

## Hepatic and Gastrointestinal Manifestation of COVID-19

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### Abstract

Coronavirus disease of 2019 (COVID-19) is a disease resultant of a novel coronavirus, severe acute respiratory syndrome coronavirus 2. It emerged at the end of 2019 and spread almost in all the countries. Because of high infectivity rate, it was declared as pandemic in March 2020. The leading method of spreading is through airway droplets with a median incubation period is 5.1 days. Spectrum of illness varies from mild to severe with majority suffering with mild symptoms. Coronavirus disease of 2019 involves mainly the respiratory system but other organs like heart, kidney, liver, intestine may also be affected. Major hepatic and gastrointestinal manifestations include elevation of liver enzymes, nausea, vomiting and diarrhoea. Pathophysiology of these symptoms is explained by presence of the ACE-2 receptors in the biliary tree and intestinal mucosa. This virus has been isolated from the stool specimens of COVID-19 patients. Based on its disease extent and involvement of hepatic and gastrointestinal systems, COVID-19 poses a high risk for gastroenterologist and precautions during endoscopic procedures are required.

**Keywords:** SARS-CoV-2; COVID 19; Pandemic; Gastrointestinal; Manifestation

### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel corona virus which resulted in an outbreak in the last few months of 2019. It emerged in Wuhan, China. Severe acute respiratory syndrome coronavirus 2 is a virus of coronavirus family which has the largest genome of all known RNA viruses. Seven coronavirus species are known to cause human disease, among them three are highly pathogenic human coronavirus caused SARS-CoV in 2002, Middle East respiratory syndrome coronavirus MERS-CoV in 2012 and novel coronavirus-SARS-CoV-2 in 2019 [1]. SARS-CoV-2 has a high infectivity rate and has a significant burden on whole population. The spectrum of illness varies from mild to severe with respiratory system being the most frequently involved. These three corona viruses SARS-CoV, MERS-CoV and SARS-CoV-2 can cause respiratory, intestinal, hepatic and neurological disease. In severe stage there is a risk of developing acute respiratory distress syndrome (ARDS), multiorgan failure (MOF) and death [2-4].

### Epidemiology and pathophysiology

The outbreak of novel coronavirus SARS-CoV-2 started in Wuhan city of China in December 2019 and since then it has involved more than 200 countries across the world. Severe acute respiratory syndrome coronavirus 2 infection was declared as pandemic by World

Health Organisation (WHO) on March 11, 2020 [4]. This speedy transmission was predominantly because of its high contagiousness, prolonged asymptomatic period and undisturbed international travel [5]. Upon detection and isolation of this new virus, the disease was named as coronavirus disease of 2019 (COVID 19). Coronavirus disease of 2019 is caused by the SARS-CoV-2 virus. The leading method of spreading SARS-CoV-2 is through airway droplets. The average incubation period of this disease is 5.1 days and 97.5% patients become symptomatic within 11.5 days of infection [6]. Severe acute respiratory syndrome coronavirus 2 infection occurred after attachment of viral spike protein to human angiotensin converting enzyme-2 (ACE-2) receptor which are expressed in the lungs, heart, intestine, bile ducts, kidneys and blood vessels. The virus enters by endocytosis after contact of S1 spike glycoprotein with receptor binding domain of ACE receptors. Immune response after SARS-CoV-2 infection is accountable for resolution of illness and its pathogenesis. This disease involves multiple system due to cytokine storm and damage caused by these inflammatory cytokines. The ribonucleic acid (RNA) of virus acts as pathogenic molecule which attaches to toll like receptors (TLR) TLR3, TLR7, TLR8 and TLR9. Triggering of this immune pathway leads to production of interferon beta (IFN- $\beta$ ), interleukins-1(IL-1), IL-2, IL-4, IL-6 and IL-10. Among these cytokines IL-6 is the most important for pathogenesis. This huge release of cytokines results in increased vascular permeability, alveolar epithelial damage, ARDS, followed by multiorgan failure [7].

### Clinical presentation of COVID-19

As COVID-19 involve the respiratory system, intestine, liver, kidney and blood vessels with the help of ACE-2 receptors. There is paucity of data on extrapulmonary manifestations of COVID-19. In this article we tried to analyse clinical features and pathogenesis of liver and gut manifestations caused by SARS-CoV-2.

### Coronavirus disease of 2019 and Liver

Hepatic manifestations have been observed in SARS-CoV and MERS-CoV infected subjects [8,9]. Hepatic involvement has been observed in up to 60% of patients with SARS. Multiple published case studies have reported the clinical features of patients with COVID-19 and have shown that patients may develop different degree of liver dysfunction (Table 1). These studies revealed that 2 - 11% of subjects with COVID-19 had hepatic comorbidities and the incidence of hepatic injury ranged from 14.8% to 78% predominantly with high alanine aminotransferase (ALT) and aspartate aminotransferase (AST), followed by slight increase in bilirubin levels [10-21]. Higher rates of abnormal levels were observed in severe COVID-19 cases [20]. In a study elevation of AST was more in intensive care unit (ICU) patients compared to who did not require ICU care (62% vs 25%) [19]. Elevated alkaline phosphatase (ALP) levels were observed in 1-8% of patients with COVID-19 during hospitalisation. Available literature suggests that ACE-2 receptor expression is increased in cholangiocytes signifying that SARS-CoV-2 might directly adhere to ACE-2 positive cholangiocytes to disturb liver functions [22]. However, histological study of liver tissue from a subject who lost his life due to COVID-19 revealed that viral inclusions were not present in the liver [23]. Though expression of ACE-2 receptors increased on cholangiocytes, recently published studies reveal that gamma-glutamyl transferase (GGT) was increased in 54% of COVID-19 patients while only 1.8% of subjects had increased alkaline phosphatase [24]. In critically ill patients with COVID-19, immune mediated inflammation may lead to liver damage. Published literature revealed that inflammatory cytokine storm is linked to unfavourable results of SARS-CoV [25]. Consequently, the typical lymphopenia in SARS-CoV-2 infection may lead to increase in levels of IL-6, IL-10, IL-2 and IFN- $\gamma$  and exaggerated inflammatory reaction resulting not only in lung damage but also damage to extra-pulmonary organs [26]. In one study lymphopenia and c-reactive protein (CRP) level were independently related to liver damage in COVID-19 patients, proving the role of inflammatory cytokine storm [27]. Increased positive end expiratory pressure can lead to liver congestion by impeding venous return and it may also result in liver damage. However, the distribution of AST and ALT levels in subjects with COVID-19 does not indicate hypoxic hepatitis [28]. Drug induced hepatic injury is a common cause of liver injury in COVID-19 patients. Various drugs like antivirals (lopinavir/ritonavir), antibiotics (macrolides, quinolones), antipyretics (paracetamol) or steroids can cause liver injury [29]. In a study on 12 subjects with COVID-19, three admitted patients who were administered remdesivir, reported

altered liver functions [30]. Recent studies on COVID-19, have shown that serum albumin is decreased in severe cases and the level of albumin is around 26.3 - 30.9 gm/l [14].

Published study	Number of Patients with COVID-19 (n)	Patients with abnormal biochemical liver profile n (%)	Patients with pre-existing liver co-morbidities n (%)
Guan., <i>et al.</i> [10]	1099	Abnormal ALT, 158/741 (21.3%): - 19.8% in non-severe COVID-19 - 28.1% in severe COVID-19 Abnormal AST, 168/757 (22.2%): - 18.2% in non-severe COVID-19 - 39.4% in severe COVID-19 Abnormal total bilirubin 76/722 (10.5%) - 9.9% in non-severe COVID-19 - 13.3% in severe COVID-19	23 (2.1%)
Cai., <i>et al.</i> [11]	298	44 (14.8%) 9.6% in non-severe COVID-19 36.2% in severe COVID-19	8 (2.7%)
Fan., <i>et al.</i> [12]	148	75 (50.7%) - Abnormal ALT (18.2%) - Abnormal AST (21.6%) - Abnormal total bilirubin (6.1%)	6 (8%)
Wang., <i>et al.</i> [13]	138	Mild elevation of ALT and AST	4 (2.9%)
Chen., <i>et al.</i> [14]	99	43 (43%) - Abnormal ALT 28% - Abnormal AST 35% - Abnormal total bilirubin 18% - Abnormal albumin 98%	NA
Lu., <i>et al.</i> [15]	85	33 (38.8%)	6 (7%)
Shi., <i>et al.</i> [16]	81	43(53%)	7 (9%)
Xu., <i>et al.</i> [17]	62	10(16%)	7 (11%)
Yang., <i>et al.</i> [18]	52	15(29%)	NA
Huang., <i>et al.</i> [19]	41	15(31%)	1 (2%)
Zhang., <i>et al.</i> [20]	82, death	64 (78%) - Abnormal ALT 30.6% - Abnormal AST 61.1% - Abnormal total bilirubin 30.6%	2 (2.4%)
Huang., <i>et al.</i> [21]	36, Non-survivor	- Abnormal ALT 13% - Abnormal AST 58% - Abnormal total bilirubin 12.9%	NA

**Table 1:** Characteristics of liver biochemical profile in published COVID-19 case studies. SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; NA: Not Available.

**Coronavirus disease of 2019 and pre-existing liver disease**

Chronic liver disease is a considerable disease burden worldwide which mainly includes chronic viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. It is a matter of interest, various underlying liver comorbidities affects liver damage in subjects with COVID-19. However, there is lack of data on relation between pre-existing liver comorbidity and COVID-19. In a research on 1099 subjects with COVID-19, 23(2.1%) had hepatitis B infection. Patients with severe disease had more hepatitis B virus (HBV) infection (2.4% vs 0.6%) compared to those with mild disease [10]. Patients of SARS with HBV/hepatitis C virus (HCV) infection were more likely to develop severe hepatitis, due to increased viral replication during SARS-CoV infection [31]. Other comorbidities like diabetes, cardiovascular disease, hypertension and non-alcoholic fatty liver disease increase the susceptibility for further hepatic damage. Till date in subjects of COVID-19 with autoimmune hepatitis, the effect of steroids on disease outcome is uncertain. In subjects with primary biliary cholangitis the effect on cholestasis due to SARS-CoV-2 infection is also unclear [24]. Patients of cirrhosis and hepatocellular carcinoma are more prone to infections because of their low systemic immunity. A study published from Wuhan, revealed an incidence of 17% of COVID-19 in 101 patients of liver cirrhosis, where precautionary measures had not been implemented compared to those who followed precautionary measures [32]. There is also a chance of transmission of SARS-CoV-2 from donor to recipient during liver transplant as revealed in past SARS epidemic [33]. A recently published study also described the risk related to transplant in COVID-19 recipients [34]. The Italian Transplant Authority advised nasopharyngeal swab or bronchoalveolar lavage to detect SARS-CoV-2 before donation [35].

**Coronavirus disease of 2019 and the gastrointestinal tract**

About 2-10% subjects with COVID-19 presents with loose motions and SARS-CoV-2 RNA has been identified in stool and blood samples [36]. The stool sample of the first reported COVID-19 subject from USA showed SARS-CoV-2 RNA, after which gastrointestinal tract infection by SARS-CoV-2 was also closely monitored [37]. Initial studies on COVID-19 revealed that simultaneous gastrointestinal manifestations are also common in these subjects [38]. One study showed that nausea along with vomiting and diarrhoea were reported in 5.6% and 3.8% patients respectively [14]. Another cross-sectional study on 204 COVID-19 patients from Hubei reported that 99 (48.5%) patients came to hospital with gastrointestinal manifestations as main symptoms including 7 patients who did not have any pulmonary complaints [39]. These early reports on COVID-19 patient, warns gastroenterologists to suspect COVID 19 in at risk patients presenting with digestive symptoms rather than waiting for pulmonary complaints to come. This facilitates early detection of COVID-19 with prior isolation and management. Patients of COVID-19 without gastrointestinal complaints have higher cure rate and discharge (60% versus 34.3%) compared to those with gastrointestinal complaints. This is likely because of viral multiplication in the gastrointestinal tract resulting in severe disease [37]. Multiple hypothesis were given for digestive symptoms of COVID-19, but the exact molecular mechanism need to be investigated. Firstly, interaction between SARS-CoV-2 and ACE-2 receptors in glandular cells of gastric and duodenal epithelium can lead to diarrhoea [40]. Another study revealed that there is increased expression of ACE-2 receptors on proximal and distal enterocytes [41]. The intestinal mucosal cells attacked by SARS-CoV-2 lead to decrease absorption, increased intestinal secretion and trigger enteric nervous system, resulting in diarrhoea [42]. Secondly, there is indirect injury to gastrointestinal tract by inflammatory cytokines due to SARS-CoV-2 infection. Antibiotic associated diarrhoea is another contributory factor for digestive symptoms in COVID-19 patients. Further research is required to know the pathogenesis of gastrointestinal tract involvement in COVID-19. An autopsy study of a 85 year old male with COVID-19 revealed focal dilatation and stenosis of small intestine [42]. Based on proof of stool excretion of SARS-CoV and MERS-CoV, it is likely that the gastrointestinal tract may act as an another route for SARS-CoV-2 infection. Another study revealed that in more than half of the subjects, stool samples were positive for SARS-CoV-2 RNA for 11.2 days even after clearance of virus from respiratory tract [43]. As per recent guidelines, a patient of COVID-19 is to be discharged after negative RT-PCR report for SARS-CoV-2 from respiratory tract specimen. Hence, it is advised to consider, routine faecal sample testing with RT-PCR and preventive measures should be followed if faecal test is positive.

Subjects with malignancy are more prone to infection, however whether subjects with gastrointestinal malignancy are prone to SARS-CoV-2 infection than healthy subjects remains unrevealed. Subjects with inflammatory bowel disease (IBD) on biological therapy and im-

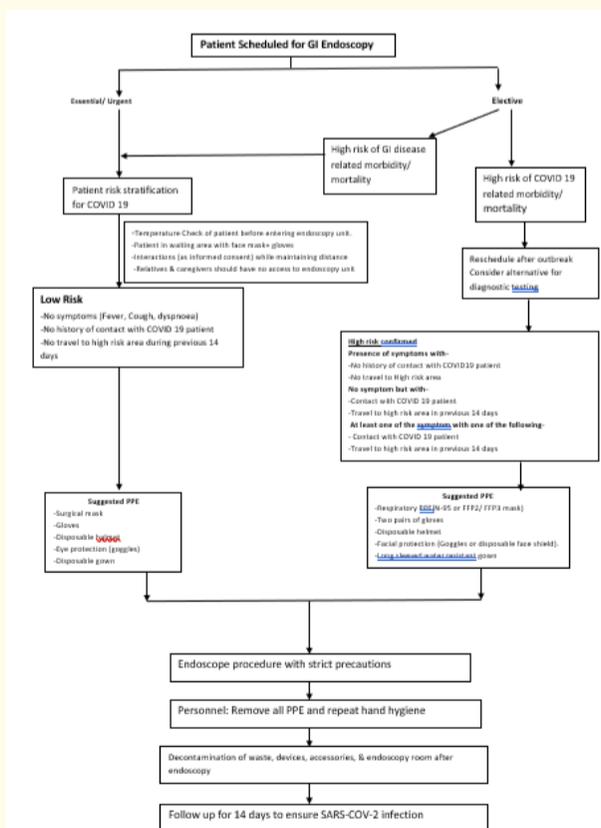
munosuppressive drugs are at enhanced risk of recurrent and grave infections and could be more prone to severe SARS-CoV-2 infection [44]. None of the 318 patients of IBD developed SARS-CoV-2 infection due to early preventive measures in the Wuhan IBD registry [45]. These preventive measures involved, guidelines for the use of immunosuppressive drugs, biological therapy, nutrition and deliberate delay in elective surgical and endoscopic procedures as well as personal protective provisions [46].

**Coronavirus disease of 2019 patient and endoscopy**

As people all over the world are advised to confine to their houses to reduce SARS-CoV-2 transmission, resulted in a decrease in the number of endoscopy procedures. China’s National Health Commission data revealed that around 3300 medical staff have been infected till March 2020 [47]. Medical staff functioning in endoscopy rooms are at enhanced risk of inhaling airborne droplets, conjunctival contact, and touch contamination even though they are not personally handling COVID-19 patients. Spread among humans results primarily via infected droplets [48]. The risk of exposure is not only restricted to gastroduodenoscopy but also in colonoscopy through faecal shedding [49]. All endoscopic units should follow preventive measure for the control of COVID-19 in association with infection control team [50]. Based on available data on COVID-19 the following measures should be carried out in endoscopy units:

1. Minimise unnecessary exposure to SARS-CoV-2: It is advised to consider only emergency endoscopic procedures to manage patients of acute gastrointestinal bleeding, foreign bodies and acute cholangitis [51].
2. Negative-pressure units: Ideally, endoscopic procedures should be done in a separate room with negative pressure. If such facility is not possible, endoscopy should be done in a properly ventilated room [52].
3. Protection of endoscopy staff: The personal protective equipment (PPE) in endoscopy rooms should constitute of at least gloves, hair cover, eye protection equipments (goggles or face shield), water-resistant gowns, and pulmonary protective wear based on the level of risk [50]. The endoscopy staff should also be made aware about airborne precautions and principles of handling probable COVID-19 patients [53].
4. Disinfection of endoscopes and accessories: SARS-CoV-2 can be deactivated by disinfectants chemicals with viricidal action [54]. Advanced level disinfection is advised for endoscopes, and other “semi-critical” equipments while sterilization is advised for “critical” equipments such as biopsy forceps, polypectomy snares and sphincterotomes. Single use accessories are a substitute to sterilization of reusable devices [55].
5. Endoscopy unit decontamination: It includes cleansing all surfaces in the endoscopy room to remove soil and biofilm, followed by adequate disinfection. Floor should be cleaned using chlorinated detergents every day [54].

To limit the spread of SARS-CoV-2 endoscopy rooms during this pandemic, a workflow is advised (Figure 1) as per with recommendations of endoscopic societies [50-55].



**Figure 1:** Workflow to prevent SARS-CoV-2 transmission in endoscopy units during the current outbreak.

### Conclusion

In conclusion hepatic and gastrointestinal manifestation are common with COVID 19. Patients may present with these symptoms to gastroenterologists without respiratory symptoms. Presence of ACE-2 receptors on enterocytes and cholangiocytes is responsible for these manifestations. Gastro-experts need to suspect when at risk subjects present with gastrointestinal manifestations rather than waiting for pulmonary complaints to appear, this will allow in prompt detection of COVID 19. Only emergency endoscopic procedures should be considered with proper PPE.

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### Conflict of Interest

The authors declare no conflict of interest related to this work.

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