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

Sahu T *et al*. Updates of COVID-19 on gastrointestinal disease

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**Abstract**

The novel coronavirus disease-2019 (COVID-19) is caused by a positive-sense single-stranded RNA virus belongs to the corona viridae family. In March 2019 the World Health Organization declared that COVID-19 as 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 the 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 the liver cells. Together these results indicate that GI tract is a potential target of SARS-CoV-2. Therefore, in present review summarized the vital information available to date on COVID-19 and gastrointestinal aspects.

**Keywords:** 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 summarised the vital information available to date on COVID-19 and gastrointestinal aspects.

**INTRODUCTION**

World populations are currently facing unprecedented health emergency due to the spread of novel coronavirus disease-2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization (WHO), COVID-19 health crisis has spread over 205 countries including United States, India, Russia, Brazil, and Colombia[1-3]. The most common symptoms of COVID-19 moderate infection include fever, dry cough, tiredness, sore throat or dyspnea. However, the pulmonary system is the main organ involved in the clinical manifestation of the disease. Patients infected with this virus suffer from other potential damage to vital organs, such as gastrointestinal (GI), cardiac, renal and nervous systems[4-6]. Before COVID-19, many infectious diseases affected global populations, including 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) of China is 0.66%, the diamond princess ship is 2.3% and the large meta-analysis of 36 European countries showed the range of 4% to 4.5% mortality[12-14].

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

Several studies have identified the 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 GI epithelial cells of the intestinal mucosa[21,22]. 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 diseases. In this critical circumstance, depth work 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 GI aspects. We recognize the ever-changing literature and aim to update future publications with the most up-to-date information available.

**GI MANIFESTATION 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 lung is the primary target organ of this virus, they cause discomfort in patients with detrimental oxygen saturation effects, causing shortness of breath. We should not close our eyes to the symptoms of GI tract. Anorexia is the most common GI symptom, mainly due to the depression, inflammatory state and side effects of drugs[23-26]. If the virus enters the food canal directly it may cause diarrhea. In patients with high viral load, anorexia, anosmia, and dyspepsia are the main GI symptoms[27,28] Further, the anti-viral drugs give rise to nausea, vomiting and diarrhea (Table 1).

The SARS-CoV-2 can be detected in the GI tract. The SARS-CoV-2 virus can invade epithelial cells on 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 because there are more possibilities for transmission of infection due to lack of information/knowledge about GI complications[21,29-31]. A course of alveolar events, GI spread and the manifestation of SARS-CoV-2 infection are given in Figure 1.

A meta-analysis using 60 studies from 6 countries found that 4243 patients with SARS-CoV-2 infection had GI symptoms, among them diarrhea (12.5%), nausea/vomiting (10.2%), anorexia (26.8%) and abdominal pain (9.2%) are most common[32]. Another hospital-based study reported that out of 1099 patients, nausea or vomiting and diarrhea respectively in 5% and 3.8% of patients[21]. Another study showed that in 148 Chinese SARS-CoV-2 positive patients, half of the patients seemed to have an abnormal liver function at the time of admission[33]. Further study has shown similar results with non-typical findings in hepatic enzymes[34,35]. 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 female patients (38.36%)[36]. Gender differences in susceptibility towards other diseases were also reported owing to their physiological differences[37].

**CLINICAL SIGNIFICANCE OF COVID-19**

The SARS-CoV-2 when entering the body causes viraemia with associated pneumonia and the main clinical features of this disease are fever, severe headache, fatigue, diarrhea and other associated potential comorbidities[38,39]. The estimated average duration of incubation is 1-14 d (3-7 d common). Viruses enter the body and proliferate mainly in lungs, the GI tract, and the heart. SARS-CoV-2 is believed to be concentrated in tissues that express ACE2[40,41]. Recently, some studies have reported that anorexia, nausea, vomiting and diarrhea as the most common GI tract symptoms in almost 40% of patients[42,43]. However, one-tenth of patients complain of GI symptoms without major difficulty in breathing or mild fever[44]. SARS-CoV-2 has been correlated with a hyper-coagulable condition with a major risk of venous thromboembolism[45]. Neurological indications like severe headache, dizziness, and loss of consciousness, strokes, and muscle injury have also been observed[46]. Detailed clinical manifestations were shown in Table 2. GI manifestations of SARS-CoV-2 infection are also indicated for altering the nutrient absorption via modulating the expression and activity of nutrient transporters, such as the neutral amino acid transporter BAT1. The BAT1 has been implicated in the manifestation of the psychiatric sequelae of COVID-19. Modulation of the psychoneuroimune axis in COVID-19 is speculated to affect the physiological and neuropsychiatric quality of life[47,48]. Potential SARS-CoV-2 infection triggered physiological and anatomical damages related to GI tract along with systemic influence is summarized in Figure 2.

**EXISTING LIVER DISEASE PATIENTS CARE**

***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 centre for inflammatory response[49,50]. 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[51]. According to a retrospective study, 39 of the 202 confirmed COVID-19 patients had higher body mass index (BMI) and higher NAFLD co-morbidity 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[52]. Interestingly, patients with NAFLD and SARS-CoV-2 infection in less than 60 years of age are associated with an elevated risk of severe disease[53]. NAFLD patients with increased non-invasive liver fibrosis scores are more likely, despite metabolic comorbidities, to develop severe COVID-19 disease[54].

***Viral hepatitis***

Almost 5 billion people in the Asia-Pacific region have chronic viral hepatitis[55]. Unlike metabolic liver disorder, there is little or no evidence that chronic viral hepatitis affects the progression of COVID-19 disease. Corticosteroid and tocilizumab are administered to critically serious people with COVID-19, which can lead to a reactivation of hepatitis B virus (HBV) and lead 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[56]. 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 drugs used to treat COVID-19 and HBV may occur. Besides, 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, the treatment of alternative drugs in patients with HBV during the pandemic should be addressed prior to the medication's onset. 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. Care should be given to interactions between these drugs used in the treatment of COVID 19, and those used to treat HBV and HCV.

***Autoimmune liver disease***

Patients with autoimmune liver disease are already experiencing 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 with COVID-19. There is still concern that patients who are still taking elevated doses of corticosteroids may be more vulnerable to SARS-CoV-2 infection and serious COVID-19 infection. Patients who are already on corticosteroids when developing COVID-19 infection 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 infections of disease 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[57-59].

***Liver cirrhosis***

Patients with cirrhosis are mainly 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 for 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 conditions. There is no specific consideration to date for cirrhosis patients who have been infected with SARS-CoV-2 because the drug used to control COVID-19 may increase the risk of other infections and viral shedding[57,60,61].

***Liver transplant recipients***

Patients with liver transplantation are at high risk of severe infection with SARS-CoV-2 and related deaths. The risk of transmission of SARS-CoV-2 through liver transplantation remains 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 distance or not travel during the outbreak of COVID-19. Telehealth home surveillance is efficient and useful for liver transplant recipients; consequently, it must be available to most transplant centers and applied to pre-transplant patients where telehealth services are available. Unrecognised COVID-19 significantly increases the risk of severe immune suppression and post-transplant infection in liver transplant recipients, leading to multiple organ failure or even death. Reduction of immunosuppressive therapy for liver transplant recipients should not be considered to prevent disease with SARS-CoV-2. Reduction can only be addressed 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 of 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[62-65].

**DIAGNOSIS OF GI COVID-19 EFFECT**

COVID-19 is an air-born outbreak affecting not only the respiratory tract, cardiovascular, and central nervous systems but also badly influence the GI system. Previously, established findings demonstrated that several patients with COVID-19 have many low to moderate GI complications, including diarrhea during the disease course[27]. Until recently, there is 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 of COVID-19 patients. Further, calprotectin measurement could play an important role in the monitoring, diagnosis, and follow up of COVID-19 associated diarrhea and GI complications. Therefore, the participation of GI to COVID-19 would need to consider and explore under several clinical policies and practices like the incorporation of rectal swab testing before the discharge of COVID-19 patients[66], as well as our future preparation for personal protective equipment in the endoscopy, ultrasound and another relevant diagnostic settings. These implementations will act as a promising tool to eradicate COVID-19 from the root[67].

***GI endoscopy***

Endoscopy is a very complex procedure in gastro clinical settings. In COVID-19 patients, it becomes a high-risk process for healthcare professionals because of their high exposure while performing upper GI endoscopy, which makes them more prone to infection by patient’s aerosol[68]. Currently, a published study reported the presence of SARS-CoV-2 RNA in a patient's stool samples. These finding raises suspicion and support the potential fecal-oral transmission route of infection. Furthermore, a novel virus is possibly transmitted through fecal contamination *via* inhalation, conjunctival splash contact, or direct contact with faces during colonoscopy[21]. To restrict the aerosol transmission of COVID-19 virus within/between the endoscopy team and hospital various 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 personal protective equipment (PPE) kit. According to recent data, it was estimated that the half-life of the COVID-19 virus particle in the air is estimated at around 1.1 h[69]. To prevent viral load, patient to patient cross-infection, transmission the current guidelines suggest performing endoscopy in negative pressure isolated room[70]. All COVID-19 patients should undergo prescreening before arrival at the endoscopy room. During this current outbreak of novel COVID-19, many experts recommended indications for urgent endoscopy which are limited to acute GI bleeding, GI obstruction requiring stenting or dilatation, biliary sepsis, execution of GI perforations and leakage, foreign body retrieval, and establishment of entrée for enteral nutrition. According to recent guidelines, we would like to recommend some 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 test. However, when it comes to operative and non-operative endoscopic procedures, it should consider all safety measures concerning medical health worker exposure. There are three criteria and routes for the endoscopic procedure: (1) Oral route: any procedure through mouth or nose; (2) Anal or stomal route: any procedure is passing through the anus or an entero-cutaneous stoma; and (3) Capsule endoscopy.

The following vital parameters should be under consideration and collected before performing endoscopy; fever of more than 37.5 ℃, contact history, travel history, occupational exposure, clustering[71]. 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 team 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 overcome the load of COVID-19 within one minute of the exposure period[72].

Endoscopy is a very advanced tool, and here we would like to recommend all elective endoscopies during this current COVID-19 outbreak for diagnosis purposes until any promising cure. This diagnostic strategy helps to protect the surge capacity of health care 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 virus between the patients and healthcare staff, particularly at the early stage of the COVID-19 pandemic[73]. 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, which is essential to overcome the spread of COVID-19 within health care staff.

***Abdominal ultrasound and computed tomography imaging***

Classically, 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, the early radiological study focused on imaging of chest with high resolution computed tomography (CT), which measure the peripheral patches of ground-glass densities with or without consolidations with bilateral basal predominance, organising pneumonia pattern, crazy paving, mild bronchiectasis, and vascular engorgement may be encountered as well[74,75]. Radiography of the chest, apart from its wide use and low cost, also has low diagnostic sensitivity for pneumonia in COVID-19 patients[76]. Unlike this, lung CT is considered the sensitive imaging technique for early detection of pulmonary severity in infected patients[77]. Recently, a finding established that CT imaging is superior to RT-PCR (98% *vs* 71%, respectively, *P* < 0.001) in the diagnosis of COVID-19[78]. However, it is complicated to envision a situation where CT is systematically performed in all suspected and positive cases due to cost, exposure to radiation, time consumption, and the probability of cross-contamination.

Ultrasound (US) is an easily portable, low cost, and relatively fast experienced procedure with real-time visualization. In the current pandemic US is considered as a potent technique for the diagnosis of suspected and confirmed COVID-19 cases to facilitate better treatment strategy with the real-time examination. Using the US has advantages as it restricts the exposure of multiple staff to confirmed cases. Additionally, point-of-care ultrasound is recently recommended to manage COVID-19 cases to reduce the use of medical equipment and the number of health care staff that ultimately minimises the cross-infection. More recently, some authors reported the high diagnostic accuracy of ultrasound compared with radiography when evaluating lung abnormalities[79,80]. However, image 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 test particularly serum bilirubin followed by elevated renal function test in 14.6% of patients[81]. Tullie *et al*[82] conducted abdomen ultrasound and CT imaging in pediatric COVID-19 confirmed patients and found that ultrasound is the only diagnostic imaging tool in patients with GI symptoms.

Further, they reported that ultrasound findings were in line with lymphadenopathy and the presence of inflammatory fat throughout the mesentery with visible thickening of the terminal ileum. Thus, image finding ultrasound and CT may accelerate the understanding of abdominal complications in COVID-19 patients[82]. Therefore, we strongly recommend the use of abdominal ultrasound imaging for the diagnosis of patients with GI manifestations when investigating for possible appendicitis.

**RISK FACTORS DURING PERFORMING ENDOSCOPY ON COVID-19 PATIENTS**

Endoscopy or minimal- invasive technique is usually recommended to evaluate ulcers/ polyps, gastritis, stomach pain, dysphagia, digestive tract bleeding, and sometimes for biopsy[83]. It is a safe, out of harm and anodyne practice; yet the technique does possess the risk of adverse events averting the completion of the procedure and result in complications ranging from low to potentially rare or mild to lethal[84]. At any given moment during clinical practice from pre-procedure to post-procedure, there are various pieces of adverse reactions expected, listing in infectious accidents, cardiopulmonary actions, bleeding, thromboembolism *etc.* Over now, as per the current situation, more than 44 million infection cases with over 1 million deaths are recorded by COVID-19[85]. It has been verified that this infection is contagious and chiefly ascribed to transmit *via* respiratory droplets (> 5 to 10 μm in diameter) or close by contact (usually within 1 m) with anyone involved in coughing or sneezing activities. The alarming element concerning the delivery of COVID-19 is an airborne transmission that may also be feasible in some medical circumstances. Certain clinical practices like endotracheal intubation, bronchoscopy, nebulization *etc*, produces aerosols resulting in aerial spread while faecal-oral route transmission (fomites) could also result in contamination[86,87].

Paramasivam and his team documented a review referencing the report of Quality Committee of American Society for Gastrointestinal Endoscopy where they mentioned the key three rudiments tangled in defining endoscopic risk factors, *i.e*, the complexity of procedure (procedure-related), co-morbidity and clinical status (patient-related) and individual expertise (operator-related)[88,89]. Complexity encompasses clinical and perceived risk elements. Technically more sophisticated approaches are often riskier. The treatment action of endoscopic retrograde cholangiopancreatography (ERCP) in conjunction with or without of sphincter division (sphincterotomy), colonic polyps as well as peptic ulcer elimination, bear high complication rates of therapeutic endoscopy procedures[90]. Artificial ventilation or positive insufflation practice may pose a significant threat of aerosol generation due to short physical distance during endoscopy, raising the chances of infection to the staff, medical personnel, anesthesiologist and others[91,92]. The supervision tactic has progressed to endo-luminal from the surgical methodology with the escalation and advancement of endoscopic expertise innovation and accrued considerable experience to combat this pandemic outburst[90,91].

Although, different procedure of endoscopy displays the specific hitches, such as post-ERCP pancreatitis in ERCP or asthma &haemoptysis in bronchoscopy[90,93]. However, perforation, hypoxemia and bleeding are the most commonly recorded complications of all forms[90]. It has been documented that the bleeding rate arrays from low to high with the intensification of invasive procedures like in endoscopic biliary sphincterotomy, endoscopy dilatation or colonoscopic polypectomy during the diagnosis[94-96]. Medical guidelines recommend that endoscopy is carried through within 24 h of presentation of patients with acute upper GI bleeding[97]. Compared to other partaking risks endoscopic mediated bleeding, typically facilitates rapid and rigorous treatment to control or minimise other risks[94]. Still, the debate about endoscopy in COVID-19 patients, however, gives rise to specific management decisions. A case study by Cavaliere *et al*[92] documented that an endotracheal tube intubation practice during upper endoscopy surgery on a COVID-19 patient is formidable, increasing the mortality rate. Coagulopathy linked to COVID is another explanation for GI bleeding; therefore, in these patients for stratification, prothrombin time, platelet count and D-dimers amount measurement are recommended[98]. Since the complications of endoscopy could surpass these benefits, clinicians agreed to cautiously treat these patients with a blood transfusion (when necessary), proton pump inhibitor drip, and regular surveillance of GI symptoms and haemoglobin vital signs[92].

Similar to the bleeding, perforation has also been recognised as an important risk factor because of its high incidence of occurrence with numerous procedures, but embraces unusual place in GI trials and often employ clinical intercession[84]. The sigmoid colon serves as the most prominent site for the occurrence of perforations. Three approaches are considered liable or accountable for perforation: air insufflation driven barotrauma, therapeutic procedures and colonoscopy or an instrument triggered mechanical injury[99,100]. Perforations occurring during ERCP arise when there is a transmural extension of sphincterotomy beyond the sphincter and are archetypally asymptomatic. The threat factor includes adhesions, dysfunctioning of the sphincter of Oddi, biliary stricture dilation, snare polypectomy *etc*[84].

The inexperience of the operator has been designated as a significant complication risk factor. Researchers found that a prolonged treatment in conjunction with the elevated sedation dose could be attributed to part of the higher proportion of complications. Over-sedation may increase the risk of severe casualties (such as perforation and bleeding), which can stump the pain response[101,102]. Owing to the 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 a safe way to sedate (senior) patients in the correct dose, while risks including haemodynamic and breathing depression continue to occur and accelerate during upper GI endoscopic procedure[84]. Under severe sedation, a patient undergoing difficult colonoscopy tend to vomit or spew up resulting in pulmonary aspiration. This builds needless misperception for medical personnel and caretaker as the signs of pneumonia arose by pulmonary aspiration are quite parallel to COVID-19[103].

Respiratory and cardiovascular complications also hold a prominent rank among the recurrently occurring impediments. Tachycardia and bradycardia can be comprehended during invasive events. Hypertension and hypotension, syncope, are other cardiovascular complications were observed during the treatment. Clinically insignificant micro-aspiration can be considered if it does not result in pulmonary inflammation or prolonged bronchospasm[84]. 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 till the outbreak of COVID-19) and there should be a discrete unit for ‘low-risk’ and ‘high-risk’ patients. Also, the health care staff and workers must abide by asymptomatic carriers precautions and level 2 biosafety[104].

**RECOMMENDATION FOR MANAGEMENT OF LIVER DISEASE PATIENTS DURING COVID-19 (TABLE 3)**

***General recommendation***

In view of the significant multifaceted participation of pandemic, especially in chronic types of disease, liver damage would 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 ailment is often connected with a phenomenon termed as “bystander hepatitis” and the patient even in lethal course show no specific records of hepatic failure[105,106]. The personal administration of these patients relies greatly on the regional COVID-19 prevalence and the laws and guidelines officially imposed[105]. Therefore, the pragmatic structuring of strategies to address such trials and efforts must be made by the physicians and their organisations *via* strengthening electric health records (EHR) and encompassing novel technologies like remote monitoring and tele medication to restore treatment levels wherever feasible[107]. This viral epidemiology appeared uncertain. But, for some time to come, the disease's prevalence may widen and diminish in demographics chronologically. Thus, a customised and versatile encounter to patient care needs 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 facilitate the sector to make significant progress despite unimaginable global events[57].

***Standard recommendation***

Both the international societies, American Association for the Study of Liver Diseases[108] and the European Association for the Study of the Liver (EASL)[105], advocate the use of telemedicine to minimize interaction between the patients and the health workers by recommending prevention and management interventions that include sectioning of COVID-19 inpatients from other clinically healthy patients and optimisation of the use of telemedicine. For COVID-19 adults with chronic disease (particularly if other risk factors are present), EASL recommends considering early admission and with upscaled biochemical profile, must be examined for concomitant viral hepatitis B or C and impediments[109]. In patients with strong clinical suspicion of a deep venous thrombosis, or biliary blockage, diagnostic pictures must only be implemented in a variety of patients, and biopsies should be postponed, but do admit in certain cases that it may be appropriate to screen out acute refusal or to detect dire autoimmune hepatitis[105,108,109]. Besides using EHR and telemedicine in the number of cases as an alternative of in-person care, various medical centres must change their modus operandi to meet the needs of spatial recognition (social distancing)[110].

**Viral hepatitis-HCV and HBV:** Medication for HCV and HBV should be begun under general guidelines in patients lacking COVID-19[111].If the patients are already undertaking medication like anti-viral therapy for the treatment of chronic HCV/ HBV, telehealthcare, as well as clinical tests, are conducted in addition to electronic follow-up prescriptions and if initiated, additional resources including complete course of anti-viral medications with alternative therapies to prevent the uncertain effect of INF-a[57,58]. A case-by-case decision following the consultant should be taken for clients with COVID-19 with high illness flare or clinical concern for an acute HBV hepatitis to undergo antiviral therapy. Take into account the use of antiviral therapeutic interventions to avoid viral flares or reactivation in patients enduring severe, latent or healed HBV and COVID-19 immunosuppressive agents[57].

**Liver cirrhosis:** The effect that SARS-CoV-2 infection may have on patients with cirrhosis and the negative impacts of the late or amended standard of attention during the COVID-19 pandemic is especially susceptibles and every attempt must be made wherever feasible to establish the highest quality of treatment for cirrhosis patients in compliance with guidelines[57,112]. Option to postpone all regular screenings or monitoring procedures for patients with compensated cirrhosis. As per the proposal of Baveno VI consensus, low-risk patients are recommended to avoid intrusive variceal blood screening[110]. The risk of infection and associated comorbidities in cirrhosis patients is expanding, notably critical for patients who are with decompensated cirrhosis, as a result of immune dysfunction related to cirrhosis. Particular measures should be rendered 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[57]. Standardised rules and regulations to avoid and deter admission must also be strictly observed concerning GI haemorrhage, hepatic encephalopathy and prophylaxis of spontaneous bacterial peritonitis[57,112].

**NAFLD or steatohepatitis:** The metabolic complications such as the disease of hypertension, obesity and diabetes mellitus (DM) will boost the probability of an extreme condition of COVID-19 patients with NAFLD or steatohepatitis (NASH)[105,110]. The associated negative metabolic and hepatic effects from social repression, including intensified sedentary habits and intake of convenience foods should be made known to patients[57,110]. Deter the growth of liver disease through ways of living, including diet guidance, weight loss advice and managing diabetes, can hopefully minimize a severe disease with a future infection with SARS-CoV-2. In compliance with current guidelines, the prognosis of arterial hypertension should proceed. Presently, there is no indication that the blockers of angiotensin-converting enzymes or antagonists of angiotensin receptor ramp up either the risk of SARS-CoV-2 or the risk of serious complications or death from COVID-19. All sufferers with NAFLD contaminated with SARS-CoV-2 should be treated for early admission[57].

Specific recommendation for NAFLD: Patients with NAFLD are considered to be susceptible to COVID-19, so 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. For preventing the progression of liver disease, Intensive lifestyle should be followed. Maintaining body weight and obesity can help to prevent from future SARS-CoV-2 infection. Under current guidelines, treatment of arterial hypertension should be continued as there is no research to date suggesting 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 become SARS-CoV-2 infected, early admission should be considered. Whenever possible, patients with NAFLD should be hospitalized in areas physically separated from other COVID-19 patients[57].

**Alcohol-related liver disease:** Congenital alcohol intake can enhance the vulnerability of a person to SARS-CoV-2 acute respiratory distress syndrome. Social exclusion can contribute to the new and elevated use of alcohol[113], rise in enrolment associated with alcohol including further liver decompensation during and after physic distance periods should be expected. Therefore, physicians and agencies should adopt preventive actions such as patient access and telephone alcohol liaison and abstinence. While the therapy for corticosteroids has shown positive help to hospitalized COVID-19 patients[114], there is still uncertainty that patients already on elevated dosage corticosteroids are more likely to be seriously affected by COVID-19. These aspects should be addressed as therapy for patients with severe alcoholic hepatitis before beginning corticosteroids[57].

**Autoimmune liver disease:** Experts are currently suggesting that immunosuppression therapy avoid SARS-CoV-2 infection in patients with autoimmune liver disease. A decline in medication-induced lymphopenia/cytopenia or microbial/meal super-infection for extreme COVID-19 should be considered only in exceptional circumstances following deliberation with a physician[57,110]. Whereas the treatment of corticosteroids has been positive for COVID-19 hospital patients, the question remains that patients with advanced doses of corticosteroids may be more vulnerable to SARS-CoV-2 and serious COVID-19 infections. Therefore, we suggest taking budesonide as an initial aid to reduce systemic glucocorticoid exposure to cause remediation in patients with autoimmune hepatitis flare without cirrhosis[57,105]. Dexamethasone should be introduced or transformed only in patients that need hospital admission and respiratory assistance with COVID-19[114]. Patients with IgG4 associated diseases, primary sclerosing cholangitis or biliary cholangitis are deficient in data to make specific guidelines. *Streptococcus pneumoniae* and influenza should be vaccinated for all patients[57,105].

**Patient with liver transplantation:** People with decompensated cirrhosis on the liver transplantation (LT) standby list are at greater risk of serious COVID-19 and death after SARS-CoV-2 infection and is therefore advisable that LT facilities should, as far as appropriate, restore the transplant resources after the pandemic. Researchers urge the creation and enhancement of LT-donors and recipients' local and global risk layering pathways, which involve a combination of clinics. LT is a priority for those with frail short-term prognostics, such as those with acute liver failure, elevated model for end-stage liver disease and hepatocellular carcinoma (HCC) at the top of the Milan criteria, in centres with constant resource limits[57,105,109]. It is presently proposed that all SARS-CoV-2 donors be tested by reverse transcription PCR and recommend using SARS-CoV-2-infected donors livers[64]. LT applicants ought to be noticeable that SARS infection is associated with a greater risk of COVID-19 and mortality in patients who undergo significant operations; thus, the possible risk of nosocomial COVID should require consent to diagnostic and therapeutic procedures relating to transplantation[115]. 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 research drugs[57]. Case-by-case consideration should include diligent risk stratification of the donor (living) and recipient using a combination of a clinical background, chest X-rays and SARS-CoV-2 monitoring. A COVID-19 free transplant route, including strict social Isolation for patients on a housing list, wireless screening for signs and exposures before admission and peri-operative management at the designated clean intensive care facility and post-LT care unit is to be developed in high disease burden areas[57,105].

**HCC:** People living with cancer have worse COVID-19 consequences. This is likely to refer to HCC patients because they usually become older, more prone and need several medicine visits including cytotoxic chemotherapy[109,116]. Multi-factorial HCC boards may continue to operate remotely and offer clinical advice, including ongoing systemic treatment and LT assessment. Where appropriate, full HCC monitoring shall restore. 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*[57,105].

***Pharmacological management***

COVID-19 is a fast-growing area for targeted management, with a wealth of new or repatriated drugs rapidly changing into and out of favour. While no medications have been approved at present for SARS-CoV-2, in recent weeks many treatments have been tested and many still are under investigation. It is encouraged to investigate possible hepatotoxic effects at "LiverTox" and drug interaction at "HEP drug interactions" before beginning any COVID-19 medications[110]. Unique factors in the treatment trials for COVID-19 for patients with chronic liver disease are briefly summarized here. The trials in the COVID-19 patients include research on these medications.

**Remdesivir:** Remdesivir is an adenosine nucleotide analogue demonstrated to minimize the length of symptoms in 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 antiviral agent[117]. In preclinical studies, remdesivir use in randomised studies demonstrated no major effect on liver function tests relative to the sugar pill, despite the evidence of a reversible aminotransferase escalation. The elevation of aminotransferase rate in the patients accepting remdesivir with exclusion of certain liver conditions[57]. A clinical *in vitro* isolate of SARS-CoV-2 has been recently hindered and in *in-vivo* rhesus macaque model, the severity of the disease of the associated MERS-CoV infection decreased *via* the action of remdesivir[118].

**Corticosteroids:** The connection between corticosteroids and COVID-19 seems amphibious and bicameral. Those with an existing serious disease appear to ironically benefit from adding corticosteroids, while patients who have already taken corticosteroids may be more at risk for adverse effects of COVID-19[57]. Corticosteroids constrain pro-inflammatory cytokine production, and there is a risk of an increase in co-infection in the persons with decompensated cirrhosis[110]. Its use has been related to extreme intensive care units admission, ventilation or demise in patients with inflammatory bowel disease. Similarly, the rheumatological hospitalisation rating for maintenance glucocorticoids after SARS-CoV-2 infection has expanded[57]. Standard immunosuppression in patients with autoimmune hepatitis or LT, including steroids where necessary, is currently recommended. But for patients with extreme COVID-19 that need respiratory help, corticosteroids tend to be a feasible treatment choice. Dexamethasone decreased mortality in perfusing, patients, by one-third and in patients who receive added oxygen by one-fifth in June 2020 in recovery[114]. This agent is likely to be used more and more to treat serious COVID-19 even in pre-existing chronic liver disease patients[57].

**Anticoagulation:** The risk of venous thromboembolism is greater for advanced liver disease patients. The rates for venous thromboembolic diseases in patients hospitalised by COVID-19 were frighteningly high, with an observed 20% incidence on day 7, and 42% on day 21 despite thromboprophylaxis[119]. There has therefore been an extensive analysis of the role of anticoagulation in COVID patient’s studies have demonstrated that the results in extreme COVID-19 are strengthened, although there are still coherent stepped care models and processing thresholds. While reservations on the use of anticoagulation in liver cirrhosis and portal high blood pressure patients have traditionally been made, there has been no systematic evaluation indicating any excess of blood supply in cirrhosis- and portal vine thrombosis anticoagulant patients[57].

**Tocilizumab:** The main driver of "cytokine storm," interleukin-6 (IL-6), appears to be significant in lungs and other organ damage when COVID-19 is heavily affected. Tocilizumab, a humanised monoclonal antibody targeted at IL-7 has therefore proven its value in the retrospective series of COVID-19 in reducing the need for organ support and the duration of it. As it is widely used in rheumatoid arthritis and other autoinflammatory products, its liver profile is well-established[57,105,110]. Mild serum Aminotransferase elevations are common and generally self -limited, asymptomatic. However, gradual jaundice requiring LT has been reported[57,110]. In rare cases, tocilizumab is associated with the HBV reactivation[57].

**Others:** Several studies have further indicated that patients with COVID-19 have clinical effectiveness. Clinical research in patients affected is underway to better determine their effectiveness. Chloroquine phosphate or hydroxychloroquine, ritonavir-boosted lopinavir, baricitinib *etc* are some medications currently being assessed. Hydroxychloriquine impedes lysosomal acidification and autophagy, preventing *in-vitro* viral entry[110,120]. Baricitinib is a JAK 1/2-AAK1 inhibitor resulting lymphopenia, HBV activation and not recommended for liver impairment[110]. Drugs of natural origins have also been suggested to improve the COVID-19 associated clinical manifestations including GI disturbances[48].

***Limitation 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 such clinical trial results available that endorse prophylactic treatments. Therefore, repurposing old drugs is the only option to cope with this current pandemic until vaccine development. Chloroquine/hydroxychloroquine, lopinavir, ribavirin, remdesivir, favipiravir, corticosteroids, tocilizumabare the only Food and Drug Administration approved medications for COVID-19. However, even after identifying old drugs for reutilization, there are several barriers to minimise the severity of COVID-19 such as dose adjustments, route of administration, mechanism of action, GI toxicity, and choice of delivery system to administer old drugs. The limitations of using these agents are the tendency to cause acute toxicity to heart and liver. This acute toxicity can overwhelm the undetermined advantage of a particular antiviral agent. Approximately 50% of patients with lopinavir experienced adverse reactions in the recent randomized controlled trial and 14% of patients discontinued treatment due to adverse GI adverse side-effects. Lopinavir may exacerbate hepatotoxicity and liver injury such that it elevates alanine transaminase. Ribavirin causes severe dose-dependent haematological toxicity. High doses of ribavirin in SARS trials resulted in hemolytic anaemia in more than 60% of patients. Tocilizumab has been linked with HBV reactivation and thus HBV serology should be part of routine pre-treatment workup. Eventually, the lack of clinical data suggesting a specific benefit cannot explain these agents' risk[57,121].

**CONCLUSION**

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

Owing to severity, a rapid rate of spread and associated clinical complications make it difficult to diagnose the GI ailments associated with COVID-19. Conventional methods and combinatorial strategies are suggested to have a better chance for an accurate diagnosis. The presence of SARS-COV-2 in various organs and faecal discharge, even in individuals negative for their respiratory infections, indicates that GI organs also serve as a target and reservoir for the virus. As GI serves for nutrients assimilation and physiological perpetuation, viral infection to its components invite a diverse form of clinical manifestations encompassing different systems including cardiovascular, neuropsychiatric, pulmonary, and hepatic, *etc.* Therefore it is being suggested that GI disturbances in respiratory infection of SARS-COV-2 or GI-infection must be considered equally important as respiratory complications in COVID-19. These warrants are restructuring medical services' priorities to cover GI physiological disturbances in the COVID-19 therapeutic regimen.

In the absence of any specific medication and prophylactic measures, the recent pandemic is expected to persist. Nevertheless, associated clinical manifestations are not entirely known for COVID-19. Data about clinical sequelae of COVID-19 in body organs other than lungs are expected to be contributed by ongoing investigations and likely to heighten. It necessitates the preparedness of health organizations to cater to the probable downpour of GI ailment post-COVID-19 pandemic.

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Grade A (Excellent): 0

Grade B (Very good): 0

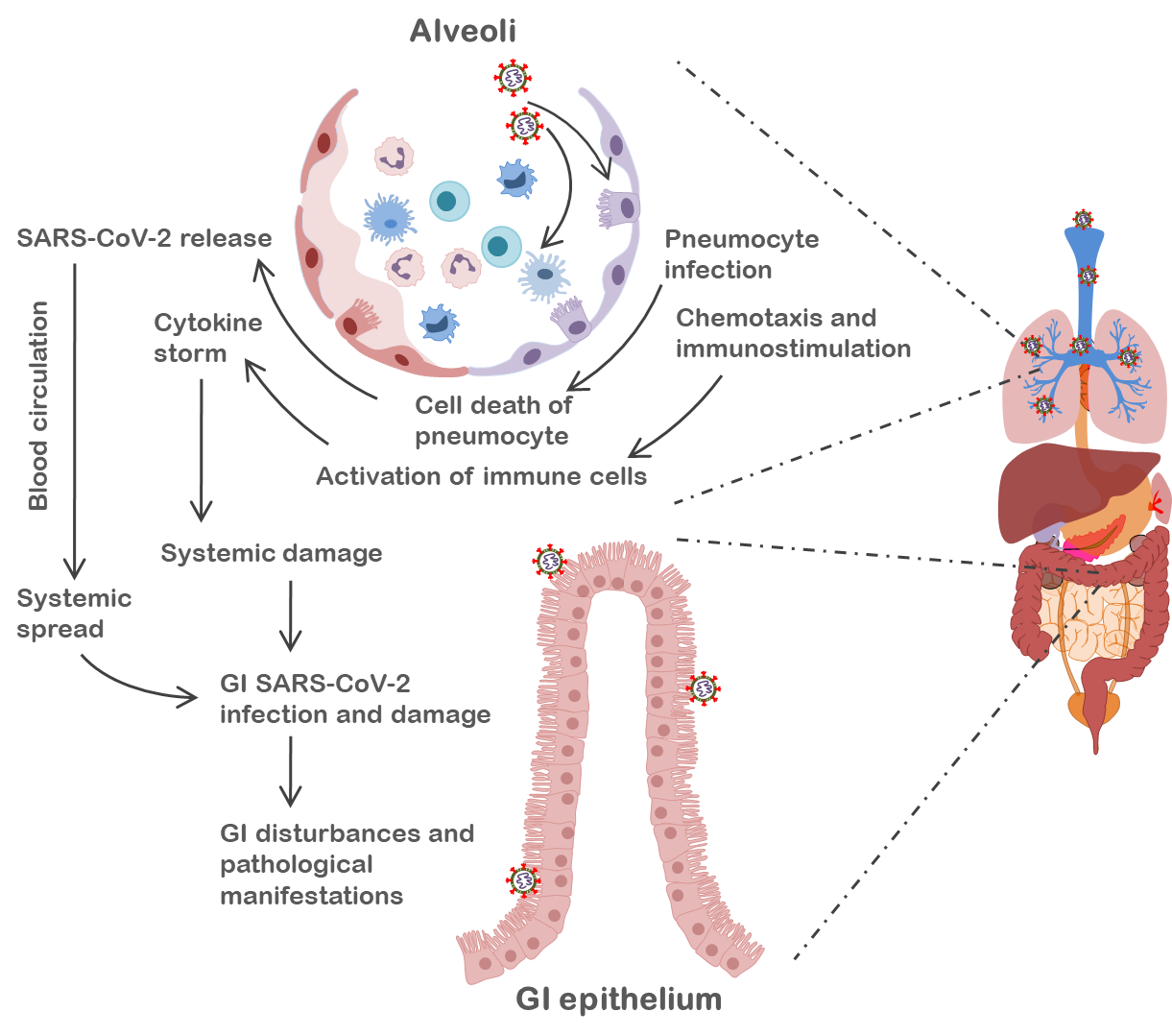
Grade C (Good): C

Grade D (Fair): 0

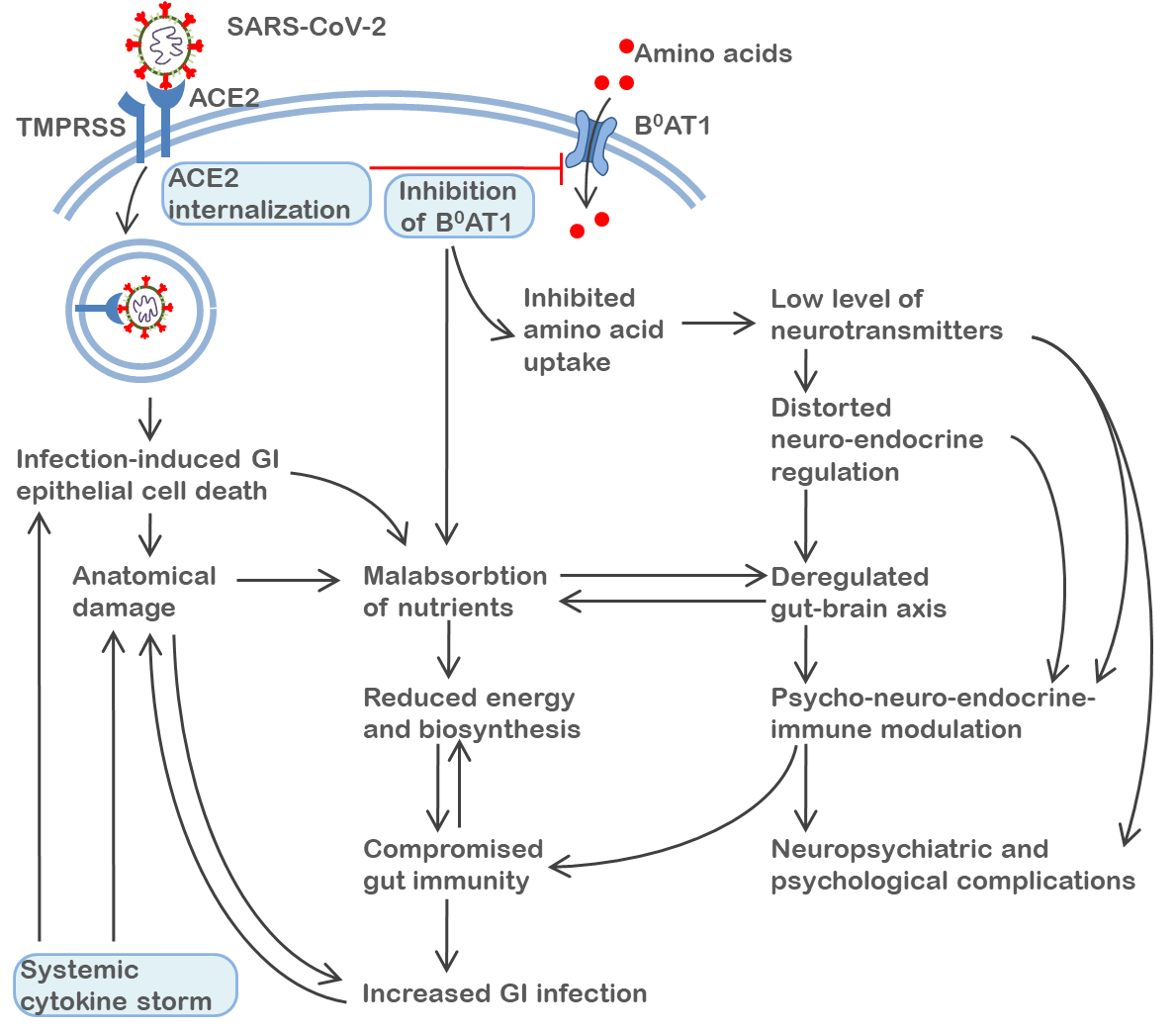
Grade E (Poor): 0

**P-Reviewer:** Nabil A **S-Editor:** Zhang H **L-Editor: P-Editor:**

**Figure Legends**

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**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.

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

**Table 1** **Gastrointestinal manifestation of coronavirus disease-2019**

|  |  |
| --- | --- |
| **Gastrointestinal manifestation** | **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.

**Table 2 Clinical significance of coronavirus disease-2019**

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

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

**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 ordering prescriptions & medications; (3) If Viral Hepatitis case: continue medication; (4) Tracking & recording alcohol usage; (5) Restraining testing, imaging & blood withdrawal; and (6) For the 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) Advancing 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 to emergent indications like 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 suites as there is high aerosol generation during clinical procedures; and (4) Postponing certain elective procedures like oesophageal variceal screening. |
| 4. | NAFLD | AASLD, EASL | (1) Notification to patients regarding adverse hepatic/metabolic implications associated with social isolation & lifestyle; (2) In line with the existing directives, arterial hypertension treatment should continue; and (3) All NAFLD patients who may be infected with SARS-CoV-2 should be deemed to 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 ordering 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) Usage 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 prioritised COVID-19 testing for patients with ACLF or deteriorating/ chronic hepatic conditions is advised; (3) Every attempt must be taken, wherever feasible, to restore the highest quality of treatment for patients; (4) Prophylactic course of action of GI haemorrhage, hepatic encephalopathy *etc*. must be trailed; (5) Usage of vasoconstrictor therapy ought to be undertaken with great consideration and carefulness; and (6) Recommendation of vaccination for *Streptococcus pneumoniae* and influenza. |
| 7. | ALD | AASLD, EASL | (1) It is directed that there should not be reduction in immunosuppressant dosing in patients with ALD & COVID-19. Under special condition, dosage may be dropped but, after consultation with clinician; (2) Monitoring of corticosteroid treatment in patients with elevated dosing as they increase susceptibility to viral infection; (3) Agents like Budesonide is recommended to use as primary treatment to cut down systemic risk of glucocorticoids; and (4) Recommendation of vaccination for *Streptococcus pneumoniae* and influenza. |
| 8. | ARLD | AASLD, EASL | (1) Reduction in consumption of alcohol; (2) Implementing anticipatory strategies like cessation and online (telephone) alcohol liaison services; (3) Monitoring of corticosteroid treatment in patients with elevated dosing as they 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, LTSI, ATS, TTS | (1) Avoiding 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 dosing should not be encouraged; (5) Edge to urgent indications/case-by-case; (6) Minimize workforces during treatment procedures; (7) Safe anaesthesia practice with appropriate PPE suites and N95 masks usage is recommended; and (8) Deferring elective procedures like 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 adjourned, then Trans-arterial bridging therapies needed to be offered; and (4) The patient needs to continue, if already up 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; LTSI: Liver Transplant Society of India; ATS: American Thoracic Society; TTS: Transplantation Society; ILCA: International Liver Cancer Association; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology.