MINIREVIEWS

COVID-19 status quo: Emphasis on gastrointestinal and liver manifestations

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Abstract
The coronavirus disease 2019 (COVID-19) has caused one of the worst public health crises in modern history. Even though severe acute respiratory syndrome coronavirus 2 primarily affects the respiratory tract, gastrointestinal manifestations are well described in literature. This review will discuss the epidemiology, virology, manifestations, immunosuppressant states, and lessons learned from COVID-19. Observations: At the time of writing, COVID-19 had infected more than 111 million people and caused over 2.5 million deaths worldwide. Multiple medical comorbidities including obesity, pre-existing liver condition and the use of proton pump inhibitor have been described as risk factor for severe COVID-19. COVID-19 most frequently causes diarrhea (12.4%), nausea/vomiting (9%) and elevation in liver enzymes (15%-20%). The current data does not suggest that patients on immunomodulators have a significantly increased risk of mortality from COVID-19. The current guidelines from American Gastroenterological Association and American Association for the Study of Liver Diseases do not recommend pre-emptive changes in patients on immunosuppression if the patients have not been infected with COVID-19. Conclusions and relevance: The COVID-19 pandemic has prompted a change in structure and shape of gastroenterology departmental activities. Endoscopy should be performed only when necessary and with strict protective measures. Online consultations in the form of telehealth services and home drug deliveries have revolutionized the field.
INTRODUCTION

Coronavirus disease 2019 (COVID-19) is considered one of the fastest expanding pandemics since the Spanish flu of 1918, and one of the most impactful public health crises in modern history. As of February 2021, the coronavirus causing COVID-19, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had infected more than 111 million people and caused over 2.5 million deaths worldwide, including 50000 in the United States[1].

It is hypothesized that SARS-CoV-2 originated from animal reservoirs and adapted to human-to-human transmission[2,3]. The first cases of severe pneumonia-like conditions were diagnosed in Wuhan, China at the end of 2019[4]. In February 2020, the international virus classification commission termed the novel coronavirus SARS-CoV-2, and its clinical disease was termed COVID-19 by the World Health Organization (WHO) [5,6]. The case fatality ratio (CFR), defined as the proportion of individuals dying of a disease, was estimated to be up to 3%[7]. Till date, CFR remains the best tool to express the severity of COVID-19 infection among confirmed cases (Table 1). In addition to CFR, many other COVID-19 risk assessment tools have been developed that try to gauge the severity of the novel disease[8] within ethnically diverse populations[9].

SARS-CoV-2 pathogenesis manifests primarily as a respiratory viral syndrome causing symptoms such as cough, fever, general malaise, dyspnea, and respiratory distress, and in a proportion of cases causes severe pulmonary manifestations with respiratory failure and death[10]. SARS-CoV-2 propagates from the respiratory tract to other organs such as the gastrointestinal (GI) tract and liver[10-12].

Due to the availability of the genomic sequence of the viral RNA, scientists and researchers have been able to understand the SARS-CoV-2 virus and develop treatment strategies. This review will discuss the epidemiology, virology, manifestations, immunosuppressant states, and lessons learned from COVID-19.

EPIDEMIOLOGY

The high degree of infectivity of the COVID-19 virus is attributed to its novelty in the human host. It can be be measured by the basic reproduction number or R0, which is a statistical tool used to describe the contagiousness of a virus. It is estimated that the SARS-CoV-2 R0 is between 2 and 3, signifying that each infected person is likely to spread the infection to 2 to 3 additional people[13,14]. The secondary attack rate characterizes the contagiousness of a virus in the close contact setting, which considers how social behaviors may influence transmissibility[15,16]. Jing et al[17] estimated the secondary attack rate of COVID-19 to be 12.4% amongst close relatives and 17.1% amongst those who share the same residential address.

Grade D (Fair): 0
Grade E (Poor): 0

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Core Tip: The coronavirus disease 2019 (COVID-19) has caused one of the worst public health crises in modern history. Even though severe acute respiratory syndrome coronavirus 2 primarily affects the respiratory tract, gastrointestinal manifestations are well described in literature. This review will discuss the epidemiology, virology, manifestations, immunosuppressant states, and lessons learned from COVID-19.

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### Table 1 Calculated case fatality rate globally and regional according to World Health Organization reports

| Region             | Cumulative confirmed cases | Cumulative death cases | CFR  |
|--------------------|----------------------------|------------------------|------|
| Global             | 111762965                  | 2479678                | 2.22%|
| Americas           | 49700102                   | 1182591                | 2.38%|
| Europa             | 37974729                   | 848644                 | 2.23%|
| South East Asia    | 13415064                   | 205814                 | 1.53%|
| Eastern Mediterranean | 6266689                | 142986                 | 2.28%|
| Africa             | 2811106                    | 71159                  | 2.53%|
| Western Pacific    | 1594530                    | 28471                  | 1.79%|

Estimated calculation with January 24, 2021 Data - World Health Organization Coronavirus (COVID-19) Dashboard, Available from: https://covid19.who.int/. CFR: Case fatality ratio.

There are many medical comorbidities identified as risk factors for increased COVID-19 severity and mortality. In a summary report from China, pre-existing comorbid conditions increase fatality rate by 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer[18]. In a retrospective cohort study of 403 COVID-19 patients from a racially diverse, urban hospital, Rustgi et al[9] identified chronic kidney disease, hypertension, congestive heart failure, coronary artery disease, malignancy, dementia, cerebrovascular disease, seizures, and COPD to be associated with increased mortality. The centers for disease control (CDC) lists diabetes and BMI as conditions associated with increased risk of severe illness[19]. In an analysis of nearly 300000 COVID-19 cases in the United States, the mortality rate was 12 times as high among patients with reported comorbidities compared to those with none[20]. Understanding the significance of these risk factors can be vital when triaging and treating patients with COVID-19.

Few GI and liver-specific risk factors have also been identified. In a retrospective study of 2780 COVID-19 patients, Galiero et al[21] examined the effect of pre-existing liver disease (including NAFLD, NASH, and cirrhosis) on mortality. Patients with liver disease had a significantly higher risk of mortality. Another gastroenterology-specific risk factor identified is the use of proton pump inhibitors (PPIs). Luxenburger et al[22] reported that in hospitalized patients with COVID-19, the use of a PPI significantly increased the risk of developing secondary infection (48.4% vs 20.0%, P ≤ 0.001), ARDS (27.4% vs 12.2%, P = 0.02), and mortality (19.4% vs 5.6%, P = 0.01)[22]. One proposed mechanism is that PPI use suppresses gastric acid production leading to increased gastric microbiota which, in turn, can lead to micro-aspiration and subsequent bacterial colonization of the lung[23]. In addition, there is growing evidence that PPIs can also modulate immune responses by inhibiting neutrophil function with anti-inflammatory activity[24].

Age is another notable variable that affects mortality rates with older patients at much higher risk of death. One study in China showed that the mortality rate could be up to 3 times higher in patients who are 80 years or older[18]. Race and ethnicity have also been shown to affect mortality rates, though there is limited literature. Rustgi et al[9] showed that White, Blacks, Asians, and Hispanics all have significantly different mortality rates[9]. In a meta-analysis of more than 3 million reported global cases, male patients compared to females had increased odds of ICU admission (OR, 2.84; 95%CI: 2.06-3.92) and mortality (OR,1.39; 95%CI: 1.31-1.47)[25]. COVID-19 mortality rates also vary significantly by country. For example, France had a CFR of 15.2% whereas Korea had a CFR of 2.1%[26]. Unique delivery systems and healthcare infrastructure in these countries play a major role in influencing COVID-19 mortality.

### VIROLOGY

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus of the Coronaviridae family[2]. The coronaviruses can infect a wide range of vertebrates, including snakes, bats, pangolins, and humans. Sequence similarities with the bat and pangolin coronavirus virus RaTG13 strains suggest that the SARS-CoV-2 has a
zoonotic origin[2,3,27].

Human infection happens by aerosol droplets or carried on fomites. Upon inhalation, the SARS-CoV-2 enters host respiratory cells via the angiotensin-converting enzyme 2 (ACE2) receptor and activating receptors such as the transmembrane protease serine 2 or cathepsin (Figure 1)[27,28]. Viral replication in the infected cells causes immune cells to proliferate and produce large amounts of cytokines and chemokines such as TNF-alpha, interferon-gamma, interleukin 6 (IL-6), IL-8, and IL-10 (Figure 1)[28,29]. This process causes a cascade of inflammatory reactions with toxic damage to the lungs (Figure 2). These mechanisms have also been utilized as targets for therapy. After the initial focus on hydroxychloroquine, emphasis has more recently been on polymerase inhibitors (Remdesivir), binding agents such as convalescent plasma therapy and IL-6 inhibitors such as Tocilizumab[30,31]. Vaccines, such as mRNA-based (Pfizer-BioNTech, Moderna), adenovirus-based (AstraZeneca, Sputnik V, Convidecia, ZF2001), inactivated viral particles (CoronaVac, BBIBP-CorV, Covaxin, CoviVac), non-replicating viral vector (Janssen), and peptide (EpiVacCorona) (Figure 3) are areas of active evolution[30-33]. Adenovirus based intra-nasal COVID vaccines are currently undergoing evaluation via clinical trials. These vaccines with different mechanisms of action trigger immune responses and are of great benefit to systematically stop the COVID-19 pandemic[34].

GI symptoms such as diarrhea, nausea, vomiting, or abdominal pain have been reported in approximately 10%-15% of COVID-19 patients before, during or after clinical disease[28,35]. Stool samples from infected patients may test positive for the presence of SARS-CoV-2[36]. In vitro studies have demonstrated that enterocyte organoids may harbor and be capable of supporting SARS-CoV-2 replication[37]. In addition, in-vivo reports indicate that viral RNA is detectable by RT-PCR in biopsies from the esophagus, stomach, duodenum, and rectum[38]. These limited studies suggest that the SARS-CoV-2 virus can actively infect and replicate in the GI tract causing direct organ dysfunction.

The liver may suffer injury in 35%-56% of COVID-19 patients as shown by elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase and/or bilirubin levels[12,38,39]. Interestingly, SARS-CoV-2 RNA sequences have been detected by RT-PCR in liver tissues of infected individuals, suggesting that hepatic injury may be related to direct viral infection[40]. Biopsy findings have demonstrated non-specific inflammatory changes such as hepatocyte swelling and steatosis, mild proliferation of hepatic sinusoid cells, hyperplasia of Kupffer cells and infiltration of lymphocytes[41-43]. SARS-CoV-2 injury in the liver may be mediated by high ACE-2 expression in liver cholangiocytes as well as TROP-2 Liver progenitor cells[41].

Ischemia-perfusion injury has been reported as a complication of COVID-19 in both the GI and liver and has been more frequently observed in those COVID-19 patients admitted to intensive care units[44-46]. This injury may be due to coagulopathy, vasculopathy, hypoxia and shock caused by COVID-19 and thromboembolic events[47-49]. Under these conditions, there is an increase in reactive oxygen species which, in turn, activate transcription factors and initiate the release of various pro-inflammatory factors that lead to tissue damage (Figure 2)[49,50].

**GI MANIFESTATIONS**

GI symptoms are common in COVID-19[51]. The most commonly reported GI manifestations are diarrhea, nausea, vomiting, and abdominal pain[52]. Loss of appetite and dysgeusia have also been described[53]. Viral particles have been isolated in fecal samples suggesting the possibility of fecal transmission of the virus[54]. A minority of patients with positive stool testing lacked GI symptoms suggesting asymptomatic carriage of disease[55]. These findings highlight the importance of fecal-aerosol-mucosal transmission among individuals exposed to contaminated feces, including public toilets or areas with poor sanitation. This provides a concerning avenue for infectious spread in under-developed regions of the globe, including many regions in Africa and South Asia which lack comprehensive wastewater treatment facilities. Disease control guidelines have emphasized effective management and disinfection of potentially contaminated feces in COVID19 patients, and aggressive vaccination programs in areas at higher risk for fecal-oral spread[43].

Initial case series from China revealed diarrhea as the most prevalent GI symptom, occurring in 2%-36% of cases, followed by nausea (1%-17%), vomiting (1%-6%), and abdominal pain (2%-6%)[56]. As the pandemic has spread, additional reviews and
meta-analyses have confirmed the prevalence of GI symptoms in other population groups, although much of the reported data remains from cohorts of Chinese patients. A large meta-analysis of 59254 patients predominantly from the Hubei province (75.8), showed that 9% of all patients experience GI symptoms (Table 2)\[57\]. A more recent meta-analysis by Tariq et al\[52\] focused specifically on GI manifestations of disease, including 12797 patients from 11 countries. Of the patients included, 12.4% reported diarrhea and 9% nausea and/or vomiting. Abdominal pain was also reported in 6.2% of patients. Comparative analysis by patient location revealed a significantly higher proportion of symptoms of diarrhea and nausea/vomiting in the non-China subgroup while loss of appetite was similar between groups.

Anosmia and ageusia are frequently reported with important implications. Ageusia was reported in 20% of patients in one recent review while the rates of anosmia varied greatly across studies from 22%-68%\[53\]. Anosmia and dysgeusia were more likely to be associated with concurrent nausea or loss of appetite (16.9 vs 6.5%, \( P = 0.006\)).

GI symptoms generally occur with modest frequency compared with respiratory symptoms and fever; however, there are a small number of patients who present with GI symptoms as the only manifestation of disease\[58\]. Among these patients with isolated symptoms, there is frequently a more delayed hospital presentation compared to respiratory symptoms (9.0 d vs 7.3 d)\[59\]. The American Gastroenterological Association (AGA) has recommended COVID-19 testing in patients with new onset GI symptoms as these may precede pulmonary symptoms\[60\]. Several studies have attempted to correlate GI symptoms with severity of disease and mortality with mixed results. A recent United States-based case-control series of 150 patients with GI symptoms did not demonstrate increased mortality, intubation, or hospital length of stay compared with controls who lacked GI symptoms\[61\]. This is in contrast to some initial series from China which linked digestive symptoms to longer length of stay\[62\]. Further investigation into this area is needed.
Table 2 Gastrointestinal manifestations in coronavirus disease 2019

| Ref.            | Number of subjects | Diarrhea | Nausea | Vomiting | Abdominal pain |
|-----------------|--------------------|----------|--------|----------|----------------|
| Lin et al[35], 2020 | 95                 | 24%      | 18%    | 4%       | 2%             |
| Wong et al[56], 2020 | 2230              | 2%-36%   | 1%-17% | 1%-6%    | 2%-6%          |
| Tariq et al[52], 2020 | 12797             | 12%      | 9%     | 9%       | 6%             |

*Study presented “nausea and/or vomiting” as one statistic.

While critically ill patients still experience many of the same GI symptoms including diarrhea and vomiting, more severe complications noted have included bowel ischemia (3.8%), ileus (55.8%), and Ogilvie-like syndrome (1.9%), as demonstrated in one series of 141 COVID ICU patients[44]. A recent review compared GI complications between critically ill patients with COVID and those with non-COVID ARDS and found that the COVID cohort developed more GI complications (74% vs 37%, \( P < 0.001 \))[63]. While many symptoms have been identified, data describing the significance of the GI symptoms in predicting disease course and outcomes has been limited, variable, and sometimes contradictory.

**COVID-19 AND LIVER MANIFESTATIONS**

COVID-19 infection has been shown to directly affect the liver and cause laboratory abnormalities via previously described mechanisms based on abundant ACE2 receptors found on hepatocytes and cholangiocytes to directly enter cells and cause significant liver dysfunction and injury[35,63]. Hospitals in China reported abnormal liver enzymes in approximately 14%-76% of cases hospitalized for COVID-19[64,65].
According to a systematic review and meta-analysis of 47 studies with 10890 total patients with COVID-19, approximately 15% to 20% were identified to have abnormal liver enzymes with a higher prevalence identified in studies performed outside of China (Table 3)[60].

Hospitalized patients found to have abnormal liver enzymes, may have also shown a higher likelihood of developing severe disease, as well as increased risk of intensive care admission and death[57]. This lack of data has recently prompted the AGA to recommend obtaining baseline liver enzymes and consider monitoring liver enzymes in patients throughout the course of their infection[60].

Treatments for COVID-19 have been associated with elevated liver enzymes and subsequent injury, most notably with remdesivir use. Remdesivir use in early trials and series was associated with 10%-50% of patients developing transient, mild to moderate (< 5 times upper limit or normal) elevations in AST and ALT within 5 da of therapy. Nine percent of patients in reported trials showed at least moderate elevations, but resolved with discontinuation and were not associated with clinically significant injury. Pharmacology guidelines recommend close monitoring of liver enzymes and early discontinuation of infusions if elevations rise > 10 times the upper limit of normal[66,67]. Dexamethasone remains a treatment for severe COVID-19 infection. It should be acknowledged that prolonged use of corticosteroid therapy can cause hepatic steatosis as well as increase the risk of developing reactivation of latent infections, such as viral hepatitis B.
Table 3 Liver manifestations in coronavirus disease 2019

| Ref.                  | Number of subjects | Abnormal LFTs (any) | ALT | AST | Tbili |
|-----------------------|--------------------|---------------------|-----|-----|-------|
| Lin et al[35], 2020   | 95                 | -                   | 5%  | 4%  | 23%   |
| Wang et al[36], 2020  | 105                | 56%                 | 16% | 9%  | 2%    |
| Fan et al[39], 2020   | 148                | 37%                 | 18% | 22% | 6%    |
| Zhang et al[65], 2020 | 1628               | 14%-53%             | -   | -   | -     |
| Cai et al[65], 2020   | 417                | 76%                 | -   | -   | -     |
| Sultan et al[60], 2020| 10890              | -                   | 15% | 15% | 17%   |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

COVID-19 AND IMMUNOSUPPRESSED STATES

Corticosteroids, immunomodulators (thiopurines, methotrexate) and biologic therapies (such as anti-TNF agents) are frequently used to manage inflammatory bowel disease (IBD), liver transplant recipients and patients with autoimmune hepatitis[68]. These medications block the intracellular signals necessary for host immunity and are associated with high rates of viral and bacterial infections including pneumonia[69, 70]. Therefore, it is plausible that immunosuppressed patients would increase the risk of infection with SARS-CoV-2. However, it is also plausible that these medications reduce mortality in COVID-19 by blocking the cytokine storm of SARS-CoV-2[71]. Hence, how a gastroenterologist should handle immunosuppressive therapies in patients with suspected or confirmed COVID-19 is a challenging clinical question.

The SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion – IBD) database consists of reported cases of COVID-19 in IBD patients[72]. The data suggests that the prevalence of severe COVID-19 is low in patients on immunomodulator therapy and biologic therapy; 25% needed hospitalization on immunomodulator monotherapy whereas 19% needed hospitalization while on anti-TNF agents[73]. Fortunately, mortality rates were low with 2% in the immunomodulator monotherapy group and 1% in the anti-TNF cohort[72]. Thus, the AGA recommends that IBD therapies be continued with a goal of maintaining remission and adjustment being made as necessary[74].

Similar to SECURE-IBD, SECURE-Cirrhosis (Surveillance Epidemiology of Coronavirus Under Research Exclusion - Cirrhosis) is a registry for all COVID-19 cases in patients with chronic liver disease as well as liver transplant recipients[75]. The data from this registry suggests that patients with chronic liver disease but without cirrhosis have a similar risk of mortality from COVID-19 as patients without liver disease. However, patients with cirrhosis have an increased risk with mortality of 32% [75,76]. The data from the registry also suggests that liver transplantation was not associated with an increase in mortality with SARS-CoV-2 infection[77]. The American Association For The Study Of Liver Diseases (AASLD) recommends that anticipatory changes in immunosuppressive regimen should not be made for post-transplant patients and autoimmune patients without COVID-19[78]. In patients on immunosuppression, AASLD recommends lowering the dosages based on the general principles to manage infections in these patients[78].

In summary, the current data does not suggest that patients on immunomodulators have an increased risk of mortality from COVID-19. The current guidelines from AGA and AASLD do not recommend pre-emptive changes in patients on immunosuppression if the patients have not been infected with COVID-19. However, the dosages may be adjusted in patients with COVID-19 on the basis of general principles[74,78].

CONCLUSION

The WHO and CDC have developed ongoing recommendations to be followed during the COVID-19 pandemic. The mechanism of injury and cascade of events due to COVID-19 (Figure 2) have been studied in great detail. These have helped develop targets for therapy and vaccines. The current literature does not reveal that immunosuppressed patients are at higher risk of COVID-19 infection[74,78]. However,
the impact of the COVID-19 vaccine on specific organs such as liver and GI tract are still uncertain. Further research is necessary to evaluate the long-term effects of the vaccine in relation to GI tract. Despite lack of long-term data, patients and physicians are encouraged to get vaccinated as universal vaccination is of great societal and global benefit.

The pandemic has prompted a change in structure and shape of gastroenterology departmental activities. 27% of the centers in the United States and Canada had implemented routine endotracheal intubation for upper endoscopic procedures[79]. The reshcping has been aimed to address urgent and emergent needs of the community and decreasing patient exposures in the hospital. Most of the practices had altered coverage schedule for the physicians. Strict protective measures during endoscopic procedures such as gowns, gloves, face shields, N95 masks, hairnets, double gloves, shoe covers, have also been implemented[79]. The patients are screened at arrival for symptoms and exposures. During the pandemic, only highly urgent endoscopic procedures are being performed on COVID-19 patients[80]. Endoscopy should be performed only when necessary and in a negative pressure flow room for COVID-19 patients if such a room is available. Where a negative pressure flow room for COVID-19 is not possible, strict sanitation measures are recommended[80].

Online consultations in the form of telehealth services and home drug deliveries have been important. Virtual clinics have been started by majority of the institutions as chronic digestive diseases can be managed safely at home. The patients are screened and 11 Canadian Centers in May 2020 [96% (70/73) of the practices had adopted telehealth as revealed in the survey of 62 U.S and 11 Canadian Centers in May 2020[80].

The evaluation of inpatients should be judicious to prevent unnecessary exposure of patients, hospital personnel to COVID-19. Clearly, society as well as healthcare delivery will continue to evolve and adapt for this and future crisis.

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