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Severe Gastrointestinal Manifestations of COVID-19

Tavia M Buysse[1]; Sameer Bhalla[1]; VIkram S Kotwal[2]*

[1]Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA.

[2]Division of Gastroenterology and Hepatology, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, USA.

***Corresponding Author(s): Vikram S Kotwal**

Assistant Professor, Division of Gastroenterology and Hepatology John H Stroger, Jr Hospital of Cook County, 1969 W Ogden Avenue, Chicago, IL, 60612, USA.

Tel: 312-864-6000; Email: drvikramkotwal@gmail.com

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic began almost 2 years ago but new and rare complications are still being reported. It is well known that COVID-19 infection is commonly accompanied by Gastrointestinal (GI) symptoms, including dysgeusia, nausea, vomiting, diarrhea, and abdominal discomfort [1-3). In fact, GI symptoms may be the sole presenting concern in patients found to have COVID-19 infection and a small proportion may not experience any respiratory symptoms [4]. Many previous reviews have focused on the presenting GI symptoms and relatively mild conditions associated with SARS-CoV-2, such as liver function test abnormalities [3,5,6]. Efforts to better understand the association and mechanism leading to GI symptoms and complications of COVID-19 are ongoing. However, it has been established that COVID-19 is able to directly infect many cells of the GI tract via the Angiotensin-Converting Enzyme 2 (ACE2) receptor and tissue biopsies from multiple areas of the GI tract have been positive for COVID-19 RNA by PCR [7,8]. Furthermore, COVID-19 has been found in substances produced by the GI tract, including bile and stool, suggesting fecal-oral transmission of the virus is possible [9,10]. Severe GI manifestations of COVID-19 infection are less commonly described but are important causes of comorbidity and mortality in patients with active or recently recovered from SARS-CoV-2 infection [11]. We present a compre-

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hensive overview of known severe manifestations of COVID-19 infection involving the GI and hepatobiliary organs that has been published in the literature to date.

Methods

Leading gastroenterology journals were queried for articles related to severe gastrointestinal pathology from January 2020 to December 2021. Search phrases used included COVID, COVID-19, coronavirus, and SARS-CoV-2. Articles selected for inclusion were those that focused on manifestations in the GI tract that were attributed to SARS-CoV-2.

Esophagus

Cases of esophagitis and esophageal ulcers have been reported in association with COVID-19 infection, as well as rare instances of hemorrhagic esophagitis and acute esophageal necrosis [4,12-14]. Esophageal mucosal biopsies showed small vessel thrombosis and mucosal necrosis [13]. COVID-19 infection is known to cause a pro-thrombotic state, and micro thrombi leading to mucosal necrosis has been suggested as the underlying mechanism for these cases [13]. A previous study has demonstrated that the esophageal epithelium expresses high amounts of ACE2 receptors and may explain the severe manifestations of COVID in the esophagus described above [1]. Virus-like particles have been found on electron microscopy of epithelial and endothelial cells in the esophagus [4]. Additionally, esophageal brushings have tested positive for SARS-CoV-2 RNA [14]. This provides strong evidence for the idea that COVID is able to directly invade the esophageal mucosa. Esophageal involvement by COVID typically presents with odynophagia, dysphagia, regurgitation of food, and signs of bleeding such as melena or hematemesis [4,12,13,15].

SARS-CoV-2 has known neurological complications, from which the esophagus is not spared. A case of rumination syndrome associated with COVID-19 was reported in a young man who presented with persistent regurgitation of swallowed food and weight loss. Rumination syndrome was diagnosed after negative gastric emptying study, barium swallow, esophageal pH impedance testing, and esophageal manometry [16]. In another case, a woman with a history of GERD status post Toupet fundoplication presented with new onset worsening heartburn not responsive to anti-reflux medications one week after testing positive for COVID-19. Gastric emptying study, upper GI series, and EGD were unremarkable and she was diagnosed with esophageal hypersensitivity after symptoms resolved two months later when she tested negative for SARS-CoV-2. COVID-19 infection of the vagus nerve leading to hypersensitivity and allodynia was suggested as a potential mechanism for her diagnosis [17].

Stomach

Similar to the esophagus, cases of gastric ulcerations and ischemia attributed to SARS-CoV-2 infection have been reported [15]. Gastric ischemia in combination with COVID-19 infection may present with severe abdominal pain typically accompanied by vomiting with signs of bleeding, such as hematemesis or coffee ground emesis and less commonly melena [15,18-20]. Endoscopic evaluation of these patients showed diffuse erosions and oozing, gastric ulcers, and severe mucosal ischemia [15,20]. Multiple cases of gastric pneumatosis have been described in the literature. Most cases were diagnosed with Computed Tomography (CT) showing gastric pneumatosis and signs of ischemia. Associated findings in the abdominal vasculature were commonly seen on imaging, ranging from thrombosis and gas in the portal system to total occlusion of the superior mesenteric artery [18-20]. The underlying pathophysiology leading to these severe manifestations may be due to direct infection of the gastric mucosa, small vessel thrombosis, systemic hypercoagulability, or a combination thereof. One case was attributed to macrophage activation syndrome and treated with intravenous immunoglobulins [21].

One unique case describes a woman diagnosed with COVID-19 one month prior who presented with coffee ground emesis. CT angiography showed extensive thrombosis involving the celiac trunk, common hepatic artery, splenic and left gastric arteries, and complete splenic infarction [22]. She developed a large gastrosplenic fistula seen on imaging and EGD that was managed conservatively with a percutaneous drain. Her severe thrombotic disease was attributed to a combination of COVID-19 coagulopathy and Factor V Leiden heterozygosity.

COVID-19 has also been implicated in cases of gastroparesis. One case report describes a man with COVID-19 pneumonia who developed abdominal distention and nausea. Abdominal x-ray and CT showed gastric distention and concern for gastric outlet obstruction. His symptoms resolved after nasogastric tube decompression and promotility agents, and he was diagnosed with acute gastroparesis [23]. This case is corroborated by a retrospective cohort study of patients with a history of COVID-19 who underwent a gastric emptying study and found that over half of these patients were confirmed to have gastroparesis [24]. Although neither of these studies establish causality between COVID-19 infection and gastroparesis, an association between the two diseases is likely.

Small and large intestine

As in the esophagus and stomach, COVID has been associated with inflammation, ulceration, and ischemia of the small bowel and colon. Patients diagnosed with colitis or enteritis primarily presented with abdominal pain, diarrhea, or hematochezia [25]. Numerous cases of ischemic colitis associated with SARS-CoV-2 have been reported. Several cases report small or large bowel ischemia with pneumatosis intestinal is, typically diagnosed on imaging or endoscopy [25,26]. Many cases are associated with venous or arterial thrombosis suggesting hypercoagulability induced by COVID-19 as the underlying etiology of bowel ischemia [26]. In addition, some cases of colonic ischemia associated with COVID-19 were severe enough to lead to toxic megacolon and bowel perforation [27-30]. Few of these patients had endoscopies; however, one patient with ischemic enteritis and SMA thrombosis had a small bowel resection with pathology consistent with ischemic injury and electron microscopy showing viral particles within enterocytes [31].

However, there are other cases of enteritis and colitis associated with SARS-CoV-2 without evidence of ischemia. One patient with CT findings suggestive of acute ileitis underwent a colonoscopy with ileal mucosal biopsy positive for COVID-19 RNA [7]. Interestingly, this patient had negative prior COVID stool testing. This again suggests that direct infection of the gastrointestinal mucosa may explain these cases of enteritis and colitis.

COVID-19 has also been implicated in cases of colonic dysmotility and Small Bowel Obstruction (SBO) [32,33]. One patient diagnosed with a partial SBO on abdominal CT underwent an exploratory laparotomy but pathology was nonspecific and

inflammatory versus ischemic etiologies could not be ruled out [32]. Multiple cases of acute colonic pseudoobstruction, or Ogilvie syndrome, have been diagnosed in patients with concurrent COVID-19 infection [11,34]. This provides further evidence that COVID-19 may cause gastrointestinal dysmotility. However, critically ill patients in intensive care units, such as those being treated for COVID ARDS, are already at an increased risk of colonic dysmotility from a variety of factors and makes it difficult to establish a direct relationship between COVID-19 and colonic pseudoobstruction.

Infections, both viral and bacterial, are known triggers of Inflammatory Bowel Disease (IBD), and SARS-CoV-2 is no different [35,36]. In the published literature, there are several cases of de novo Crohn's disease and ulcerative colitis thought to have been triggered by COVID-19 infection [37]. There was initial concern that patients with IBD would be more susceptible to COVID-19 than the general population, as many are on immunosuppressive medications and the ACE2 receptor was previously shown to be upregulated in IBD [38]. However, large cohort studies have shown no increased rates of COVID-19 infection in IBD patients [39]. In fact, it has been suggested that the COVID-19 infection rate in patients with IBD may be lower than that of the general population [40].

However, outcomes in this patient population may be dependent on a variety of factors and more studies are needed to further investigate this possibility.

Pancreas

COVID-19 infection has been associated with severe pancreatic manifestations. Existing studies have shown that concomitant SARS-CoV-2 infection in patients with Acute Pancreatitis (AP) leads to more severe disease and higher mortality [41,42]. A meta-analysis showed that compared to patients without COVID-19, patients with acute pancreatitis and COVID-19 had three times the incidence of idiopathic pancreatitis, greater severity of AP (Bedside Index of Severity in Acute Pancreatitis (BISAP) in four studies), increased risk of pancreatic necrosis, increased intensive care unit admissions, increased need for mechanical ventilation, more persistent organ failure, and increased mortality [43,44]. This may be due to immune dysfunction and cytokine storm caused by SARS-CoV-2, but it still remains unclear if SARS-CoV-2 infection can directly cause pancreatitis [45]. ACE2 receptors are found in the pancreas, and infection of the pancreatic islet and exocrine glands may explain the pancreatic manifestations in SARS-CoV-2 infection [46].

Biliary tract

Severe biliary tract injury resembling Sclerosing Cholangitis of Critically Ill Patients (SC-CIP) has been reported in patients with COVID-19. All reported cases occurred in severely ill patients who required ICU admission and mechanical ventilation [47,48]. Patients were predominantly men with mean time to recognition over 3 months after initial COVID-19 diagnosis and the terminology "post COVID-19 cholangiopathy" has been proposed to describe this syndrome [47,48]. Patients have cholestatic or mixed cholestatic/hepatocellular injury patterns, but the predominant feature is marked elevation in serum alkaline phosphatase levels. MRI shows bile duct inflammation with multifocal stricturing and beading [47]. Biopsies in one case series showed acute/chronic large duct obstruction without obvious bile duct loss [47], while another case series showed cholangiocyte injury, loss of bile ducts with accompanying microvascular changes, and portal/periportal fibrosis [48]. The mechanism of injury is proposed to be ischemic, related to microvascular coagulopathy and/or hypotension during severe illness. Direct virus-mediated injury to the biliary epithelium may be involved as there is widespread expression of ACE2 receptors in cholangiocytes [47,48].

On prolonged follow up (up to 12 months), bile duct injury appeared to be stable or worsening and patients may eventually require liver transplant [47]. There have also been case reports of biliary casts which may be associated with post COVID-19 cholangiopathy and ERCP with removal of the casts may not lead to normalization of liver enzymes [49,50]. As seen during other severe illnesses, acalculous cholecystitis has also been described as a complication of COVID-19 infection [51].

Liver

COVID-19 can affect the liver, causing a range of manifestations from transient hepatitis to fulminant liver failure. Reported rates of transient transaminitis in hospitalized patients with COVID-19 ranges from 10.5 - 69% [52-56]. Additionally, one meta-analysis of twenty-two studies found that deranged liver chemistries may indicate COVID-19 severity and predict mortality [57,58]. Case reports also note that fulminant liver failure can occur during COVID-19 infection in the absence of respiratory symptoms and in patients without prior liver disease [59]. All reported cases of liver failure in the setting of COVID-19 occurred in patients greater than age 75. Proposed mechanisms of liver injury in COVID-19 include hypotension due to sepsis, direct viral cytotoxicity through ACE-2, drug-induced liver injury, immune-mediated damage, and passive congestion.

Discussion

Acute infection with SARS-CoV-2 often presents with gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal discomfort. However, COVID-19 has also been implicated as the underlying etiology of gastrointestinal pathologies that have developed in patients both during and after their initial infection. This narrative review focused on summarizing abstracts, case reports, and case series published in gastroenterology journals to date. Additional articles describing the myriad of gastrointestinal diseases and disorders associated with but not attributed to SARS-CoV-2 are important reports but are beyond the scope of this review. Furthermore, it can be difficult to delineate which manifestations can truly be attributed to COVID-19 and which are simply complications of critical illness and extended hospitalizations in COVID-19 patients. Many reports include pathology that supports the case as a direct result of COVID-19 infection and suggest an underlying mechanism for the manifestation, but our review ultimately relies on author analysis to determine this. Severe manifestations of COVID in the GI tract and the hepatobiliary system are important causes of morbidity and mortality that gastroenterologists and intensivists should be aware of as the SARS-CoV-2 pandemic continues.

Author contributions

Tavia Buysse contributed to the literature review and manuscript writing, this author has approved the final draft for submission.

Sameer Bhalla contributed to the literature review and manuscript writing. This author has approved the final draft for submission.

Vikram Kotwal contributed to the article conception, manuscript writing, and manuscript editing. This author has approved the final draft for submission.

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