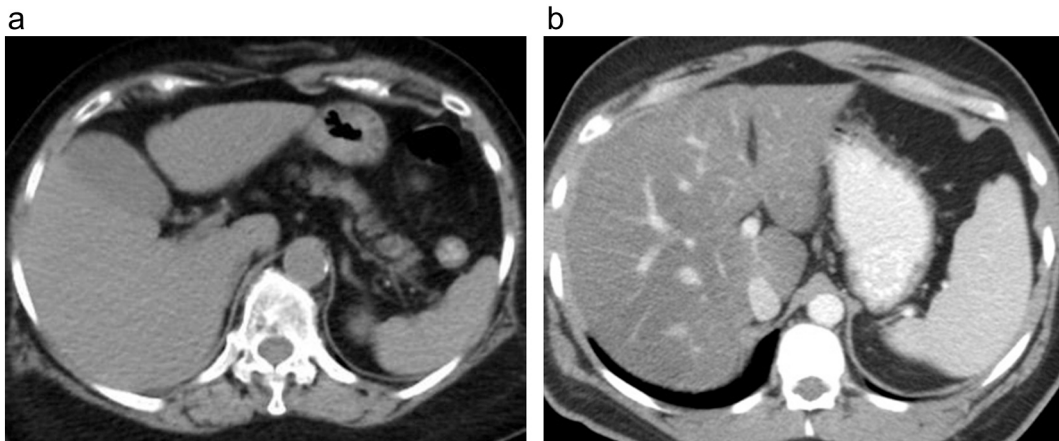


Fig. 3. 65-year-old woman with COVID-19 and elevated liver enzymes due to hepatic steatosis. (a) Axial non-enhanced CT image shows diffuse hypoattenuation of the liver whose attenuation was greater than 10 HU lower than the spleen. (b) Subsequent contrast-enhanced CT images shows marked hypoattenuation of the liver whose attenuation was greater than 30 HU lower than the spleen.

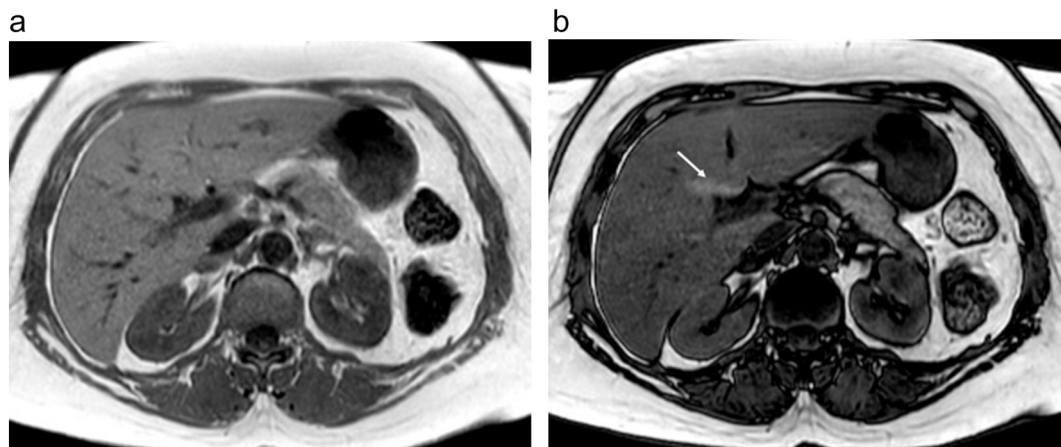


Fig. 4. Hepatic steatosis in a 44 year old male with COVID-19 and elevated liver enzymes.

(a) Axial in and (b) out-of-phase MRI images show loss of signal in the liver parenchyma on the out of phase sequence consistent with intracellular fat. Note focal high signal due to fatty sparing in the medial segment of the left lobe (arrow).

early acute stages. Color Doppler images may show total or partial absence of flow in the vein. On contrast-enhanced CT or MRI, portal vein thrombosis appears as non-enhancing filling defect within the main or intrahepatic branches (Fig. 6). Clots may be occlusive or non-occlusive and may expand the involved vein.

2.1.3. Biliary stasis

Biliary stasis is quite common in COVID-19, manifesting as gallbladder distention, gallbladder sludge and/or biliary ductal dilatation on imaging. In a retrospective study of 37 COVID-19 patients who underwent abdominal imaging, gallbladder sludge and distension were reported in 54% of patients who underwent right upper quadrant ultrasound [4]. Acalculous cholecystitis has been reported in patients with COVID-19, although it is unclear if this is due direct viral injury or due to the multiple confounding factors of general sepsis, prolonged parenteral nutrition, or systemic cytokine release [20]. SARS-CoV-2 RNA has been detected in the gallbladder wall [21]. There are reports of patients developing acalculous cholecystitis several weeks after mild COVID-19 infection, suggesting there may be residual gallbladder stasis or endothelial injury [20]. In a large retrospective study of 80 COVID-19 patients with positive findings on abdominal imaging, abnormalities of the gallbladder and biliary system were found in 25% of patients, including gallbladder findings in 15% and biliary ductal dilatation in 10% [14]. Gallbladder findings included distention (6.2%), mural edema (2.5%) and possible or definite acute cholecystitis (5%).

On imaging, biliary stasis may manifest as increased gallbladder distention (typically defined as ≥ 5 cm) and sludge, and acalculous cholecystitis is suggested when there is superimposed gallbladder mural thickening and pericholecystic fluid [20] (Fig. 7). Prolonged biliary stasis may obstruct the biliary tree and result in cholangitis. This is demonstrated on imaging as extrahepatic or intrahepatic biliary ductal dilatation, and increased biliary ductal mural thickening and enhancement (Fig. 8). Gallstones should be excluded on ultrasound, as cholelithiasis is a more common cause of biliary infection.

The management of acute cholecystitis in COVID-19 patients is controversial. Intravenous antibiotics alone or with percutaneous cholecystostomy are advocated by many as a bridging agent to cholecystectomy [22] (Fig. 9). Since it remains unknown the extent to which SARS-CoV-2 remains in the smoke generated by electrocautery [23], some recommend conservative management [24]. Others advocate an individualized approach based on the severity of cholecystitis and available resources during the pandemic [25].

Imaging plays a role in the diagnosis of cholecystitis as well as in the detection of complications of percutaneous cholecystostomy. These complications include placement in the wrong site, catheter

dislodgement, intraabdominal hemorrhage or bile leak. Fistulae to the liver can develop when catheters are left in for extended periods of time. In order to avoid potential cholecystostomy risks, some institutions offer surgery in COVID-19 patients as first-line therapy [24].

2.1.4. Pancreatic injury

Pancreatic involvement in COVID-19 is much less common than hepatic or biliary involvement, and may occur from direct viral injury or secondary to general inflammation and systemic illness. Pancreatic islet cells contain ACE2 receptors that may permit direct viral entry, while the host immune-mediated cytokine response can also incite pancreatic damage. In a study of 52 patients hospitalized for COVID-19 pneumonia, 9 (17%) had pancreatic injury defined as elevation of amylase or lipase with only one requiring mechanical ventilation. None had clinically severe pancreatitis [26]. In a larger study of hospitalized COVID-19 patients, almost 11% (13 of 121) had elevated pancreatic enzymes [6]. Only 1–2% of patients with mild viral illness had elevated pancreatic enzymes while almost 18% of patients with severe illness had elevated pancreatic enzymes. On CT scan, no patients had evidence of necrosis and only 7.5% (5 of 67) patients with severe illness had imaging evidence of pancreatitis described mainly as focal pancreatic enlargement or dilatation of the pancreatic duct. Although reported cases of pancreatic injury in COVID-19 tend to be mild, the role of pancreatitis in aggravating systemic inflammation, contributing to ARDS or leading to potential chronic pancreatitis later on remains unknown [6]. Recurrent acute pancreatitis has been reported several weeks after resolution of COVID-19 infection [27]. Finally, in two larger retrospective studies of abdominal imaging findings in hospitalized COVID-19 patients [4,14], only one patient had reported pancreatitis [4].

Imaging findings of pancreatitis in COVID-19 patients mimic those in other settings, with CT demonstrating diffuse or focal pancreatic enlargement, decreased pancreatic attenuation due to edema, surrounding fat stranding and indistinct gland margins. MRI shows similar manifestations, with the gland appearing enlarged with poorly defined margins, and with edema and free fluid appearing bright on T2 weighted images (Figs. 10,11).

2.2. Genitourinary derangement

2.2.1. Acute kidney injury

Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection, seen in about one third of hospitalized COVID-19 patients [28]. Patients with AKI have a higher associated morbidity and mortality with one meta-analysis showing 77% of patients developing a more severe infection, 5% requiring renal replacement therapy and

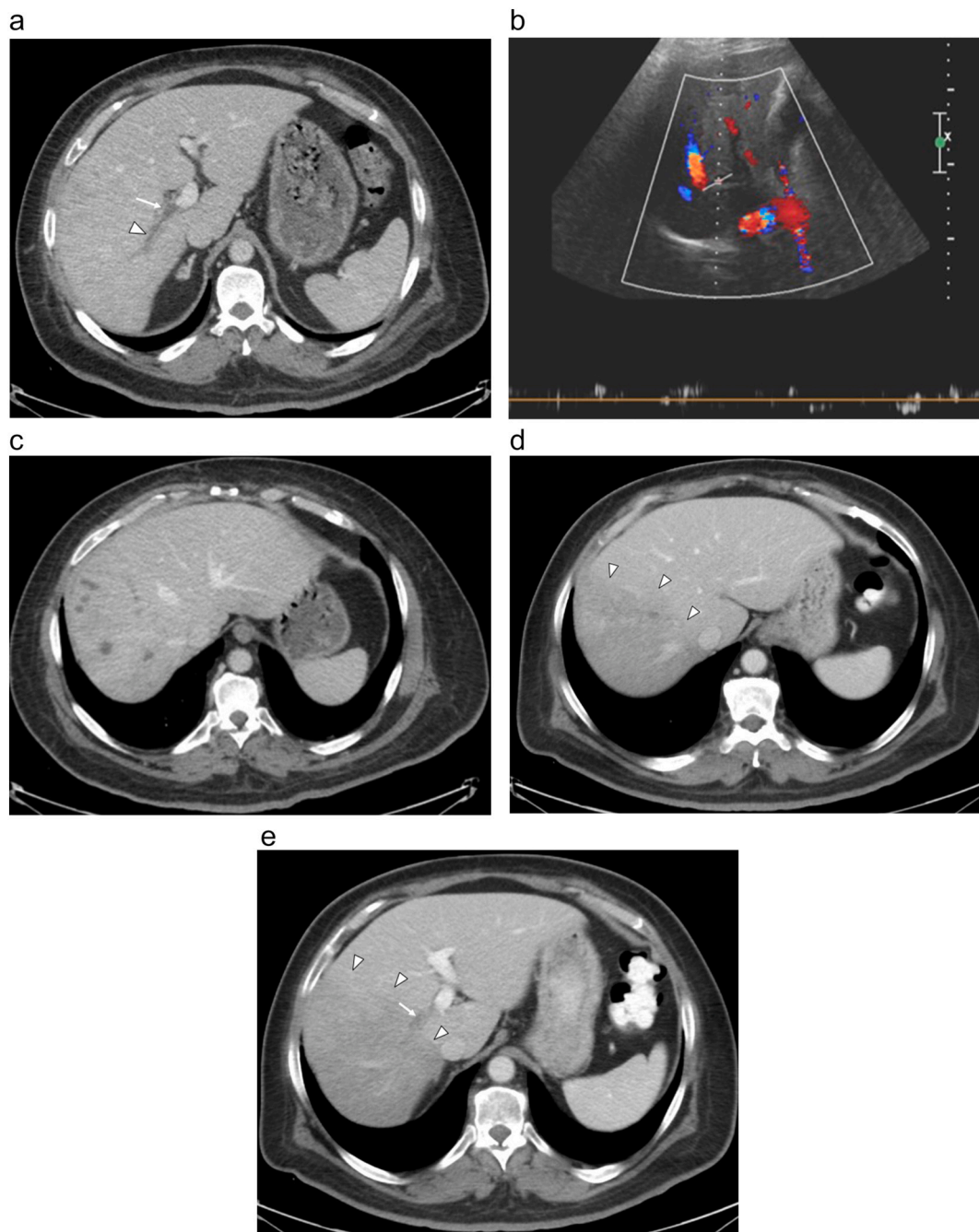


Fig. 5. 49-year-old man with COVID-19 pneumonia who has a history of coronary artery disease and diabetes mellitus. (a) Axial contrast-enhanced CT image shows hypodense thrombus in the distal right portal vein (arrow) extending into the posterior segmental branch (arrowhead) with associated heterogeneous right lobe enhancement. (b) Sagittal Color Doppler US image shows absent flow and no spectral waveform consistent with occlusive thrombus. (c) More cephalic image shows heterogeneous hepatic enhancement with several rounded hypoattenuated foci consistent with parenchymal inflammation and abscesses. The patient was treated with anticoagulation and antibiotics. (d,e) Axial contrast-enhanced CT images 3 months later shows gross resolution of abscesses with persistent geographic hypoattenuation due to perfusion change (arrowheads) with only slight decrease in right portal vein thrombosis (arrow).

having an overall increased mortality rate of 50% [29]. Among the patients who developed AKI and survived, only a third recovered renal function at the time of discharge, and about a third of patients failed to recover to baseline even on subsequent follow-up [30]. In addition, patients with chronic renal disease are at a higher risk of developing severe upper respiratory infection and pneumonia following exposure to COVID-19, secondary to their inherent proinflammatory state and diminished immunity [2,31].

The mechanism of kidney injury in COVID-19 is likely multifactorial. Both the increased expression of ACE2 receptors in the kidneys and

certain genetic traits and polymorphism of renal ACE2 receptors enable SARS-CoV-2 binding and viral cell entry [32]. The pathogenesis of AKI involves both direct and indirect effects. The direct effect of the virus causes endothelial damage, inflammatory response, coagulopathy and complement activation while the indirect effects are sequelae of the systemic effects of multisystem involvement including hypovolemia, critical care interventions and organ crosstalk [32]. Organ crosstalk is a complex communication network between distant organs that communicate by signaling factors such as cytokines, growth factors and release of damage associated molecular patterns (DAMPs) from injured tissue.

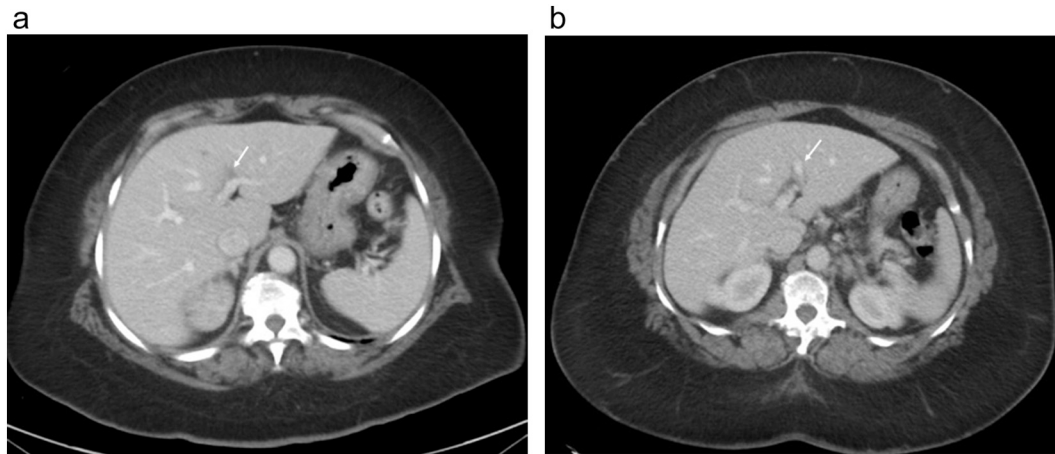


Fig. 6. 73-year-old obese woman with COVID-19 pneumonia and increasing liver function tests. (a) Axial contrast-enhanced CT image shows hypodense thrombus in the medial segmental branch of the left portal vein (arrow). (b) Corresponding image from an older exam demonstrates the branch to be patent (arrow).



Fig. 7. 77-year-old man with rising bilirubin, fever and abdominal pain, with concern for acalculous cholecystitis. Sagittal gray-scale ultrasound image shows gallbladder distension and sludge (arrow). Findings were attributed to biliary stasis and not acalculous cholecystitis due to lack of mural thickening, hyperemia and sonographic Murphy's sign.

Histologic evaluation of COVID-19 patients has revealed varying types of injury including collapsing glomerulopathy, proximal tubular injury, microthrombi and microangiopathy [32].

On ultrasound, the kidneys of COVID-19 patients with AKI typically demonstrate increased or heterogeneous parenchymal echogenicity, with possible loss of corticomedullary differentiation [7] [Fig. 12]. Involved kidneys typically have preserved cortical thickness, which helps differentiate them from those with chronic kidney disease. Additionally, a combination of nonspecific findings including increased renal parenchymal echogenicity, loss of corticomedullary differentiation, increased resistive indices and decreased color Doppler flow can be seen in COVID-19 patients with collapsing focal segmental glomerulosclerosis [33]. On non-contrast CT, perinephric fat stranding and thickening of Gerota's fascia correlated with higher serum creatinine levels in patients with AKI, suggesting more severe inflammation and parenchymal injury [34]. Following the administration of contrast, geographic hypodense areas maybe observed in the periphery of the kidneys from hypoperfusion attributed to vasculopathy [35] [Fig. 13].

2.2.2. Cystitis

Increased urinary frequency has been reported in COVID-19 patients. It is believed that expression of ACE2 receptors in the urinary bladder,

although not as high as the kidneys, predisposes patients to interstitial or hemorrhagic cystitis. It is unclear whether the receptors are expressed on the basal or luminal bladder surface. However, infection arises both from urine along the luminal surface and from blood via the basal surface [36]. Viral RNA and inflammatory cytokines have been identified in the urine of COVID-19 patients [36–38]. Additionally, endotheliitis may be a factor in local bladder inflammation [36].

Imaging findings include diffuse and irregular bladder wall thickening on ultrasound and diffuse thickening and enhancement of the bladder wall on CT, with adjacent perivesicular stranding [7,39] [Fig. 14].

2.3. Solid organ infarction

Thromboembolic solid organ events in COVID-19 patients can be arterial or venous in origin [40–43]. In a retrospective study of 141 COVID-19 patients with abdominal pain, 18% had solid organ infarct and vascular thrombosis [14]. The mechanism of organ infarction in COVID-19 is likely multifactorial. There is a direct cytopathic effect of SARS-CoV-2 which results in a viral mediated platelet-dependent endothelial inflammation causing endothelial dysfunction and rise in proinflammatory cytokines, leading to an increase in tissue factor expression [40,44,45]. Hypoxia in COVID-19 patients causes increased blood viscosity and the resulting hypoxia inducible transcription factors promote thrombosis [2,46,47]. Additionally, hypercoagulability from increased levels of coagulation factors and antiphospholipid antibodies along with decreased levels of anticoagulation proteins contribute to the increased incidence of thrombotic events in COVID-19 patients [48]. In a study of 82 patients with COVID-19 who underwent imaging, nine patients (11%) had thromboembolic findings, four of which were solid organ insults [19]. Three splenic and one renal infarct were identified with patent vasculature on contrast-enhanced CT. One additional case of renal vein thrombus was reported without reported renal infarct. This supports disseminated microvascular thrombosis in the etiology of solid organ infarction [19].

2.3.1. Renal infarction

Although relatively uncommon, renal infarcts have been reported in COVID-19 patients [40,49]. Based on a retrospective study of 141 COVID-19 patients with abdominal symptoms, the incidence of renal infarct was 5% on CT scans [14].

On ultrasound, renal infarcts appear as wedge shaped heterogeneous hypoechoic areas with decreased or absent perfusion on color Doppler images [7]. On CT and MRI, renal infarcts may appear as geographic focal or multifocal areas of diminished or absent parenchymal

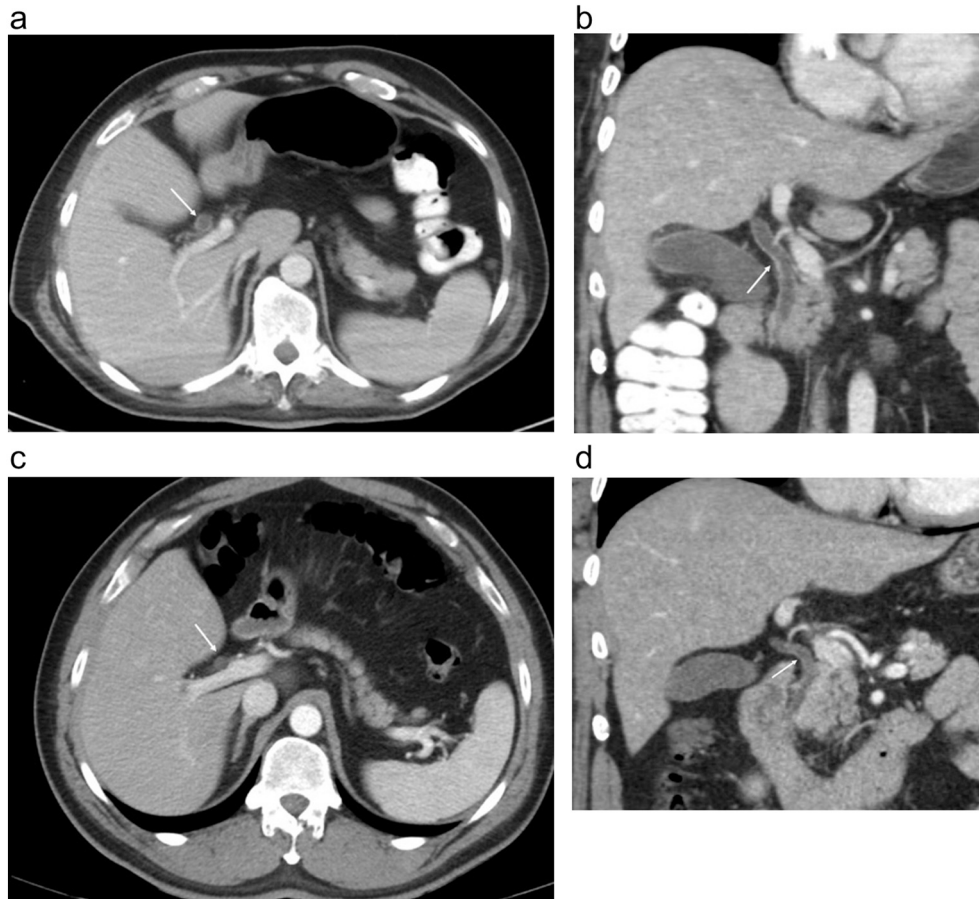


Fig. 8. 54-year-old man with COVID-19 with history of obesity and diabetes mellitus. (a,b) Axial and coronal contrast-enhanced CT images show mild dilatation (8 mm) and mural hyperenhancement of the common bile duct (arrow). Ultrasound (not shown) shows absence of gallstones. (c,d) Axial and coronal images from CT from 1-year prior show a normal common bile duct (arrow).

enhancement in one or both kidneys. The renal defects are typically wedge-shaped spanning the cortex and medulla with their apex towards the hilum and extending to the renal capsule. Several days after acute onset they typically have overlying thin capsular enhancement (“rim sign”) due to preserved collateral capsular perfusion. Segmental infarcts have a characteristic geographic appearance that follows the distribution of the anterior and posterior branch vessels of the renal artery [50]. On MRI, infarcts vary with age and are usually hypointense on T1-weighted and T2-weighted images acutely, becoming higher in signal on T2-weighted images over the next few days as coagulation necrosis occurs. They may appear hyperintense on T1-weighted images if hemorrhage occurs. Healed or chronic infarcts have progressively decreased signal due to fibrosis and atrophy. There is often loss of normal corticomedullary differentiation in the infarcted segment and corresponding wedge-shaped areas of hypoenhancement on post contrast images [51]. Less commonly, a filling defect may be seen in the renal artery on post-contrast images [Fig. 15] or vein [Fig. 16].

2.3.2. Splenic infarction

Although relatively uncommon, splenic infarcts have been reported in COVID-19 patients. Based on a retrospective study of 141 COVID-19 patients with abdominal symptoms, the incidence of splenic infarct was 5% on CT scans [14]. In an autopsy series studying the spleens of 10 COVID-19 patients, one had splenic infarct [52]. In a case series of 3 patients with abdominal visceral infarction associated with severe COVID-19 infection, two had splenic infarcts [53]. One patient had both multifocal splenic infarcts and unilateral focal renal infarct and the other had small bowel necrosis and massive splenic infarction requiring

surgery. Asymptomatic splenic infarct incidentally noted on CT scan performed for suspected pulmonary embolism has also been reported [54].

On CT and MRI, splenic infarcts appear as single or multiple peripheral wedge-shaped hypoenhancing defects, with their apex pointed towards the hilum [Fig. 17]. They can also be rounded or linear in shape. Their appearance varies with age, being vague hypodense areas on CT with mottled enhancement in the first 24 h, and becoming progressively better defined non-enhancing hypodense defects over the next week [55]. On MRI, splenic infarcts are typically hypointense on T1- and T2-weighted images without enhancement on the post contrast images. However, their appearance varies based on the presence of hemorrhage and with their age. Acute and hemorrhagic infarcts are hyperintense on T1-weighted images and hypointense on T2-weighted images. Subacute infarcts have fluid signal. Chronic infarcts may fully resolve or become hypointense on T2 and T2-weighted images [56,57]. Less commonly, a filling defect may be seen in the splenic vein or artery on post-contrast images [Fig. 18].

2.4. Gastrointestinal derangement

The mechanism of SARS-CoV-2 induced gastrointestinal symptoms is not fully understood and may in part be due to direct viral entry into enterocytes. A single-cell transcriptomic study of enteric and lung cells determined that co-expression of ACE2 and TMPRSS2 cell receptors is necessary to permit SARS-CoV-2 entry. Co-expression was found not only in the lung but also in the esophageal upper epithelial and gland cells, the ileum and colon [58].

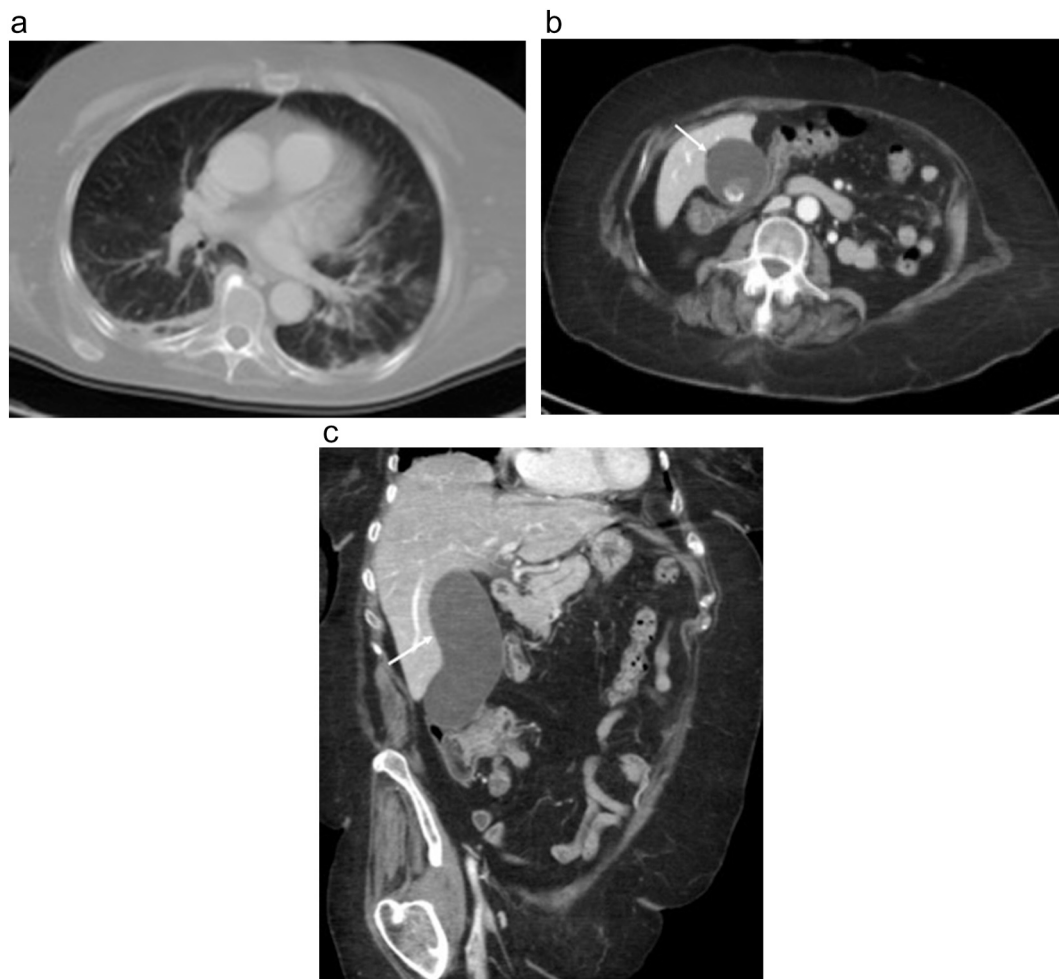


Fig. 9. 60-year-old man with history of hypertension and asthma hospitalized for COVID-19 pneumonia with respiratory distress requiring oxygen supplementation and with diffuse abdominal pain and leukocytosis. (a) Axial CT image with lung windows shows bibasilar infiltrates. (b,c) Axial and coronal contrast-enhanced CT images show a hydroptic gallbladder with stones (arrow). Hepatobiliary iminodiacetic acid (HIDA) scan was positive confirming acute cholecystitis. Percutaneous cholecystostomy was performed with clear yellow bile drained. Cholecystectomy was performed 4 weeks later revealing chronic cholecystitis and stones. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

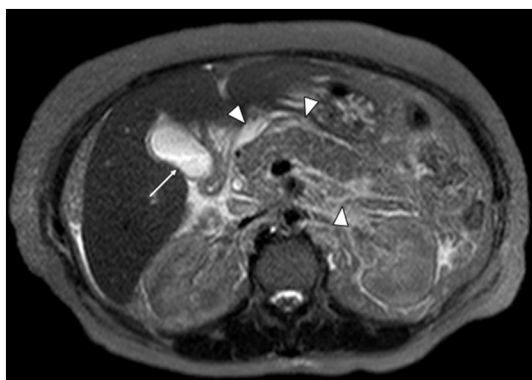


Fig. 10. 57-year-old woman with history of coronary artery disease, chronic kidney disease and COVID-19 pneumonia who developed abdominal pain and an elevated lipase. Axial T2-weighted image with fat saturation reveals hyperintense edema and fluid surrounding the pancreas (arrowheads), trace perihepatic and left perirenal ascites, and gallbladder sludge (arrow). No gallstones were seen on ultrasound (not shown).



Fig. 11. 44-year-old man with diabetes and mild obesity hospitalized with COVID-pneumonia who developed acute kidney injury requiring dialysis and acute respiratory distress syndrome. His liver enzymes and lipase levels increased. Right upper quadrant ultrasound and non-contrast CT of the abdomen and pelvis were notable for increased hepatic and renal echogenicity (not shown). Balanced Turbo Field Echo (BTFE) axial MRI image shows mild T2 hyperintense stranding of the peripancreatic fat (arrowheads) surrounding the pancreatic tail. Mild hepatic steatosis was also present (not shown).

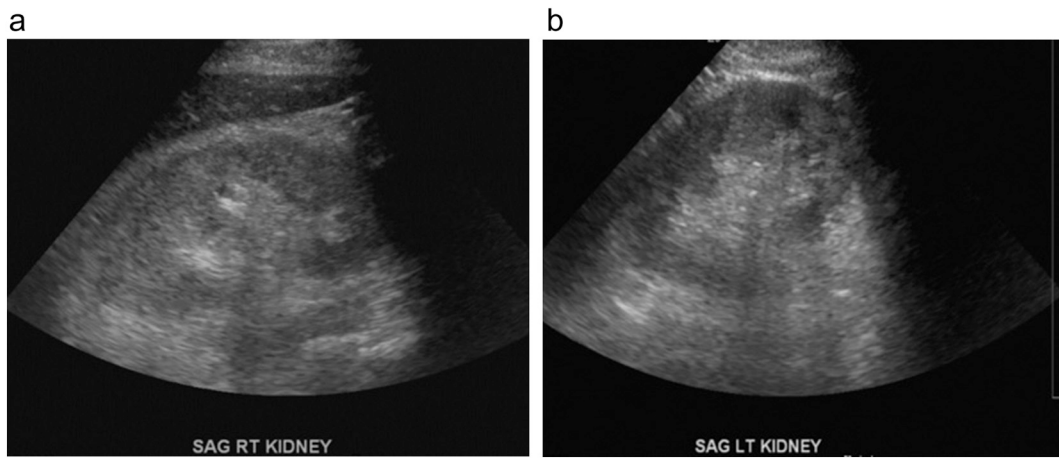


Fig. 12. 68-year-old woman with history of diabetes, hypertension and asthma presented to the hospital with COVID-19 pneumonia and elevated creatinine due to acute kidney injury. (a,b) Sagittal gray-scale ultrasound images of the right and left kidneys show increased renal parenchymal echogenicity and loss of cortico-medullary differentiation with preserved cortical thickness.

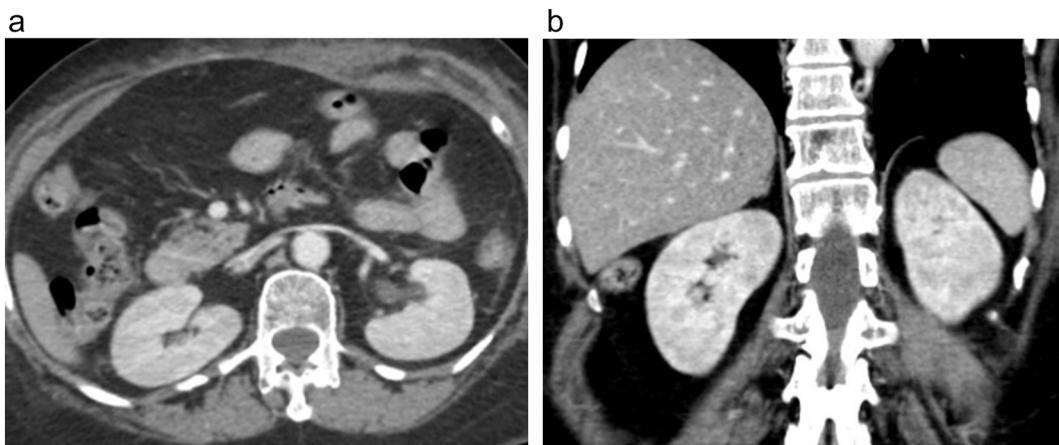


Fig. 13. 65-year-old woman with COVID-19 pneumonia presented with elevated creatinine and acute kidney injury. Her past medical history was notable for hypertension and remote history of breast cancer. (a) Axial and (b) coronal contrast-enhanced CT images show patchy mottled inhomogeneous renal enhancement of both kidneys that are of normal size.

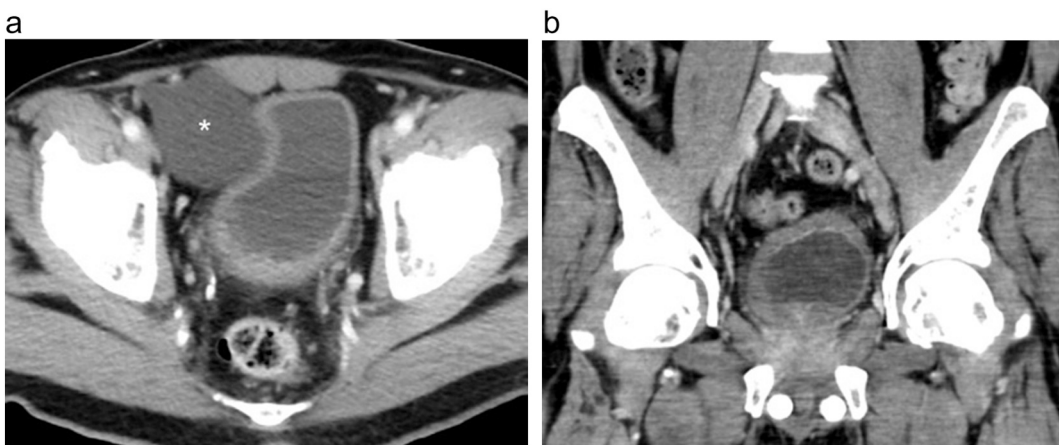


Fig. 14. 63-year-old man with past medical history of diabetes and hypertension, presented with COVID-19 pneumonia and two days of dysuria and hematuria. (a) Axial and (b) coronal contrast-enhanced CT images demonstrate marked mural thickening of the urinary bladder with mild adjacent perivesicular stranding. The patient has a penile prosthesis with a reservoir (asterisk) in the right anterior pelvis.

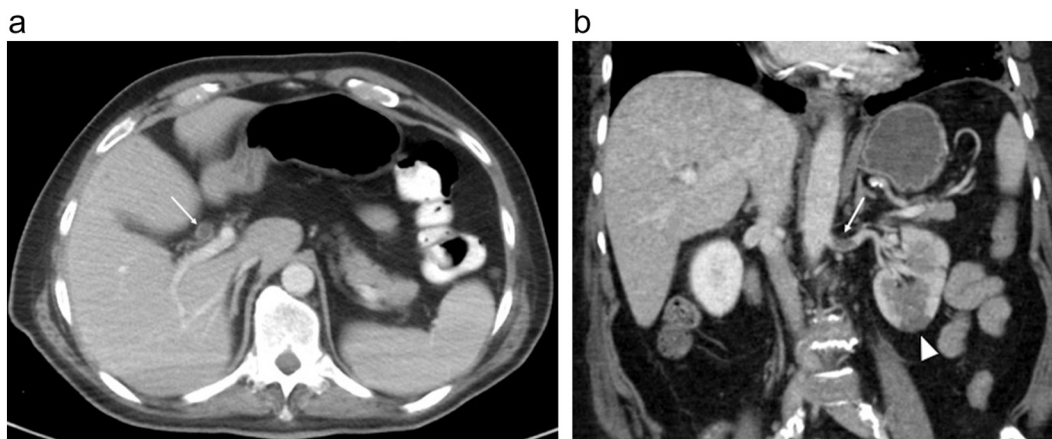


Fig. 15. 69-year-old woman with history of hypertension, coronary artery disease and congestive heart failure presented to the Emergency Room with cough and chest tightness. She was diagnosed with COVID-19 pneumonia and found to have acute kidney injury. (a) Coronal contrast-enhanced CT image shows multiple wedge-shaped non-enhancing defects in the left kidney (arrowheads). Also seen is perinephric fat stranding around the right kidney with thickening of the adjacent Gerota's fascia (arrows). (b) A more anterior coronal contrast-enhanced CT image shows a focal hypodense filling defect in the proximal left renal artery (arrow) consistent with thrombus.



Fig. 16. 71-year-old woman from a nursing home with history of dementia, schizophrenia and obstructive sleep apnea, found to be COVID-19 positive and presented to the Emergency Room unresponsive and with acute kidney injury. Axial contrast-enhanced CT image shows a hypodense filling defect distending the left renal vein consistent with non-occlusive renal vein thrombus (arrow).

Gastrointestinal symptoms in COVID-19 are relatively frequent. In a large meta-analysis of 43 studies of gastrointestinal manifestations of COVID-19 including over 18,000 patients, diarrhea was the most common GI symptom (11.5%), followed by nausea and vomiting (6.3%), and abdominal pain (2.3%) [59]. Among symptomatic patients, 17.5% had severe COVID-19 illness and 9.8% had a milder illness. In a retrospective study of 141 patients with severe COVID-19 in the ICU, 45% had gastrointestinal symptoms on admission including abdominal pain, diarrhea and vomiting [60]. In a meta-analysis of 36 studies reporting abdominal imaging in COVID-19, 16% of patients presented solely with gastrointestinal symptoms [61].

Gastrointestinal symptoms in COVID-19 may be due to hepatobiliary or enteric involvement and, in some, may be due to side effects of drug therapy or advanced sepsis. In addition, when enteric involvement occurs, the mechanism of bowel disease remains unclear with postulations including cytokine storm and inflammation, edema, or ischemia [61]. Further studies are needed to determine if there is a direct correlation between viral entry into enterocytes and imaging findings of enteritis or colitis, as mild cases are managed without operative intervention or definitive tissue diagnosis. The origin of bowel involvement in mild

cases is therefore unknown and may be infectious, ischemic or due to an alternative cause.

Finally, it has also been reported that many patients with abdominal complaints lack abdominal imaging findings. In a study of abdominal CT scans of 23 patients whose lung bases had findings typical of COVID-19 and presented with abdominal complaints, there were no bowel abnormalities detected [62]. In a larger study of abdominal CT scans of hospitalized patients with COVID-19, 43% lacked abdominal imaging findings [14]. Of those who lacked abdominal findings in the study, 64% had basilar lung findings on CT. In another study of 43 hospitalized COVID-19 patients who underwent CT for abdominal complaints, 63% had no abdominal abnormality [63]. Therefore, it is not clear how often COVID-19 patients have relevant bowel involvement when symptomatic. Since abdominal symptoms are common, it can be postulated that some cases are due to nonspecific viral-induced pain or referred symptoms from basilar pneumonia.

2.4.1. Bowel imaging patterns of COVID-19

The most common and consistently reported imaging manifestations of COVID-19 affecting the bowel include mural thickening, non-specific ileus, fluid-filled colon, and pneumatosis intestinalis. Portal vein gas and pneumoperitoneum are less commonly seen [61,64]. In a retrospective review of 141 COVID-19 patients in the ICU, 56% had clinically or radiologically diagnosed ileus, 2% had Ogilvie-like syndrome, 4% had bowel ischemia (3% small bowel, 1% small and large bowel and 1% cecal), 11% had GI bleeding and 4% had *Clostridium difficile* colitis [60]. Out of 81 hospitalized COVID-19 patients who underwent abdominal CT, 24% had intestinal findings of which colorectal thickening (5%), small bowel thickening (12%), and ileus (18%) were the most common, while pneumatosis (1%) and perforation (1%) were relatively rare [64]. In a retrospective study of 42 hospitalized COVID-19 patients who underwent CT, 31% had bowel wall abnormality [4]. Small bowel thickening was reported in 12%, all of who were in the ICU. Colonic or rectal thickening was reported in 17%, of which nearly half were in the ICU. In another larger retrospective study of hospitalized COVID-19 patients who underwent CT for abdominal symptoms, 57% had positive abdominal imaging findings [14]. Bowel wall thickening was found at a lower rate of 15%, including mostly colonic and small bowel, with rare cases of esophageal and gastric thickening. An even smaller rate of bowel abnormalities was reported in a retrospective study of 32 hospitalized COVID-19 patients who underwent CT, where only 7% had nonspecific enteritis, with pneumatosis intestinalis in one patient [63].

Colonic mural thickening on CT has been reported in a patient with



Fig. 17. 58-year-old male with history of hypertension and diabetes presented to the Emergency Room with worsening abdominal pain who tested positive for SARS-CoV2 1 week ago and lacked respiratory symptoms. (a) Axial and (b) coronal contrast-enhanced CT demonstrates multiple geographic wedge shaped non-enhancing splenic defects (arrowheads). (c) Axial contrast-enhanced CT 4 months later shows small linear band like areas of hypoattenuation with overlying capsular retraction consistent with scarring (arrowheads).



Fig. 18. 69-year-old man with history of atrial fibrillation hospitalized with COVID-19 pneumonia that developed a cerebrovascular attack in the ICU and required intubation for respiratory compromise. Prior to PEG placement CT of the abdomen and pelvis was performed to assess his anatomy. Axial contrast-enhanced CT image demonstrates a large wedge-shaped non-enhancing splenic infarct (asterisk) and diffuse hypodense filling defect in the splenic artery (arrows) consistent with thrombus. Enhancing splenic vein is noted (arrowhead). The patient did not survive.

symptomatic colitis in COVID-19 including one patient with hemorrhagic colitis confirmed on colonoscopy [65,66]. Mucosal hyper-enhancement and mural thickening of the colon, mild mesenteric vascular congestion and small adjacent lymph nodes have been reported on CT in patients with colitis [67].

Finally, Horvat et al. found the presence of intestinal findings on CT in hospitalized COVID-19 patients positively correlated with a higher risk of worse clinical outcome including death or assisted ventilation [64].

2.4.2. Ileus

Ileus can manifest as gaseous distention of the small bowel, colon or both and is relatively common in hospitalized COVID-19 patients (Fig. 19). Kaafarani et al. reported that 56% of patients in their case series of 141 patients with severe COVID-19 requiring ICU care had a clinical or radiographic diagnosis of ileus [60]. The pathophysiology of ileus in COVID-19 is likely multifactorial. In severely ill COVID-19 patients, ileus is commonly caused by metabolic and/or electrolyte derangements but may also be reactive to other complications of COVID-19 [60,68] or due to direct viral entry into enterocytes with resultant intestinal inflammation and ensuing ileus [68]. A few cases of severe colonic ileus have been reported in patients with severe pulmonary COVID-19 infection [68,69], some of which were complicated by bowel ischemia [68,69] and some of which were indistinguishable from Ogilvie syndrome [69].

2.4.3. Mesenteric Ischemia

Acute mesenteric ischemia is a serious and not uncommon complication of COVID-19 infection with a high mortality. It is theorized to



Fig. 19. 72-year-old woman in the Emergency Room with weakness, nausea and abdominal pain who tested positive for SARS-CoV-2. Supine portable radiograph shows mild prominence of air-filled small bowel that is minimally distended and mild prominence of non-dilated segments of colon consistent with ileus. No further imaging was performed. The patient was treated conservatively with supportive therapy and discharged 3 days later.

occur secondary to viral-induced hypercoagulability or thromboinflammation leading to thrombosis, as opposed to direct viral infection of the gastrointestinal tract [70,71]. Patients with mesenteric ischemia classically present with pain out of proportion to their physical exam and other gastrointestinal symptoms such as vomiting and diarrhea [71]. It is surmised that mucosal bowel ischemia expedites viral spread from the bowel wall leading to more rapid clinical deterioration because of the sudden increase in viral load [72]. If COVID-19 patients present with suspicious symptoms, there should be a low threshold to initiate a search for acute mesenteric ischemia with CT angiogram of the abdomen and pelvis.

Acute mesenteric ischemia can be caused by thromboembolic arterial or venous occlusion of medium or large mesenteric vessels or by microthrombosis of small vessels. A systematic literature review of studies reporting mesenteric ischemia in COVID-19 patients who had at least one gastrointestinal finding on imaging, defined as mesenteric arterial or venous thromboembolism or signs of small bowel ischemia, yielded 22 studies and 31 patients [73]. Nine (29%) had superior mesenteric arterial thromboembolism, 6 (19%) had occlusive thrombosis of the portal system or superior mesenteric vein and 16 (52%) had no visible vascular occlusion. More than two-thirds (64%) of all patients required laparotomy and bowel resection. The overall mortality was 39%. In this meta-analysis, almost half of patients with bowel ischemia had macrovascular arterial/venous thrombosis and half did not.

Imaging findings of COVID-19 related bowel ischemia on CT angiogram of the abdomen and pelvis are not unique and include mural thickening, a targetoid mural enhancement pattern, absent or diminished mural enhancement, mural hyperenhancement, ileus [Fig. 20], mesenteric vascular engorgement, mesenteric fat stranding and ascites. Pneumatosis and/or portomesenteric venous gas may reflect ischemia or infarction, but when seen together typically indicate infarction [74,75] [Fig. 21]. Arterial filling defects or zones of vascular narrowing may occur in arterial ischemia with preservation or thinning of bowel wall thickness. Venous filling defects may occur in venous ischemia typically with associated mesenteric venous engorgement, mural thickening and ascites. In nonocclusive mesenteric ischemia, bowel wall may be normal

or thickened due to reperfusion. Mesenteric fat stranding and ascites are also common [74].

A few CT imaging reports of mesenteric ischemia in COVID-19 with confirmed bowel necrosis on surgical intervention have been reported. These include one case of non-enhancing distal ileal loops with adjacent free air and patent mesenteric vessels [76] and two cases of small bowel pneumatosis or portal venous gas suggestive of ischemia [4]. All three patients were reported to have yellow discoloration of the necrotic bowel on surgical exploration [4,76]. The first patient had unsalvageable necrotic bowel from the ligament of Treitz to the transverse colon and died shortly after surgery with presumed microvascular thrombosis [76]. One of the other two patients underwent small bowel resection, revealing patchy necrosis ranging from mucosal to full-thickness necrosis with submucosal arteriolar microthromboses [4].

Finally, pneumatosis or portal venous gas is reported in COVID-19 patients with bowel ischemia in up to 20% (4 of 20) of ICU patients, and is typically considered a marker for possible mesenteric ischemia [4]. However, in the absence of clinical symptomatology, like in non-COVID-19 patients, it may not on its own indicate ischemia or mandate surgical intervention. Meini et al. report a patient hospitalized for COVID-19 pneumonia that was successfully managed conservatively for asymptomatic intraperitoneal air bubbles and pneumatosis of the cecum and ascending colon noticed on chest CT performed for pulmonary embolism [77]. The etiology was theorized to be bowel wall injury and gut flora impairment during SARS-CoV-2 infection.

2.4.4. Ischemic colitis

Ischemic colitis has been reported rarely in patients hospitalized with COVID-19 illness with bloody diarrhea. In one case it was attributed to shock and hemodynamic compromise triggered by small vessel vasoconstriction and mesenteric hypoperfusion [78] and in the other to inflammatory cytokine storm in a patient with risk factors for ischemic colitis but without hemodynamic compromise [79].

2.4.5. Pneumoperitoneum

Pneumoperitoneum in hospitalized COVID-19 patients has many causes including recent surgery, iatrogenic procedural trauma, bowel perforation, ischemia, and benign causes such as barotrauma in ventilated patients. Benign pneumomediastinum and pneumoperitoneum can be due to pulmonary interstitial emphysema, known as the Macklin effect [80]. In the setting of barotrauma, typically due to invasive mechanical ventilation, alveoli can rupture leading to small pockets of air tracking along the peribronchovascular sheaths into the mediastinum. Once air collects within the mediastinum, it can dissect into the peritoneal cavity, causing pneumoperitoneum via major diaphragmatic portals [Fig. 22]. Alternatively, even if pneumomediastinum is absent, air can track directly through pleural or diaphragmatic defects leading to isolated pneumoperitoneum [81]. Duarte et al. report a case of pneumoperitoneum in a hospitalized COVID-19 patient who developed pulmonary interstitial edema from nasal cannula oxygen supplementation leading to benign pneumoperitoneum [81]. Intrathoracic barotrauma has been reported in 15% of COVID-19 patients on assisted mechanical ventilation and is more likely to occur in younger patients [82].

When unexpected pneumoperitoneum is detected in a COVID-19 patient on chest radiograph or abdominal imaging, it is essential to rule out potential bowel perforation or ischemia. If no cause is determined on abdominal CT, the patient should be observed closely to ensure bowel perforation or ischemia was not missed, and that the pneumoperitoneum is regressing. Given the high morbidity and mortality associated with exploratory laparotomy in hospitalized COVID-19 patients, there should be a high threshold for surgical intervention [81]. In certain situations, if a chest CT is performed, the Macklin effect can be confirmed by visualizing thin linear collections of air tracking along the bronchovascular sheath.

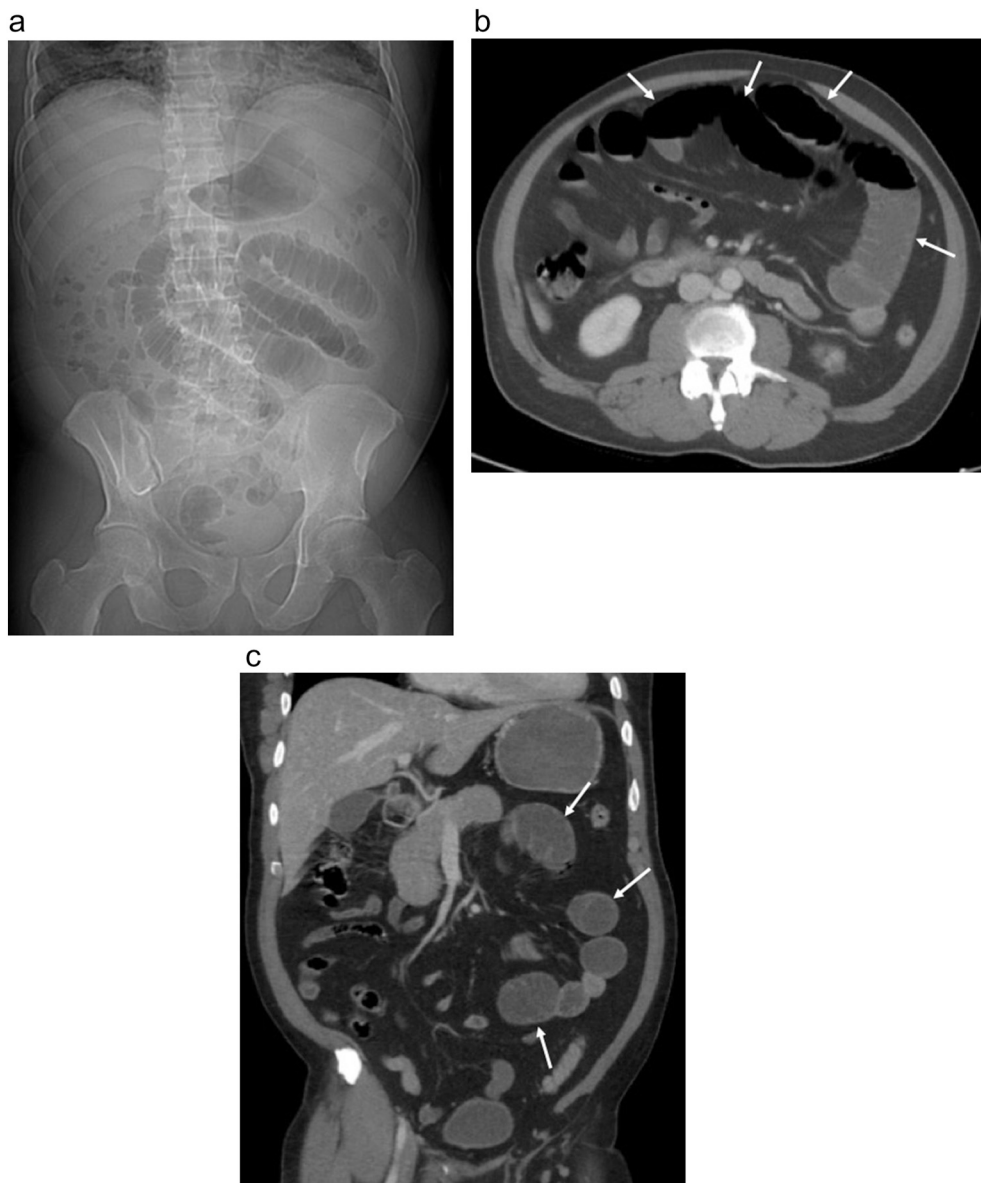


Fig. 20. 67-year-old man hospitalized with COVID-19 requiring ventilation who developed acute kidney injury, nausea and abdominal distension with a tender abdomen and peritoneal signs on physical exam on day three of his hospital course. (a) Supine scout from CT shows dilated small bowel in the left mid abdomen and bibasilar interstitial infiltrates. (b,c) Axial and coronal contrast-enhanced CT images show dilated proximal and mid small bowel loops (arrows) with non-distended distal small bowel and small amount of colonic air with no discrete transition zone. Findings are most suggestive of a severe ileus pattern, somewhat mimicking a small bowel obstruction. Exploratory laparotomy was performed revealing a friable mesentery with several areas of ecchymosis, dilated, hyperemic, thickened and dusky small bowel. The abdomen was left open. No obstruction was found and findings were deemed to be secondary to COVID-19 related ischemia. Re-exploration 10 days later revealed normal small bowel and resolution of ileus. The patient improved and was later discharged to rehabilitation center.

2.4.6. GI bleeding

Although the exact incidence of GI bleeding in COVID-19 is unknown, GI bleeding is not uncommonly observed in hospitalized COVID-19 patients, and in some cases may be the primary indication for abdominopelvic CT scan. In one retrospective study, 5% of hospitalized COVID-19 patients had GI bleeding as the indication for abdominal CT [4]. Patients may also present with symptoms of perforated gastric or duodenal ulcers, which has been attributed to stress-related mucosal damage in the setting of severe illness or anticoagulation, rather than direct infection or ischemia of the gastrointestinal tract [83]. In a large case series of 4871 patients in Northern Italy, 23 patients developed upper GI bleeds (0.5%), 78% of whom were on anticoagulation at the time bleeding, including 44% on full dose anticoagulation [84]. While most patients in the case series developed bleeding during their hospital course, 26% of patients initially presented to the emergency room for GI bleeding and then tested positive for COVID-19 infection, suggesting that in some cases bleeding may be directly due to COVID-19 infection rather than stress-related mucosal damage or anticoagulation [84].

A multicenter international study of 114 endoscopies performed on COVID-19 patients for acute GI bleeds, found that 25% of bleeds were caused by ulcers, 16% by erosive/ulcerative gastro-duodenopathy and

9% by petechial or hemorrhagic gastropathy [85]. Utilizing multivariate regression analysis, the authors found that ICU admission, pre-existing frailty, and extended hospitalization had no impact on the risk of a positive endoscopy finding [85].

Dedicated CT angiogram with a GI bleeding protocol, including non-contrast, arterial and portal venous phase images can detect foci of active bleeding at a rate of 0.3–0.5 ml/min which is less sensitive than RBC scanning (0.1–0.5 ml/min) but more sensitive than fluoroscopic angiography (0.5–1.0 ml/min) [86]. Alternatively, on a dual energy scanner, images may be acquired in the arterial and portal venous phase with reconstruction of a virtual non-contrast image set [86]. On non-contrast exam, luminal blood product is hyperdense with attenuations ranging from 30 to 45 HU when unclotted and from 45 to 70 HU when clotted [87,88]. Active extravasation of contrast appears as an area of intraluminal enhancement on arterial phase images that changes shape and attenuation on portal venous phase [89] (Artigas). In patients with intermittent bleeding or in stable patients with elevated creatinine, a technetium 99 m (^{99m}Tc) nuclear medicine scan with a sulfur colloid or red blood cell pharmaceutical agent may be used as an alternative imaging modality. ^{99m}Tc scintigraphy has a high sensitivity but poor anatomic localization of acute GI bleed [90]. CT angiogram has the

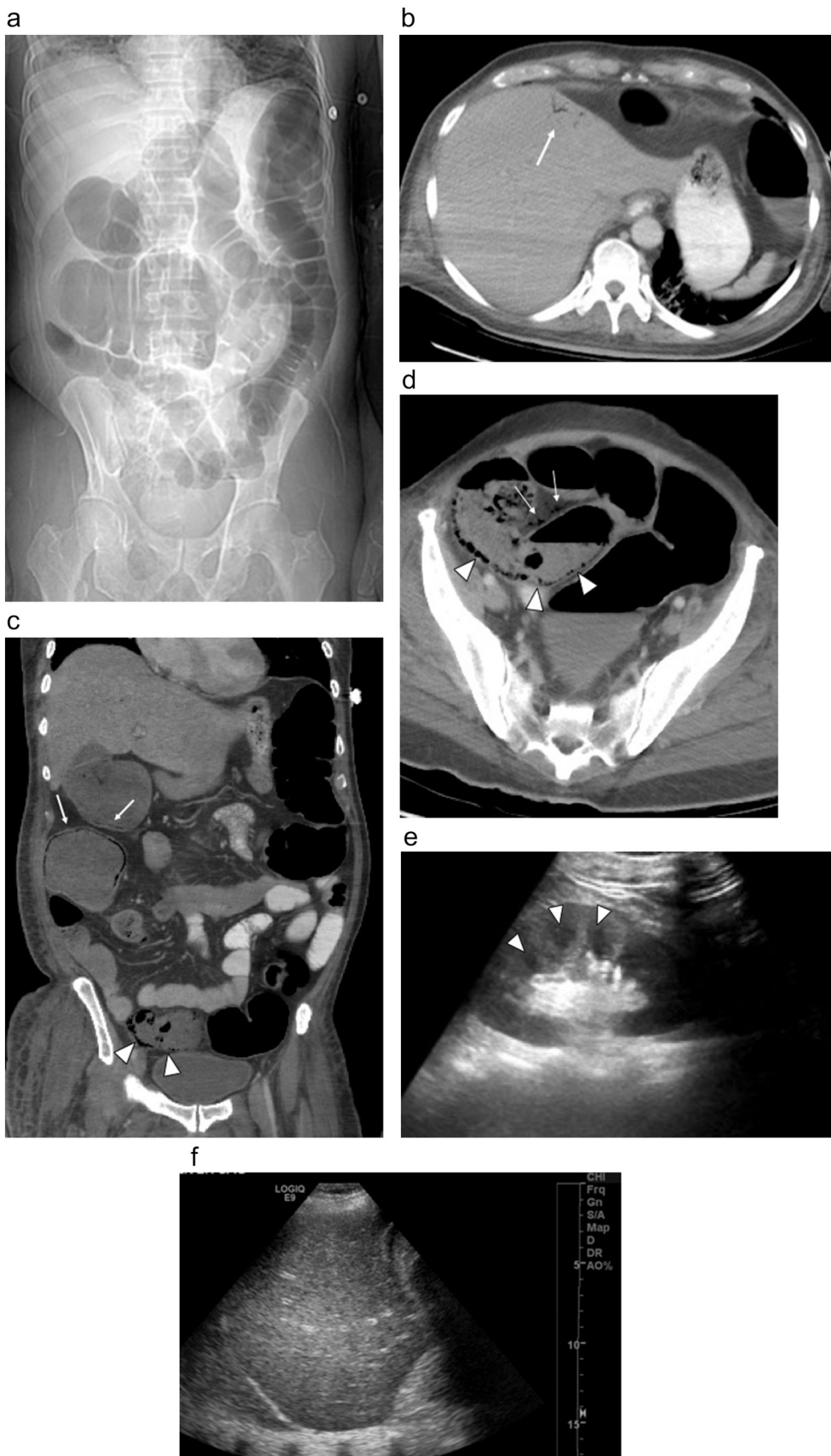


Fig. 21. 61-year-old man with no significant past medical history in the ICU for one month for respiratory failure due to COVID-19 pneumonia underwent CT scan of the chest, abdomen and pelvis because of persistent fever and leukocytosis despite broad spectrum antibiotics. (a) Supine scout shows bilateral interstitial infiltrates and marked colonic ileus. (b) Axial contrast-enhanced CT image shows portal venous gas (arrow) in the periphery of the left hepatic lobe. (c) Coronal CT images shows pneumatosis of the entire right colon (arrow) and a distal ileal loop (arrowhead) with mild mesenteric haziness. (d) Axial CT image shows extensive distal ileal pneumatosis (arrowhead) with adjacent branching mesenteric venous gas (thin arrows). Despite the findings of bowel ischemia, due to the patient's advanced septic condition, he was not a surgical candidate and died the following day. Additional imaging during his hospital course confirmed evidence of acute kidney injury with (e) longitudinal ultrasound image of his left kidney showing increased cortical echogenicity with increased conspicuity of the pyramids (arrowheads). He also had signs of liver injury with rising liver function tests and (f) longitudinal ultrasound image of the right hepatic lobe showing increased echogenicity suggestive of steatosis.

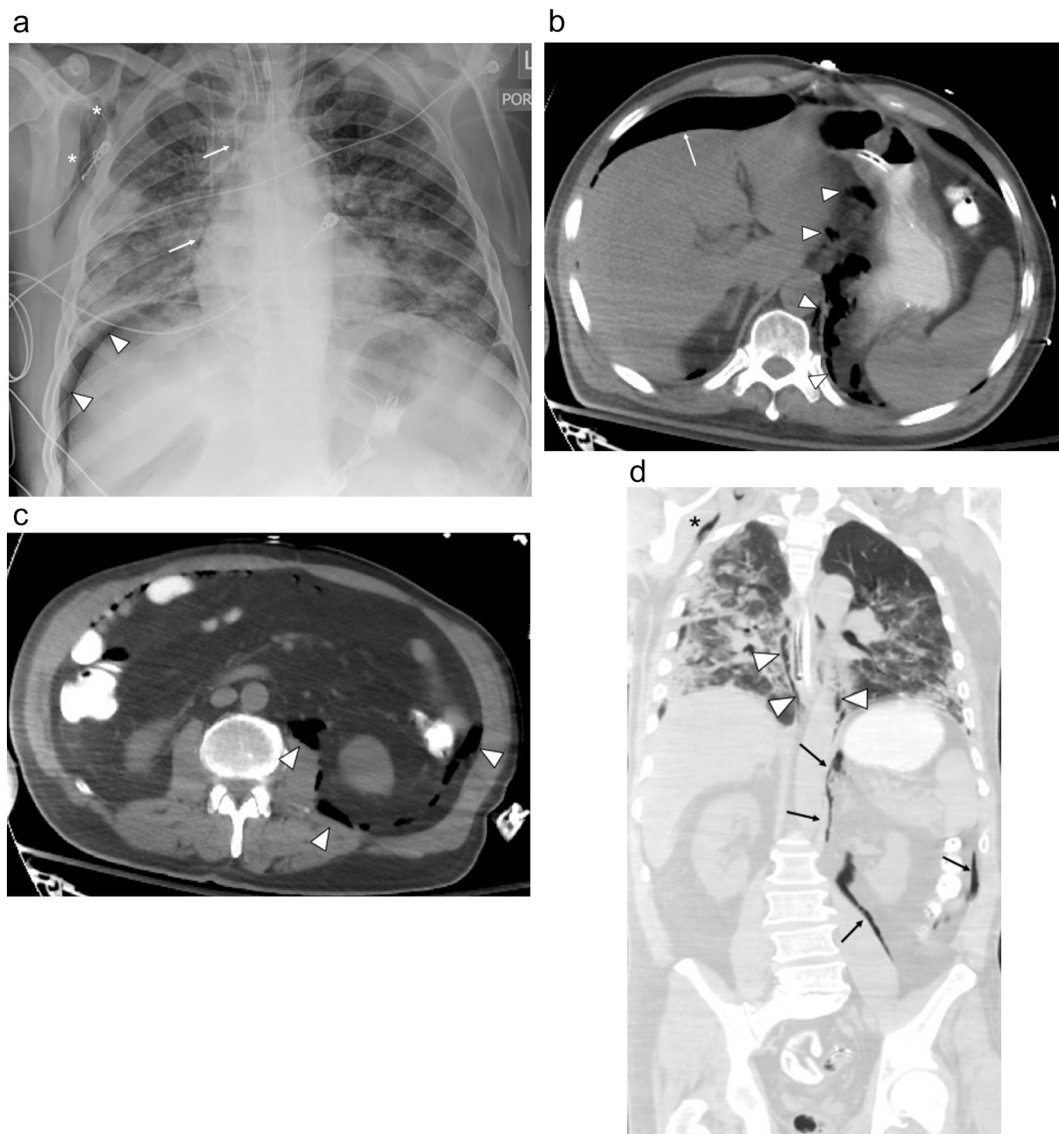


Fig. 22. 67-year-old man with stage III colon cancer hospitalized for COVID-19 pneumonia requiring mechanical ventilation for worsening respiratory distress. (a) Portable chest radiograph shows bilateral infiltrates consistent with pneumonia, with subcutaneous emphysema in the right axilla and neck (asterisk), pneumoperitoneum under the right hemidiaphragm (arrowheads), and small pneumomediastinum (arrows). Bilateral cervical central lines and endotracheal tube are present. (b) Subsequent non-contrast CT image performed with oral contrast via a nasogastric tube showed no extravasation of oral contrast. Pneumoperitoneum ventral to the liver (arrow) and tracking along the gastrohepatic ligament and subjacent left precrucal retroperitoneum (arrowheads) is noted. (c) More caudal CT image shows continuous tracking of retroperitoneal gas in the left retroperitoneum (arrowheads) anterior to the left psoas and in the left posterior pararenal space and left paracolic gutter. Small foci of extraluminal gas are visible in the right anterior abdomen. (d) Coronal CT image of the chest, abdomen and pelvis with lung windows shows the tracking nature of the pneumomediastinal air (arrowheads) coursing below the diaphragm (black arrows) into the left retroperitoneum and left paracolic gutter. Subcutaneous emphysema in the right axilla is noted (black asterisk). Bilateral pneumonia is noted and the nasogastric is partially visualized.

added benefit of detecting free air prompting a search for perforated gastric or duodenal ulcer as a source of GI bleed [Figs. 23,24].

2.4.7. Pseudomembranous colitis

Clostridium difficile colitis is frequently seen in severely ill COVID-19 patients after treatment with broad-spectrum antibiotics, which were given frequently early on in the pandemic and are still routinely given to COVID-19 patients with severe sepsis. In addition to antibiotic use, direct infection of enterocytes by the SARS-CoV-2 virus may disrupt the gut microbiome, increasing a patient's susceptibility to gastrointestinal infection, including *Clostridium difficile* [91]. Elderly patients, especially those living in long-term care facilities, have both an increased risk of severe COVID-19 illness and baseline elevated rates of *Clostridium difficile* colonization. This confounds our understanding of the true impact of

COVID-19 infection on the development of *Clostridium difficile* colitis [91]. In a retrospective clinical laboratory review of hospitalized patients with *Clostridium difficile* infection, 9 patients co-infected with COVID-19 were found, all of whom had severe COVID-19 illness and developed symptomatic *Clostridium difficile* colitis during their hospital course, all related to antibiotic administration [92].

Pseudomembranous colitis should be suggested whenever abdominopelvic CT scan shows a pattern of long segment colitis [Fig. 25] most commonly involving the rectosigmoid but which can be also be segmental involving the right or transverse colon or pan-colonic in extent. It is characterized by a more extensive pattern of circumferential mural thickening than other causes of colitis, with low attenuation intramural edema, and associated features including the “accordion sign,” the “target sign,” pericolonic stranding and ascites. Mural

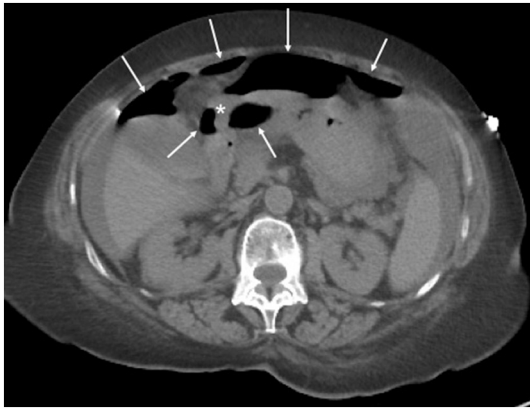


Fig. 23. 73-year-old woman found collapsed in her home was brought to the Emergency Room for abdominal pain and shortness of breath due to COVID-19 pneumonia. Non-contrast CT scan of the chest, abdomen and pelvis revealed multifocal pneumonia in the lung bases (not shown), moderate upper abdominal pneumoperitoneum (arrows) and moderate ascites with mild mesenteric and subcutaneous edema. The underlying duodenal bulbar region (*) is surrounded by free air. Exploratory laparotomy revealed a 1 cm anterior bulbar perforation that was repaired.

thickening is marked with a reported mean of 15 mm (range 3–32 mm), and is often irregular and shaggy [93].

3. Multisystem inflammatory syndrome in the pediatric population

Children with COVID-19 experience far less severe pulmonary disease than adults and account for only a minority of confirmed COVID-19 cases (2–8%) [94,95]. Although the majority of symptomatic children with COVID-19 have a respiratory illness, gastrointestinal symptoms have been reported in 33–35% of cases, with vomiting, diarrhea and abdominal most common [96,97]. This review will focus on the multifaceted post-infectious clinical and imaging manifestations of COVID-19 unique to children, coined multisystem inflammatory syndrome in children (MIS-C).

Although infected children tended to be only mildly symptomatic during the early months of the pandemic, by April and May of 2020, several medical centers in Europe and North America reported children with a multiorgan Kawasaki disease-like syndrome, consisting of fever and mucocutaneous rash, sometimes with features of toxic shock syndrome [98–100]. This syndrome was previously given various

overlapping definitions, however as more cases subsequently arose around the globe, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have given this entity the preferred label of “Multisystem Inflammatory Syndrome in Children” (MIS-C) [101,102].

MIS-C is an acute febrile illness characterized by inflammation, gastrointestinal symptoms, and cardiac manifestations [103,104]. Although SARS-CoV-2 is not definitively known to cause MIS-C, temporal occurrences to outbreaks in Europe and America are highly suggestive of a link, and some cases even occur in the presence of an acute respiratory infection [104,105]. Some MIS-C patients test positive for SARS-CoV-2 IgM and IgG antibodies, rather than testing positive for the virus on RT-PCR, and a minority of patients have recorded COVID-19 symptoms a few weeks prior to onset of MIS-C [95,103,106–108]. These findings raise the possibility that MIS-C represents a post-infectious immune-mediated phenomenon, rather than an acute viral infection [95,107,109].

While some features of MIS-C, such as fever, conjunctival injection, oropharyngeal erythema, and maculopapular rash, overlap with Kawasaki disease, the two syndromes appear to be separate entities [96,104,107]. MIS-C is characterized by various elevated inflammatory laboratory values (erythrocyte sedimentation rate, C-reactive protein, procalcitonin, interleukin-6, lactate dehydrogenase, D-dimer, and lymphopenia), myocardial dysfunction (elevated troponins, elevated pro-B-type natriuretic peptide, depressed ejection fraction), hypotension, shock, and acute kidney injury [98,108–112]. Kawasaki disease has lower rates of myocardial involvement than MIS-C, and is more frequently associated with coronary artery aneurysms. Kawasaki disease typically presents before 5 years of age, with the highest incidence of disease in Asia. In contrast, MIS-C usually occurs in older children and adolescents, and has not been reported in China or Japan.

Treatment of MIS-C is both supportive and directed, consisting of fluid resuscitation, vasopressors and inotropic support, anticoagulation, intravenous immune globulin (IVIG), glucocorticoids, and other immunomodulatory and antiviral drugs [95,98,105,106,109,110]. Critical cases may require mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Despite the severity of MIS-C at initial presentation, short-term outcomes are favorable, with the majority of patients recovering between a few days up to two weeks [110,113].

The diagnosis of MIS-C is made on clinical grounds, and imaging is not routinely indicated. However, imaging may be requested to exclude other acute pathologies, and imaging abnormalities are associated with fulminant illness [104]. While the vast majority of MIS-C patients experience gastrointestinal symptoms, a wide-ranged incidence

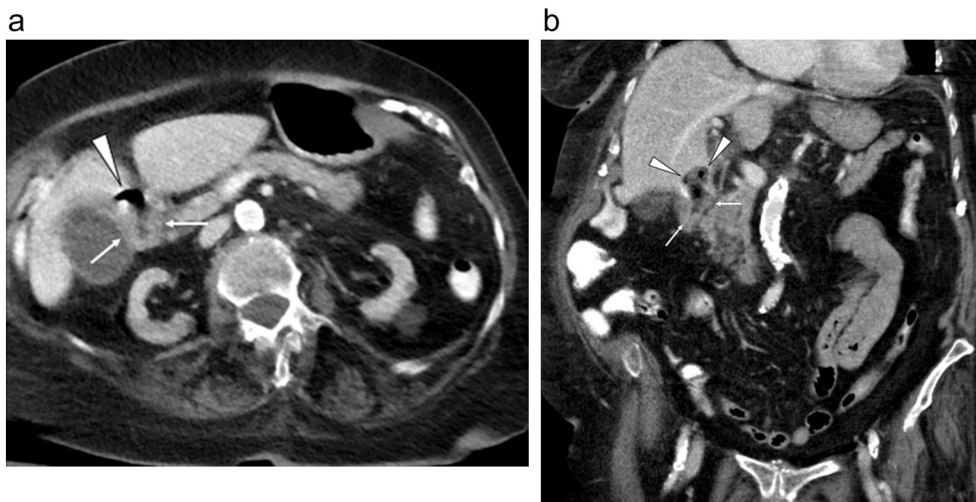


Fig. 24. 82-year-old woman with chronic obstructive pulmonary disease and end-stage renal disease sent from the nursing home 4 weeks after testing positive for COVID-19 with leukocytosis. (a) Axial contrast-enhanced CT image show a mildly thick-walled duodenal bulbar region (arrows) with a small anterior defect and extraluminal gas (arrowhead) consistent with locally perforated ulcer. Two small left renal cysts are present. (b) Coronal CT image shows a small walled off fluid collection with fluid and gas (arrowheads) in the adjacent right hepatic lobe at the level of the ulcer defect. Arrows indicate the thickened duodenal bulbar wall. Since the patient was not a candidate for surgical intervention she was treated conservatively with IV antibiotics.

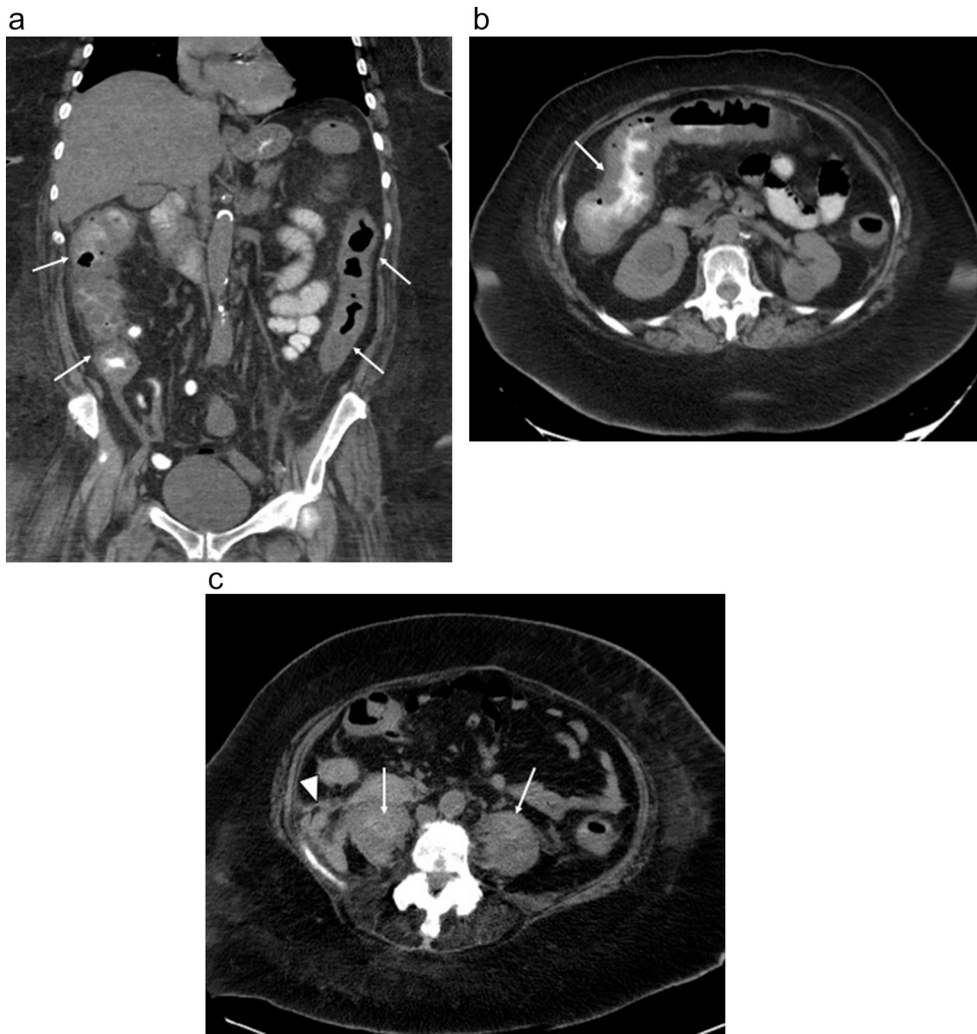


Fig. 25. 74-year-old morbidly obese woman with history of breast cancer and prolonged ICU hospitalization for severe COVID-19 pneumonia causing acute respiratory failure. One week after discharge to a nursing home, she was readmitted to the hospital for fever, hypotension and diarrhea. (a) Coronal non-contrast CT image with oral contrast shows prominent right and left colonic mural thickening (arrows) which involved the entire colon (not shown). (b) Axial image better shows the extent of mural thickening in the right colon (arrow) due to luminal contrast. *Clostridium difficile* infection was confirmed and she improved after treatment with oral Vancomycin and IV Flagyl. Her course was subsequently further complicated by gastrointestinal bleeding and retroperitoneal hemorrhage due to anticoagulation. (c) Axial non-contrast CT image shows hyperdense content expanding both psoas muscles (arrows), and in the right paracolic gutter (arrowhead).

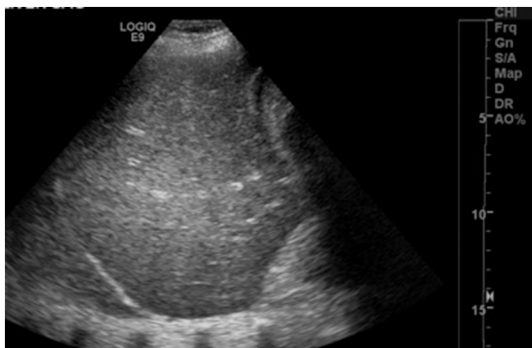


Fig. 26. Chest radiographs in two patients with MIS-C. 9-year-old girl with previously healthy girl who presented with cardiogenic shock and acute renal failure. Frontal chest radiograph shows symmetric hazy airspace opacities, increased interstitial markings, and bilateral small pleural effusions.

(5–70%) of respiratory symptoms has been reported [105,106,108–110,112]. Although this review is focused on the extrapulmonary manifestations of COVID-19, the cardiothoracic imaging findings of MIS-C will be included because the majority of MIS-C patients have pulmonary findings that are slightly different than those of routine COVID-19 pneumonia and may have associated cardiac sequelae.

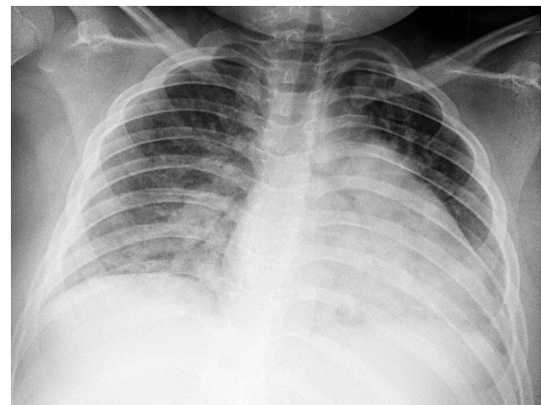


Fig. 27. Chest radiographs in two patients with MIS-C. 9-year-old boy with history of asthma, who presented with high fever, rash and abdominal pain. Frontal chest radiographs shows mild cardiomegaly and bilateral symmetric central consolidative airspace opacities.

3.1. Thoracic manifestations of MIS-C

The most common respiratory complaint in MIS-C is tachypnea, although some patients may progress to respiratory failure requiring mechanical ventilation, likely secondary to shock and cardiac

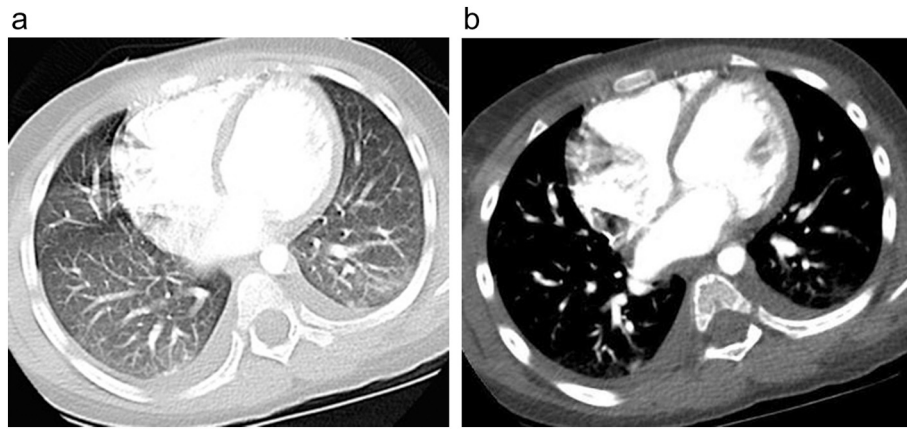


Fig. 28. 5-year-old girl with COVID-19 and MIS-C who presented with fever, conjunctivitis and vomiting. Axial chest CT image with lung (a) and soft tissue (b) windows shows mild dependent ground-glass opacities in both lungs, and bilateral small pleural effusions.

dysfunction [106,108,110,114]. While initial chest radiographs can be normal, as the disease progresses, common radiographic findings include bilateral diffuse airspace opacities with basilar predominance, peribronchial thickening or interstitial opacities, bilateral pleural effusions, and cardiomegaly [112,114–117] (Figs. 26,27). The pulmonary opacities tend to be hazy and symmetric, suggesting that they reflect pulmonary edema, ARDS, and/or third spacing. These phenomena may be secondary to cardiac dysfunction, the hyperinflammatory status of the patient, or possibly even the sequelae of aggressive fluid resuscitation [112,116–118]. Although chest radiograph findings in MIS-C can overlap with acute COVID-19 pneumonia, COVID usually presents as non-diffuse peripheral or subpleural opacities without pleural effusions and MIS-C usually presents as diffuse opacities with lower lobe predominance with pleural effusions [112,117]. It is interesting to note that patients with MIS-C may demonstrate abnormalities on chest radiographs even in the absence of lower respiratory tract symptoms

[114,117].

Chest CT is not routinely performed in MIS-C, but may be indicated in patients with sepsis or suspected pulmonary embolism [114,116]. The most common chest CT findings are bibasilar consolidation with atelectasis and bilateral pleural effusions, with diffuse ground-glass opacity, septal thickening, and mild hilar lymphadenopathy less common [114] (Fig. 28).

3.2. Cardiac manifestations of MIS-C

Echocardiography is routinely performed at baseline and in follow-up of patients with MIS-C. The most common finding is depressed left ventricular ejection fraction, with other findings including valvular regurgitation and small pericardial effusion [110,111,119,120]. Coronary artery ectasia or aneurysms have been seen in a minority of patients on echocardiogram and cardiac CT [111,114,121]. Postinfectious

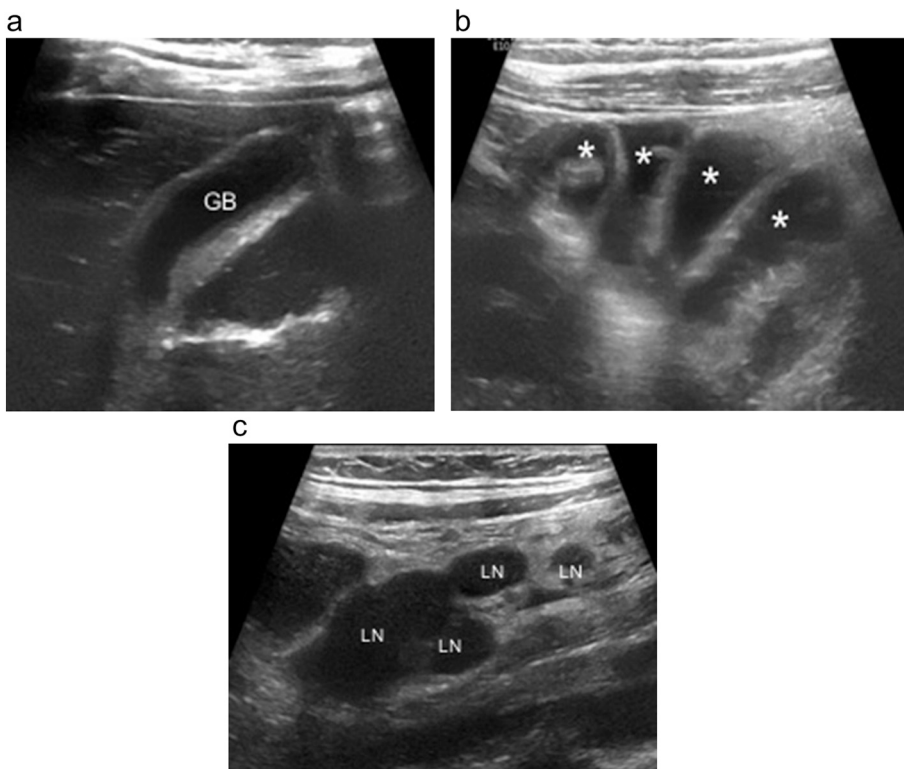


Fig. 29. 9-year-old girl with MIS-C who presented with abdominal pain, vomiting, fever, hypotension and acute renal failure. (a) Transverse gray-scale ultrasound image of the right upper quadrant shows mild wall thickening of the gallbladder (GB). (b) Transverse gray-scale ultrasound image of the right lower quadrant demonstrates multiple fluid-filled thick-walled loops of small bowel (*). (c) Sagittal gray-scale ultrasound image of the right lower quadrant shows multiple enlarged hypochoic mesenteric lymph nodes (LN) lacking echogenic hila, with thickening of the surrounding fat.



Fig. 30. 8-year-old girl with MIS-C who presented with abdominal pain, diarrhea, fever, tachycardia and hypotension. Coronal contrast-enhanced CT image demonstrates a cluster of enlarged mesenteric lymph nodes in the right lower quadrant (arrows). There is diffuse mild fluid distention of small and large bowel consistent with ileus.

myocarditis characterized by diffuse myocardial edema and hyperemia without evidence of fibrosis on delayed gadolinium-enhanced images has been reported on cardiac MRI [122].

3.3. Vascular manifestations of MIS-C

While adult COVID-19 patients are vulnerable to vascular complications, it remains unclear whether children with SARS-CoV-2 infection have an increased risk of thrombosis [123–127]. Data on thrombotic complications in pediatric COVID-19 and MIS-C is limited, likely due to

its low incidence, and currently published guidelines for thromboprophylaxis in children are extrapolated from the adult population. The highest reported rate of symptomatic imaging-confirmed thromboembolic disease (deep venous thrombosis or pulmonary embolism) in one multicenter registry of MIS-C was 7% [106]. It is thought that children with COVID-19 and/or MIS-C who experience hospital-associated thrombotic events have markedly elevated plasma D-dimer levels, or have one or more superimposed risk factors (e.g. prior history of venous thrombosis, indwelling central line, active malignancy, etc) [124,126]. Imaging is not necessarily required prior to initiation of therapy if a thromboembolic event is suspected, but can be obtained at the time of discharge, in order to guide the length and intensity of the anti-coagulation regimen [125]

3.4. Abdominal manifestations of MIS-C

Since patients with MIS-C most commonly present with gastrointestinal symptoms, often mimicking acute appendicitis, abdominal imaging is sometimes obtained even prior to recognition of the MIS-C diagnosis [98,114,128]. Commonly reported findings on abdominal radiographs, ultrasound, and CT include an ileus bowel gas pattern, mild ascites, gallbladder wall thickening, gallbladder sludge, bowel wall thickening, mesenteric lymphadenopathy, mesenteric edema or inflammatory change, and urinary bladder wall thickening [114,116,117,129] (Figs. 29,30,31). Bowel wall thickening, lymphadenopathy, and mesenteric changes can occur anywhere in the abdomen but are most commonly located in the right lower quadrant [130] (Fig. 32). A minority of patients has also demonstrated hepatosplenomegaly, splenic infarction, and increased renal echogenicity [114,116,131]. Acute hepatitis, defined as elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, was found in 43% of subjects in a single-center report, and may account for some of the abdominal ultrasound findings in MIS-C such as hepatomegaly, gallbladder wall thickening, and ascites [132].

3.5. Neurologic manifestations of MIS-C

Of patients with MIS-C who have undergone brain imaging, MRI is usually normal, however there are isolated reports of cortical signal abnormalities, papilledema, and infarct [114,117]. Cervical

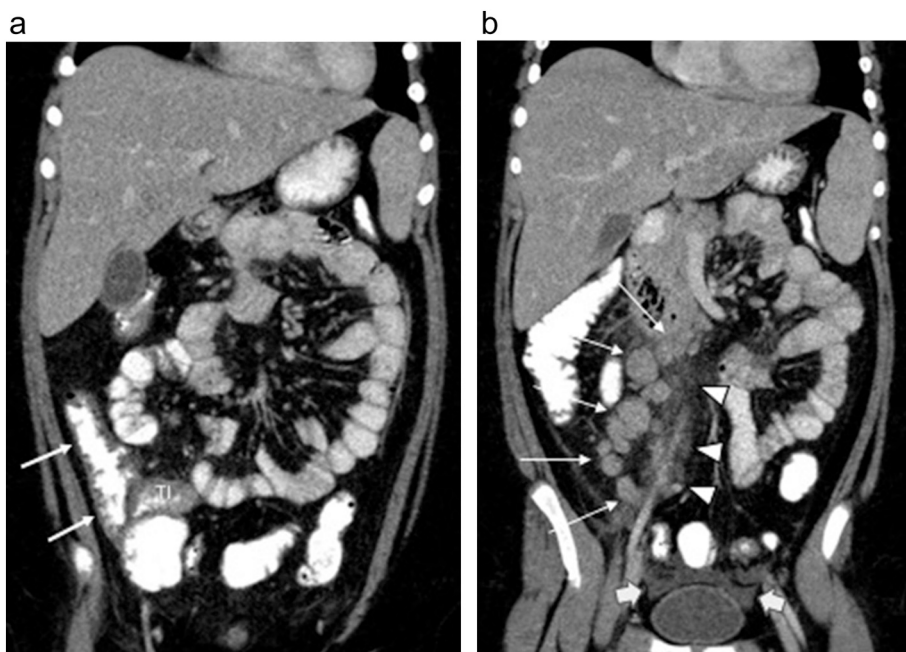


Fig. 31. 13-year-old boy with MIS-C who presented with abdominal pain, vomiting, diarrhea, fever, hypotension and elevated liver function tests. (a) Coronal contrast-enhanced CT image demonstrates mural thickening of the ascending colon (arrows) and terminal ileum (TI). Gallbladder wall thickening is noted. (b) Coronal image in a more posterior location shows a chain of enlarged mesenteric lymph nodes (thin arrows), with hazy infiltration of the mesentery (arrowheads). There is also small pelvic ascites (thick arrows).

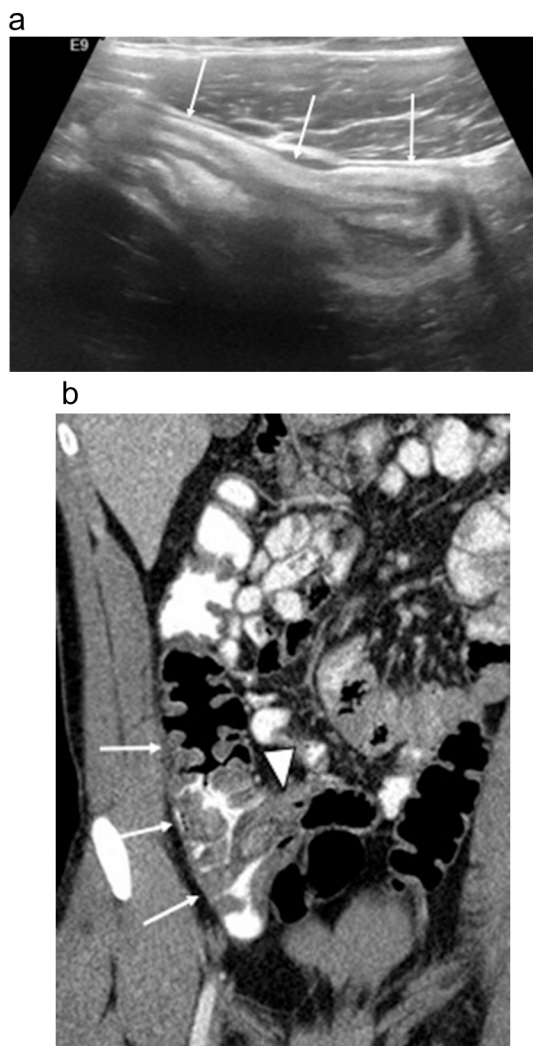


Fig. 32. 18-year-old man with MIS-C who presented with headache, right lower quadrant abdominal pain and elevated inflammatory markers. (a) Sagittal gray-scale ultrasound image of the right lower quadrant demonstrates wall thickening of the ascending colon and cecum (arrows). (b) Coronal contrast-enhanced CT image confirms moderate wall thickening of the right colon (arrows) and thickening of the terminal ileum (arrowhead).

lymphadenopathy has also been reported [112,117].

4. Conclusion

The SARS-CoV-2 virus has many extrathoracic facets in adults with a host of abdominal manifestations increasingly recognized. MIS-C is a unique postinfectious manifestation in children that encompasses gastrointestinal symptoms most commonly, but also includes unique pulmonary and cardiac manifestation different than those of typical COVID-19 respiratory infection. It is important for radiologists to have a better understanding of the pathophysiology of this disease and incidence of its involvement in various organ systems, along with improved familiarity with the broad spectrum of imaging manifestations of COVID-19. This will improve our ability to more accurately search for and diagnose COVID-19 sequelae and hopefully better assist clinicians in managing this complex disease. As the long-term effects of COVID-19 continue to emerge, we must stay vigilant and closely watch and monitor patients for any future unexpected manifestations of this novel COVID-19 disease.

References

- WHO Coronavirus Disease (COVID-19) Dashboard. WHO COVID-19 homepage. <https://covid19.who.int>.
- Benedetti C, Waldman M, Zaza G, Riella LV, Cravedi P. COVID-19 and the kidneys: an update. *Front Med* 2020;7:423. <https://doi.org/10.3389/fmed.2020.00423> [PMID: 32793615; PMCID: PMC7385132].
- Revzin MV, Raza S, Warhaws R, D'Agostino C, Srivastava NC, Bader AS, et al. Multisystem imaging manifestations of COVID-19, part 1: viral pathogenesis and pulmonary and vascular system complications. *RadioGraphics* 2020;40(6):1574–99. <https://doi.org/10.1148/rg.2020200149>.
- Bhayana R, Som A, Li MD, Carey DE, Anderson MA, Blake MA, et al. Abdominal imaging findings in COVID-19: preliminary observations. *Radiology* 2020 Oct;297(1):E207–E215. <https://doi.org/10.1148/radiol.2020201908> [Epub 2020 May 11. PMID: 32391742; PMCID: PMC7508000].
- Kumar A, Faiq MA, Pareek V, Raza K, Narayan RK, Prasoon P, et al. Relevance of SARS-CoV-2 related factors ACE2 and TMPRSS2 expressions in gastrointestinal tissue with pathogenesis of digestive symptoms, diabetes-associated mortality, and disease recurrence in COVID-19 patients. *Med Hypotheses* 2020;144:110271. <https://doi.org/10.1016/j.mehy.2020.110271>.
- Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol* 2020;18(9):2128–2130.e2. <https://doi.org/10.1016/j.cgh.2020.04.040>.
- Revzin MV, Raza S, Srivastava NC, Warshawsky R, D'Agostino C, Malhotra A, et al. Multisystem imaging manifestations of COVID-19, part 2: from cardiac complications to pediatric manifestations. *Radiographics* 2020;40(7):1866–92. <https://doi.org/10.1148/rg.2020200195> [PMID: 33136488; PMCID: PMC7646410].
- Lei P, Zhang L, Han P, Zheng C, Tong Q, Shang H, et al. Liver injury in patients with COVID-19: clinical profiles, CT findings, the correlation of the severity with liver injury. *Hepatol Int* 2020;14:733–42. <https://doi.org/10.1007/s12072-020-10087-1>.
- Zhao JN, Fan Y, Wu SD. Liver injury in COVID-19: a minireview. *World J Clin Cases* 2020;8(19):4303–10. <https://doi.org/10.12998/wjcc.v8.i19.4303>.
- Díaz LA, Idalosoaga F, Cannistra M, Candia R, Cabrera D, Barrera F, et al. High prevalence of hepatic steatosis and vascular thrombosis in COVID-19: a systematic review and meta-analysis of autopsy data. *World J Gastroenterol* 2020 Dec 28;26(48):7693–706. <https://doi.org/10.3748/wjg.v26.i48.7693> [PMID: 33505145; PMCID: PMC7789052].
- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020 May;5(5):428–30. [https://doi.org/10.1016/S2468-1253\(20\)30057-1](https://doi.org/10.1016/S2468-1253(20)30057-1) [Epub 2020 Mar 4. PMID: 32145190; PMCID: PMC7129165].
- Abdelmohsen MA, Alkandari BM, Gupta VK, ElBeheiry AA. Diagnostic value of abdominal sonography in confirmed COVID-19 intensive care patients. *Egypt J Radiol Nucl Med* 2020;51(1):198. <https://doi.org/10.1186/s43055-020-00317-9>.
- Medeiros AK, Barbisan CC, Cruz IR, et al. Higher frequency of hepatic steatosis at CT among COVID-19-positive patients. *Abdom Radiol* 2020;45(9):2748–54. <https://doi.org/10.1007/s00261-020-02648-7>.
- Goldberg-Stein S, Fink A, Paroder V, Kobi M, Yee J, Chernyak V. Abdominopelvic CT findings in patients with novel coronavirus disease 2019 (COVID-19). *Abdom Radiol* 2020 Sep;45(9):2613–23. <https://doi.org/10.1007/s00261-020-02669-2> [Epub 2020 Aug 6. PMID: 32761402; PMCID: PMC7406871].
- Franco-Moreno A, Piniella-Ruiz E, Montoya-Adarraga J, et al. Portal vein thrombosis in a patient with COVID-19. *Thromb Res* 2020;194:150–2. <https://doi.org/10.1016/j.thromres.2020.06.019>.
- Borazjani R, Seraj SR, Fallahi MJ, et al. Acute portal vein thrombosis secondary to COVID-19: a case report. *BMC Gastroenterol* 2020;20:386. <https://doi.org/10.1186/s12876-020-01518-2>.
- Ofori Andrew, Ramai Daryl, Novikov Anastasia, Sushma Venugopal. Portal vein thrombosis in a patient with COVID-19. *Am J Gastroenterol* September 2020;115(9):1545–6. <https://doi.org/10.14309/ajg.0000000000000781>.
- Jafari SH, Naseri R, Khalili N, Haseli S, Bahmani M. Portal vein thrombosis associated with COVID-19: points to consider. *BJR Case Rep* 2020;6:320200089. <https://doi.org/10.1093/bjr/abaa089>.
- Dane B, Smereka P, Wain R, Kim D, S Katz D. Hypercoagulability in patients with Coronavirus Disease (COVID-19): identification of arterial and venous thromboembolism in the abdomen, pelvis, and lower extremities. *AJR Am J Roentgenol* 2021 Jan;216(1):104–5. <https://doi.org/10.2214/AJR.20.23617> [Epub 2020 Sep 22. PMID: 32603220].
- Alhassan SM, Iqbal P, Fikrey L, MIM Ibrahim, Qamar MS, Chaponda M, et al. Post COVID 19 acute acalculous cholecystitis raising the possibility of underlying dysregulated immune response, a case report. *Ann Med Surg* 2020;60:434–7. <https://doi.org/10.1016/j.amsu.2020.11.031>.
- Balaphas A, Gkoufa K, Meyer J, Peloso A, Bornand A, McKee TA, et al. COVID-19 can mimic acute cholecystitis and is associated with the presence of viral RNA in the gallbladder wall. *J Hepatol* 2020;73(6):1566–8. <https://doi.org/10.1016/j.jhep.2020.08.020>.
- Somuncu E, Kara Y, Kızılkaya MC, Bozdağ E, Yıldız ZB, Özkan C, et al. Percutaneous cholecystostomy instead of laparoscopy to treat acute cholecystitis during the COVID-19 pandemic period: single center experience. *Ulus Travma Acil Cerrahi Derg* 2021;27(1):89–94 [English. doi: 10.14744/tjtes.2020.69804. PMID: 33394477].
- Campanile F, Podda M, Arezzo A, Botteri E, Sartori A, Guerrieri M, et al. *World J Emerg Surg* 2020;15:38. <https://doi.org/10.1186/s13017-020-00317-0>.
- Peckham-Cooper A, Coe PO, Clarke RW, Burke J, Lee MJ. The role of cholecystostomy drains in the management of acute cholecystitis during the

- SARS-CoV-2 pandemic. What can we expect? *Br J Surg* 2020;2020(107). <https://doi.org/10.1002/bjs.11907> [e447-e447].
- [25] Strasberg S, Hughes T. BRIEF Outline of Management of Symptomatic Gallbladder Disease and Acute Cholecystitis During the COVID-19 Pan Epidemic. https://www.facs.org/media/files/covid19/symptomatic_gallbladder_recommendations.ashx.
- [26] Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with coronavirus disease 19 pneumonia. *Gastroenterology* 2020;159(1):367–70. <https://doi.org/10.1053/j.gastro.2020.03.055>.
- [27] Cheung S, Delgado Fuentes A, Fetterman AD. Recurrent acute pancreatitis in a patient with COVID-19 infection. *Am J Case Rep* 2020;21:e927076. <https://doi.org/10.12659/AJCR.927076> [PMID: 32833954; PMCID: PMC7476744].
- [28] Silver SA, Beaubien-Souigny W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. *Kidney Med* 2021;3(1). <https://doi.org/10.1016/j.xkmc.2020.11.008> [83-98.e1, Epub 2020 Dec 9. PMID: 33319190; PMCID: PMC7723763].
- [29] Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, et al. Outcomes for patients with COVID-19 and acute kidney injury: a systematic review and meta-analysis. *Kidney Int Rep* 2020 Jun 25;5(8):1149–60. <https://doi.org/10.1016/j.ekir.2020.06.013> [PMID: 32775814; PMCID: PMC7314696].
- [30] Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. Mount Sinai COVID Informatics Center (MSCIC). AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 2021 Jan;32(1):151–60. <https://doi.org/10.1681/ASN.2020050615> [Epub 2020 Sep 3. PMID: 32883700; PMCID: PMC7894657].
- [31] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020 May;97(5):829–38. <https://doi.org/10.1016/j.kint.2020.03.005> [Epub 2020 Mar 20. PMID: 32247631; PMCID: PMC7110296].
- [32] Nadim MK, Forni LG, Mehta RL, Connor Jr MJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 2020;16(12):747–64. <https://doi.org/10.1038/s41581-020-00356-5> [Epub 2020 Oct 15. Erratum in: *Nat Rev Nephrol*. 2020 Nov 2; PMID: 33060844; PMCID: PMC7561246].
- [33] Tancredi T, DeWaters A, McGillen KL. Renal ultrasound findings secondary to COVID-19 related collapsing focal segmental glomerulosclerosis - a case report. *Clin Imaging* 2021 Mar;71:34–8. <https://doi.org/10.1016/j.clinimag.2020.11.011> [Epub 2020 Nov 5. PMID: 33171364; PMCID: PMC7644181].
- [34] Huang Q, Li J, Lyu S, Liang W, Yang R, Zhang R, et al. COVID-19 associated kidney impairment in adult: qualitative and quantitative analyses with non-enhanced CT on admission. *Eur J Radiol* 2020;131:109240. <https://doi.org/10.1016/j.ejrad.2020.109240> [Epub 2020 Aug 26. PMID: 32920219; PMCID: PMC7448815].
- [35] Faqeh S, Madkhali R. Acute reversible renal failure requiring temporary dialysis in a patient with COVID-19. *Radiol Case Rep* 2020;15(11):2449–52. <https://doi.org/10.1016/j.radcr.2020.08.049> [Epub 2020 Aug 25. PMID: 32864030; PMCID: PMC7447211].
- [36] Mumm JN, Osterman A, Ruzicka M, Stihl C, Vilsmaier T, Munker D, et al. Urinary frequency as a possibly overlooked symptom in COVID-19 patients: does SARS-CoV-2 cause viral cystitis? *Eur Urol* 2020 Oct;78(4):624–8. <https://doi.org/10.1016/j.eururo.2020.05.013> [Epub 2020 May 19. PMID: 32475747; PMCID: PMC7236674].
- [37] Lamb LE, Dhar N, Timar R, Wills M, Dhar S, Chancellor MB. COVID-19 inflammation results in urine cytokine elevation and causes COVID-19 associated cystitis (CAC). *Med Hypotheses* 2020;145:110375. <https://doi.org/10.1016/j.mehy.2020.110375> [Epub 2020 Nov 5. PMID: 33213997; PMCID: PMC7644255].
- [38] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020 Apr 30;382(18):1708–20. <https://doi.org/10.1056/NEJMoa2002032> [Epub 2020 Feb 28. PMID: 32109013; PMCID: PMC7092819].
- [39] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020 May 2;395(10234):1417–8. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5) [Epub 2020 Apr 21. PMID: 32325026; PMCID: PMC7172722].
- [40] Post A, den Deurwaarder ESG, Bakker SJL, de Haas RJ, van Meurs M, Gansevoort RT, et al. Kidney infarction in patients with COVID-19. *Am J Kidney Dis* 2020 Sep;76(3):431–5. <https://doi.org/10.1053/j.ajkd.2020.05.004> [Epub 2020 May 29. PMID: 32479921; PMCID: PMC7258815].
- [41] Wang T, Chen R, Liu C, Liang W, Guan W, Tang R, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol* 2020 May;7(5):e362–e363. [https://doi.org/10.1016/S2352-3026\(20\)30109-5](https://doi.org/10.1016/S2352-3026(20)30109-5) [Epub 2020 Apr 9. PMID: 32278361; PMCID: PMC7158946].
- [42] Klok FA, Kruijff MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020 Jul;191:145–7. <https://doi.org/10.1016/j.thromres.2020.04.013> [Epub 2020 Apr 10. PMID: 32291094; PMCID: PMC7146714].
- [43] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382(17):e38. <https://doi.org/10.1056/NEJMc2007575> [Epub 2020 Apr 8. PMID: 32268022; PMCID: PMC7161262].
- [44] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med* 2020 May 11;9(5):1417. <https://doi.org/10.3390/jcm9051417> [PMID: 32403217; PMCID: PMC7290769].
- [45] Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. *Front Pediatr* 2018;6:142. <https://doi.org/10.3389/fped.2018.00142> [PMID: 29876337; PMCID: PMC5974100].
- [46] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020 May;18(5):1094–9. <https://doi.org/10.1111/jth.14817> [Epub 2020 Apr 27. PMID: 32220112].
- [47] Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res* 2019 Sep;181:77–83. <https://doi.org/10.1016/j.thromres.2019.07.013> [Epub 2019 Jul 15. PMID: 31376606].
- [48] Piazza G, Morrow DA. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. *JAMA* 2020;324(24):2548–9. <https://doi.org/10.1001/jama.2020.23422> [PMID: 33226423].
- [49] Akin IB, Altay C, Eren Kutsoylu O, Secil M. Possible radiologic renal signs of COVID-19. *Abdom Radiol* 2021;46(2):692–5. <https://doi.org/10.1007/s00261-020-02671-8>.
- [50] Urban BA, Fishman EK. Tailored helical CT evaluation of acute abdomen. *Radiographics* 2000 May-Jun;20(3):725–49. <https://doi.org/10.1148/radiographics.20.3.g00ma12725> [Erratum in: *Radiographics* 2000 Sep-Oct;20(5):1494. PMID: 10835125].
- [51] Jeong JY, Kim SH, Lee HJ, Sim JS. Atypical low-signal-intensity renal parenchyma: causes and patterns. *Radiographics* 2002;22(4):833–46. <https://doi.org/10.1148/radiographics.22.4.g02j104833>. Jul-Aug. [PMID: 12110713].
- [52] Xu X, Chang XN, Pan HX, Su H, Huang B, Yang M, et al. Pathological changes of the spleen in ten patients with coronavirus disease 2019 (COVID-19) by postmortem needle autopsy. *Zhonghua Bing Li Xue Za Zhi* 2020;49(6):576–82. <https://doi.org/10.3760/cma.j.cn112151-20200401-00278> [PMID: 32340089].
- [53] Besutti G, Bonacini R, Iotti V, Marini G, Riva N, Dolci G, et al. Abdominal visceral infarction in 3 patients with COVID-19. *Emerg Infect Dis* 2020;26(8):1926–8. <https://doi.org/10.3201/eid2608.201161>.
- [54] Ghalib N, Pophali P, Chamorro-Pareja N, et al. Incidental asymptomatic splenic infarct in a COVID-19 patient. *Cureus Infect Dis* 2021;13(2):e13065. <https://doi.org/10.7759/cureus.13065>.
- [55] Balcar I, Se Seltzer, Davis S, Geller S. CT patterns of splenic infarction: a clinical and experimental study. *Radiology* 1984;151(3):723–9.
- [56] Luna A, Ribes R, Caro P, et al. MRI of focal splenic lesions without and with dynamic gadolinium enhancement. *AJR* 2006;186:1533–47.
- [57] Urrutia M, Mergo PJ, Ros LH, et al. Cystic masses of the spleen: radiologic-pathologic correlation. *Radiographics* 1996;16:107–29.
- [58] Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* 2020;69(6):1010–8. <https://doi.org/10.1136/gutjnl-2020-320953>.
- [59] Silva FAFD, Brito BB, Santos MLC, et al. COVID-19 gastrointestinal manifestations: a systematic review. *Rev Soc Bras Med Trop* 2020;53:e20200714. Published 2020 Nov 25. <https://doi.org/10.1590/0037-8682-0714-2020>.
- [60] Kaafarani HMA, El Moheb M, Hwabebjire JO, Naar L, Christensen MA, Breen K, et al. Gastrointestinal complications in critically ill patients with COVID-19. *Ann Surg* 2020;272(2):e61–e2. Epub 2020/07/18. <https://doi.org/10.1097/S.LA.0000000000004004> [PubMed PMID: 32675498; PubMed Central PMCID: PMC7268843].
- [61] Lui K, Wilson MP, Low G. Abdominal imaging findings in patients with SARS-CoV-2 infection: a scoping review. *Abdom Radiol* 2021;46(3):1249–55. <https://doi.org/10.1007/s00261-020-02739-5>.
- [62] Dane B, Brusca-Augello G, Kim D, Katz DS. Unexpected findings of Coronavirus Disease (COVID-19) at the lung bases on Abdominopelvic CT. *AJR Am J Roentgenol* 2020 Sep;215(3):603–6. <https://doi.org/10.2214/AJR.20.23240> [Epub 2020 Apr 22. PMID: 32319792].
- [63] Barkmeier DT, Stein EB, Bojicic K, Otemuyiwa B, Vummidi D, Chughtai A, et al. Abdominal CT in COVID-19 patients: incidence, indications, and findings. *Abdom Radiol* 2021 Mar;46(3):1256–62. <https://doi.org/10.1007/s00261-020-02747-5> [Epub 2020 Sep 19. PMID: 32949274; PMCID: PMC7501764].
- [64] Horvat N, Pinto PVA, Araujo-Filho JAB, Santos JMMM, Dias AB, Miranda JA, et al. Abdominal gastrointestinal imaging findings on computed tomography in patients with COVID-19 and correlation with clinical outcomes. *Eur J Radiol Open* 2021;8:100326. <https://doi.org/10.1016/j.ejro.2021.100326> [Epub 2021 Jan 18. PMID: 33495735; PMCID: PMC7816627].
- [65] Takifuji K, Terasawa H, Oka M, Sahara M, Hara T, Itoh H. Computerized tomography scan findings of a patient with severe enterocolitis associated with the coronavirus disease 2019: a case report. *Res Square* 2020. <https://doi.org/10.21203/rs.3.rs-21006/v1> [Accessed July 20, 2020].
- [66] Carvalho A, Alqusairi R, Adams A, et al. SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease. *Am J Gastroenterol* 2020;115(6):942–6. <https://doi.org/10.14309/ajg.0000000000000667>.
- [67] Khader M, Bishawi Ahmed Al, Kambal Aalaa, Abdelmajid Alaaeldin. SARS-CoV-2 infection presenting as colitis with chest and abdomen CT findings. *Radiol Case Rep* 2020;15(11):2427–32.
- [68] Ibrahim YS, Karuppasamy G, Parambil JV, Alsoub H, Al-Shokri SD. Case report: paralytic ileus: a potential extrapulmonary manifestation of severe COVID-19. *Am J Trop Med Hyg* 2020;103(4):1600–3. Epub 2020/09/03. <https://doi.org/10.4269/ajtmh.20-0894> [PubMed PMID: 32876011; PubMed Central PMCID: PMC7543796].

- [69] Hwabejire JO, Saillant N, King R, Velmahos GC, HMA Kaafarani. Colonic paralytic ileus in Covid-19 patients. *ACS Case Rev Surg* 2020;3(1):65–71.
- [70] Lakshmanan S, Toubia N. Pneumatosis Intestinalis in COVID-19. *Clin Gastroenterol Hepatol* 2020. <https://doi.org/10.1016/j.cgh.2020.05.048>. Epub 2020/06/03. [PubMed PMID: 32485300; PubMed Central PMCID: PMC7260506].
- [71] Al Mahruqi G, Stephen E, Abdelhedy I, Al Wahaibi K. Our early experience with mesenteric ischemia in COVID-19 positive patients. *Ann Vasc Surg* 2021. <https://doi.org/10.1016/j.avsg.2021.01.064>. Epub 2021/01/29. [PubMed PMID: 33508450; PubMed Central PMCID: PMC7839392].
- [72] Ignat M, Philouze G, Aussenac-Belle L, Faucher V, Collange O, Mutter D, et al. Small bowel ischemia and SARS-CoV-2 infection: an underdiagnosed distinct clinical entity. *Surgery* 2020;168(1):14–6. Epub 2020/06/01. <https://doi.org/10.1016/j.surg.2020.04.035> [PubMed PMID: 32473831; PubMed Central PMCID: PMC7198136].
- [73] Keshavarz P, Raffie F, Kavandi H, Goudarzi S, Heidari F, Gholamrezaezhad A. Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation [published online ahead of print, 2020 Dec 8]. *Clin Imaging* 2020;73:86–95. <https://doi.org/10.1016/j.clinimag.2020.11.054>.
- [74] Furukawa A, Kanasaki S, Kono K, Wakamiya M, Tanaka T, Takahashi M, et al. CT diagnosis of acute mesenteric ischemia from various causes. *Am J Roentgenol* 2009;192(2):408–16.
- [75] Kernagis LY, Levine MS, Jacobs JE. Pneumatosis intestinalis in patients with ischemia: correlation of CT findings with viability of the bowel. *AJR Am J Roentgenol* 2003;180(3):733–6. <https://doi.org/10.2214/ajr.180.3.1800733>. Mar. [PMID: 12591685].
- [76] Gartland RM, Velmahos GC. Bowel necrosis in the setting of COVID-19. *J Gastrointest Surg* 2020;24(12):2888–9. Epub 2020/05/05. <https://doi.org/10.1007/s11605-020-04632-4> [PubMed PMID: 32363540; PubMed Central PMCID: PMC7196179].
- [77] Meini S, Zini C, Passaleva MT, Frullini A, Fusco F, Carpi R, et al. Pneumatosis intestinalis in COVID-19. *BMJ Open Gastroenterol* 2020;7(1). <https://doi.org/10.1136/bmjgast-2020-000434>. Epub 2020/06/12. [PubMed PMID: 32522754; PubMed Central PMCID: PMC7287500].
- [78] Paul T, Joy AR, Alsoub HARS, Parambil JV. Case report: ischemic colitis in severe COVID-19 pneumonia: an unforeseen gastrointestinal complication. *Am J Trop Med Hyg* 2021 Jan;104(1):63–5. <https://doi.org/10.4269/ajtmh.20-1262> [PMID: 33146121; PMCID: PMC790084].
- [79] Chan KH, Lim SL, Damati A, et al. Coronavirus disease 2019 (COVID-19) and ischemic colitis: an under-recognized complication. *Am J Emerg Med* 2020;38(12):2758.e1–4. <https://doi.org/10.1016/j.ajem.2020.05.072>.
- [80] Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: interpretation of the clinical literature in the light of laboratory experiment. *Medicine* 1944;23:281–358 [PubMed PMID: 00005792-194412000-00001].
- [81] Vidrio Duarte R, Vidrio Duarte E, Gutierrez Ochoa J, Gaviria Leiva MC, Pimentel-Hayashi JA. Pneumoperitoneum in a COVID-19 patient due to the Macklin Effect. *Cureus* 2021;13(2):e13200. Epub 2021/02/13. <https://doi.org/10.7759/cureus.13200> [PubMed PMID: 33575160; PubMed Central PMCID: PMC7870111].
- [82] McGuinness G, Zhan C, Rosenberg N, Azour L, Wickstrom M, Mason DM, et al. Increased incidence of barotrauma in patients with COVID-19 on invasive mechanical ventilation. *Radiology* 2020;297(2):E252–62.
- [83] Kangas-Dick A, et al. Gastrointestinal perforation in a critically ill patient with COVID-19 pneumonia. *SAGE Open Med Case Rep* 2020;8:2050313X20940570.
- [84] Mauro A, De Grazia F, Lenti MV, Penagini R, Frego R, Ardizzone S, et al. Upper gastrointestinal bleeding in COVID-19 inpatients: incidence and management in a multicenter experience from Northern Italy. *Clin Res Hepatol Gastroenterol* 2020; 45(3):1–8. 101521, Epub 2020/09/06. <https://doi.org/10.1016/j.clinre.2020.07.025>. PubMed PMID: 32888875; PubMed Central PMCID: PMC7427596.
- [85] Vanella G, Capurso G, Burti C, Fanti L, Ricciardiello L, Souza Lino A, et al. Gastrointestinal mucosal damage in patients with COVID-19 undergoing endoscopy: an international multicentre study. *BMJ Open Gastroenterol* 2021;8(1). <https://doi.org/10.1136/bmjgast-2020-000578>. Epub 2021/02/26. [PubMed PMID: 33627313; PubMed Central PMCID: PMC7907837].
- [86] Wells ML, Hansel SL, Bruining DH, Fletcher JG, Froemming AT, Barlow JM, et al. CT for evaluation of acute gastrointestinal bleeding. *Radiographics* 2018;38(4): 1089–107. <https://doi.org/10.1148/rg.2018170138> [Epub 2018 Jun 8. PMID: 29883267].
- [87] Hamilton JD, Kumaravel M, Censullo ML, Cohen AM, Kievlan DS, West OC. Multidetector CT evaluation of active extravasation in blunt abdominal and pelvic trauma patients. *Radiographics* 2008;28(6):1603–16. <https://doi.org/10.1148/rg.286085522>. Oct. [PMID: 18936024].
- [88] Lubner M, Menias C, Rucker C, Bhalla S, Peterson CM, Wang L, et al. Blood in the belly: CT findings of hemoperitoneum. *Radiographics* 2007;27(1):109–25. <https://doi.org/10.1148/rg.271065042>. Jan-Feb. [PMID: 17235002].
- [89] Artigas JM, Martí M, Soto JA, Esteban H, Pinilla I, Guillén E. Multidetector CT angiography for acute gastrointestinal bleeding: technique and findings. *Radiographics* 2013;33(5):1453–70. <https://doi.org/10.1148/rg.335125072>. Sep-Oct. [PMID: 24025935].
- [90] Alavi A, Dann RW, Baum S, Biery DN. Scintigraphic detection of acute gastrointestinal bleeding. *Radiology* 1977;124(3):753–6. <https://doi.org/10.1148/124.3.753>. Sep. [PMID: 302010].
- [91] Spigaglia P. Clostridioides difficile infection in the COVID-19 era: old and new problems. *Pol Arch Intern Med* 2021;131(2):118–20. Epub 2021/03/02. <https://doi.org/10.20452/pamw.15838> [PubMed PMID: 33641318].
- [92] Sandhu A, Tillotson G, Polistico J, Salimnia H, Cranis M, Moshos J, et al. Clostridioides difficile in COVID-19 patients, Detroit, Michigan, USA, March–April 2020. *Emerg Infect Dis* 2020;26(9). <https://doi.org/10.3201/eid2609.202126>. Epub 2020/05/23. [PubMed PMID: 32441243; PubMed Central PMCID: PMC7454075].
- [93] Kawamoto S, Horton KM, Fishman EK. Pseudomembranous colitis: spectrum of imaging findings with clinical and pathologic correlation. *RadioGraphics* 1999;19(4):887–97.
- [94] Carsetti R, Quintarelli C, Quinti I, Mortari E, Piano, Zumla A, Ippolito G, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? *Lancet Child Adolesc Health* 2020;4:414–6. [https://doi.org/10.1016/s2352-4642\(20\)30135-8](https://doi.org/10.1016/s2352-4642(20)30135-8).
- [95] Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis* 2020;20:e276–88. [https://doi.org/10.1016/s1473-3099\(20\)30651-4](https://doi.org/10.1016/s1473-3099(20)30651-4).
- [96] Pousa PA, Mendonça TSC, Oliveira EA, Simões ESAC. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations. *J Pediatr* 2020. <https://doi.org/10.1016/j.jpeds.2020.08.007>.
- [97] Miller J, Martinez M, Margolis K. Gastrointestinal symptoms prevalent in both children with MIS-C and those with COVID-19. *Gastroenterology* 2021. <https://doi.org/10.1053/j.gastro.2021.01.016>.
- [98] Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020;383:334–46. <https://doi.org/10.1056/NEJMoa2021680>.
- [99] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; 395:1607–8. [https://doi.org/10.1016/s0140-6736\(20\)31094-1](https://doi.org/10.1016/s0140-6736(20)31094-1).
- [100] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–8. [https://doi.org/10.1016/s0140-6736\(20\)31103-x](https://doi.org/10.1016/s0140-6736(20)31103-x).
- [101] CDC Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19). Accessed March 5 2021. Available at, <https://emergency.cdc.gov/han/2020/han00432.asp>.
- [102] World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Accessed March 5, 2021. Available at, <https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>.
- [103] Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med* 2020;383:347–58. <https://doi.org/10.1056/NEJMoa2021756>.
- [104] Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC, Herberg J, Bajolle F, Randanne PC, et al. Multisystem inflammatory syndrome in children: an international survey. *Pediatrics* 2021;147. <https://doi.org/10.1542/peds.2020-024554>.
- [105] Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev* 2020. <https://doi.org/10.1016/j.prvr.2020.08.001>.
- [106] Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Tenforde syndrome in pediatric COVID-19 patients: a meta-analysis. *World J Pediatr* 2021;1–11. <https://doi.org/10.1007/s12519-021-00419-y>.
- [107] Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol* 2020;20:453–4. <https://doi.org/10.1038/s41577-020-0367-5>.
- [108] Reiff DD, Mannion ML, Samuy N, Scalici P, Cron RQ. Distinguishing active pediatric COVID-19 pneumonia from MIS-C. *Pediatr Rheumatol Online J* 2021; 19:21. <https://doi.org/10.1186/s12969-021-00508-2>.
- [109] Toraih EA, Hussein MH, Elshazli RM, Kline A, Munshi R, Sultana N, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation* 2020;142:429–36. <https://doi.org/10.1161/circulationaha.120.048360>.
- [110] Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): a multi-institutional Study from New York City. *J Pediatr* 2020;224:24–9. <https://doi.org/10.1016/j.jpeds.2020.06.045>.
- [111] Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. *J Am Coll Cardiol* 2020; 76:1947–61. <https://doi.org/10.1016/j.jacc.2020.08.056>.
- [112] Rostad BS, Shah JH, Rostad CA, Jaggi P, Richer EJ, Linam LE, et al. Chest radiograph features of multisystem inflammatory syndrome in children (MIS-C) compared to pediatric COVID-19. *Pediatr Radiol* 2021;51:231–8. <https://doi.org/10.1007/s00247-020-04921-9>.
- [113] Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. *Circulation* 2021;143:78–88. <https://doi.org/10.1161/circulationaha.120.049836>.
- [114] Hameed S, Elbaaly H, Reid CEL, Santos RMF, Shivamurthy V, Wong J, et al. Spectrum of imaging findings at chest radiography, US, CT, and MRI in multisystem inflammatory syndrome in children associated with COVID-19. *Radiology* 2021;298:E1–e10. <https://doi.org/10.1148/radiol.2020202543>.
- [115] Biko DM, Ramirez-Suarez KI, Barrera CA, Banerjee A, Matsubara D, Kaplan SL, et al. Imaging of children with COVID-19: experience from a tertiary children's

- hospital in the United States. *Pediatr Radiol* 2021;51:239–47. <https://doi.org/10.1007/s00247-020-04830-x>.
- [116] Blumfield E, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging findings in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease (COVID-19). *AJR Am J Roentgenol* 2021;216:507–17. <https://doi.org/10.2214/ajr.20.24032>.
- [117] Fenlon Iii EP, Chen S, Ruzal-Shapiro CB, Jaramillo D, Maddocks ABR. Extracardiac imaging findings in COVID-19-associated multisystem inflammatory syndrome in children. *Pediatr Radiol* 2021:1–9. <https://doi.org/10.1007/s00247-020-04929-1>.
- [118] Trout AT, Westra SJ. Imaging in support of the clinical diagnoses of COVID-19 and multisystem inflammatory syndrome in children. *Pediatr Radiol* 2021:1–2. <https://doi.org/10.1007/s00247-021-04999-9>.
- [119] Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. *EclinicalMedicine* 2020;26:100527. <https://doi.org/10.1016/j.eclinm.2020.100527>.
- [120] Theocharis P, Wong J, Pushparajah K, Mathur SK, Simpson JM, Pascall E, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020. <https://doi.org/10.1093/ehjci/jeaa212>.
- [121] Sperotto F, Friedman KG, Son MFB, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr* 2021;180:307–22. <https://doi.org/10.1007/s00431-020-03766-6>.
- [122] Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. *Radiology* 2020;297:E283–e288. <https://doi.org/10.1148/radiol.2020202288>.
- [123] Al-Ghafry M, Aygun B, Appiah-Kubi A, Vlachos A, Ostovar G, Capone C, et al. Are children with SARS-CoV-2 infection at high risk for thrombosis? Viscoelastic testing and coagulation profiles in a case series of pediatric patients. *Pediatr Blood Cancer* 2020;67:e28737. <https://doi.org/10.1002/pbc.28737>.
- [124] Goldenberg NA, Sochet A, Albisetti M, Biss T, Bonduel M, Jaffray J, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. *J Thromb Haemost* 2020;18:3099–105. <https://doi.org/10.1111/jth.15073>.
- [125] Karimi M, Bozorgi H, Zarei T, Bordbar M, Amanati A, Safaei A, et al. Antithrombotic prophylaxis in children and adolescents' patients with SARS-CoV-2 (COVID-19) infection: a practical guidance for clinicians. *Acta Biomed* 2020;91:e2020170. <https://doi.org/10.23750/abm.v91i4.10720>.
126. Loi M, Branchford B, Kim J, Self C, Nuss R. COVID-19 anticoagulation recommendations in children. *Pediatr Blood Cancer* 2020;67:e28485. <https://doi.org/10.1002/pbc.28485>.
- [127] Del Borrello G, Giraudo I, Bondone C, Denina M, Garazzino S, Linari C, et al. SARS-CoV-2-associated coagulopathy and thromboembolism prophylaxis in children: a single-center observational study. *J Thromb Haemost* 2021;19:522–30. <https://doi.org/10.1111/jth.15216>.
128. Tullie L, Ford K, Bisharat M, Watson T, Thakkar H, Mullassery D, et al. Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children. *Lancet Child Adolesc Health* 2020;4:e19–20. [https://doi.org/10.1016/s2352-4642\(20\)30165-6](https://doi.org/10.1016/s2352-4642(20)30165-6).
- [129] Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to Coronavirus Disease 2019: a single center experience of 44 cases. *Gastroenterology* 2020;159. <https://doi.org/10.1053/j.gastro.2020.05.079> (1571–1574.e1572).
- [130] Sahn B, Eze OP, Edelman MC, Chougar CE, Thomas RM, Schleien CL, et al. Features of intestinal disease associated with COVID-related multisystem inflammatory syndrome in children. *J Pediatr Gastroenterol Nutr* 2021;72:384–7. <https://doi.org/10.1097/MPG.0000000000002953>.
- [131] Morparia K, Park MJ, Kalyanaraman M, McQueen D, Bergel M, Phatak T. Abdominal imaging findings in critically ill children with multisystem inflammatory syndrome associated with COVID-19. *Pediatr Infect Dis J* 2021;40:e82–3. <https://doi.org/10.1097/inf.0000000000002967>.
- [132] Cantor A, Miller J, Zachariah P, DaSilva B, Margolis K, Martinez M. Acute hepatitis is a prominent presentation of the multisystem inflammatory syndrome in children: a single-center report. *Hepatology* 2020;72:1522–7. <https://doi.org/10.1002/hep.31526>.