

# World Journal of *Clinical Cases*

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## Practical points that gastrointestinal fellows should know in management of COVID-19

Tevhide Sahin, Cem Simsek, Hatice Yasemin Balaban

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### Abstract

Pandemics obligate providers to transform their clinical practice. An extensive effort has been put to find out feasible approaches for gastrointestinal diseases and also to manage coronavirus disease 2019 (COVID-19) related gastrointestinal conditions. Diarrhea, hepatitis, and pancreatitis can be seen in the COVID-19 course. Endoscopic procedures increase the risk of contamination for medical staff and patients despite precautions, therefore indications should be tailored to balance risks *vs* benefits. Furthermore, whether the immunosuppression in inflammatory bowel diseases, liver transplantation, and autoimmune liver diseases increases COVID-19 related risks and how to modify immunosuppression are topics of ongoing debate. This review aims to provide most up to date practical approaches that a gastrointestinal fellow should be aware on the problems and management of gastrointestinal and hepatobiliary diseases during the COVID-19 pandemic.

**Key Words:** COVID-19; Gastrointestinal diseases; Practical points; Endoscopy; Gastrointestinal fellows

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**Core Tip:** Along with the rise of new gastrointestinal and hepatopancreatic problems during the coronavirus disease 2019 (COVID-19) pandemic, patients and physicians involved in gastroenterology faced serious challenges in managing diseases. All these necessitated modifying our daily clinical practice in COVID-19 era. Here this review provides guidance for diarrhea, pancreatitis, hepatitis, inflammatory bowel disease, autoimmune hepatitis, liver transplantation, and endoscopic procedures based on most current evidence from the literature.



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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is on an anniversary of its emerging as a global health problem. Throughout last year, all medical fields' practices have been modified. These modifications were in accordance with the COVID-19 precautions as well as the patients' best possible care with limited resource utilization. From the perspective of a gastroenterologist, there are many COVID-19 implications in our practice. First, gastrointestinal symptoms can be presenting symptoms for COVID-19 or they can emerge during the course of diseases that warrant diagnostic and management strategies. Second, endoscopic procedures pose risk to the patients as well as the endoscopy team, therefore the indications have to be reevaluated. Third, we care for a great number of patients at risk for COVID-19 and related outcomes. The population at risk include but not limited to patients with cirrhosis, autoimmune liver diseases, and inflammatory bowel disease (IBD), as well as liver transplant recipients. All these patients need updated algorithms during the course of pandemics that have been constantly being updated with the emergence of new data.

## PRACTICAL POINTS

### *Gut-lung axis*

Microbiota-containing tissues, such as the gastrointestinal and respiratory tracts, serve as entrance points for pathogens and hence are regions prone to infection. The endogenous microbiota regulates pathogen entrance into the host and by exposing the microbiota to food-borne antigens, pathogens, and metabolites in the gut, it establishes a complicated regulatory system. Disruption of this complex system results in pathologies such as IBD, allergies, and metabolic disorders. Microbiota plays an essential role in immune response regulation[1]. The lower respiratory tract has a range of microbial communities. In diseased and healthy lungs, there are multiple microbial communities[2-4]. The lung and gut microbiota interact bi-directionally: The gut microbiome influences respiratory immunity and contributes to the differentiation of the extra-intestinal T cell population, which is required for systemic immunity. When intestinal bacteria invade, Th17 cells are induced[5]. In a preliminary study, it was discovered that COVID-19 patients had a higher prevalence of opportunistic pathogens in their feces than the control group. In another study, high prevalence of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* was connected with the severity of COVID-19[6]. Another study revealed that the Bacteroidetes group was more prevalent in COVID-19 positive patients than in the control group[7].

In the midst of rapidly emerging data for every field, it has become a matter of continuous effort to stay up-to-date with the recommended clinical practice. Therefore, we aim to provide a pragmatic and brief summary of evidence and guidance regarding the most common and highly specialized areas in gastroenterology.

### ***How should the practice of endoscopy adapt to the COVID-19 pandemic in terms of triage of endoscopic indications and protection rules for the endoscopist and patients?***

Studies suggest the possibility of fecal-oral transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is extensively reviewed by Simsek C *et al* at this Topic Highlight for Gastrointestinal System in COVID-19. Therefore, new strategies for endoscopy suits are mandated with the rising prevalence of COVID-19.

A joint message from The American Association for the Study of Liver (AASLD), American College of Gastroenterology (ACG), American Gastroenterology Association (AGA), and American Society for Gastrointestinal Endoscopy (ASGE) societies recommends to consider rescheduling non-urgent endoscopic procedures[8]. This recommendation is also in line with the recommendations of British Society of Gastroenterology (BSG) and Joint Advisory Group (JAG) which prioritize procedures into three as: Emergent/essential, deferrable, and discussable. The first group includes bleeding, foreign bodies, luminal obstruction, hepatobiliary obstruction and infected pancreatic fluids, inpatient nutrition support, and endoscopic therapy for leaks and perforations. In cases such as EUS for cancer staging/treatment planning, planned endoscopic mucosal resection (EMR)/endoscopic mucosal dissection (ESD) for high risk lesions, new suspected acute colitis, and variceal banding in high risk cases, it should be evaluated by the clinician according to the patient's condition. Planned procedures for reasons such as all screening colonoscopy, surveillance (polyps, IBD, Barrett's esophagus, and varices), bariatric endoscopy, endosonography (EUS) for non-malignant lesions, elective procedures, and IBD evaluation



should be postponed[9].

A joint panel from AASLD, ACG, AGA, and ASGE recommends pre-screening all patients if they have high risk exposure or COVID-19 relatable symptoms. As expected, the panel also recommends personal protective gear for all endoscopy staff. All patients should be questioned for symptoms and exposure, those aged > 65 years or those identified as being risky by the Centers for Disease Control and Prevention (CDC) should not accompany the patients, the endoscopy team should wear appropriate personal protective equipment (PPE), the temperature of the patients coming to the endoscopy unit should be measured, the appropriate distance between the patients should be approximately 6 feet (about 180 cm), and COVID-19 positive patients with or waiting for the test result should be treated in a negative pressure room[8].

The joint panel does not comment on SARS-CoV-2 polymerase chain reaction (PCR) test prescreening [8]. Besides, other joint statements from BSG and JAG, The European Society of Gastrointestinal Endoscopy (ESGE), and The ESGE Nurses and Associates (ESGENA) did not provide guidance regarding SARS-CoV-2 PCR testing, only commenting on questioning for symptoms and contacts[9,10]. A PCR pretesting strategy has been advocated by AGA where asymptomatic SARS-CoV-2 infection prevalence is 0.5%-2%[11]. An economic feasibility analysis concluded that COVID-19 PCR pre-testing is effective in restarting endoscopic procedures[12]. In endoscopy centers where asymptomatic SARS-CoV-2 infection is < 0.5%, most of the gastroenterologists may choose to use mask of National Institute for Occupational Safety and Health filter series, namely, N95/99 or powered air-purifying respirator (PAPRs) if PPE is present. N95/99 or PAPRs should be used in emergent upper and lower endoscopy in areas with a high number of cases. In centers with a 0.5%-2% asymptomatic SARS-CoV-2 infection prevalence, endoscopist can use surgical masks while performing upper and lower endoscopy in patients with negative PCR testing. Before coming to the endoscopy unit, patients should be questioned for symptoms. Everyone should wear masks in the endoscopy unit. The number of individuals coming to the unit should be limited (patient, staff, and visitor), and there should be at least 6 feet space between patients in the waiting room[11].

The endoscopy unit should be cleaned with virucidal agent after the procedure for every patient in the case of high risk for COVID-19 or after known COVID-19 infection. One day before endoscopy and on the day of endoscopy, patients should be risk stratified by questioning symptoms and contact or by testing for SARS-CoV-2 infection. While the patient is being evaluated in the endoscopy center, employees and patients should wear surgical masks and the distance should be at least 1-2 meters. All patients' temperature should be measured before entering the unit. Caregivers and relatives should not be taken into the endoscopy unit. There should be no personnel not related to the process in the processing room, and the number of personnel should be minimized to reduce exposure. Personnel change should be avoided during operations. Pre-post endoscopy timeframes should be arranged for patients with a high risk of infection. PPE should be used according to the patient's risk situation. Endoscopies of patients with a high risk or known to be positive should be performed by experienced personnel in a negative pressure room. If there is no negative pressure room, it should be done with appropriate ventilation in the allocated rooms[10]. AGA recommends using a negative pressure chamber if COVID-19 is known or highly possible. After the procedure, scopes must be cleaned according to standard endoscopic disinfection and reprocessing protocol regardless of the COVID-19 status[13].

During the pandemic, endoscopic procedures should be planned and categorized according to their urgency in accordance with protection rules for the endoscopist and the patients. Those with elective indications should be postponed in accordance with the guidelines. Since PCR based tests have increased availability and accessibility, we recommend the routine use of them for prescreening before endoscopic procedures to detect asymptomatic patients, and so to prevent the spread of COVID-19.

### **Acute diarrhea before or during COVID-19?**

The gastrointestinal system is frequently affected by COVID-19, although the primary target of SARS-CoV-2 is the respiratory system. The epidemiology of gastrointestinal symptoms and their prognostic value are discussed in detail by Usta B *et al* at this Topic Highlight series for Gastrointestinal System in COVID-19. The most common gastrointestinal symptom is diarrhea which occurs in 2-50% of patients as initial symptom or during the course of disease. Furthermore, the management of diarrhea is also important for possible fecal-oral transmission of SARS-CoV-2.

AGA Institute estimated the frequency of diarrhea in COVID-19 through a meta-analysis involving 10676 COVID-19 patients with positive PCR tests. The pooled prevalence of diarrhea was 7.7% (95% confidence interval [CI]: 7.2%-8.2%), which was slightly higher in hospitalized patients than in outpatients [10.4% (95%CI: 9.4-10.7) *vs* 4.0% (95%CI: 3.1%-5.1%)] [14].

Diarrhea is a confounder for the management of COVID-19, because patients may present with diarrhea in the absence of respiratory symptoms[14,15]. However, a meta-analysis with limited data found that preceding diarrhea is much rarer than expected[14]. Two studies by Ai *et al* and Wang *et al* found that only 2 of 102 and 14 of 138 hospitalized patients had diarrhea as initial symptom[14,16,17]. Even though, AGA recommends taking a thorough history regarding the risk contact exposure as well as the specific symptoms for COVID-19. For outpatients with diarrhea, it is recommended to follow them for few days for the development of other symptoms. However, testing should not be delayed in

high prevalence settings[14].

In summary, COVID-19 often causes respiratory symptoms, but the initial presentation can be with gastrointestinal complaints, especially diarrhea. COVID-19 should be considered in those who have acute diarrhea coming from areas with a high incidence of COVID-19. The symptom questioning should be performed in detail, and if necessary, PCR should be done without any delay.

### **Should the treatment of IBD patients be changed during COVID-19 pandemic?**

Ulcerative colitis and Crohn's disease are chronic inflammatory diseases of the bowel with exacerbations that warrant immunosuppressive or immunomodulatory treatments[18]. Such treatment strategies pose a theoretical risk for COVID-19, which has been addressed by a number of studies.

COVID-19 outcomes in pediatric and adult IBD patients were evaluated using an international database of Surveillance Epidemiology of Coronavirus under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD). The report included 525 confirmed IBD patients with COVID-19 from 33 countries. The risk factors were assessed for severe COVID-19 outcome which was defined as need for intensive care unit admission, ventilator use, or death. Multivariate analysis demonstrated risk factors as use of systemic corticosteroids (adjusted odds ratio [aOR] = 6.9; 95%CI: 2.3-20.5) and use of sulfasalazine or 5-aminosalicylate (aOR = 3.1; 95%CI: 1.3-7.7). Although monotherapy with tumor necrosis factor (TNF) antagonist was not associated with severe COVID-19 (aOR = 0.9; 95%CI: 0.4-2.2), combination of anti-TNF with an immunomodulatory agent had a higher risk for hospitalization or death than monotherapy (aOR = 5.0; 95%CI: 2.0-12.3)[19].

In another study using the SECURE-IBD database, the relationship of different drug classes and combinations with severe COVID-19 was analyzed among 1439 confirmed COVID-19 patients with IBD from 47 countries. Anti-TNF monotherapy was compared with thiopurine monotherapy and their combination. Combination therapy (aOR = 4.01; 95%CI: 1.65-9.78) and thiopurine monotherapy (aOR = 4.08; 95%CI: 1.73-9.61) were found to be associated with an increased risk of serious COVID-19. On multivariable analysis, anti-TNF therapy, in contrast to corticosteroids, was not found to be associated with severe COVID-19. Mesalamine/sulfasalazine monotherapies were found to be associated with severe COVID-19 when compared to anti-TNF monotherapy (aOR = 3.52; 95%CI: 1.93-6.45). When evaluated with respect to age, mesalamine/sulfasalazine treatments after the age of 50 years had a significant risk of COVID-19 in comparison to anti-TNF monotherapy. However, no statistically significant difference was found in patients under 50 years of age. In an exploratory analysis, there was no significant difference associated with COVID-19 when mesalamine/sulfasalazine and non-drug users were compared. When low and high dose mesalamine/sulfasalazine was compared, no difference was observed in terms of serious COVID-19 risk. Similarly, interleukin-12/23 and integrin antagonists did not increase severe COVID-19 risk when compared to anti-TNF monotherapy[20].

In a prospective observational cohort study from Italy, 79 IBD patients diagnosed with COVID-19 were examined with respect to IBD treatments and outcomes. IBD treatments (corticosteroids, thiopurines, anti-TNF, and vedolizumab) were not found to be associated with increased risks of COVID-19 pneumonia or hospitalization. Active IBD, advanced age, and comorbidities were found to be associated with negative COVID-19 outcomes (pneumonia, hospitalization, need for mechanic ventilation, and death)[21].

A matched cohort study compared the clinical outcomes of COVID-19 patients with or without IBD (80 *vs* 160 patients). Corticosteroid use was found to be higher in patients with COVID-19, but no difference was found in the use of biologics, immunomodulators, or aminosaliclates. When the users of biological agents (anti-TNF, vedolizumab, and ustekinumab) were compared, no significant difference was found in terms of emergency service admission or hospitalization. COVID-19 was observed at similar rates in patients who received biological therapy (anti-TNF, vedolizumab, ustekinumab, and tofacitinib)[22].

In a similar population-based retrospective cohort study using a federal research data set, COVID-19 patients with IBD were compared with those without. Out of 196403 IBD patients, 1901 were tested for COVID-19, in whom 232 were positive, whereas the non-IBD COVID-19 group consisted of 19776 patients. When IBD patients who took immunosuppressive treatment in the previous year were compared to those who did not, there was no high risk of severe COVID-19. IBD patients who were using steroids within the previous 3 mo of COVID-19 diagnosis had an increased risk of severe COVID-19 when compared to those who were not[23].

In another retrospective cohort study using United States Veterans Affairs healthcare system data, 36 COVID-19 patients were identified among 37857 patients with IBD between January 1 and May 15, 2020. Thiopurine and anti-TNF were found not to significantly increased the risk for COVID-19[24].

Both BSG and The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) recommend not to cease treatments in IBD patients in order to avoid COVID-19[25,26]. However, BSG recommends avoidance and rapid tapering of corticosteroids if possible. Otherwise, corticosteroids should be switched to budesonide or beclomethasone, if possible. Budesonide (9 mg/d for 8 wk) should be considered in active small bowel and ileocecal Crohn's disease. Immunomodulator monotherapy may not be suitable at the beginning and combination therapy with biologics can be started by carefully discussing the risks and benefits. Patients with significant comorbidities who are in remission with thiopurines or those aged > 60 years may consider discontinuing after discussion. There is also no

evidence that anti-TNF increases the risk of COVID-19 infection or impacts the outcome. Starting with monotherapy is suggested with a special emphasis on adalimumab, as it is self-injectable and has lower immunogenicity when compared to infliximab. However, intravenous to subcutaneous switching is not recommended. Salicylates, anti-interleukins 12 and 23, vedolizumab, and tofacitinib did not have any evidence regarding their impacts on COVID-19 or related risks[25].

AGA advises IBD patients to continue their current treatment regimens. Switching to elective injectable therapies is not recommended. Switching to home infusion is a presented option but not a strong recommendation. In IBD patients with COVID-19 but without symptoms, AGA recommends a dose reduction of prednisolone and if possible, switch to budesonide. Thiopurine, methotrexate, and tofacitinib are advised to be paused as well as monoclonal antibody treatments (anti-TNF, ustekinumab, vedolizumab) for 2 wk while observing the clinical course of COVID-19. If COVID-19 manifestations do not develop, the treatments could be re-started after 2 wk. In IBD patients confirmed with COVID-19, aminosalicylate, topical rectal treatment, dietary management, and antibiotics are considered safe and can be used. Oral budesonide is also considered safe; it can be continued to control the disease. Systemic steroids should be avoided and, if possible, discontinued. Thiopurine, methotrexate, and tofacitinib should not be used in acute illness, as well as anti-TNF and ustekinumab. Following complete resolution of symptoms or a negative PCR test, these treatments can be resumed[27].

We suggest that during the pandemic, there should be no change in the treatment of IBD patients without COVID-19, since most treatments have been found to be safe according to the studies. In patients with asymptomatic or symptomatic COVID-19, the dose of prednisolone should be reduced as quickly as possible and immune modulators and biologic treatments should be hold for 2 wk.

### ***How should management and follow-up of IBD patients be modified in order to decrease the risk for COVID-19?***

Along with the risks elaborated in the previous section, there have been several recommendations regarding the management of IBD patients during the pandemic.

BSG provided the most comprehensive recommendation set that includes healthcare providing strategies as well as diagnosis, surveillance, and management of IBD. As expected, infusion services is recommended to comply with social distance rules. Since subcutaneous drugs provide home care in IBD patients, they should be preferred first. A telephone/email helpline should be established for IBD patients with immunosuppressive/biological drug management or exacerbation complaints. Clinical appointments should be provided by telephone or the official telemedicine system, if possible. Routine blood tests should be delayed according to local capacity. The fecal calprotectin test can be used as a potential alternative to endoscopy and its combined use with clinical disease activity scores may assist in the treatment decision more objectively. Non-emergency endoscopies should not be performed and IBD surveillance procedures should be postponed, or replaced with alternative methods such as biomarkers, radiology, or capsule endoscopy. Urgently suspected new cases of IBD should be discussed on a case-by-case basis to decide the timing of the diagnostic endoscopy. If centers delay evaluating new IBD patients, a telephone triage system should be implemented to assess clinical urgency. For patients with a higher risk of hospitalization, daily clinics with a limited number of patients should be considered for their timely evaluation and management. Complex IBD surgery should be postponed if possible and its optimal timing should be determined by the multidisciplinary team. Yet, emergency procedures should continue as part of routine care[25].

AGA also provided guidance on the topic focusing mostly on general precautions and use of endoscopy. It is advocated that during the pandemic, endoscopy can be performed for biopsy in the diagnosis of new severe IBD, or to exclude CMV if non-invasive tests are suspicious, or in cases of serious disease or cancer[27]. AGA endorses precautions that include prescreening for COVID-19 symptoms or exposure, temperature measurement at the door, appropriate distance between chairs, use of gloves and masks by caregivers, and appropriate deep cleaning after the patient leaves[27]. IOIBD panel recommended ambulatory infusions to be continued in centers with COVID-19 screening protocols[26].

Our recommendation for IBD patients is that they should be managed as much as possible without going to the hospital. Patients should be followed by phone calls, telemedicine, and non-invasive methods, depending on the facilities of the center.

### ***Does proton pump inhibitor treatment increase the risk for COVID-19?***

COVID-19 pandemic brought up a concern on the treatment of proton pump inhibitors (PPIs), which are well known to increase the risks for enteric infections and pneumonia[28-30]. Several studies were conducted to investigate potential harmful effects of PPIs on COVID-19 development and progression.

The studies on the infection rate among PPI users had contradictory results. An online national health survey was conducted from May 3 to June 24, 2020, and 3386 (6.4%) of 53130 adult participants reported a positive COVID-19 test. The regression analysis showed that the rate of COVID-19 was significantly increased among individuals using PPIs once a day (aOR = 2.15; 95%CI: 1.90-2.44) or twice a day (aOR = 3.67; 95%CI: 2.93-4.60) in comparison to PPI non-users. The infection rate did not increased by histamine 2 receptor antagonists[31]. However, a prospective study from France had contradictory results. Out of



179 elderly people with SARS-CoV-2 contacts and followed for COVID-19 transmission, 89 of them became PCR positive. SARS-CoV-2 infection was found to be 2.3 times less likely to develop in patients who received PPIs (OR = 0.4381; 95%CI: 0.2331-0.8175,  $P = 0.053$ )[32].

The Korean national cohort study included 132316 patients (111911 PPI non-users, 14163 current PPI users during the past 30 d, and 6242 past PPI users in the last year through 31 to 365 d). After propensity score matching, the relationship could not be demonstrated between PCR positivity and current or past PPI use, which implied that PPIs did not predispose to COVID-19. However, current PPI use was associated with a 90% increased risk of severe COVID-19 (intensive care unit, ventilation, or death)[33]. Supporting the association between PPI use and severe COVID-19, the *post hoc* analysis of the same study revealed that patients who received two or more PPIs per day compared to those who did not take PPI had higher risks of oxygen treatment, intensive care, invasive ventilation, or mortality[34]. A matched case-control study in Scotland was designed based on the prescription records given in primary care in the last 240 d and those who were discharged from the hospital since June 2015. Since the beginning of the epidemic, 4272 severe COVID-19 cases were matched with 36948 controls. PPI usage was associated with an increased risk for severe COVID-19[35].

The increased rate of secondary pulmonary infections among PPI user hospitalized for COVID-19 might explain the association between PPIs and poor prognosis of severe disease. In a retrospective cohort study, 295 hospitalized COVID-19 patients were included, in whom 15.6% (46 patients) were using PPIs at home before admission. The mortality and risk for developing acute respiratory distress syndrome (ARDS) were 2.3 times higher in patients using PPIs than those in non-users. The effect of PPIs on mortality in patients < 60 years old was independent from other factors, such as cardiovascular risk factors and comorbidities[36]. Similarly, in another study with 152 patients hospitalized for COVID-19, of whom 62 (48.4%) received PPIs regularly, secondary infection was developed in 48 patients during hospitalization. The use of PPIs was found to be an important risk factor for secondary infection in hospitalized patients ( $P < 0.001$ ). Moreover, PPI use had an indirect effect on the development of ARDS by causing secondary infection, and was associated with a significantly higher mortality ( $P = 0.01$ )[37].

PPIs are one of the most commonly used drugs. However, the review of current literature indicated that the usage of PPIs is associated with poor clinical outcomes of COVID-19. No matter how much emphasized it is less that, PPIs should be used in clinical practice, especially during the pandemic period, only when indicated and at the lowest effective dose.

### **Does COVID-19 related acute pancreatitis have effect on severity of COVID-19?**

SARS-CoV-2 can cause acute pancreatitis, similar to other viral infections such as mumps, coxsackie, hepatitis B virus, cytomegalovirus, varicella-zoster virus, and herpes simplex virus[38]. SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) expressed in human exocrine glands and pancreatic islets, and cause pancreatic damage[39].

Hospitalized COVID-19 patients from six US centers were included in a retrospective cohort study. Hyperlipasemia was observed in 12.1% (9/71) of patients, and 2.8% (2 patients) had lipase elevated three times the upper limit of normal. But none of them developed acute pancreatitis, and hyperlipasemia was not associated with poor outcome[40]. Serum amylase and lipase levels were determined retrospectively in 42 COVID-19 patients diagnosed by PCR. Amylase and lipase levels were discovered to be elevated by 33% and 24.1%, respectively. Of note, neither elevated amylase nor lipase levels were not related with severe COVID-19 or death[41]. A cohort of 52 COVID-19 pneumonia patients were evaluated according to the presence of pancreatic injury which was defined as any abnormality in amylase or lipase, with heart injury observed in 33% of the patients, liver injury in 29%, pancreatic injury in 17%, and diarrhea in 2%. The groups with and without pancreatic injury did not had a significant difference in terms of steroid therapy and mechanical ventilation. However, the patients with pancreatic injury had more severe disease with high levels of AST, GGT, LDH, and sedimentation rate on admission to hospital, and their CD3+ and CD4+ T cell counts were lower[42]. The cytokine patterns in the early stages of acute pancreatitis and COVID-19 were examined in a meta-analysis which included 12 studies on acute pancreatitis and 9 studies on COVID-19. The change in pattern of cytokines was similar in severe acute pancreatitis and COVID-19. Both diseases were found to have high levels of IL-6, IL-8, and IL-10 during severe disease course[43].

An international, multicenter, prospective cohort study included 1777 patients who were hospitalized with acute pancreatitis during the pandemic period between March 1 and June 23, 2020. The acute pancreatitis coinfecting with SARS-CoV-2 was detected in 8.3% (149) of patients. Patients with SARS-CoV-2 positive acute pancreatitis significantly more frequently developed severe form of acute pancreatitis (22.6% *vs* 6.3%,  $P < 0.001$ ) and ARDS (13.6% *vs* 4%,  $P < 0.001$ )[44]. In another prospective study, 316 hospitalized patients with COVID-19 pneumonia were grouped according to the development of acute pancreatitis. The revised Atlanta Criteria were used for diagnosis, which requires the presence two of three criteria, namely, a 3-fold increase in amylase and lipase values, and typical clinical pain or radiological findings compatible with acute pancreatitis. Acute pancreatitis was detected in 12.6% of the patients. Acute pancreatitis did not develop in patients with mild COVID-19, but in 32.5% of critical cases. The hospitalization and mortality rates were higher in COVID-19 patients with acute pancreatitis ( $P = 0.0038$  and  $P < 0.0001$ )[45].

Acute pancreatitis might develop with SARS-CoV-2 infection, although its pathogenesis is not thoroughly delineated. Patients with COVID-19 associated acute pancreatitis had more severe disease course with higher rates of hospitalization, ARDS, and mortality.

### **What are the mechanisms of acute liver injury in patients with COVID-19?**

The liver is one of the major target organs for SARS-CoV-2 infection, since both hepatic parenchymal cells, namely, hepatocytes and cholangiocytes, express ACE2 that is the cellular entry receptor for the virus. As reviewed in detail by Usta B *et al* at this Topic Highlight for Gastrointestinal System in COVID-19, liver injury occurs in one forth to fifth of COVID-19 patients. Acute liver injury might develop through several mechanisms, some of which is discussed here. Apart from its prognostic value, differential diagnosis of the underlying cause is necessary to decide upon pharmacological treatment for COVID-19 and liver disease.

In a prospective study conducted in Brazil, 406 patients hospitalized with a diagnosis of COVID-19 were examined. The prevalences for high ALT and AST levels ( $> 2 \times \text{ULN}$ ) on admission were 14% (95%CI: 11.0-17.8) and 12.9% (95%CI: 10.0-16.6), respectively. In patients with high aminotransferase on admissions, in-hospital mortality rate was found to be significantly increased according to age and gender[46]. Another retrospective cohort study was conducted in three hospitals, and included 2273 patients with positive PCR and 1108 patients with negative test. Among positive patients, ALT at baseline was above the upper limit of normal in 24% of patients; 5.9% of patients had  $> 2 \text{ ULN}$  and 1.3% of patient had  $> 5 \text{ ULN}$ . In the multivariable analysis, severe acute liver injury was significantly associated with the elevation of inflammatory markers, such as ferritin and IL-6, and also serious clinical consequences. Patients with severe liver injury had high rates of intensive care unit admission (69%), intubation (65%), renal replacement therapy (33%), and mortality (42%)[47].

A retrospective analysis performed in Wuhan included 675 confirmed COVID-19 positive hospitalized patients. Liver abnormalities and liver injury were respectively defined as ALT, AST, or total bilirubin value above the upper limit and ALT value  $> 3 \times \text{ULN}$ , respectively. Abnormal liver function was found in 37.5% of patients and liver injury in 7.7%. Of 52 patients with liver injury, the liver injury developed on admission in 25 patients and during hospitalization in 27 patients. The highest risk for mortality was associated with AST levels (*i.e.*,  $> 3 \text{ ULN}$ ) ( $P < 0.0001$ )[48].

Although it is among the proposed mechanisms, the existence of “direct” liver injury associated with SARS-COV-2 is not yet fully known[49]. The ACE2 receptor expression in hepatocytes and especially cholangiocytes (20 times more than hepatocytes) suggests that liver injury may be mediated by bile duct cells. Another possibility is that SARS-COV-2 can cause liver injury through ACE2 receptor expressed on endothelial cells which play an active role in the development of hepatic ischemia-reperfusion injury and of oxidant stress with increased reactive oxygen products and nitric oxide derivatives[50]. In addition to ACE2 receptor, other receptors, such as L-SIGN and DC-SIGN, are proposed to contribute to direct liver injury of SARS-COV-2[51].

Alternative or opposing views have also been made to these assertions. First, mild to moderate liver dysfunction is mostly observed, and it rarely leads to liver failure. There is no correlation between the duration of symptoms and liver damage, and it is unknown if other respiratory viruses cause comparable liver failure as a result of immunological interactions[52]. Other respiratory viruses might also induce comparable liver damage as a result of immunological interactions. In addition, although ACE2 expression is higher in cholangiocytes than in hepatocytes, no significant elevations were observed in bile duct injury markers such as ALP, bilirubin, and GGT. Furthermore, the hepatocyte or bile duct cell injury that could support this hypothesis was not found histopathologically, although bile duct cells are thought to be precursor cells in liver injury[49].

Autopsy samples showed microvesicular steatosis, and mild lobular and portal activity implying direct injury by SARS-CoV-2 (hepatocyte apoptosis and caspase pathways)[50,53,54]. In one study, although viral inclusion-like structures were observed in postmortem liver biopsy samples, the presence of viral nucleic acid was not supported by PCR. It is not known whether these inclusions found within the parenchymal cells are cholesterol crystals or a different structure. Findings observed in biopsy materials were evaluated as being non-specific[55]. In the light of all these, it can be thought that COVID-19 associated liver dysfunction may be a secondary liver injury[49]. Although the direct effect of SARS-CoV-2 on hepatocytes is possible, it seems less likely than other mechanisms[53].

Proinflammatory cytokines, which are mediators of the hyperimmune response triggered by viral infections, can injury many organs including the liver[56]. It is well known that hepatocytes are highly sensitive to proinflammatory cytokines[57]. It is a known situation that causes liver inflammation and damage as a result of triggering the innate immune system and cytokine release by many factors[58]. In the light of all this information, increased immune response can be considered as an important mechanism in the development of COVID 19-related liver injury. Therefore, early control of cytokine dysregulation may be useful in preventing disease progression[56]. In some case series, a correlation was observed between lymphopenia and liver injury, and  $\text{CRP} \geq 20 \text{ mg/L}$  and lymphocyte  $< 1.1 \times 10^9/\text{L}$  were independent risk factors for liver injury[59]. In a retrospective observational research, a correlation was found between liver damage and cytokine storm which is characterized by elevated CRP, LDH, ferritin, and IL-6 levels[60].

Hypoxia causes ischemic hepatitis in several conditions, and 90% of these patients have heart failure, respiratory failure, and sepsis as the underlying diseases[61]. The deep hypoxia observed in COVID-19 has been thought to be one of the physiopathological factors involved in liver injury[62]. ARDS, sepsis, myocardial involvement, and endothelitis at the microvascular level are the main manifestations of severe SARS COV 2 infection. All of these cause hypoxia to be refractory to treatment, which causes ischemic hepatitis related liver injury. However, the liver injury associated with SARS-COV-2 is usually moderate, and enzyme levels are elevated less than  $5 \times \text{ULN}$ . In this sense, liver dysfunction observed in patients does not fully meet the diagnostic criteria for hypoxic hepatitis[63].

Drugs used in the treatment of COVID-19 can also cause liver injury. Total bilirubin and GGT levels were found to be higher in patients who were hospitalized and treated with lopinavir/ritonavir ( $P < 0.004$ ). The use of lopinavir/ritonavir increased the risk of liver injury four times[64]. The pharmacovigilance analysis of VigiBase data was performed on COVID-19 patients with remdesivir treatment. Out of 387 events, 34% (130) were hepatic side effects (increased liver transaminases, increased bilirubin, and hepatic failure), and remdesivir was the only suspect drug in 94% of cases[65]. A randomized, open label, phase 3 study was conducted in hospitalized patients with confirmed SARS-CoV-2 infection. After 5 d *vs* 10 d use of remdesivir, an increase in ALT and AST occurred in 6% *vs* 8% and in 5% *vs* 7% of patients[66]. A retrospective study performed in 32 severe COVID-19 patients found an elevation of serum ALT or AST in 15% of patients who were given tocilizumab treatment[67]. In a randomized, open-label, phase 3 trial in 19 patients with mild-moderate symptoms, abnormal liver chemistry was found in 6.8% of patients on favipravir treatment[68].

The mechanism of COVID-19 associated liver injury is not yet clearly understood, and is multifactorial. The increase in liver enzymes is most of the time mild to moderate, and secondary to the conditions associated with COVID-19. Therefore, there is no specific treatment for liver injury rather than treating the triggering conditions in patients infected with SARS-CoV-2.

### ***Is liver transplantation an urgent or elective procedure?***

Liver transplantation process includes different steps such as preparation, transplantation, and follow-up, all of which are challenged by COVID-19. For some patients, transplantation is an urgent rather than elective procedure. A study revealed that the mortality rates according to presence of cirrhosis and COVID-19 were 5.2% for patients with cirrhosis, 10.6% for SARS-CoV-2 positive patients, and 17.1% for patients with both cirrhosis and SARS-CoV-2. In cirrhotic patients who were positive for SARS-CoV-2, the mortality rates increased from 12.8% in compensated cirrhosis to 27.3% in decompensated cirrhosis [69]. The avoidance of transplant patients from coming to the hospital has increased deaths due to cirrhosis complications. Therefore, the follow-up of the patients should not be delayed, and must be done even by telemedicine.

Organ allocation requires an extensive team and significant infrastructure/equipment support. It creates a burden for hospital resources to be used during the pandemic period. For this reason, in the early stages of the pandemic, while transplantation was trending downwards all over the world, it started to increase again with the establishment of appropriate conditions by the hospitals. Proper surveillance of the recipient, donor, and transplant team by PCR is very important. Due to the immunosuppressive treatments to be used after transplantation, the timing should be done correctly. Immune suppressants need to be dosed well and monitored in a way that minimizes hospital visits. APASL recommends limiting the number of liver transplants, taking into account the pandemic course and resources, and transplanting only to emergency cases with a poor prognosis (acute liver damage, high MELD, high risk of HCC progression, etc.)[70].

During the pandemic period, emergency transplantation plan should be done. Centers should arrange their own protocol, considering the risk of COVID-19 during the hospitalization and capacity of intensive care bed.

### ***Should and how immunosuppressive drugs be modified in patients with autoimmune liver diseases or liver transplantation?***

Managing autoimmune liver diseases and liver transplant recipients require constant immunosuppression. How immunosuppression impacts COVID-19 rates and outcomes is a field for active investigation.

**Patients with autoimmune liver diseases:** In a study from Northern Italy, a telephone questionnaire was applied to 138 patients who were followed up with a diagnosis of autoimmune hepatitis (AIH; 71 patients) and primary biliary cholangitis (PBC; 67 patients). Symptomatic COVID-19 developed and was diagnosed by nasal swap PCR test in 3.6% of patients (4 AIH and 1 PBC). Although two AIH patients recovered at home, other two AIH patients were hospitalized for respiratory distress, and treated with lopinavir/ritonavir and hydroxychloroquine[71].

Laboratory confirmed COVID-19 patients with AIH were collected from R-LIVER COVID-19 registry, the SECURE-Cirrhosis registry, and COVID-Hep.net registry data from 25 March to 24 October, 2020. Out of 932 patients from 35 countries with chronic liver disease, 70 had a diagnosis of AIH, and 83% received immunosuppressive therapy with prednisone, thiopurines, mycophenolate mofetil (MMF), tacrolimus, and budesonide. There were no significant difference between AIH and non-AIH chronic

liver disease groups for rates of hospitalization (76% *vs* 85%;  $P = 0.06$ ), ICU admission (29% *vs* 23%;  $P = 0.240$ ), and mortality (23% *vs* 20%;  $P = 0.643$ ). In the multivariable analysis, death was associated with age and Child-Turcotte-Pugh (CTP) groups B and C cirrhosis. However, no relationship was found between the use of immunosuppression and mortality[72]. Therefore, when the hazards of discontinuing immunosuppression in AIH are weighed against the possibility of contracting COVID-19 infection, we recommend maintaining pharmacological treatment in this patient group.

**Liver transplant recipients:** A prospective national study in Spain included 111 liver transplant recipients with confirmed COVID-19, and the majority of the patients were under immunosuppression. COVID-19 was symptomatic in 93% of patients. The most common symptoms were fever (74.8%) and cough (70.3%). In this cohort, 96 (86.5%) patients were hospitalized, 22 (19.8%) needed respiratory support, and 12 (10.8%) were followed in the ICU. However, the mortality rate was 18%, which was lower than that in the matched general population. Baseline MMF, especially at doses higher than 1000 mg/d, was found to increase the risk of severe COVID-19 in hospitalized liver transplant recipients ( $P = 0.003$ ). This adverse effect could not be demonstrated with calcineurin inhibitors and mTOR inhibitors [73].

Another European multicenter prospective cohort study analyzed 57 liver transplant recipients with SARS-CoV-2 infection confirmed by microbiological assay. The most frequently reported symptoms at the time of diagnosis were fever (79%), cough (55%), dyspnea (46%), fatigue or myalgia (56%), and gastrointestinal symptoms (33%). Out of 41 (72%) patients who needed hospitalization, 11 developed ARDS and 7 (17%) died, all of which were hospitalized for ARDS[74].

European Liver Transplant Association (ELITA) and European Liver Transplant Registry (ELRT) included 243 adult symptomatic liver transplant recipients with confirmed COVID-19 from 36 European centers. Most of the patients were hospitalized (84%; 204 patients) and 19.1% (39 patients) of them were treated in the ICU. The mortality rate was 20.2% (49 patients) on average at 13.5 d after the COVID-19 diagnosis. Multivariable analysis showed that advanced age ( $> 70$ ) was independently associated with risk of mortality (hazard ratio = 4.16; 95%CI: 1.78-9.73). In the second model that excluded the age of patients, diabetes and chronic kidney failure were predictors of mortality. Tacrolimus use was independently associated with a reduced risk of mortality (hazard ratio = 0.55; 95%CI: 0.31-0.99)[75].

The current literature does not show any evidence for increased risks of COVID-19 in patients neither with AIH nor liver transplantation recipients. Therefore, we recommend to continue the immunosuppression at the lowest effective doses in these patient groups. However, the data to make specific recommendations and adjustments for particular drugs or drug classes are still pending.

## CONCLUSION

In this review, we brief current practice evidence and guidance for relevant gastrointestinal diseases and conditions during ongoing COVID-19 pandemic. The knowledge is rapidly expanding and evolving. The overall current strategy can be summarized as maximizing precautions and minimizing interventions that put patients or providers at higher risk for COVID-19. Of course, many questions remain unsolved and further studies are needed to prime our practice with the constantly changing paradigm.

## FOOTNOTES

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