

## Gastrointestinal and Hepatobiliary Manifestations of SARS-CoV-2 Virus in COVID-19 Patients

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### Abstract

COVID-19 disease is an ongoing severe respiratory viral disease that emerged in December 2019. COVID-19 is caused by a novel coronavirus, first isolated in January 2020, known as SARS-CoV-2. COVID-19 has been declared as a global pandemic by the World Health Organization as it has already spread across the continents. SARS-CoV-2 virus enters the cells via the ACE-2 receptor. The ACE-2 receptor is highly expressed in the lungs in addition to other organs in the gastrointestinal tract, such as the esophagus, small and large intestines, ileum, colon and cholangiocytes. Although COVID-19 frequently present with fever, body aches, respiratory symptoms such as cough, shortness of breath, it can rarely present with gastrointestinal symptoms. Diarrhea is the most common gastrointestinal manifestation; however, nausea, vomiting and abdominal pain have been reported. Acute liver injury and pancreatic injury are not uncommon in patients with severe COVID-19. It is, therefore, vital for the clinicians to recognize gastrointestinal and hepatobiliary manifestations in patients suspected with COVID-19 and conduct early diagnostic workup.

**Keywords:** SARS-CoV-2; COVID-19; Pandemic; Symptoms of COVID-19; Gastrointestinal manifestations of COVID-19; Liver Injury in COVID-19; Novel Corona Virus; Diarrhea in COVID-19; Pancreatitis in COVID-19

### Introduction

“Corona Virus Disease 2019”, or popularly known as “COVID-19” disease, is an ongoing severe respiratory viral disease that emerged first in Wuhan, China, in December 2019 [1]. COVID-19 is caused by a novel coronavirus, first isolated in January 2020, known as SARS-CoV-2 [2,3]. COVID-19 has been declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020 as it has already spread across the continents [4]. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths [5]. As of April 22, at the time of this manuscript was finalized, more than 2,500,000 cases have been reported, with more than 175,000 total deaths worldwide. COVID-19 cases have been reported in 185 countries and territories with varying rates of infection. Mode of transmission was initially thought to be ‘zoonotic’ based on that the large number on infected individuals were exposed to routinely sold exotic animals, such as bats and pangolins, in Wuhan City’s wet markets [5]. The first case of direct human-to-human transmission

was reported in Gansu Province after a lag of 4 days followed by 6 family clusters were identified over 12 days [6,7]. Fecal oral transmission was also reported in various cases [8]. The majority of these cases occurred in adults with more fatalities in older adults and those with comorbidities [9].

The common symptoms of COVID-19 include fever, dry cough, shortness of breath, fatigue, malaise and severe body aches, among many other clinical features. A small percentage of patients with SARS-CoV-2 infection was asymptomatic. The virus may also lead to several complications, such as pneumonia and acute respiratory distress syndrome [10]. The mean incubation period of SARS-CoV-2 is 5.2 days but may extend up to 14 days while the basic reproductive number is estimated to be 2.2 [11]. Li, *et al.* reported a mean interval of 9.1 to 12.5 days between the onset of COVID-19 disease and hospitalization [12].

Laboratory findings of the SARS-CoV-2 comprise lymphopenia, prolonged prothrombin time, elevated D-dimer, and elevated inflammatory markers such as ferritin, C-reactive protein, and lactate dehydrogenase. Olfactory and gustatory dysfunctions were also reported [13,14]. Additionally, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, creatine kinase, cardiac troponin I and N-terminal pro-brain natriuretic peptide have been observed [15]. Classic radiographic findings of COVID-19 are patchy bilateral infiltrates and ground-glass opacities in the lungs bilaterally, seen best on computerized tomography (CT) scans. A study, in which CT findings on admission were compared with CT findings later after disease progression, found that the initial pulmonary lesions were more diffusely distributed in the lung lobes with patchy, crazy-paving pattern [16]. Hypertension, diabetes and heart disease were found to be associated with severe presentations of COVID-19 [17]. Many factors have been found to increase in-hospital deaths such as cardiovascular comorbidities in addition to older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1 µg/mL on hospital admission [18]. Moreover, individuals with advanced age are more likely to suffer from severe forms of COVID-19 as the highest mortality rate of COVID-19 has been observed in individuals who are older than 68 years of age. Specifically, approximately 80% of all COVID-19 deaths come from patients older than 65 years of age [9]. No intensive care unit (ICU) admissions or deaths were reported among COVID-19 patients aged ≤ 19 years in the same study [9].

The higher mortality rate has been reported in males with COVID-19, compared to their female counterparts [19]. COVID-19 is also associated with numerous life-threatening complications such as acute respiratory distress syndrome (ARDS), cardiac arrhythmias, redistributive shock secondary to sepsis, acute cardiac injury and heart failure, acute kidney injury, and hypoxic encephalopathy [18].

### Viral features of SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus that belongs to the beta coronavirus genus [20]. Since the SARS-CoV outbreak in 2002, the structural analysis of SARS-CoV has been conducted to identify its molecular characteristics. SARS-CoV-2 enters the cells via the angiotensin-converting enzyme-2 (ACE-2) receptor, which has a high affinity for this novel coronavirus [21-23]. The host's ACE-2 receptors regulate both human-to-human and interspecies transmission [22]. The ACE-2 receptor is highly expressed in the lungs in addition to other organs in the gastrointestinal tract, such as the esophagus, small and large intestines, ileum, colon and cholangiocytes. Thus, it is likely that those organs with ACE-2 receptors could be affected by SARS-CoV-2. Indeed, SARS-CoV-2 RNA has been identified in rectal swabs and stool specimens of COVID-19 patients on day 7 of presentation [21]. Furthermore, SARS-CoV-2 was demonstrated inside the enterocytes by electron microscopy [24]. All these findings indicate that SARS-CoV-2 may survive in the gastrointestinal tract much longer after the resolution of clinical symptoms by up to 30 days [21].

### Gastrointestinal manifestations of COVID-19

Given the patterns of SARS-CoV-2 expressions in the gastrointestinal (GI) tract that has been described earlier in this review, many gastrointestinal manifestations have been described among COVID-19 patients [25]. The first COVID-19 patient in the United States presented with a 2-day history of nausea and vomiting on admission followed by diarrhea on day 2 in the hospital [21]. Up to 79% of COVID-19

infected patients in Wuhan presented with GI symptoms such as diarrhea, anorexia, nausea, vomiting, abdominal pain and GI bleeding during hospitalization [26]. Diarrhea is among one of the earliest symptoms to appear in many COVID-19 patients before the diagnosis is established. GI bleeding is most common in critically ill patients [26].

### Hepatobiliary manifestations of COVID-19

COVID-19 also affects the hepatobiliary system, consistent with the evidence of the influence of SARS-CoV-2 on the cholangiocytes [21]. Acute liver injury (ALI) with liver synthetic dysfunction, including elevated aminotransferases, hypoalbuminemia and prolonged prothrombin time, has been reported in COVID-19 cases. Cai Q, *et al.* reported that 76.3% of 417 COVID-19 patients developed abnormal liver chemistry tests while 21.5% of these cases resulted in liver injury during hospitalization. 26.7% of COVID-19 cases with abnormal liver tests progressed to severe pneumonia [27]. Notably, 60% of patients with SARS virus infection also developed liver impairment, signifying the similarities between SARS and SARS-CoV-2 viruses [28]. Studies have shown that many underlying liver diseases such as NAFLD, alcoholic liver disease and chronic hepatitis B are common in COVID-19 patients with liver injury. Besides, patients with elevated liver chemistry tests are much more likely to progress into a severe COVID-19 infection. Specifically, COVID-19 patients show abnormal levels of AST and ALT during disease progression. Mild elevation in serum bilirubin has been reported which could be secondary to cholestasis from systemic inflammatory response syndrome (SIRS) in addition to SARS-CoV-2's direct impact on cholangiocytes injury [21]. The histopathological findings from the autopsy reports of COVID-19 patients revealed microvesicular steatosis and non-specific mild lobular activity, although these findings could be contributed to drug-induced liver injury (DILI) from the use of various anti-microbial agents [21]. It is uncertain that SARS-CoV-2 imposes direct injury to hepatocytes.

Wang, *et al.* reported the evidence of pancreatic injury in patients with COVID-19 has also been reported [29]. Acute pancreatitis is characterized as an elevated lipase level of 3 times upper normal limits, along with classic periumbilical abdominal pain or radiographic evidence of pancreatic inflammation. The study did not suggest the pancreatic injury as a distinct complication of COVID-19 as most patients with pancreatic injury also had diarrhea. Enteritis may contribute to elevated pancreatic enzymes without a true pancreatic injury. It is too premature to state that COVID-19 can present with acute pancreatitis [29].

### Summary

In summary, scientific evidence indicates a strong influence of SARS-CoV-2 on the gastrointestinal and hepatobiliary organ-system, in addition to its impact on the pulmonary system. Diarrhea is the most common gastrointestinal presentation among individuals with COVID-19. Varying degree of acute liver and pancreatic injury can be seen in COVID-19 patients; however, it is uncertain at this time if these injuries are the direct cause of SARS-CoV-2 infection or the indirect consequences secondary to a severe systemic inflammatory response. It is, therefore, vital for the clinicians to recognize gastrointestinal and hepatobiliary manifestations in patients suspected with COVID-19 and conduct early diagnostic workup.

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