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Current understanding of the impact of COVID-19 on gastrointestinal disease: Challenges and openings

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Abstract

The novel coronavirus disease-2019 (COVID-19) is caused by a positive-sense single-stranded RNA virus which belongs to the Coronaviridae family. In March 2019 the World Health Organization declared that COVID-19 was a pandemic. COVID-19 patients typically have a fever, dry cough, dyspnea, fatigue, and anosmia. Some patients also report gastrointestinal (GI) symptoms, including diarrhea, nausea, vomiting, and abdominal pain, as well as liver enzyme abnormalities. Surprisingly, many studies have found severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA in rectal swabs and stool specimens of asymptomatic COVID-19 patients. In addition, viral receptor angiotensin-converting enzyme 2 and transmembrane protease serine-type 2, were also found to be highly expressed in gastrointestinal epithelial cells of the intestinal mucosa. Furthermore, SARS-CoV-2 can dynamically infect and replicate in both GI and liver cells. Taken together these results indicate that the GI tract is a potential target of SARS-CoV-2. Therefore, the present review summarizes the vital information available to date on COVID-19 and its impact on GI aspects.

Key Words: SARS-CoV-2; COVID-19; Gastrointestinal symptoms; Recommendation; Diagnosis; Therapeutics

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Core Tip: The landscape of coronavirus disease-2019 (COVID-19) is evolving dramatically, with new information increasing at an alarming rate. It is a challenge to make sense of these data and to interpret what is crucial and high-quality evidence. In this critical circumstance, in-depth work is highly important for the future treatment and management of the disease. In this review, we summarize the vital information available to date on COVID-19 and its impact on gastrointestinal aspects.

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INTRODUCTION

Populations worldwide are currently facing an unprecedented health emergency due to the spread of novel coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization (WHO), the COVID-19 health crisis has spread to over 205 countries including the United States, India, Russia, Brazil, and Colombia^[1-3]. The most common symptoms of moderate COVID-19 include fever, dry cough, tiredness, sore throat or dyspnea. However, the pulmonary system is the main system involved in the clinical manifestation of the disease. Patients infected with this virus can suffer potential damage to other vital organs, such as the gastrointestinal (GI), cardiac, renal and nervous systems^[4-6]. Before COVID-19, many infectious diseases affected global populations, including the plague, Spanish flu, cholera, swine flu (H1N1), and severe acute respiratory syndrome-coronavirus (SARS-CoV)^[7-11]. Recent studies have shown that the mortality ratio (MR) due to COVID-19 in China is 0.66%, on the Diamond Princess ship it is 2.3% and a large meta-analysis of 36 European countries showed that the MR ranged from 4% to 4.5%^[12-14].

To date, there are no vaccines or medicines available to combat this pandemic. However, several clinical trials of both therapeutics and vaccine candidates are underway. Furthermore, it was proven that convalescent plasma transfusion (CPT) is useful in patients with severe COVID-19^[15,16]. As the landscape of COVID-19 is evolving dramatically, it is becoming a challenge to determine high-quality evidence as data is being generated at an alarming rate.

Several studies have identified SARS-CoV-2 viral RNA in rectal swabs^[17,18], and stool specimens of asymptomatic COVID-19 patients^[19,20]. This raises the issue of GI viral infection and the route of fecal-oral transmission. Furthermore, viral receptor angiotensin-converting enzyme 2 (ACE2) is expressed in epithelial cells of GI mucosa^[21,22]. Taken together, these results indicate that SARS-CoV-2 can dynamically infect and replicate in the GI tract and liver cells. However, this has important implications for the management, transmission and control of the disease. Thus, in-depth research is essential for the future treatment and management of the disease. In this review, we summarized the vital information available to date on COVID-19 and its impact on GI aspects. We recognize the ever-changing literature and aim to update future publications with the most up-to-date information available.

GI MANIFESTATIONS OF COVID-19

There are more than 40 million cases of COVID-19 worldwide, and studies that can confirm the symptoms and manifestations associated with SARS-CoV-2 are now critical. Although the lung is the primary target organ of this virus, this causes discomfort in patients with detrimental oxygen saturation effects, causing shortness of breath. However, GI symptoms have also been observed in COVID patients^[23-25]. If the virus enters *via* food it may cause diarrhea. In patients with high viral load, anorexia, anosmia, and dyspepsia are the main GI symptoms^[26,27]. Furthermore, anti-viral drugs can give rise to nausea, vomiting and diarrhea (Table 1).

Table 1 Gastrointestinal manifestations of coronavirus disease-2019

| Gastrointestinal manifestations | Clinical findings |
|---------------------------------|--------------------|
| Lack of appetite | Elevated AST |
| Anorexia | Elevated ALT |
| Anosmia | Elevated bilirubin |
| Vomiting | Elevated LDH |
| Dysgeusia | |
| Nausea | |
| Abdominal pain | |
| Bloody diarrhea | |
| Intestinal dysfunction | |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase.

SARS-CoV-2 can be detected in the GI tract. The virus can invade epithelial cells in the stomach, intestine and colon surface and cause symptoms in the GI tract. As the world is now facing the second wave of this current pandemic, the GI manifestations of COVID-19 require much more attention as there are more possibilities for transmission of the infection due to lack of information/knowledge on GI complications^[21,28-30]. The course of alveolar events, GI spread and the manifestations of SARS-CoV-2 infection are shown in **Figure 1**.

A meta-analysis of 60 studies from 6 countries found that 4243 patients with SARS-CoV-2 infection had GI symptoms, including diarrhea (12.5%), nausea/vomiting (10.2%), anorexia (26.8%) and abdominal pain (9.2%), which were the most common symptoms^[31]. Another hospital-based study reported that of 1099 patients, nausea or vomiting and diarrhea occurred in 5% and 3.8% of patients, respectively^[21]. Another study showed that in 148 Chinese SARS-CoV-2 positive patients, half of the patients seemed to have abnormal liver function at the time of admission^[32]. A further study showed similar results with non-typical findings in hepatic enzymes^[33,34]. Patients were expected to have moderate to high fever with elevated liver function, and these tests were remarkably more frequent in male patients (68.67%) than in female patients (38.36%)^[35].

CLINICAL SIGNIFICANCE OF COVID-19

SARS-CoV-2 when entering the body causes viremia with associated pneumonia and the main clinical features of this disease are fever, severe headache, fatigue, diarrhea and other potential associated comorbidities^[36,37]. The estimated average duration of incubation is 1-14 d (commonly 3-7 d). Viruses enter the body and proliferate mainly in the lungs, GI tract, and heart. SARS-CoV-2 is believed to be concentrated in tissues that express ACE2^[38,39]. Recently, studies have reported that anorexia, nausea, vomiting and diarrhea were the most common GI tract symptoms in almost 40% of patients^[40,41]. However, one-tenth of patients complained of GI symptoms without major difficulty in breathing or mild fever^[42]. SARS-CoV-2 has been correlated with a hyper-coagulable condition with a major risk of venous thromboembolism^[43]. Neurological indications such as severe headache, dizziness, and loss of consciousness, stroke, and muscle injury have also been observed^[44]. Detailed clinical manifestations are shown in **Table 2**. GI manifestations of SARS-CoV-2 infection are also indicated to alter nutrient absorption by modulating the expression and activity of nutrient transporters, such as the neutral amino acid transporter BAT1. SARS-CoV-2 infection which potentially triggers physiological and anatomical damage related to the GI tract along with its systemic influence is summarized in **Figure 2**.

Table 2 Clinical significance of coronavirus disease-2019

| Stage | Symptoms |
|----------|--|
| Mild | Initial symptoms are mild or negligible with no sign of pneumonia on imaging. |
| Moderate | Cough, moderate fever, myalgia, gastrointestinal symptoms, anosmia and respiratory signs with radiological imaging findings of pneumonia. |
| Severe | The presence of one of the following: (1) Shortness of breath (RR ≥ 30 breaths/min); (2) Oxygen saturation $\leq 93\%$ at rest; (3) Arterial partial pressure of oxygen/fraction of inspired oxygen ≤ 300 mmHg (1 mmHg = 0.133 kPa); and (4) In less than 24-48 h, more than half of patients with radiological imaging show clear lesion progression. |
| Critical | Any of the following: (1) Lung failure or requiring mechanical ventilation; (2) Septic shock; and (3) Multiple organ failure (other organ failure that requires HDU/ICU critical care.) |

RR: Risk ratio; HDU: High dependency unit; ICU: Intensive care unit.

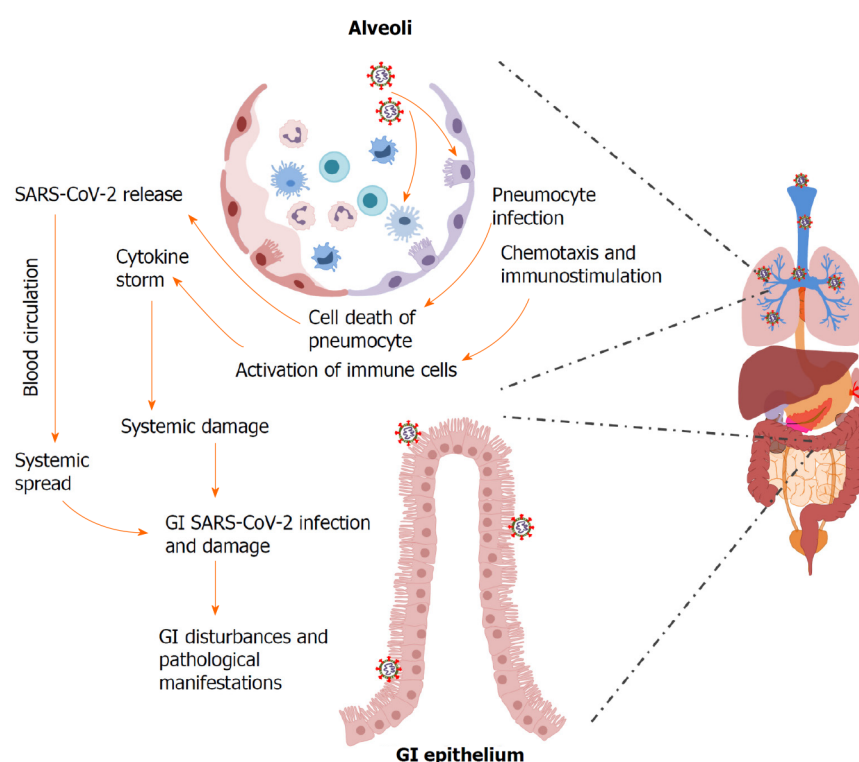


Figure 1 Systematic representation of the course of alveolar events, gastrointestinal spread and manifestations of severe acute respiratory syndrome coronavirus 2 infection. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; GI: Gastrointestinal.

CARE OF PATIENTS WITH EXISTING LIVER DISEASE

Non-alcoholic fatty liver

Obesity is a major risk factor for severe COVID-19 because pneumonia is mainly exacerbated in obese people as adipose tissue can act as a viral repository and is, therefore, an immunological center for the inflammatory response^[45,46]. Since non-alcoholic fatty liver disease (NAFLD) is associated with metabolic comorbidities such as type 2 diabetes, hypertension and obesity, NAFLD patients are at higher risk of having severe COVID-19^[47]. According to a retrospective study, 39 of 202 confirmed COVID-19 patients had higher body mass index (BMI) and higher NAFLD comorbidity rates. The study also found that NAFLD patients had a higher risk of disease progression to severe COVID-19, and these patients also had a longer duration of viral shedding^[48]. Interestingly, patients with NAFLD and SARS-CoV-2 infection less than 60 years of age are associated with an elevated risk of severe disease^[49]. NAFLD patients with increased non-invasive liver fibrosis scores are more likely, despite metabolic comorbidities, to develop severe COVID-19 disease^[50].

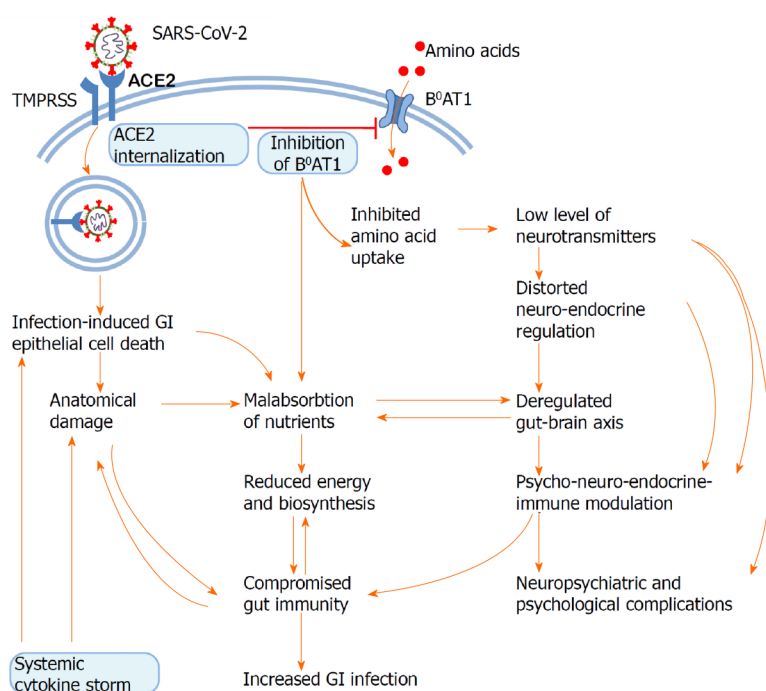


Figure 2 Potential events caused by severe acute respiratory syndrome coronavirus 2 infection in gastrointestinal physiological and anatomical damage with systemic influence. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; GI: Gastrointestinal.

Viral hepatitis

Almost 5 billion people in the Asia-Pacific region have chronic viral hepatitis^[51]. Unlike metabolic liver disorder, there is little or no evidence that chronic viral hepatitis affects the progression of COVID-19. Corticosteroid and tocilizumab are administered to critically ill patients with COVID-19, which can lead to reactivation of hepatitis B virus (HBV) and to severe liver failure in patients with long-term HBV infection. Therefore, HBsAg screening should be performed in patients with severe COVID-19 with a positive HBsAg test at the time of corticosteroid therapy^[52]. It is essential to initiate antiviral medication in newly diagnosed HBV patients affected by COVID-19 when HBV DNA is more than 2000 IU/mL and alanine aminotransferase is above the upper limit of normal. Drug-drug interactions between agents used to treat COVID-19 and HBV may occur. In addition, patients with HBV and HBC should continue to receive antiviral drugs. Considering the uncertain effect of interferon-alpha on the systemic inflammation associated with COVID-19, treatment with alternative drugs in patients with HBV during the pandemic should be addressed prior to medication administration. In COVID-19 patients, initiation of treatment for HBV and hepatitis C virus (HCV) is usually not required and should be delayed until recovery from COVID-19 is achieved. Interactions between the drugs used in the treatment of COVID 19, and those used to treat HBV and HCV should be carefully monitored.

Autoimmune liver disease

Patients with autoimmune liver disease can experience severe liver problems. Therefore, the reduction of immunosuppressive drugs in the prevention of SARS-CoV-2 is generally not recommended. The reduction should only be performed under special conditions (such as drug-induced cytopenia or bacterial super-infection) after consultation with a specialist. Treatment with corticosteroids was found to be promising in hospital patients seeking respiratory support for COVID-19. There is still concern that patients who are taking elevated doses of corticosteroids may be more vulnerable to SARS-CoV-2 infection and serious COVID-19. Patients who are already taking corticosteroids when they develop COVID-19 should have an adequate dose of corticosteroids to prevent adrenal insufficiency. Adding or switching to dexamethasone can only be addressed in patients with COVID-19 who require hospitalization and respiratory assistance. Liver enzymes such as transaminases, alkaline phosphatase and gamma-glutamyltranspeptidase may be increased in patients with confirmed COVID-19 or suspected SARS-CoV-2 infection. Thus, it is

strongly recommended that suspected infection should be confirmed by biopsy. However, if there is a strong suspicion of autoimmune hepatitis, empiric therapy may be initiated without histological confirmation at the standard treatment dose^[53-55].

Liver cirrhosis

Patients with cirrhosis are susceptible to SARS-CoV-2 infection, new and worsening hepatic decompensation, severe COVID-19 and death. Patients with new or deteriorating hepatic decompensation should be given priority to SARS-CoV-2 screening even in the absence of respiratory symptoms. For patients with cirrhosis who are infected with SARS-CoV-2, rapid admission must be considered to prevent further worsening of their condition. There is no specific consideration to date for cirrhosis patients who have been infected with SARS-CoV-2 as the drug used to control COVID-19 may increase the risk of other infections and viral shedding^[53,56,57].

Liver transplant recipients

Patients who have undergone liver transplantation are at high risk of severe infection with SARS-CoV-2 and death. The risk of transmission of SARS-CoV-2 through liver transplantation is unknown; therefore, it is recommended that all donors should be screened for SARS-CoV-2 infection with real-time reverse transcription polymerase chain reaction (RT-PCR). Considering that SARS-CoV-2 can spread from asymptomatic people, including children, patients undergoing liver transplantation should strictly follow physical distancing or not travel during the COVID-19 pandemic. Telehealth home surveillance is efficient and useful for liver transplant recipients; consequently, it must be available in most transplant centers and applied to pre-transplant patients where telehealth services are available. Unrecognized COVID-19 significantly increases the risk of severe immune suppression and post-transplant infection in liver transplant recipients, leading to multiple organ failure and even death. A reduction of immunosuppressive therapy in liver transplant recipients should not be considered to prevent SARS-CoV-2 infection. Such a reduction can only be carried out under exceptional conditions (including drug-induced lymphopenia or bacterial/fungal super-infection in the event of SARS-CoV-2 infection) after consultation with a specialist. Calcineurin inhibitor dosage levels and mechanistic targeting by rapamycin inhibitors should be closely monitored as they are offered in conjunction with drugs such as hydroxychloroquine, protease inhibitors or recent COVID-19 test drugs^[58-61].

DIAGNOSIS OF GI COVID-19 EFFECTS

COVID-19 is spread by air-borne viral particles and affects not only the respiratory tract, cardiovascular, and central nervous systems but also affects the GI system. Previous findings demonstrated that several patients with COVID-19 had many low to moderate GI complications, including diarrhea during the disease course^[26]. Until recently, there was no evidence on the potential of anti-GI drugs but sufficient frequent rehydration and potassium ion monitoring were conducted in COVID-19 patients. Therefore, it might be hypothesized that diarrhea should be considered an awareness parameter and must be investigated to reach an early diagnosis in COVID-19 patients. Furthermore, measurement of calprotectin could play an important role in the monitoring, diagnosis, and follow-up of COVID-19-associated diarrhea and GI complications. Therefore, participation of the GI tract in COVID-19 should be considered and explored under several clinical policies and practices such as the incorporation of rectal swab testing before the discharge of COVID-19 patients^[62], as well as our future supply of personal protective equipment (PPE) in the endoscopy, ultrasound and another relevant diagnostic settings. These implementations will act as promising tools to eradicate COVID-19^[63].

GI endoscopy

Endoscopy is a very complex procedure in GI clinical settings. In COVID-19 patients, it is a high-risk process for healthcare professionals due to potential high exposure while performing upper GI endoscopy, and makes them more prone to infection as a result of the patient's aerosol^[64]. A study reported the presence of SARS-CoV-2 RNA in a patient's stool samples. These findings raise suspicion and support the potential fecal-oral transmission route of infection. Furthermore, the novel virus is possibly transmitted through fecal contamination *via* inhalation, conjunctival splash contact, or direct contact with feces during colonoscopy^[21]. To restrict the aerosol transmission of

SARS-CoV-2 within/between the endoscopy team, various hospital infection control guidelines and protocols should be established. All endoscopic procedures should be conducted in an isolated aseptic environment with one set of endoscopy equipment and a PPE kit. According to recent data, it was estimated that the half-life of SARS-CoV-2 virus particles in the air is estimated at around 1.1 h^[65]. To prevent viral load, patient to patient cross-infection, and transmission, the current guidelines suggest performing endoscopy in a negative pressure isolated room^[66]. All COVID-19 patients should undergo prescreening before arrival at the endoscopy room. During this current outbreak of COVID-19, many experts have recommended the indications for urgent endoscopy which are limited to acute GI bleeding, GI obstruction requiring stenting or dilatation, biliary sepsis, repair of GI perforations and leakage, foreign body retrieval, and the establishment of enteral nutrition. According to recent guidelines, we would like to recommend other criteria including a minimum number of staff with specifically one proficient endoscopist and two nurses for each endoscopy platform. Adequate time should be allowed for infection control measures before and after endoscopy. It should be kept in mind that the same staff should serve the same room for the whole session while performing the procedure. However, when it comes to operative and non-operative endoscopic procedures, all safety measures concerning medical health worker exposure should be considered. There are three criteria and routes for the endoscopic procedure: (1) Oral route: any procedure *via* the mouth or nose; (2) Anal or stomal route: any procedure passing through the anus or an enterocutaneous stoma; and (3) Capsule endoscopy.

The following vital parameters should be documented before performing endoscopy; fever of more than 37.5°C, contact history, travel history, occupational exposure, and clustering^[67]. For all suspected and positive cases, the clinical preparation for endoscopy should be reviewed, and preferably patients with a medical emergency, life-threatening conditions should receive endoscopy. Moreover, all endoscopy teams and staff should receive proper training on the use of PPE and infection control management. Various disinfectants such as ethanol (62%-71% concentration), 2% glutaraldehyde, and 0.1%-0.5% sodium hypochlorite are frequently used before and after each case. All these practices can help to reduce the viral load within one minute of the exposure period^[68].

Endoscopy is a very advanced tool, and we would like to recommend all elective endoscopies during the current COVID-19 pandemic for diagnosis purposes be limited until there is a promising cure. This diagnostic strategy helps to protect health care capacity to handle many suspected and positive cases of COVID-19 strategically. However, this approach will act as a potential protective measure to reduce the cross-transmission of COVID-19 between patients and healthcare staff, particularly at the early stage of the COVID-19 pandemic^[69]. All these measures aid some significant effort to reduce the risk of cross-infection, the spread of the virus and preserve the use of PPE, are essential in overcoming the spread of COVID-19 within healthcare staff.

Abdominal ultrasound and computed tomography imaging

In COVID-19 patients, fever and dry cough are the most commonly observed symptoms? RT-PCR is the most frequently use confirmatory test to diagnose and identify genomic RNA of SARS-CoV-2. However, early radiological studies focused on imaging of the chest using high resolution computed tomography (CT), which measures peripheral patches of ground-glass densities with or without consolidations with bilateral basal predominance, organizing pneumonia pattern, crazy paving, mild bronchiectasis, and vascular engorgement may also be observed^[70,71]. Radiography of the chest, apart from its widespread use and low cost, also has low diagnostic sensitivity for pneumonia in COVID-19 patients^[72]. Unlike radiography, lung CT is considered a sensitive imaging technique for early detection of pulmonary severity in infected patients^[73]. A recent study found that CT imaging is superior to RT-PCR (98% *vs* 71%, respectively, $P < 0.001$) in the diagnosis of COVID-19^[74]. However, it is difficult to imagine a situation where CT is systematically performed in all suspected and positive cases due to cost, exposure to radiation, time required, and the probability of cross-contamination.

Ultrasound (US) is a portable, low cost, and relatively fast procedure with real-time visualization. In the current pandemic, US is considered a potent technique for the diagnosis of suspected and confirmed COVID-19 cases to facilitate better treatment strategies. The use of US has advantages as it restricts exposure of multiple staff to confirmed cases. Additionally, point-of-care US has recently been recommended to manage COVID-19 cases to reduce the use of medical equipment and the number of healthcare staff, which ultimately minimizes cross-infection. More recently, some authors have reported the high diagnostic accuracy of US compared with radiography

when evaluating lung abnormalities^[75,76]. However, imaging findings may also increase the understanding of abdominal manifestations in COVID-19 patients. Recently, Abdelmohsen and coworkers conducted abdominal imaging studies (sonographic examination) at 30 intensive care units with 41 confirmed COVID-19 patients with abdominal complications. They reported that 51.2% of patients had increased liver function tests, particularly serum bilirubin, followed by elevated renal function tests in 14.6% of patients^[77]. Tullie *et al*^[78] conducted abdominal US and CT imaging in pediatric COVID-19 confirmed patients and found that US was the best diagnostic imaging tool in patients with GI symptoms.

Furthermore, they reported that US findings were in line with lymphadenopathy and the presence of inflammatory fat throughout the mesentery with visible thickening of the terminal ileum. Thus, US and CT may accelerate the understanding of abdominal complications in COVID-19 patients^[78]. Therefore, we strongly recommend the use of abdominal US imaging for the diagnosis of patients with GI manifestations when investigating for possible appendicitis.

RISK FACTORS DURING ENDOSCOPY IN COVID-19 PATIENTS

Endoscopy is a minimally-invasive technique and is usually recommended for the evaluation of ulcers/polyps, gastritis, stomach pain, dysphagia, digestive tract bleeding, and sometimes for biopsy^[79]. It is a safe and common practice; however, it does have the risk of adverse events preventing completion of the procedure and can result in complications ranging from low to potentially rare or mild to lethal complications^[80]. During clinical practice from pre-procedure to post-procedure, various adverse reactions can occur, such as infections, cardiopulmonary disorders, bleeding, thromboembolism *etc.* To date, more than 44 million COVID-19 cases with over 1 million deaths have been recorded^[81]. It has been verified that this infection is contagious and is chiefly transmitted *via* respiratory droplets (> 5 to 10 µm in diameter) or by close contact (usually within 1 m) to an infected individual while coughing or sneezing. The alarming element concerning COVID-19 is its airborne transmission that may also be feasible in some medical circumstances. Certain clinical practices such as endotracheal intubation, bronchoscopy, nebulization *etc.*, produces aerosols resulting in aerial spread, while fecal-oral route transmission (fomites) can also result in contamination^[82,83].

Paramasivam and his team conducted a review referencing the report of the Quality Committee of American Society for Gastrointestinal Endoscopy where they mentioned the three key rudiments in defining endoscopic risk factors, *i.e.*, the complexity of the procedure (procedure-related), co-morbidity and clinical status (patient-related) and individual expertise (operator-related)^[84,85]. Complexity encompasses clinical and perceived risk elements. Technically more sophisticated approaches are often riskier. Treatment with endoscopic retrograde cholangiopancreatography (ERCP) in conjunction with or without sphincter division (sphincterotomy), colonic polyps as well as peptic ulcer elimination, have high complication rates following therapeutic endoscopy procedures^[86]. Artificial ventilation or positive insufflation practice may cause significant aerosol generation due to short physical distancing during endoscopy, increasing the risk of infection in staff, medical personnel, anesthesiologist and others^[87,88]. Techniques have progressed to endo-luminal from surgical methods with the escalation and advancement of endoscopic expertise, innovation and has accrued considerable experience to combat this pandemic^[86,87].

Although, different endoscopic procedures have specific complications, such as post-ERCP pancreatitis in ERCP or asthma and hemoptysis in bronchoscopy^[86,89]; however, perforation, hypoxemia and bleeding are the most commonly recorded complications of all forms of endoscopy^[86]. It has been documented that the bleeding rate ranges from low to high with the intensification of invasive procedures such as endoscopic biliary sphincterotomy, endoscopy dilatation or colonoscopic polypectomy during diagnosis^[90-92]. Medical guidelines recommend that endoscopy is carried out within 24 h of the patient presenting with acute upper GI bleeding^[93]. Compared to other risks, endoscopic-mediated bleeding, typically improves after rapid and rigorous treatment and controls or minimizes other risks^[90]. However, the debate about endoscopy in COVID-19 patients, gives rise to specific management decisions. A case study by Cavaliere *et al*^[88] documented that endotracheal tube intubation during upper endoscopy surgery in a COVID-19 patient is challenging, and may increase the mortality rate. Coagulopathy linked to COVID is another explanation for GI bleeding; therefore, for stratification, prothrombin time, platelet count and D-dimer

measurement are recommended^[94]. Since the complications of endoscopy could surpass the benefits, clinicians have agreed to cautiously treat these patients with a blood transfusion (when necessary), proton pump inhibitor drip, and regular surveillance of GI symptoms, hemoglobin level and other vital signs^[88].

Similar to bleeding, perforation has also been recognized as an important risk factor due to its high incidence during numerous procedures, it has been studied in GI trials and clinical interventions are often employed^[80]. Perforations are frequently found in the sigmoid colon. Three approaches are considered to cause perforations: air insufflation driven barotrauma, therapeutic procedures and colonoscopy or an instrument triggered mechanical injury^[95,96]. Perforations occurring during ERCP arise when there is a transmural extension of sphincterotomy beyond the sphincter and are archetypally asymptomatic. Other factors include adhesions, dysfunction of the sphincter of Oddi, biliary stricture dilation, snare polypectomy *etc*^[80].

Operator inexperience has also been designated a significant risk factor. Researchers found that prolonged treatment in conjunction with elevated sedation dose could be attributed, in part, to a higher proportion of complications. Over-sedation may increase the risk of severe complications (such as perforation and bleeding), which can inhibit the pain response^[97,98]. Due to its short recovery duration, propofol is among the most widely used agents and has lower complication rates than conventional sedative agents as its mean sedation period is shorter and the sedation depth is higher. Propofol is thought to be safe for sedating (senior) patients when given the correct dose, while the risks including hemodynamic and breathing depression occur and accelerate during upper GI endoscopic procedures^[80]. Under severe sedation, patients undergoing difficult colonoscopy tend to vomit resulting in pulmonary aspiration. This can lead to needless misperception in medical personnel and caretakers as the signs of pneumonia due to pulmonary aspiration are similar to those in COVID-19^[99].

Respiratory and cardiovascular complications have also been observed. Tachycardia and bradycardia can be found during invasive events. Hypertension, hypotension, and syncope were observed during treatment. Clinical micro-aspiration can be considered insignificant if it does not result in pulmonary inflammation or prolonged bronchospasm^[80]. As soon as these risk factors have been identified and defined, standard operating procedures and detailed protocols can be set up to reduce the risk of complications before or during the planning phase. The compulsory pre-screening test should be carried out before entry (conditionally carried out to the outbreak of COVID-19) and there should be a discrete unit for 'low-risk' and 'high-risk' patients. Also, healthcare staff and workers must abide by asymptomatic carrier precautions and level 2 biosafety^[100].

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH LIVER DISEASE DURING COVID-19

General recommendations

In view of the significant multifaceted effects of the pandemic, especially in chronic diseases, liver damage can be highly variable and complex, leading to the activation of an intra-hepatic immune response, triggering microvascular thrombosis, hepatic obstruction and systemic inflammation in addition to drug toxicity. In conjunction, this systemic disorder is often associated with a phenomenon known as "bystander hepatitis" and the patient can have a lethal course and show no specific signs of hepatic failure^[101,102]. The personal care of these patients relies greatly on the regional COVID-19 prevalence and the laws and guidelines imposed^[101]. Therefore, the pragmatic structuring of strategies to address this issue must be made by physicians and their organizations by strengthening electronic health records (EHR) and encompassing novel technologies such as remote monitoring and telemedicine to restore treatment levels wherever feasible^[103]. The epidemiology of this virus appears uncertain. However, for some time to come, its prevalence may increase and diminish chronologically. Thus, a customized and versatile patient care strategy is needed to align nationwide SARS-CoV-2 infection dynamics, public infrastructure accessibility, and the degree of frequency of existing hepatic disease in an individual. Finally, it is necessary to restart clinical trial registration to make significant progress despite unimaginable global events^[53] (Table 3).

Standard recommendations

Both the American Association for the Study of Liver Diseases^[104] and the European

Table 3 Recommendation guidelines for the management of patients with liver disease during coronavirus disease-2019

| S. No. | Clinical condition | Consulting organization | Recommendation guidelines for management during COVID-19 |
|--------|-----------------------------------|-------------------------------------|--|
| 1 | Out-patient care | AASLD, EASL-ESCMID | (1) Offering telehealth; (2) Mail order of prescriptions & medications; (3) If viral hepatitis occurs: continue medication; (4) Tracking & recording alcohol usage; (5) Limiting testing, imaging & blood withdrawal; and (6) For patients with autoimmune liver disease, immunosuppression medication is continued. |
| 2 | In-patient care | AASLD, EASL-ESCMID | (1) Clustering COVID-19 & non-COVID-19 patients separately; (2) Minimizing personnel on rounds; (3) Safe discharge planning; (4) Usage of remote care-telehealth communications & video monitoring; (5) Limiting patient visitors; (6) Minimizing testing, imaging & blood withdrawal; and (7) Avoiding inter/intra-transfer between facilities. |
| 3 | Endoscopy | AASLD, EASL, APSDE, AGA, ESGE, ASGE | (1) Limiting emergent indications such as ERCP (for cholangitis), severe GI bleeding or variceal bleeding; (2) Minimizing personnel during procedures; (3) Every clinician/personnel recommended to use N95 masks and PPE as there is high aerosol generation during clinical procedures; and (4) Postponing certain elective procedures such as esophageal variceal screening. |
| 4 | NAFLD | AASLD, EASL | (1) Notification to patients regarding adverse hepatic/metabolic implications associated with social isolation & lifestyle; (2) In line with existing directives, arterial hypertension treatment should continue; and (3) All NAFLD patients who may be infected with SARS-CoV-2 should have early admission. |
| 5 | Viral hepatitis (HBV & HCV) | AASLD, EASL | (1) If under care, continue treatment for chronic HCV and chronic HBV; (2) For follow-up patients, offer telehealth and laboratory testing; (3) Mail order of direct-acting anti-viral prescriptions & medications, if initiated; (4) Alternative therapy should be considered as associated risks of IFN- α is unknown; (5) Case-by-case basis decision in consultation with a medical specialist should be undertaken for patients with COVID-19 and high disease flare; and (6) Use of anti-viral therapy is considered in individuals with resolved or chronic HBV and COVID-19 conditions undertaking immunosuppressive therapy. |
| 6 | Liver cirrhosis | AASLD, EASL | (1) Clustering COVID-19 & non-COVID-19 patients separately; (2) Early admission and prioritized COVID-19 testing for patients with ACLF or deteriorating/chronic hepatic conditions is advised; (3) Every attempt must be made, wherever feasible, to restore highest quality treatment for patients; (4) Prophylactic course of action for GI hemorrhage, hepatic encephalopathy <i>etc.</i> must be trialed; (5) Use of vasoconstrictor therapy ought to be undertaken with great consideration and care; and (6) Vaccination recommended for <i>Streptococcus pneumoniae</i> and influenza. |
| 7 | ALD | AASLD, EASL | (1) It is recommended that there should be no reduction in immunosuppressant dosing in patients with ALD & COVID-19. Under special conditions, dosage may be decreased but, after consultation with a clinician; (2) Monitoring of corticosteroid treatment in patients with elevated doses as they have increase susceptibility to viral infection; (3) Agents such as budesonide is recommended as a primary treatment to reduce the systemic risk of glucocorticoids; and (4) Vaccination is recommended for <i>Streptococcus pneumoniae</i> and influenza. |
| 8 | ARLD | AASLD, EASL | (1) Reduction in consumption of alcohol; (2) Implementing strategies such as cessation and online (telephone) alcohol liaison services; (3) Monitoring of corticosteroid treatment in patients with elevated doses as they have an increase susceptibility to viral infection; (4) Awareness of online circulation of misinformation or fabrication concerning alcoholic effects. |
| 9 | Liver transplantation and surgery | AASLD, EASL, ILTS, LTSL, ATS, TTS | (1) Avoid evaluation of in-patient transplants; (2) Screening of recipients and donors for COVID-19; (3) Reduction in immunosuppression in chronic COVID patients; (4) Routine reduction in immunosuppression doses should not be encouraged; (5) Edge to urgent indications/case-by-case; (6) Minimize workforce during treatment procedures; (7) Safe anesthesia practice with appropriate PPE and N95 masks use is recommended; and (8) Deferring elective procedures such as hepatic resection. |
| 10 | Hepatocellular carcinoma | AASLD, EASL, ILCA, ASCO, ESMO | (1) Postponing HCC screening for some months; (2) Pausing enrolment in clinical trials; (3) If surgery or extirpation are delayed, then trans-arterial bridging therapies should be offered; and (4) The patient needs to continue, if already taking tyrosine kinase inhibitor medications. |

NAFLD: Non-alcoholic fatty liver disease; ALD: Auto-immune liver disease; ARLD: Alcohol-related liver disease; COVID-19: Coronavirus disease-2019; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal; PPE: Personal protective equipment; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ACLF: Acute-on-chronic liver failure; ALD: Alcoholic liver disease; HCC: Hepatocellular carcinoma; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; APSDE: Asian Pacific Society for Digestive Endoscopy; AGA: American Gastroenterological Association; ESGE: European Society of Gastrointestinal Endoscopy; ASGE: American Society for Gastrointestinal Endoscopy; ILTS: International Liver Transplantation Society; LTSL: Liver Transplant Society of India; ATS: American Thoracic Society; TTS: Transplantation Society; ILCA:

Association for the Study of the Liver (EASL)^[101], advocate the use of telemedicine to minimize interaction between patients and health workers by recommending prevention and management interventions that include sectioning of COVID-19 inpatients from other clinically healthy patients and optimization of the use of telemedicine. For COVID-19 adults with chronic disease (particularly if other risk factors are present), the EASL recommends considering early admission and with an upscaled biochemical profile, must be examined for concomitant viral hepatitis B or C infections^[105]. In patients with strong clinical suspicion of deep venous thrombosis, or biliary blockage, diagnostic imaging must only be implemented in selected patients, and biopsies should be postponed, but certain cases should be admitted to detect autoimmune hepatitis^[101,104,105]. Besides using EHR and telemedicine in some patients as an alternative to in-person care, various medical centers must change their modus operandi to meet the needs of social distancing^[106].

Viral hepatitis-HCV and HBV: Medication for HCV and HBV should be administered following the general guidelines in patients without COVID-19^[107]. If the patients are already taking medication such as anti-viral therapy for the treatment of chronic HCV/ HBV, telehealthcare, as well as clinical tests, should be conducted in addition to electronic follow-up prescriptions and if initiated, additional resources including a complete course of anti-viral medications with alternative therapies to prevent the uncertain effect of INF- α ^[53,54]. A case-by-case decision by the consultant should be taken for clients with COVID-19 and a high disease flare or a clinical concern of acute HBV hepatitis, and then patients should undergo antiviral therapy. The use of antiviral therapeutic interventions should be taken into account to avoid viral flares or reactivation in patients with severe, latent or healed HBV and COVID-19 treated with immunosuppressive agents^[53].

Liver cirrhosis: The effect of SARS-CoV-2 infection on patients with cirrhosis and the negative impacts of late or amended treatment during the COVID-19 pandemic is especially important and every attempt must be made wherever possible to establish the highest quality treatment for cirrhosis patients in compliance with guidelines^[53,108]. The option to postpone all regular screenings or monitoring procedures for patients with compensated cirrhosis should be available. As per the proposal of the Baveno VI consensus, it is recommended that low-risk patients should avoid intrusive variceal blood screening^[106]. The risk of infection and associated comorbidities in cirrhosis patients is expanding, and is critical for patients who have decompensated cirrhosis, as a result of immune dysfunction related to cirrhosis. Particular measures should be carried out for those patients with cirrhosis admitted for reasons other than COVID-19 in a designated non-COVID-19 station, ideally side-rooms, in an attempt to mitigate the risk of SARS-CoV-2 nosocomial contamination^[53]. Standardized rules and regulations to avoid and deter admission must also be strictly observed concerning GI hemorrhage, hepatic encephalopathy and prophylaxis of spontaneous bacterial peritonitis^[53,108].

NAFLD or steatohepatitis: Metabolic complications such as hypertension, obesity and diabetes mellitus (DM) will increase the probability of severe COVID-19 in patients with NAFLD or steatohepatitis (NASH)^[101,106]. The associated negative metabolic and hepatic effects due to social repression, including intensified sedentary habits and intake of convenience foods should be made known to patients^[53,106]. The development of liver disease may be prevented by activities such as diet guidance, weight loss advice and managing DM, which may minimize severe disease following future infection with SARS-CoV-2. The treatment of arterial hypertension should follow current guidelines. There is currently no indication that angiotensin-converting enzyme blockers or angiotensin receptor antagonists increase either the risk of SARS-CoV-2 or the risk of serious complications or death from COVID-19. All patients with NAFLD and SARS-CoV-2 should be admitted to hospital promptly^[53].

Specific recommendations for NAFLD: Patients with NAFLD are considered to be susceptible to COVID-19; therefore, specific recommendations should be followed. Patients with NAFLD should be mindful of the possible detrimental effects of social isolation on metabolic and hepatic function, as more unhealthy lifestyles and excessive intake of refined foods may exacerbate the condition. To prevent the progression of liver disease, good lifestyle choices should be made. Maintaining body weight and avoiding obesity can help to prevent future SARS-CoV-2 infection. Under current

guidelines, treatment of arterial hypertension should be continued as there is no research at present to suggest that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers raise the risk of SARS-CoV-2 infection or the risk of experiencing serious complications or death from COVID-19. For all NAFLD patients who develop COVID-19 admission should be considered. Whenever possible, patients with NAFLD should be hospitalized in areas physically separated from other COVID-19 patients^[53].

Alcohol-related liver disease: Alcohol intake can enhance the vulnerability of a person to SARS-CoV-2 infection. Social exclusion can contribute to new and elevated use of alcohol^[109], a rise in alcohol consumption may be associated with further liver decompensation. Therefore, physicians and agencies should adopt preventive actions such as patient access to telephone alcohol liaison and abstinence. While therapy with corticosteroids has shown a positive benefit in hospitalized COVID-19 patients^[110], there is still uncertainty as to whether patients already on elevated doses of corticosteroids are more likely to be seriously affected by COVID-19. These aspects should be addressed in patients with severe alcoholic hepatitis before the initiation of corticosteroids^[53].

Autoimmune liver disease: Experts are currently suggesting that immunosuppression therapy should be avoided in COVID-19 patients with autoimmune liver disease. A decline in medication following lymphopenia/cytopenia or microbial super-infection in patients with severe COVID-19 should be considered only in exceptional circumstances following consultation with a physician^[53,106]. Although corticosteroid treatment has had a positive effect in hospitalized COVID-19 patients, it is unknown whether patients treated with high doses of corticosteroids may be more vulnerable to SARS-CoV-2 infection and severe COVID-19. Therefore, we suggest the initial administration of budesonide to reduce systemic glucocorticoid exposure in patients with autoimmune hepatitis flare without cirrhosis^[53,101]. Dexamethasone should be introduced or added only in COVID-19 patients who require hospital admission and respiratory assistance^[110]. There is insufficient information on patients with IgG4-associated diseases, primary sclerosing cholangitis and biliary cholangitis to formulate specific guidelines. All patients should be vaccinated against *Streptococcus pneumoniae* and influenza^[53,101].

Patients who have undergone liver transplantation: Patients with decompensated cirrhosis on the liver transplantation (LT) standby list are at greater risk of serious COVID-19 and death; therefore it is advisable that LT facilities should, as far as appropriate, be restored after the pandemic. Researchers urge the creation and enhancement of LT-donors and recipients' local and global risk pathways, which involve a combination of clinics. LT is a priority for those with a short-term prognosis, such as those with acute liver failure, elevated Model for End-stage Liver Disease score and hepatocellular carcinoma (HCC) at the top of the Milan criteria, in centers with constant resources^[53,101,105]. It is currently proposed that all SARS-CoV-2 donors be tested using reverse transcription PCR before using SARS-CoV-2-infected donor livers^[60]. It should be noted that patients with SARS infection waiting for LT are associated with a greater risk of COVID-19 and mortality following significant surgery; thus, the possible risk of nosocomial COVID should require consent for diagnostic and therapeutic procedures relating to transplantation^[111]. Calcineurin-inhibitor drug levels and rapamycin inhibitor mechanistic targets should be closely monitored when used in combination with medications such as hydroxychloroquine, protease inhibitors or experimental COVID-19 drugs^[53]. Case-by-case consideration should include diligent risk stratification of the donor (living) and recipient using a combination of the clinical background, chest X-rays and SARS-CoV-2 monitoring. A COVID-19-free transplant plan, including strict social isolation for patients on a housing list, wireless screening for signs and exposures before admission and peri-operative management in a designated clean intensive care facility and post-LT care unit should be developed in areas with high disease burden^[53,101].

HCC: People living with cancer have worse COVID-19 consequences. This is likely to apply to HCC patients as they are usually older, more vulnerable and require several medications including cytotoxic chemotherapy^[105,112]. Multi-factorial HCC boards may continue to operate remotely and offer clinical advice, including ongoing systemic treatment and LT assessment. When appropriate, full HCC monitoring shall be restored. Where resource constraints exist, priority should be given, by public HCC risk stratification ratings, to patients at higher risk, including those with elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, NASH/diabetes,

etc^[53,101].

Pharmacological management

COVID-19 is a fast-growing area for targeted management, with a wealth of new or repurposed drugs rapidly being in and out of favor. While no medications have been approved at present for SARS-CoV-2, in recent weeks many treatments have been tested and many are still under investigation. It is encouraged to investigate possible hepatotoxic effects at "LiverTox" and drug interactions at "HEP drug interactions" before beginning any COVID-19 medications^[106]. Unique factors in treatment trials for COVID-19 patients with chronic liver disease are briefly summarized here. Trials in COVID-19 patients include research on the following medications:

Remdesivir: Remdesivir is an adenosine nucleotide analogue demonstrated to minimize the length of symptoms following early use as a potential contender for COVID-19 therapy. It induced termination of the RNA chain and was first developed as an anti-Ebola agent^[113]. In preclinical studies, remdesivir use in randomized studies demonstrated no major effect on liver function tests relative to a sugar pill, despite evidence of a reversible aminotransferase elevation. The elevation in aminotransferase was seen in patients on remdesivir after exclusion of certain liver conditions^[53]. A clinical *in vitro* isolate of SARS-CoV-2 has recently been inhibited and in an *in-vivo* rhesus macaque model, the severity of the associated MERS-CoV infection was decreased by remdesivir^[114].

Corticosteroids: The association between corticosteroids and COVID-19 seems inconclusive. Those with an existing serious disease appear to benefit from the addition of corticosteroids, while patients who have already taken corticosteroids may be more at risk of COVID-19 adverse effects^[53]. Corticosteroids reduce pro-inflammatory cytokine production, and there is a risk of an increase in co-infection in persons with decompensated cirrhosis^[106]. Their use has been related to intensive care unit admission, artificial ventilation or death in patients with inflammatory bowel disease. Similarly, the rheumatological hospitalization rating for maintenance glucocorticoids after SARS-CoV-2 infection has expanded^[53]. Standard immunosuppression in patients with autoimmune hepatitis or LT, including steroids where necessary, is currently recommended. However, for patients with severe COVID-19 who require respiratory assistance, corticosteroids are a feasible treatment choice. Dexamethasone decreased mortality in perfusing patients by one-third and in patients who received additional oxygen by one-fifth in June 2020^[110]. This agent is likely to be used more and more to treat serious COVID-19 even in patients with pre-existing chronic liver disease^[53].

Anticoagulation: The risk of venous thromboembolism is greater in patients with advanced liver disease. The rate of venous thromboembolic disease in patients hospitalized due to COVID-19 is frighteningly high, with an observed 20% incidence on day 7, and 42% on day 21 despite thromboprophylaxis^[115]. Therefore extensive analysis of the role of anticoagulation in COVID patients has demonstrated that the results in extreme COVID-19 are strengthened, although there are still coherent stepped care models and processing thresholds. While there are reservations regarding the use of anticoagulation in patients with liver cirrhosis and portal hypertension, there has been no systematic evaluation indicating excess blood disorders in cirrhosis- and portal vein thrombosis anticoagulated patients^[53].

Tocilizumab: The main driver of the "cytokine storm," interleukin-6 (IL-6), appears to be significant in lungs and other organs due to severe COVID-19. Tocilizumab, a humanized monoclonal antibody targeting IL-6 has shown value in retrospective series of COVID-19 by reducing the need for and duration of organ support. As this agent is widely used in rheumatoid arthritis and other autoinflammatory diseases, its liver profile is well-established^[53,101,106]. Mild serum aminotransferase elevations are common and are generally self-limited and asymptomatic. However, gradual jaundice requiring LT has been reported^[53,106]. In rare cases, tocilizumab is associated with HBV reactivation^[53].

Others: Several studies have indicated that other drugs have shown clinical effectiveness in patients with COVID-19. Clinical research in patients affected is underway to better determine their effectiveness. Chloroquine phosphate or hydroxychloroquine, ritonavir-boosted lopinavir, baricitinib *etc* are some of the

medications currently being assessed. Hydroxychloroquine impedes lysosomal acidification and autophagy, preventing *in-vitro* viral entry^[106,116]. Baricitinib is a JAK 1/2-AAK1 inhibitor resulting in lymphopenia, HBV activation and is not recommended in those with liver impairment^[106]. Drugs with natural origins have also been suggested to improve COVID-19-associated clinical manifestations including GI disturbances.

Limitations of existing therapy

At present, there is no evidence from clinical trials which shows the effectiveness of drugs in patients with either suspected or confirmed COVID-19, and there are no clinical trial results available that endorse prophylactic treatments. Therefore, repurposing old drugs is the only option to cope with the current pandemic until vaccines are developed. Chloroquine/hydroxychloroquine, lopinavir, ribavirin, remdesivir, favipiravir, corticosteroids, and tocilizumab are the only Food and Drug Administration approved medications for COVID-19. However, even after identifying old drugs for reutilization, there are several barriers to minimize the severity of COVID-19 such as dose adjustments, route of administration, mechanism of action, GI toxicity, and choice of delivery system to administer these old drugs. The limitations of using these agents are a tendency to cause acute heart and liver toxicity. This acute toxicity can overwhelm the undetermined advantage of a particular antiviral agent. Approximately 50% of patients treated with lopinavir experienced adverse reactions in a recent randomized controlled trial and 14% of patients discontinued treatment due to GI side-effects. Lopinavir may exacerbate hepatotoxicity and liver injury as it elevates alanine transaminase. Ribavirin causes severe dose-dependent hematological toxicity. High doses of ribavirin in SARS trials resulted in hemolytic anemia in more than 60% of patients. Tocilizumab has been linked to HBV reactivation and thus HBV serology should be part of the routine pre-treatment workup. The lack of clinical data suggesting a specific benefit of these agents do not explain their risks^[53,117].

CONCLUSION

The recent COVID-19 pandemic has posed an unprecedented burden on human health. The lungs are the primary infection site for the causative agent of this COVID-19 pandemic, *i.e.*, SARS-CoV-2 and, therefore, initial investigations have mainly focused on its community spread and consequent pulmonary disorders. With the quantity of studies from various medical, bio-medical as well as allied fields, it is now established that the effects of SARS-CoV-2 are not limited to only the lungs. Systemic infection and pathological manifestations have been confirmed including those in the GI system. Considering the critical role of the GI system in physiological maintenance, it is essential to combat the SARS-CoV-2 infection-triggered anatomical damage. GI disturbances in COVID-19 also result in complications which are challenging in the clinical management of patients with co-morbidities including obesity, hyperglycemia, hypertensive disorders, liver diseases, cardiovascular disorders, *etc.* Although most of the symptoms in SARS-CoV-2 infected patients are similar to those known to arise in other respiratory viral infections, its novel nature and the degree of uncertainty regarding the outcome of therapeutic interventions make treatment challenging. Moreover, the steps taken to prevent the ongoing pandemic (social distancing, lockdown, stay-home strategies) also drive disturbances in physiological and mental well-being. This will contribute to GI anomalies due to altered daily routine, leisure activities, dietary habits, and hormonal imbalance (reduced vitamin D due to less sunlight exposure).

Due to its severity, rapid rate of spread and associated clinical complications, it is difficult to diagnose the GI ailments associated with COVID-19. Conventional methods and combinatorial strategies are suggested to provide an accurate diagnosis. The presence of SARS-COV-2 in various organs and fecal discharge, even in individuals negative for respiratory infections, indicates that GI organs also serve as a target and reservoir for the virus. As the GI system is involved in nutrient assimilation and physiological processes, viral infection results in diverse clinical manifestations in different systems including cardiovascular, neuropsychiatric, pulmonary, and hepatic, *etc.* Therefore, it is suggested that GI disturbances due to SARS-COV-2 infection must be considered as important as respiratory complications in COVID-19. This warrants the restructuring of medical service priorities to cover GI physiological disturbances in the treatment of COVID-19.

In the absence of any specific medication and prophylactic measures, the recent pandemic is expected to persist. However, the associated clinical manifestations of COVID-19 are not entirely known. Data on the clinical sequelae of COVID-19 in organs other than lungs are expected from ongoing investigations which are likely to increase. This requires the preparedness of health organizations to respond to the probable increase in GI disorders during and after the COVID-19 pandemic.

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