COVID-19 and its Implication on Gastroenterology: An Overview

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Abstract
Emerging pandemics show that humans are not infallible and communities need to be prepared. Coronavirus outbreak was first reported towards the end of 2019 and has now been declared a pandemic by the World Health Organization. Since then many researches are going worldwide to understand this coronavirus disease, its impact on human body, prevention and treatment. As of now it has been observed that its can affect every organ of body and it’s not only the respiratory manifestation but it has shown other clinical sign and symptoms in various patients. This review article is highlighting the impact of covid-19 on Gastroenterology which helps us to understand the various manifestations in our digestive system and guide us to diagnose at earlier stage and prevents cross infection among society.

Introduction
A pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or novel coronavirus disease (COVID-19) started in December 2019 in the Wuhan province of China and swept through the world by April 2020, affecting 187 of the 192 countries of the world with varying severity.¹⁻³ As of October 2020, WHO has reported there have been 43 million confirmed cases of COVID-19, including 1,155,553 deaths.⁴

Respiratory tract manifestations such as fever and cough are the most commonly reported symptoms in patients with COVID-19.⁵ Evidence of digestive system involvement in patients with COVID-19 was first reported by a group in China. Emerging data showed that the gastrointestinal tract and liver might also represent target organs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the basis of the findings that angiotensin-converting enzyme 2 (ACE2), the major receptor of SARS-CoV-2, is expressed in the gastrointestinal tract as well as liver cells.⁶⁻⁷

The detection of SARS-CoV-2 viral RNA in patients’ stool and the potential for faecal–oral transmission has raised great concern and could pose a challenge for the control and prevention of COVID-19. However further research is warranted in this space.

COVID 19 and Gastro Intestinal Symptoms

In The Lancet Gastroenterology and Hepatology, Ren Mao and colleagues report findings of a systematic review and meta-analysis of data from 35 studies, including 6686 patients with COVID-19. In 29 studies (6064 cases) reporting gastrointestinal symptoms in patients with COVID-19, the pooled prevalence of digestive symptoms was 15%, the most common of which were nausea or vomiting, diarrhoea, and anorexia. The pooled prevalence of diarrhoea was 9%, nausea or vomiting 6%, loss of appetite 21%, and abdominal pain 3%. Of note, the authors report that around 10% of patients presented with gastrointestinal symptoms only. Wang and colleagues also found that around 10% of patients initially presented with diarrhoea and nausea 1–2 days before the development of fever and dyspnoea. Patients with digestive symptoms had a variety of manifestations, such as loss of appetite, diarrhoea, vomiting, and abdominal pain.⁸⁻¹⁰

A link between gastrointestinal involvement and disease severity of COVID-19 has been proposed. In a multicentre study, Pan and colleagues investigated the prevalence and outcomes of patients with COVID-19 with digestive symptoms. In 99 patients who presented with digestive symptoms compared with those without gastrointestinal symptoms. However, the risk of severe disease was not increased among patients with digestive comorbidities compared with patients without these comorbidities. Patients with gastrointestinal symptoms had an increased risk of acute respiratory distress syndrome and liver injury. However, the pooled rates of discharge, length of hospital stay, and mortality were similar between patients with and without gastrointestinal symptoms.⁹⁻¹¹

Over the course of the COVID-19 pandemic, some patients have initially presented with abdominal symptoms without fever or respiratory manifestations. In a large multicentre study of 204 patients with COVID-19 in three heavily affected hospitals during the initial outbreak in China, 103 (50%) patients presented with digestive symptoms as their chief complaint. Six (3%) patients presented with digestive symptoms but no respiratory symptoms. In a large case series (n=1141) of patients admitted to hospital with COVID-19, 183 (16%) presented with gastrointestinal symptoms only. Wang and colleagues also found that around 10% of patients initially presented with diarrhoea and nausea 1–2 days before the development of fever and dyspnoea. Patients with digestive symptoms had a variety of manifestations, such as loss of appetite, diarrhoea, vomiting, and abdominal pain.⁸⁻¹¹

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Received: 03.11.2020; Accepted: 04.02.2021
patients without digestive symptoms (9.0 days vs 7.3 days). As the severity of the disease increased, digestive symptoms became more numerous. Patients without digestive symptoms were more likely to be cured and discharged than were patients with digestive symptoms (60% vs 34%).

This finding was consistent with the study from Wang and colleagues, who found that patients admitted to the ICU were more likely to have abdominal pain and loss of appetite compared with non-ICU patients. A higher prevalence of abdominal pain in patients with severe COVID-19 than in those with non-severe disease has also been frequently noted in our clinical settings. More data analysis is warranted in such settings as well.

Emerging data suggest the prolonged presence of SARS-CoV-2 RNA in stool samples or rectal swabs even after the patients’ respiratory specimens become negative. Much attention has been paid to the possibility of viral shedding from the gastrointestinal tract and faecal–oral transmission. Data from Wu and colleagues suggest the possibility of extended duration of viral shedding in faeces, for nearly 5 weeks after the patients’ respiratory samples tested negative for SARS-CoV-2. However, the clinical implications of prolonged viral excretion in faeces, including the association with disease course, severity, and even recurrence of COVID-19, remains unclear. More studies are needed to show the virus’ replication competence, abundance in stool, and stability in the environment.

**COVID 19 and Liver Injury**

In addition to digestive symptoms, patients with COVID-19 are also at risk of developing liver injury. Studies have shown that patients had varying degrees of liver function abnormalities—the incidence ranging from 1% to 53%—mainly indicated by abnormal ALT and AST concentrations, accompanied by slightly increased bilirubin concentrations as seen in prominent literature. Albumin was decreased in severe cases (around 26.3–30.9 g/L).

Acute liver injury is common in patients who test positive for SARS-CoV-2, but is most often mild. However, among patients with severe lung injury, a severe disease course should be anticipated. In addition, patients with severe COVID-19 may be more likely to have liver injury than patients with less severe disease or asymptomatic carriers. Although cholestasis and liver synthetic function abnormalities appear to be rare, hypoaalbuminemia is emerging as a consistent risk factor for severe disease, even among patients without chronic illness.

Emerging data suggest that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are common among patients with COVID-19 with AST and ALT elevations found in 38%–63% and 29%–39% of patients, respectively.

The mechanism by which SARS-CoV-2 impacts the liver is not fully understood, but is thought to be a combination of direct viral mediated injury as well as the immune-mediated inflammatory response. The SARS-CoV-2 cellular receptor, the angiotensin-converting enzyme 2 (ACE2) receptor, is present in biliary and hepatic endothelial cells, providing a plausible mechanistic explanation for the observed liver injury. Among hospitalized patients, additional etiologies of liver injury must be considered, including drug-induced liver injury, sepsis, shock, congestion, and extra hepatic sources of AST.

It has been indicated that angiotensin II receptor blockers and ACE-inhibitors drugs may inhibit liver functions COVID-19 patients. In a study, elevated levels of liver enzymes were observed among participants who used ACE-Is/ARBs drugs during hospitalization, though the elevation was not significant with those who did not use these drugs. It has now been proven beyond doubt that ACE inhibitors or ARBs have no derogatory effect on patients with concomitant COVID 19 infection.

Some authors also observed that the drugs lopinavir and ritonavir contributed significantly to liver test abnormalities and liver injury. These drugs increased the odds of liver injury by four-fold. Moreover, using antibiotics in the treatment also showed an association with the increased prevalence of liver test abnormalities, however this association was not significant. Hydroxychloroquine, an antimalarial agent has not been associated with liver injury in COVID-19; however, it should be used with caution to avoid any harmful effects. Future studies would be worth conducting in determining the possible effects of drugs on liver function in COVID-19 patients.

However data pertaining to level of liver damage in COVID 19 by drugs, sepsis and shock needs to be ascertained more thoroughly.

Dysregulation of the innate immune response may be another important aspect of liver injury in COVID-19. So, the possible pathways that can be associated with liver damage in COVID-19 patients are (i) immune-mediated inflammation, such as cytokines storm and pneumonia-related hypoxia, (ii) Direct cytotoxicity because of active viral replication in the liver cells, (iii) Drug-induced liver damage: initially recommend antiviral drugs including lopinavir/ritonavir, chloroquine, remdesivir, tocilizumab, umifenovir, being potentially hepatotoxic in severe patients, (iv) Reactivation of pre-existing hepatic disease: patients with previous chronic hepatic disease are more vulnerable to hepatic damage from this viral infection, (v) Possible reactivation of hepatitis B virus with some biological drugs such as tocilizumab and baricitinib that may lead to liver dysfunction. Moreover, it is also unknown whether SARS-CoV-2 infection enhances cholestasis in patients with underlying cholestatic hepatic diseases. More mechanistic studies regarding virus entry and replication in liver cells and the potential consequences of drugs in the liver are required.

These findings indicate that one in five patients will develop liver function abnormalities, especially in patients with severe disease, thus close attention should be paid to liver dysfunction when treating patients with COVID-19 over the hospitalisation period. Liver injury was characterised by slight increases in hepatocyte-related enzymes, including ALT and AST. Cholangiocyte-related enzymes, such as alkaline phosphatase and γ-glutamyl transpeptidase, were also reported to be slightly increased in a few patients.

However, limited information is available on the interaction between pre-existing liver disease and COVID-19. A recent study examined the effects of pre-existing liver disease on outcomes in a large cohort of COVID-19 patients. The authors observed a higher proportion of comorbidities, specially diabetes mellitus and hypertension, in patients with liver disease. Fatty liver disease and non-alcoholic steatohepatitis were more frequent among patients with pre-existing liver disease. Importantly, the mortality rate was significantly higher in patients with pre-existing liver disease than patients without liver disease and the relative risk was markedly higher in patients with cirrhosis. Moreover,
patients with pre-existing liver disease required increased hospitalization. Another recent study reported a high mortality rates from COVID-19 among patients with chronic liver disease and cirrhosis. However more work is required in studying interaction between isolated pre-existing liver disease and COVID-19. In very little of our clinical experience in pre-existing liver disease patients with COVID-19, not much could be studied.

**COVID 19, the Intestine and Inflammatory Bowel Disease**

A recent study in >100 outpatients with mild courses of COVID-19 demonstrated the presence of diarrhoea in approximately 30% of patients suggesting that diarrhoea may be a frequent hallmark of mild disease. The presence of diarrhoea could be due to direct infection of GI cells. In this regard, gastric, duodenal and rectal epithelial cells rather than cells in the oesophagus were shown to express the SARS-CoV2 receptor ACE2. COVID-19 led to infection of these cells followed by expression of the viral nucleocapsid protein indicating that SARS-CoV-2 may spread from infected to uninfected cells in the GI tract. Infection was not associated with marked macroscopic inflammation on endoscopy. However, numerous infiltrating plasma cells and lymphocytes with interstitial oedema were seen in a COVID-19 patients indicating mucosal immune cell activation. In addition to local enteric infection, viraemia following lung infection may occur in few patients (approximately 1%) and may lead to a secondary attack of SARS-CoV2 on ACE2 target organs such as the kidney and the intestine.

The COVID-19 receptor ACE2 is particularly highly expressed in intestinal epithelial cells from the terminal ileum and to a lesser extent in the colon, where mucosal inflammation in patients with IBD (Crohn’s disease - CD; Ulcerative Colitis - UC) is frequently detected. In this context, ACE may act as a co-receptor for nutrient uptake, in particular for amino acid resorption from food. Cytokines expressed in IBD, such as IFN-gamma, can potentially induce ACE2 expression by cytokine signalling events driving ACE2 promoter activity consistent with the idea that mucosal inflammation may increase expression of ACE2. Finally, the fusion of SARS-CoV2 with the host cell membrane is critical for uptake in cells and is modulated by the S protein. Activation of the S protein via proteolytic cleavage is controlled by host trypsin-like proteases, whose activity is upregulated in IBD, and this effect might facilitate infection in patients with IBD. Collectively, these findings suggested the possibility that patients with IBD might be particularly susceptible to COVID-19. However, there is no evidence so far that patients with IBD are highly susceptible to COVID-19. In contrast, a recent study from Wuhan studied 318 patients with IBD (204 UC and 114 CD) during the local outbreak of the disease and did not report any COVID-19 cases. The reasons for this observation are not entirely clear but might relate to the local adjustment of protective measures to prevent infection, the particular awareness of the IBD patient cohort to hygiene and infection prevention and the modulation of immunosuppressive therapy (eg, stop of treatment with immunomodulators and biologicals). Alternatively, patients with IBD might be less susceptible to COVID-19 and further studies in this regard are highly warranted.

Mesalazine (an anti-inflammatory drug) and mercaptopurine (a thiopurine) used in IBD therapy were identified as putative repurposable drugs for potential treatment of SARS-CoV-2 through genomics and proteomics analysis using bioinformatics tools. Indeed, studies have shown that thiopurines were able to inhibit in vitro the papain-like protease of SARS-CoV and Middle East respiratory syndrome coronavirus that represents an essential antiviral target essential in viral maturation and the antagonism of interferon stimulation. Additionally, another cohort study found that thiopurines were not associated with an increased risk of developing COVID-19. However, care must be taken in evaluating mesalazine as a potential drug for COVID-19 since clinical studies showed possible pulmonary toxicities associations.

The COVID-19 receptor ACE2 and its putative membrane proteins, such as the S protein, can be blocked by neutralizing antibodies, such as Anti-TNF antibodies are frequently used for IBD therapy. As TNF inhibition may potentially affect antiviral immunity and has been shown to affect hepatitis B virus reactivation, TNF blockade could regulate the susceptibility to COVID-19. However, analyses of TNF levels in COVID-19 led to different results. One study showed no effect on TNF levels in severe COVID-19 cases in spite of the regulation of other proinflammatory cytokines. In contrast, another study reported that COVID-19 ICU patients had significantly higher serum levels of TNF than non-ICU patients. TNF may also exert pathogenic effects in COVID-19 by augmenting the expression of ACE2 or by augmenting lymphopenia through induction of direct leucocyte death via TNF/TNFRI signalling in T cells. These findings argue for a potentially protective effect of TNF inhibition in COVID-19 and further studies are needed to address this point.

In summary, there is currently no evidence for an increased risk or aggravated outcomes in patients with IBD in the context of COVID-19. Other COVID-19 risks situation comprise older patients with IBD with comorbidities as well as patients suffering from malnutrition who may be at risk for infections and severe courses of the disease, respectively. Common drugs for COVID-19 treatment like hydroxychloroquine or remdesivir may increase the risks for drug-drug interactions with established IBD medications (potentially increased risk of combination therapy with hydroxychloroquine and adalimumab/ infliximab for nerve damage). With regard to the effect of IBD on COVID-19, it should be pointed out that further studies are required in this highly dynamic situation. There is no evidence to suggest that patients with IBD should discontinue IBD-specific medications. However, older patients with IBD with comorbidities such as diabetes mellitus, obstructive lung disease, coronary heart disease and hypertension might have an increased risk for COVID-19 and further studies are urgently needed to address this point. In this context, there is an ongoing international programme initiated by the International Organization for the Study of IBD to register COVID-19 cases in patients with IBD in the
endoscopy team must be trained in cases), and 43% recommended that the or FFP2/3 masks were recommended (PPE) during the examination (gloves, reducing the number of people who examination (questionnaire regarding elective/nonurgent procedures; 86% recommended temporarily postponing recommendations for endoscopy during worldwide. To conduct an overview of the recommendations for endoscopic procedures during the COVID-19 pandemic, a total of 21 of various national and international societies have elaborated specific recommendations for endoscopy during the COVID-19 pandemic. A total of 95% recommended temporarily postponing elective/nonurgent procedures; 86% recommended stratifying patients for risk of COVID-19 before the examination (questionnaire regarding symptoms and/or taking patient’s body temperature); 38% recommended reducing the number of people who accompany patients; 33% recommended requiring self-surveillance of signs and symptoms by HCWs; and 19% recommended contacting patients 14 days after the examination to check symptoms. All societies recommended the use of personal protective equipment (PPE) during the examination (gloves, mask, goggles or face shield, gown, and hairnet; double gloves and use of N95 or FFP2/3 masks were recommended in highly suspected or confirmed cases), and 43% recommended that the endoscopy team must be trained in wearing and removing PPE. There was not any mention of using preexposure or postexposure prophylaxis for HCW. All international societies recommended following a standardized reprocessing procedure for flexible endoscopes.

Conclusion

Pandemics always come up with various life-threatening issues. COVID-19 outbreak came up with the same health issues. Though respiratory manifestations always been considered majorly but gastrointestinal manifestation’s cannot be ignored and now it has also emerged as one of the important manifestations of COVID-19. The influence of COVID-19 on digestive system which can leads to various complications due to cytokine storm.

References


