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**Gastrointestinal and hepatic diseases during COVID-19 pandemic: manifestations, mechanism and management**

Mohamed DZ *et al*. Gastrointestinal and hepatic diseases during COVID-19 pandemic

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**Abstract**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered the causative pathogen of coronavirus disease 2019 (COVID-19) and became an international danger to human health. Although respiratory transmission and symptoms are still the essential way and expression of COVID-19, the digestive system could be an unconventional or supplementary route for COVID-19 to be transmitted and manifested, most likely due to the presence of angiotensin-converting enzyme 2 (ACE2) in the gastrointestinal tract. As well, SARS-CoV-2 can trigger hepatic injury *via* direct binding to ACE2 receptor in cholangiocytes, antibody-dependent enhancement of infection, systemic inflammatory response syndrome, inflammatory cytokine storms, ischemia/reperfusion injury, and adverse events of treatment drugs. There are gastrointestinal symptoms, including anorexia, nausea, vomiting, and diarrhea, which are unusual in patients with COVID-19, and some digestive signs may occur without other respiratory symptoms. Furthermore, SARS-CoV-2 could be found in infected patients’ stool, demonstrating the likelihood of transmission through the fecal-oral route. In addition, liver function should be monitored during COVID-19 infection, particularly in more severe cases. This review summarized the evidence for extra-pulmonary manifestations, mechanisms, and management of COVID-19 infection, particularly those related to the gastrointestinal tract and liver.

**Key Words:** COVID-19; Angiotensin-converting enzyme 2; Gastrointestinal; Inflammatory bowel disease; Liver; Management

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**Core Tip:** The coronavirus disease 2019 (COVID-19) pandemic has affected millions worldwide, with high lethality. In addition to typical respiratory symptoms of COVID-19, gastrointestinal symptoms and hepatic harm have been frequently shown during COVID-19. The main purpose of this article is to focus on the manifestations, mechanisms, and management of the gastrointestinal tract and liver that occurred during COVID-19 course. Therefore, physicians must not undervalue the digestive symptoms during COVID-19 infection and rapidly adjust the treatment options for COVID-19 patients during gastrointestinal symptoms and liver enzyme abnormalities.

**INTRODUCTION**

Coronaviruses (CoV) is the largest group of spike-like viruses in Nidovirales family. The CoVs in the last two decades have instigated three worldwide outbreaks, with the most recent pandemic caused by coronavirus 2 in the recent period, coronavirus disease 2019 (COVID-19), that causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first 21st century outbreak in Guangdong Province, China, in November 2002, causes SARS-CoV (SARS-CoV-1), an extreme SARS, with 8098 fatalities globally at 9.6%[1,2]. The second outbreak in Saudi Arabia in 2012 was Middle East respiratory syndrome (MERS), caused by MERS-CoV, with 2521 confirmed deaths of 36 percent[3].

It first originated in China in December 2019 and critically threatened worldwide health[4,5]. On February 12, 2021, it has been considered that 108 million cases and 2 million deaths have been recorded across over 219 countries and regions worldwide[6]. The lung is the primary organ involved by COVID-19-infected pneumonia, and most COVID-19 patients suffered from typical respiratory symptoms (*e.g.*, dyspnea, cough with sputum production, fatigue, and in severe cases, acute respiratory distress syndrome (ARDS), respiratory failure, and even death). On the other hand, extrapulmonary clinical manifestations of COVID-19 exist and affect multiple other organs including cardiovascular (*e.g.*, arrhythmias, myocarditis, pericarditis, acute coronary syndrome, and heart failure), renal (*e.g.,* acute kidney injury and acute tubular necrosis), hepatic [*e.g.,* elevated alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and bilirubin], gastrointestinal (*e.g.*, diarrhea, nausea, vomiting, and abdominal pain), ocular (*e.g.,* epiphora, conjunctivitis, and chemosis), dermatologic (*e.g.*, erythematous rash, urticaria, and chickenpox-like vesicles), and neurological systems (*e.g.,* headache, neuropathy, encephalopathy, cerebrovascular, and dizziness)[7] (Figure 1). Considering all the previously mentioned data, this article examines the effects of gastrointestinal (GI) and hepatic symptoms, associated mechanisms, and management caused by SARS-CoV-2 infection and provides a guide for clinical prevention and treatment (Figure 2).

**DISEASE COURSE OF COVID-19**

For SARS-CoV-2, the incubation period averages 4-5 d, with most patients on symptoms 14 d before, although there have been instances where the incubation period was longer[8]. The infection and hospitalization onset was documented from 9.1 to 12.5 d and emphasizes the difficulty in the early stage of the diagnosis and isolation of populations[9]. The average period for recovering patients from initial symptoms is 22 d, and for those who succumbed the time for death is 18.5 d approximately[9].

Overall, the case fatality ratio of COVID-19 is reported to be around 1-2 percent in patients aged 80, to over 15 percent[10]. Currently, WHO data has surmised that several COVID-19 cases have mild to moderate illness signs (80%) with 13.8% of a number of cases of COVID-19 have mild to moderate signs of illness (80%) with 13.8% of serious signs described within 24-48 h by the following symptoms: shortness of breath; hypoxia < 300 and/or pulmonary infiltration > 50%; tachypnoa > 30 *per* min breaths in lung[11]. 6.1% of critical infections are shown to be septic shock, respiratory and multiple-organ failure[11,12]. Roughly, 25% of hospitalized patients require intensive care unit (ICU), and 4.3% die[12].

**GENDER AND RACE DURING COVID-19**

It has been reflected that 51% of reported cases of COVID-19 are males’ patients. This may be due to the higher levels of estrogen in women COVID-19 ones which can reduce COVID-19 deaths' severity and mortality *via* the elevation in the innate and humoral immunity[13-19]. Moreover, *in vivo* studies have demonstrated that the higher levels of angiotensin-converting enzyme 2 (ACE2) expression in male kidneys than female ones, which may explain changes in the development and COVID-19 susceptibility between male and female patients.

Whether ACE2 expression varies from men' or women's lungs in patients, however, is still unclear[20,21]. Furthermore, preclinical trials have suggested that ACE2 expression may raise the vulnerability of COVID-19 in pregnant patients[22,23].

In the same way, COVID-19 patients vary between different ethnic groups for severity and mortality. During the spread of COVID-19 pandemic, American, Hispanic, and African communities have displayed higher rates of infection and hospitalization in comparison with Caucasian residents[24]. These discrepancies may be due to the higher occurrence of heart diseases, hypertension, obesity, diabetes, and asthma in minority groups[24].

**GASTROINTESTINAL AND COVID-19**

***GI manifestations in COVID-19 patients***

Gastrointestinal symptoms including, nausea, anorexia, vomiting, diarrhea, and abdominal pain are commonly shown in COVID-19 patients (Table 1)[12,25-35]. In SARS infection of 2002-2003, diarrhea is the main feature that appears in 16%-73% of SARS patients mainly in the first week of contagion[36]. Similarly, diarrhea is considered a common digestive sign in COVID-19 patients, with incidence (1.3%-29.3%). However, the criteria for the diagnosis of diarrhea may be altered in various hospitals, and its prevalence varied in different studies[37].

Among 204 COVID-19 patients in Hubei China, only 99 (48.5%) had gastrointestinal signs as their chief complaint. Ample of COVID-19 patients had a diversity of digestive symptoms, including abdominal pain (0.4%), anorexia (83.8%), diarrhea (29.3%), and vomiting (0.8%)[38]. A retrospective study conducted by Guan *et al*[39] has reported, among 1099 COVID-19 patients from 552 centers across China, 5% of cases have nausea and vomiting, and 3.8% of cases have diarrhea. A further study indicated in 32.5% of COVID-19 patients at least one gastrointestinal tract (GIT) symptom. These symptoms include diarrhea (37.8%), anorexia (56.7%), abdominal pain (10.4%), nausea (16.5%), and vomiting (7.9%)[40]. Additionally, Luo *et al*[41] have documented that 16% of patients, out of 1141 cases, has at least one of the GIT symptoms including, anorexia (98%), nausea, vomiting (66%), diarrhea (37%), and abdominal pain (25%). Furthermore, a research study conducted by Jin *et al*[42], the first COVID-19 study outside Wuhan, have reported the incidence of 11.4% of GIT symptoms; (8.14%) Diarrhea was the most common of these symptoms[42].

In New York, GIT symptoms have been identified by the single-center-case series, including 892 cases. The most common diarrhea (19.8%), accompanied by nausea (16.6%), abdominal pain (7.8%), vomiting (10.2%), and anorexia (11.8%)[43]. An additional retrospective study conducted in New York informed that out of 1059 COVID-19 patients have (22%) diarrhea, (6%) nausea, (19%) vomiting, and (7%) abdominal pain[44]. In addition to these researches, the pooled prevalence of GI symptoms has been found at 17.6 % through a meta-analysis of 60 studies involving 4243 cases in 6 countries The most frequent symptom was anorexia (26.8%), accompanied by diarrhoea (12.5%), nausea/vomiting (10.2%) and stomach pain/discontinuity (9.2%)[45].

Furthermore, Goyal *et al*[46] has indicated that hyperlipidemia has been found in 11.7% of patients affected by SARS-CoV-2 where 92 patients out of 756 with COVID-19, had elevated serum lipase levels, resulting in acute pancreatitis. Therefore, COVID-19 patients with hyperlipidemia are, approximately, at a 3-fold higher risk of poor clinical outcomes, including the need for ICU admission, mechanical ventilation, and death[46].

As well, the study of Gadiparthi *et al*[47] showed that the higher Glasgow Blatchford bleeding score was 7 and 11 in 2 out of 3 patients on admission and represents a high risk of gastrointestinal bleed (GIB) with a need for intervention of more than 50%. However, both young patients responded by carefully controlling hemodynamic parameter, levels of hematocrit or haemoglobin, transfusion of packed red blood cells as needed and medical therapy. Although GIB has been resolved, two patients died because of respiratory failure[47].

Besides GIT symptoms, the autopsy of COVID-19 patients showed that there are gross and microscopic changes of the GIT. Segmental dilation and stenosis of the small intestine, accompanied by mucosal shedding and necrosis is described on autopsy, whereas colitis, inflammatory infiltrates, and interstitial edema, are found on histopathology imaging[48,49]. Lui *et al*[50] have shown pneumatosis, intestinalis, pneumoperitoneum, ascites, and thickening bowel wall in addition to ileus on abdominal imaging. Therefore, abnormalities of GIT can be obvious on imaging.

Based on these previous data, physicians must realize that the key characteristic of COVID-19 infection before respiratory symptoms may be digestive symptoms and, in rare instances may be the only occurring COVID-19 symptoms.

***Mechanisms of GI injury during COVID-19***

**Direct infection of gastrointestinal cells**: The entry of SARS-CoV-2 virus into host cells is the main part of cross-species transmission. All coronaviruses bind to receptors and mediate their entry *via* glycoprotein and spike proteins[51]. It has been recognized that ACE2 mainly contains receptors for SARS-CoV[52], and dipeptidyl peptidase 4, for MERS-CoV[53]. A plethora of studies has shown that the SARS-CoV-2 Spike (S) protein of SARS-CoV-2 has a high host ACE2 affinity[54], and enters host cells *via* ACE2 receptor[55] as shown in Figure 3.

In small intestinal cells, ACE2 is usually located and strongly expressed in type II epithelial cells ACE2[56,57]. It is considered an important enzyme in the renin-angiotensin system (RAS)[58,59] and plays an essential role in controlling inflammation and diarrhea[60]. Moreover, its deficiency leading to the accumulation of angiotensin II (ANG II)[61]. Consequent studies[12,62-64] have proven that SARS-CoV-2, in COVID-19 patients, may invade the gastrointestinal tract *via* ACE2 receptors, causing digestive symptoms. Lately, it is well acknowledged that the significant upsurge of ANG II level in COVID-19 patients is the cause of progression and severity of the disease.

Although in the mouse colon, the knockdown of ACE2 by the virus leads to the upsurge of ANG II levels; ACE2 doesn't primarily act *via* the intestine RAS system but controls the homeostasis of intestinal amino acids, gut microbes and expression antimicrobial peptides[65]. Mice with blocked ACE2, for example, have significantly inhibited serum tryptophan that is important to the body's niacin synthesis[66], therefore, inadequate intake of tryptophan or niacin develops pellagra[65]. It is well-recognized that tryptophan is absorbed on the lumen surface of intestinal epithelial cells *via* the B0AT1/ACE2 transport route and induced the mammalian target of rapamycin, which controlled consequently the appearance of antimicrobial peptides, thereby having a direct influence on components of intestinal flora[65]. Ultimately, above 90% of pellagra patients will develop colitis[67]. Hence, it is considered that SARS-CoV-2 attachment to the ACE2 in the gastrointestinal tract lowers the critical receptor level, disrupting the absorption of tryptophan and ultimately destroying the steady-state of the gut flora, resulting in diarrhea.

Furthermore, He *et al*[68] demonstrated that the pathological results of an autopsy of dead COVID-19 patients indicated proinflammatory cytokines (PICs) as tumor growth factor-β1, monocyte chemokine-1 (MCP-1), tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β, IL-6 were highly expressed in ACE2-expressing cells. While there is no presence for PICs in cells that do not express ACE2. Numerous PICs produce cytokine storm, which finally leads to multiple organ failure. Besides, the plasma, IL-2, recombinant human interferon (IFN)-induced protein-10, MCP-1, macrophage inflammatory protein-1A, IL-7, granulocyte colony-stimulating factor, IL-10, and TNF-α level of COVID-19 patients were more than healthy people[25]. Dendritic cells and macrophages show low levels of IFN and high levels of pro-inflammatory cytokines with chemokine in the early stage of SARS-COV infection[69-71]. Later, there is a rise in cytokines and chemokine levels, which causes severe tissue damage by a large number of inflammatory cells, such as neutrophils and monocytes. In the same manner, the SARS-CoV-2 can make cells expressed ACE2 release inflammatory cytokines, leading to cytokine storm and multiple organs failure[72]. Furthermore, Cytokine storms can have an effect on immune cells; lymphocytosis is known to be a common sign of severe cases of COVID-19, with a significant decline in number of B, CD8+ and CD4+T cells as well as in the natural cell killers., which leads to lymph node necrosis, spleen atrophy, hepatomegaly, renal hemorrhage, necrosis, and degeneration of neurons[73].

Thromboembolic complications are being progressively documented in COVID 19[74]. Acute mesenteric ischemia (AMI) has been reported in severe COVID-19 patients in addition to deep venous thrombosis and pulmonary embolism[75]. It has been disclosed that ANG II stimulates the expressions of tissue factor VIII (FVIII), von Willebrand factor, and plasminogen activator inhibitor-1 by endothelial cells, resulting in a state of hypercoagulation[76,77]. The histology of the small intestine secondary to a mesenteric thrombosis revealed a prominent endothelium of the submucosa with evidence of direct viral invasion of the endothelial cells along with diffuse endothelial swelling with mononuclear cell infiltrate. It is understood that there is a stimulation of alternate and lectin complement trajectories [C5b-9 (membrane attack complex), C4d, and mannose-binding protein-associated serine protease 2] that destroys the endothelial cells[78]. Lastly, SARS-CoV-2 infection resulted in an elevation of ANG II levels and other prothrombotic proteins, which lead to AMI[78-81].

**Gastrointestinal damage caused by lung infection:** Any change in intestinal flora constituents affects the respiratory tract, *via* the common mucous immune system. Reciprocally, any damage to the respiratory tract mainly affects the digestive tract *via* immune regulation. This effect is known as the “gut-lung axis”[82,83]. Furthermore, SARS-CoV-2 cannot be detected in COVID-19 stools in patients with digestive symptoms and thus GIT symbols may not be affected by the direct damage of certain COVID-19 patients SARS-CoV-2. The entry of CD4+ T cells is essential to immunity and chronic enteritis in the intestinal mucosa. As is known, the C-C chemical receptor type 9 (CCR9) is an important chemical receptor for the introduction of CD4+T cells into small gut cells[84]. Wang *et al*[84] showed after viral infection, CCR9+ CD4+ T lung derived cells were amplified. The small intestinal epithelium can include chemokine (C-C motif) ligand 25[85], which promote the recruitment into the small gut of CCR9+ CD4+ T cells[86], which leads to impairment of the gut's immune system and to the destruction of the intestinal flora homeostasis. This, in turn, stimulate the polarization of T helper 17 (Th17) cells in the intestine, and recruitment of neutrophils due to the production of large amounts of IL-17A[87], causing diarrhea, intestinal immune damage, and other gastrointestinal symptoms. The inflammation in the intestine may lead to the entry of intestinal flora and cytokines into the lung through the bloodstream, which affects the lung immune system[88]. Additionally, bacterial imbalance and intestinal mucosal damage can affect the gut-liver axis. In the intestine, host metabolites are transported through the portal vein to the liver and affect the function of the liver. The liver releases bioactive contents and bile acids and transfers them into the intestines through systemic circulation[89]. This may lead to liver dysfunction in COVID-19 patients, which illuminates the abnormalities that occurred[90] (Figure 3).

**Gastrointestinal symptoms caused by drug side effects:** Diarrhea accompanied by antibiotics is the most common unwanted effect on antimicrobial agents, including cephalosporins, macrolides and β-lactam. A retrospective study, in China, has demonstrated that 260 COVID-19 patients subjected to treatment with macrolides, fluoroquinolones, and cephalosporin antibiotics has been shown that 24.2% of patients have suffered from diarrhea[91]. Another study of 138 patients with SARS-CoV-2 have found that 38% had diarrhea with a medium period of 3-7 d during treatment[92]. The abovementioned data have advocated that the early use of large quantities of antimicrobial agents could be linked to symptoms of diarrhea during COVID-19. Similarly, the prevalence of diarrhea in patients using antiviral agents like oseltamivir is about 55.2%[93]. The other antiviral agents cause diarrhea as an adverse effect during the management of COVID-19 including, lopinavir, chloroquine phosphate, remdesivir, and Chinese patent medicines (*e.g.*, lianhuaqingwen capsules)[94]. Additionally, the treatment with broad-spectrum antibiotics is the major risk issue for Clostridioides difficile infection, which is considered the primary reason for nosocomial diarrhea[95]. It remains unclear whether the above-mentioned factors including, the use of antibiotics or antiviral agents and increased gut inflammation along with a decrease in mammalian target of rapamycin (mTOR) activity, and antimicrobial peptides, are partly responsible alone or in combination for the causing of diarrhea in patients infected with COVID-19 *via* alteration in the gut flora[96].

Proton pump inhibitors (PPIs) are mainly used as a therapy for peptic ulcer patients and gastroesophageal reflux disease patients. By blocking the proton pump, PPI decreases gastric acid released into the stomach. Although the decrease in stomach acid can be beneficial to stomach diseases patients, it can make the gut more susceptible to COVID-19 infections[97-99]. SARS-CoV S protein was suggested to allow the fusion in neutral pH conditions with patients' cells. Additionally, Darnell *et al*[100] also established that highly acidic pH (1-3) and alkaline pH (12-14) may lead to inactivation of SARS-CoV, while, in the case of neutral pH, the virus remains stable[101]. Zhou *et al*[102] reported that, under the conditions of pH 1.0 and 2.0, SARS-CoV-2 was inactivated and unable of infecting cells which are related to the pH of an empty stomach through creating viruses pseudotyped with SARS-CoV-2 S protein. In addition, the study Ramachandran *et al*[103] found that prehospitalization PPI-exposed patients are associated with worse clinical outcomes, involving mortality of COVID-19 patients, irrespective of the existence of cardiovascular diseases. A possible explanation for this is that the secretions of the stomach are of the pH from 1.0 to 3.5 while small and large bowels have a pH from 7.5 to 8.0. SARS-CoV-2 intakes can cause gastric acid to inactivate most virus particles. If a person takes a long period of acid suppressant like PPI, however, their pH acidity of the stomach decreases. SARS-CoV-2 can also have a higher rate or entry to the gut, which leads to viral infection.

***COVID-19 and pre-existing digestive diseases***

Generally speaking, the existence of comorbidities is associated with dramatically low outcomes in COVID-19 patients. This may cause consequences for the management of previous gastrointestinal patients[104]. Patients that have inflammatory bowel disease (IBD) and have been treated with immunosuppressive drugs are more at risk for regular and serious infections and may be more at risk for infections with SARS-CoV-2[105]. It was reported in the IBD registry in Wuhan that no patient of 318 patients (204 patients with ulcerative colitis and 114 patients with Crohn's disease) had been infected with SARS-CoV-2 with precautions for COVID-19 control and prevention[106]. This recommended the use of biologic and immunosupressants, diet, deliberate postponement of elective and endoscopical surgery and provisions on personal safety[107].

**Considerations and management of IBD medications during COVID-19 infection:** Now, it is not recommended for IBD patients to stop immunosuppressant drugs[11]. As there is a risk of disease’s reactivation for patients who discontinue their treatments, leading to severe inflammation, surgery, increase risk of hospitalization, and infection[108,109]. The non-hormonal anti-inflammatory drug use should be prohibited as adverse effects in viral respiratory infections have been associated. and triggering the reactivation of IBD[110].

No evidence-based recommendations for immunosuppressed patients have been made by clinical parties. Table 2 encapsulates the specific considerations of treatment for IBD patients mainly based on specialist beliefs. These suggestions can be edited and modernized as new evidence emerges[108,110]. Overall, the same therapies can be used by patients with moderate to serious Crohn's disease or ulcerative colitis, regardless of COVID-19 infection[110]. IBD therapies can be restarted after 14 d for asymptomatic IBD patients with SARS-CoV-2 infection and their therapy has been stopped[110].

It is noteworthy that IBD patients should stop immunosuppressant drugs until the COVID-19 infection resolves, and resume the medications after complete resolution of COVID-19 symptoms or after two negative polymerase chain reaction (PCR) tests[111].

**IBD surgery in the context of the COVID-19 pandemic**: The new strand of coronavirus has increased the risk of severe pulmonary infection and extended the hospitalization for IBD patients waiting for surgeries, which is critical for IBD immunosuppressed patients. A recent report in Wuhan, China, has demonstrated that 34 patients, with elective surgical processes during COVID-19 incubation period, have developed COVID-19 pneumonia after surgery; 44.1% of patients admitted to ICU, and 20.5% of patients died[[112](#_ENREF_132" \o "Lei, 2020 #155)]. Therefore, the majority of physicians have recommended postponing both elective and endoscopic surgeries to protect patients and healthcare personnel and to minimize the usage of healthcare services and personal protection equipment[[113](#_ENREF_133),[114](#_ENREF_134)]. Eventually, the ultimate goal is to ensure the safety of patients and health care workers.

***COVID-19 and the fecal–oral transmission route***

An ample of articles disclosed that the RNA of SARS-CoV-2 could be found in patients’ stool, suggesting that SARS-CoV-2 has the availability to transmit *via* fecal-oral route[115-117]. It has been demonstrated that some COVID-19 patients had positive fecal but negative PCR tests[118]. Wang *et al*[117] has presented that of the 153 (29%) patients receiving COVID-19, 44 were positive for the stool virus. Moreover, Xiao *et al*[49] indicated that of the 73 COVID-19 patients hospitalised in China, 39 (53.42%) screened positively in stools for SARS-CoV-2 RNA[49]. Surprisingly, 17 (23.29%) patients remained positive in the stool following negativity in respiratory testing samples and their period ranged from 1 to 12 d in the stool. Xiao *et al*[49] has directly evidenced that infectious SARS-CoV-2 may be secreted from the virus-infected gastrointestinal cells. Therefore, sample stool with real-time-PCR should be frequently tested and transmission-based precautions should be worthily taken into consideration[119].

Furthermore, SARS-CoV-2 fecal-oral transmission probability has highlighted the importance of adequate hand hygiene, especially in poorly settled areas. Strict measures must be taken to deal properly with the stool of COVID-19 patients and their sewage from hospitals. Therefore, patients with preexisting gastrointestinal diseases will be more worried when they are infected with SARS-CoV-2 in addition to the potential fecal microbiota transplant donors.

***Pharmacologic management of GI symptoms in COVID-19***

**Microecological preparation:** The intestinal flora generates various vitamins, bile acids, immune factors, and fatty acids *via* the decomposition of food and participates also in immune system regulation[120]. If there is any dysfunction or damage in the intestinal flora and/or mucosa, the virus may further stimulate infection through this pathway. Further studies have stated that probiotics have the availability to manage diarrhea caused by rotavirus[121]. Also, lactic acid bacteria and bifidobacteria can contribute to antiviral antibodies in the human body, accelerating virus removal. Therefore, probiotic treatments and/or antiviral drugs, and antibacterial drugs may enhance the symptoms of SARS-CoV-2 diarrhea. Regarding the diagnosis and treatment protocols of COVID-19 in China, the use of intestinal flora regulators is preferred to preserve the intestinal micro-environmental balance and avoid secondary bacterial infection[122].

**ACE2 inhibitors:** As previously mentioned, ACE2 binding SARS-CoV-2 reaches the cell. Therefore, it can be an efficient way to avoid viral infections by blocking the interaction between the receptor connection domain (RBD) of virus and ACE2. An ample of studies have shown that inhibitors of ACE2 can regulate bowel metabolism, innate immunity, secretion of antibacterial peptides, and intestinal microbial homeostasis[122]. It is experimentally confirmed that the ACE2 pathway on epithelial cells of the small intestine trigger mTOR *via* nutrient stimulation and/or the tryptophan-nicotinamide pathway, thus affecting the composition of intestinal flora, and decreasing GIT indications in mice[60]. Azathioprine is an immunosuppressive medicinal product similar to chloroquine; recent studies analyses azathioprine in database analyses and can be regarded as an ACE2 inhibitor[123]. Additionally, *in vitro* studies have shown that Vaccinia virus can be inhibited by azathioprine[124]. Regarding molecular immunity, azathioprine competitively binds to ACE2, using a single chain (ScFv) antibody fragment attaching to an ACE2 or SARS-CoV-2, *via* the RBD. Thus, the human recombinant ACE2 antibody Fc segment bound by the S protein works by inhibiting the virus' attachment to ACE2[55]. It has been documented that a combination between Chinese medicines (*e.g.*, baicalin in the Chinese medicine Scutellaria baicalensis, scutellarin in Erigeron breviscapus, hesperetin in lime and orange peel, glycyrrhizin in liquorice, and nicotinamide in soybean) and ACE2 resulted in the prevention of SARS CoV-2 infection.

**Diet and enteral nutrition:** A lot of COVID-19 patients have significant anorexia. For ensuring effective therapy, the basic energy, absorption, enteral and peristalsis movement of the intestine, and normal function of Gastrointestinal tract micro-organisms and mucosal immunity should be taken into account as well as the functioning of GIT and patients' nutrition[94]. Nutritional risk assessment should be performed in serious cases of COVID-19 with gastrointestinal symptoms[125]. Once the risk of enteral nutrition has been eliminated, enteral nutrition should immediately be restored. If the patient has a gastrointestinal harm and cannot withstood enteral nutrition, parenteral nutrition should be correctly supplemented with a sufficient supply of energy. Patients in poor condition can take digestive enzymes[125]. A nasogastrical tube can be used for enteral feeding in patients who have undergone mechanical ventilation and unable to take food orally. A nasal jejunal tube can be administered when patients are at high risk of reflux aspiration or cannot handle nasogastric tube feeding. Generally, the patient gastrointestinal tolerability should be estimated appropriately and the enteral nutrition program adjusted correspondingly.

**LIVER AND COVID-19**

***Clinical manifestations and pathological changes in hepatic injury in patients with COVID-19***

Hepatic injury is a frequent adverse event in both SARS-CoV and Middle East respiratory coronavirus-related patients and is associated with the severity of diseases[126]. In almost all cases, a substantial systematic study of 11 studies assessing the liver laboratory parameters of 2541 patients with COVID-19 shows increased AST and/or ALT (25%), lactate dehydrogenase (20%), bilirubin (3%) and normal alkaline phosphatase (ALP)[127]. This may mean minimal direct liver damage caused by the ACE2 overexpression in cholangiocytes. To date, A major published study of 5700 patients found that AST and ALT have been increased in both COVID-19 patients by 58.4% and 39.0%, respectively[128], Cai *et al*[129] showed that 41% of patients, gamma-glutamyl transferase (GGT) was increased more than 3 × ULN, while, another research study, GGT was raised in severe cases, but without an elevation in ALP[126].

A data of preprint meta-analysis containing 20 retrospective studies with 3428 COVID-19 patients showed that increased levels of COVID-19 were related to significant rise in levels of ALT, AST, and bilirubin[130]. Recently, a plethora of studies has reported the increase of serum ALT, AST, and GGT levels in severe patients than mild or non-severe ones[39,131]. A recent meta-analysis has associated high marker admission levels with patient mortality[132]. Other studies combine the rise in these parameters with a worse pulmonary computed tomography (CT) score[133], increased numbers of ICU patients[12] and longer hospital stays[134]. In COVID-19 mortality cases, the incidence of elevated liver parameters ranged between 58.06% to 78%[32,135].

According to a study conducted by Lei *et al*[132], AST was the first indicator that was considered high when patients were admitted to the hospital and was correlated with the highest COVID-19 death rates. A recent study carried out by Guan *et al*[39], Around 1100 Chinese patients reported elevating levels of serum AST and ALT for 18% and 26% of non-severe COVID-19 patients respectively, in comparison with 56% and 28% of COVID-19 patients. The previous findings showed the crucial role of immune-mediated systemic inflammation in liver dysfunction in serious COVID-19 cases[9]. Recently, Gordon *et al*[136] has proposed a probability that mitochondrial proteins would interact directly with the virus, providing a cause for the high level of AST prominent liver profile[136]. Wang *et al*[137] have also identified anomalies of liver enzymes, higher radiologic scores as well as a partial pressure differential between alveolar arterial oxygen, higher GGT, disease intensity, higher ferritin, lower CD4+ T and B cells and lower albumin. It has been considered that total bilirubin, AST/ALT, and ALT/ALP ratios have helped in the prediction of survival in cirrhotic COVID-19 patients[138]. Serum albumin levels were also markedly lower in patients who died because of COVID-19 infection[32]. The adverse path of COVID-19 patients has been shown to have elevated serum levels of IL-6, ferritin, procalcitonin, C-reactive protein. In addition to the reduced albumin content and platelet count, the parallel increase of the level of ferritin, ALT and IL-6 indicates a greater role for liver participation in COVID-19[32,134]. The CT imagery score for pulmonary lesions is known as a hepatic injury indicator. Therefore, patients with aggression must undergo careful monitoring of their liver function in order to identify any liver insults at an early stage[133]. Incidences of hepatic abnormalities in COVID-19 patients are depicted in Table 3.

Morphological findings regarding the interpretation and description of liver parenchymal changes accompanied by COVID-19 infection are totally rare, and most of them are post-mortem autopsies. It is noteworthy that the first post-mortem liver autopsy specimen examinations accomplished by Xu *et al*[139] showed moderate microvesicular steatosis and both portal activity and mild lobular. SARS-CoV-2 infection or drug-related hepatic damage might result in this liver insult. These results were matched with Liu *et al*[140]. A preliminary research, consisting of 49 patient COVID-19, showed that the Portal intrahepatic system was affected vascularly as acute (thrombotic and luminal ectasia) or chronic (fibrous thickening of the vascular wall) and the intrahepatic blood vessels have been abnormally configured. These findings have indicated that the major trigger for COVID-19 hepatitis pathogenesis can be considered as endothelial damage or coagulation dysfunction[141]. Additionally, in critical cases of COVID-19 there is no detection of signs of damage to bile ducts or histological changes of liver failure[140]. Several studies failed to identify viral inclusion bodies in liver tissue[139,142]. Furthermore, the study of Li and Xiao[143] demonstrated that cirrhosis and regeneration signs with macrovesicular steatosis and accumulation in hepatocytes, along with atypical lymphocytic infiltration in the portal tract, may occur due to COVID-19 infection. In the portal triad and centrilobular zones, sinusoidal expansion dilatationin zone 3, mild lymphocytic infiltrations and patchy liver necrosis were also revealed.

Moreover, the study of Ramachandran *et al*[144] showed that in hospitalized COVID-19 patients, elevated aminotransferases were associated with higher mechanical aeration concentrations and did not achieve any statistical meaning after inflammatory marker measures. In addition, patients with elevated aminotransferases did not have higher rates of mortality or prolonged length of stay as shown in Table 4.

In China, some patients recovering from extreme COVID-19 were confirmed to have experienced special manifestations of a darkened face and pigments during treatment. The key causes of darkened face and pigmentation were multiple organ injuries, in particular liver injuries[[145](#_ENREF_170" \o "SOHU News, 2020 #387),146]. The abnormal hepatic function can easily lead through three pathways to pigmentation: (1) Liver dysfunction can prevent estrogen from being inactivated[[147](#_ENREF_172" \o "Liu, 2018 #389)]. The rise in estrogen decreases thiamine inhibition of tyrosinase in vivo, thus increasing the transformation of tyrosine into melanin[[148](#_ENREF_173" \o "Jee, 1994 #391)]; (2) An abnormal liver function can cause hypofunction of adrenocortic. The liver does not metabolize the anterior pituitary gland's melanocytic stimulatory hormone which causes greater melanin secretion[[149](#_ENREF_174)]; and (3) A liver damage can cause a bleaching face to the iron in the blood that is provided to the facial skin[[150](#_ENREF_175),[151](#_ENREF_176)] (Figure 4).

***Mechanisms of liver injury during COVID‐19***

**Direct damage:** It is established that SARS-CoV-2 enters the host cells *via* its binding to ACE2 on the surface of the host cell by S protein[152,153]. However, the expression of ACE2 levels in liver tissue was estimated to be approximately 0.31% and its expression in bile duct cells was 20 times higher than that in hepatocyte on the basis of single cell sequencing and animal models analysis[154]. Furthermore, it was demonstrated that elevated levels of γ-glutamyl transferase and alkaline phosphatase have been shown in COVID-19 patients[155], and inconsistent with biliary epithelial cells injury, and approximately 10% of COVID-19 patients have high-level total bilirubin. Thus, suggesting that SARS-CoV-2 can bind to cholangiocytes expressing ACE2, resulting in their injury (Figure 5).

**Antibody-dependent enhancement:** Antibody-dependent enhancement of infection (ADE) may arise in patients with SARS[[156](#_ENREF_181" \o "Tirado, 2003 #179)]. ADE indicates that the interplay between the virus-based antibody and the CR and/or FC receptor complements increases the virus' ability to reach the macrophages, granulocytes, and monocytes (Figure 5). The virus frequently replicates in the aforementioned cells, leading to an increase in virus production and worsening of infection. Former findings have indicated that SARS-CoV antibodies activate ADE, triggering SARS-CoV in immune cells that do not have ACE2 expression or harm the immune system[[157](#_ENREF_182" \o "Wang, 2014 #180)]. Whether ADE can help SARS-CoV-2 infect immune cells through a non-ACE2-dependent pathway and participate in SARS-CoV-2 hepatic injury is an issue of concern.

**Systemic inflammatory response syndrome and cytokine storms:** Researches have revealed that the inflammatory cytokines, including endotoxin ILs, and TNF-α in SARS patients who have impairment of liver function have significantly higher levels than normal liver function patients. Therefore, systemic inflammatory response syndrome (SIRS) and cytokine storms were risk factors for liver impairment in SARS-CoV and in MERS-CoV infected patients[[158-160](#_ENREF_183" \o "Wong, 2004 #181)]. Limited pathological findings indicated that COVID-19 hepatocytes exhibit non-specific inflammatory modifications in patients with serious infection such as Kupffer-cell hyperplasia and moderate proliferation, hepatocyte swelling and steatosis and a limited number of lymphocytes. Furthermore, the amount of IL-2 and IL-6 in COVID-19 serum has been shown to be substantially increased and linked to the seriousness of the disease[[4](#_ENREF_4" \o "Zhu, 2020 #1)]. Moreover, cytokines secreted by Th1 and Th2 cells in the serum of COVID‐19 patients, such as TNF, IL-6, IL-18, IL-4, and IL-10 were significantly intensified as pro-inflammatory cells (CCR4 + CCR6 + Th17)[[25](#_ENREF_25),[30](#_ENREF_30),[139](#_ENREF_164)]. Following SARS-CoV-2 infection, a large number of immune cells activate and disclose excessive cytokines, like TNF-α, IFN-μ, IL-6, IL-8, *etc.*, leading to SIRS, acute respiratory distress syndrome, and induction of ischemia, eventually, resulting in cell destruction and necrosis as shown in Figure 4. Not only does such a vicious cycle lead to lung injury but also may progress into multiple organ damage. These results suggest that the cytokine inflammatory storms may be one of the essential trajectories of liver injury (Figure 5).

**Ischemia and hypoxia reperfusion injury**: COVID-19 Patients have varied degrees of hypoxia, as more than 40% of diseased cases required oxygen supplementation[[30](#_ENREF_30" \o "Yang, 2020 #15)]. Complications such as aspiration and multiple organ failure can cause hypoxia, ischemia and subsequent shock. The suppression of cell survival signal transduction and hepatocyte death may be caused as a result of ischemia and hypoxia, adenosine triphosphate depletion of hepatocytes, lipid accumulation, and glycogen consumption (Figure 5). Furthermore, the respiratory distress syndrome can cause oxidative stress that increases the production of reactive oxygen species (ROS). The ROS and fat peroxidation products can induce redox-sensitive transcription factors and then release various pro-inflammatory factors to lead to liver damage. These changes can exaggerate the ischemia of hepatocytes, influence the excretion of toxic metabolites and eventually stimulate liver injury. Hypoxia can also be one of the main causes of liver injury in serious patients with COVID-19[[161](#_ENREF_186)].

**Drug hepatotoxicity**: In China, the occurrence of drug-induced hepatic harm including, traditional Chinese patent medicines[162,163], antitumor drugs, antibiotics, antimalarial drugs, and anti-tuberculosis drugs[164,165], is second only to fatty liver disease and viral hepatitis (like alcoholic and nonalcoholic). Several COVID-19 patients have a fever and consequently, use antipyretic and analgesic drugs. Therefore, a drug overdose can cause hepatic harm.

Recent has been observed with the abidol, lopinavir, ritonavir and other antiviral medications controlled by COVID-19. A recent study published in JCI[166] demonstrated that CAP3A4 plays a critical role of the side-effect and metabolic pathways of ritonavir which can generate electrophilic material, radical free oxygen that can be covalently linked with liver cells leading to lipid membrane peroxidation, membrane integrity disruption and Ca2+-ATPase membrane, interruption of the internal and external Ca2+ homeostasis of the cells, and finally leading to death. Furthermore, the overdose combination of lopinavir and ritonavir can stimulate the hepatic endoplasmic reticulum stress cascade, induce inflammatory reactions, trigger hepatocyte apoptosis through the caspase mechanism, suppress hepatocyte growth, and aggravate liver damage by production of oxidative stress[167,168]. Some scientists have assumed that SARS-CoV-2 replication can be effectively inhibited by human immunodeficiency virus (HIV) protease inhibitors; although the team of Shen has stated that the risk of liver damage has increased in patients receiving hormones and HIV protease inhibitors[169]. The incidence of liver damage due to different medicine varies. The prevalence of more drug types is, however, increasing. The diagnosis of hepatic damage by medication includes a combination of medical history and appropriate testing to rule out other liver disorders and to estimate the relationship between hepatic injury and suspected medications by causality.

***COVID-19 and previously-existing liver disease***

Due to global spread of chronic liver disorder, correlations among presenting hepatic illness and COVID-19 need to be examined. A preliminary analysis showed 2%–11% of patients with hepatic comorbidity in COVID-19[170]. Regarding a study of 1099 COVID-19 patients, Hepatitis B infection occurred in 23 (2.1%) patients. Serious cases of hepatitis B infection were more likely (2.4% *vs* 0.6%) than lesser cases[39]. SARS patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections were more vulnerable to serious hepatitis, likely because viral replication was increased during the SARS-CoV infection[171]. COVID-19 patients at an older age and/or with the existence of other conditions such as diabetes, cardiovascular disease, hypertension, and nonalcoholic fatty liver disease, are more susceptible to liver injury.

Moreover, patients with liver cirrhotic disease may be more susceptible to infection because of their systemic disease[172], thus, preventing infection with COVID-19 is extremely important. There was no single patient with COVID-19 out of 111 patients with decompensated cirrhosis due to preventive precautions in Wuhan. In contrast to this, there were 17% of patients with COVID-19 among 101 ones with decompensated cirrhosis at other hospitals where preventive measures were not implemented[173]. Ultimately, the risk of viral infection transmission could be involved during liver transplantation from donor to recipient, as previously displayed in SARS infection[174]. Recently, Michaels and his colleagues have shown potential transplantation risks to COVID-19 recipients[175]. The Italian Transplant Authority has acclaimed nasopharyngeal swab to recognize COVID-19 before donation, with the subsequent exclusion of positive donors[176].

**COVID-19 in liver transplant recipients:** COVID-19's worldwide spread raises additional challenges for organ transplants. Transplant recipients with decompensating preoperative organs and chronic illness tend to contract respiratory viruses. Liver transplant patients, who are exposed to more people, during their waiting for transplantation, have increased risks for cross-infection with COVID-19. Qin *et al*[177] confirmed a COVID-19 hepatocellular carcinoma disease following liver transplantation. On the 11th day after a hepatic transplant, the patient was diagnosed with COVID-19 on the following day following a positive PCR-test, with multicenter subplant glass opacification in the left lobes. Long-term immune treatment for transplantation recipients prevents reaction to allograft rejection and significantly reduces their ability to protect them against COVID-19 infection due to the compromised immune system. A systematic study of 15 studies on 223 patients with confirming COVID-19 in liver transplantation has shown that patients with simultaneous diarrhoea are more likely to be present in liver transplants. The higher mortality rates of elderly patients living with dyspnea and diabetes were about 23% COVID-19[178]. The latest data, however, still do not confirm the susceptibility to COVID-19 infection for liver transplant patients. A number of cases in Italy indicated that children who are receiving liver transplants are not at elevated risk of serious lung disease relative to the general population despite being immunocompromised[179]. Similarly, all three COVID-19-related deaths were observed by D'Antiga[179] at an Italian transplant center were long-term patients on a minimal immunosuppression regimen, rather than recently transplanted patients with complete immunosuppression. Furthermore, a large global observational study done by Webb *et al*[180] has shown that the risk of death of COVID-19 patients cannot substantially increase liver transplantation.

***Pharmacologic management of liver injury in COVID-19***

COVID-19 causes mainly transient and indirect liver injuries, which can be caused by hypoxia, systemic inflammatory reactions, and medication. Thus, hepatic damage should be treated by elimination of the basic etiology in the COVID-19 patients. Correction of hypoxia by supplementation of oxygen or mechanical vent, renal replacement treatment for cytokine storm, and restore intravascular effectiveness can enhance liver injuries in the event of a septic shock[181]. Also crucial thing is early identifying and reducing the dosage of hepatic drug-induced harms. Hepatoprotective anti-inflammatory medicines including L-ornithine-L-aspartate can be used in extreme cases as an adjuvant treatment[182]. It is worthy to note that therapeutic drugs may be hepatotoxic, especially in chronic liver disease (CLD) patients. Furthermore, patients with immunosuppressive medicines should be closely examined due to drug interactions. Recommendations for the management of CLD, AIH, and immunosuppressed patients during a pandemic are summarized in Tables 5-7[183,184].

**COVID-19 IN THE ENDOSCOPY UNIT**

In the world, though millions of people have remained at their houses to decrease the transmission of SARS-CoV-2, the risk of COVID-19 amongst health workers is high.

For example, the Chinese National Health Commission determined that approximately 3300 health workers were infected in early March[185]. It is well-known that Endoscopic staff remains at high risk for airborne droplets infection, conjunctiva contact and contact surface contamination[182,186]. Airways suction and other cough-induced procedures face an increased risk of transmission with SARS-CoV-2[182]. It must be noted that the possible risk of exposure to faecal removal is not confined to the upper endoscopy[35].

A first prospective study conducted by Johnston *et al*[187], showed the quantification of unrecognised bacterial rate to endoscopist exposed to biological samples leading to infection transmission. In this investigation, 227 endoscopic face shields have been examined for colony-forming units (CFUs) 1-15 CFU, 91/227 (40%); 16-30 CFU, six/227 (2,6%); 30 or more CFU, 6/227 (2.6%) that significantly increased after endoscopy. Similarly, in 1999, a research study carried out by Mohandas and Gopalakrishnan[188] in a tertiary care hospital in India on 786 endoscopies (149 lower and 162 therapeutic endoscopies) concluded that the splash rate to the skin of the forearms, feet, and face was 9.5%, while the splash rate to the eyes was 4.1%.

The duodenoscopy is the most complex medical equipment that undergoes disinfection among patients[189]. Noteworthily, virus risk factors include non-compatibility with the disinfection guidelines, the promotion of biofilm deposition because of complicated nature, surface defects and infected automated endoscopes[190,191]. It is considered that endogenous infections in gut flora of patients are the most common infections after endoscopy[192]. On the other side, exogenous infections as Escherichia coli (71%), Klebsiella (14%), and Enterobacter (5%) are accompanied by infected scopes and may be avoided theoretically by efficient re-processing[192,193]. Currently, Pseudomonas aeruginosa is the most common organism which is isolated from contaminated endoscopes[194]. Other microorganisms implicated including, Mycobacteria, Helicobacter pylori, Clostridium difcile, and HBV and HCV[195]. Recently, studies of duodenoscopy-associated outbreaks including multidrug-resistant organisms, particularly carbapenem-resistant Enterobacteriaceae, have surfaced[196]. Numerous infections occurred despite sufficient reprocessing, supporting professional and government bodies to offer additional recommendations for duodenoscope processing[197,198]. To date, The Food and Drug Administration and Centers for Disease Control and Prevention have recommended efficient comprehensive cleaning followed by using high-level disinfection for reprocessing of flexible GI endoscopes[199-201].

In COVID-19 patients single-use duodeno-scopes may be important. They are however not worldwide accessible and have cost-related constraints[202]. Several societies have advocated the use of room negative pressures, particularly for COVID-19 patients, or if endoscopy is urgently needed[203]. Intraprocedural changes such as minimal verbal communication, avoiding procedures in patients with inadequate bowel preparation, and avoiding spill of GI contents *via* biopsy channel should be completed[204]. A former study has reported the use of a “double gauze technique”; one for the endoscopists and the other for technicians in a controlled fashion to prevent the “whip” effect of accessories and spillage of GIT secretions[204] Institutional requirements for the minimum staff involved in the procedure have been developed[205]. The risk of exposure among endoscopy personnel is diminished. The endoscopy technique performed in moderate sedation without the need of anaesthetic agents (endoscopy driven sedation) can also reduce the risk of transmission. However, in the case of procedures requiring general anesthesia, policymakers recently recommended the use of endotracheal intubation to diminish the risk of aerosolization with suspected or confirmed COVID-19[206]. Other methods for splaches include the use of regular precautions such as full-sleeve gowns and suitable footwear[187].

**GAPS IN KNOWLEDGE**

Though there is a theoretical risk of fecal-oral transmission, the actual risk of transmission is extremely low. Despite the risk, endoscopy units have been functioning and reopening with no significant outbreaks noted.

**CONCLUSION**

The latest COVID-19 infection can lead to a high rate of morbidity and mortality and can lead to acute respiratory infection. The main signs of COVID-19 are respiratory system reactions, and also very common gastro-intestinal symptoms. COVID-19 patients with GIT symptoms are more probably associated with severe complications like ARDS and liver damage, with poor prognosis. Hence, during diagnosis and treatment of the disease, it should be taken into consideration the GIT symptoms as well as virus transmission *via* the fecal-oral route. In addition, it is advisable to take care of patients with CLD and treatments that can suppress inflammatory responses and preserve liver function should be treated during COVID-19 infection. Furthermore, the harmful effects of some drugs on the gut and liver during hospitalization must be checked and evaluated frequently. The intrinsic relations of COVID-19 into hepatology and gastroenterology are urgently required for future studies.

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**Footnotes**

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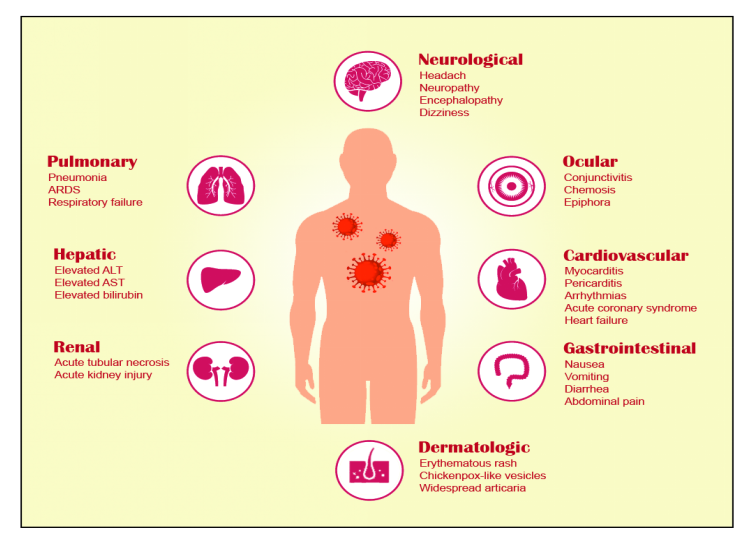
Grade C (Good): C, C, C

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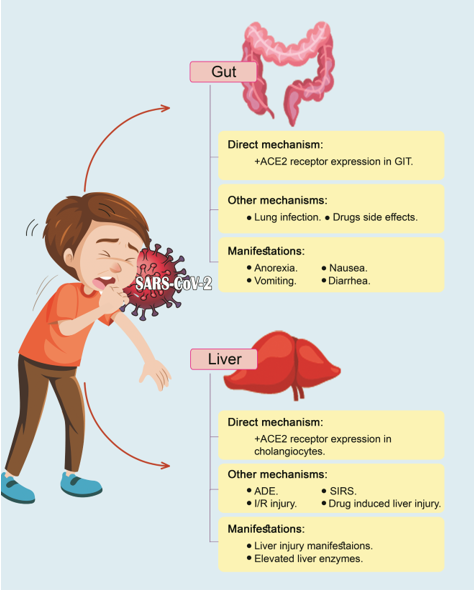
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**Figure Legends**



**Figure 1 Pulmonary and extrapulmonary manifestations of coronavirus disease 2019.** ARDS: Acute respiratory distress syndrome; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

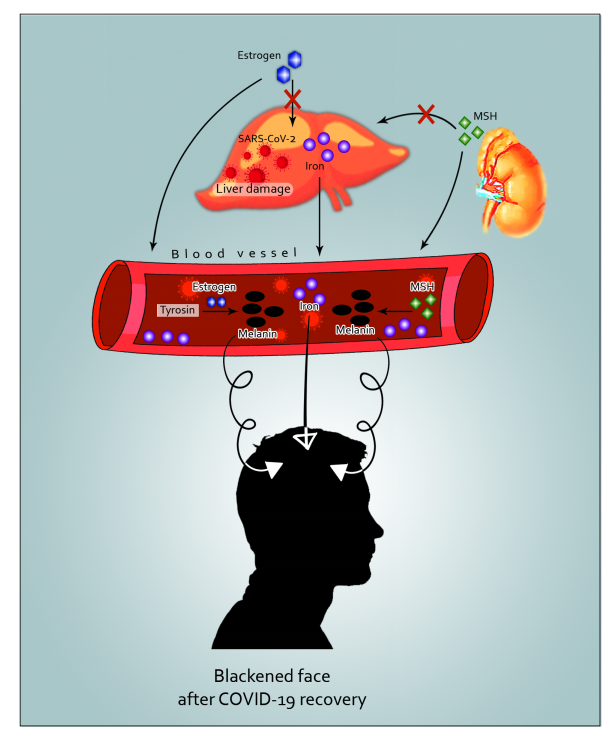


**Figure 2 Mechanisms and manifestations coronavirus disease 2019 in gut and liver.** SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2:Angiotensin-converting enzyme 2; GIT: gastrointestinal tract; ADE: Antibody-dependent enhancement of infection; SIRS: Systemic inflammatory response syndrome; I/R: Ischemia and hypoxia reperfusion injury.

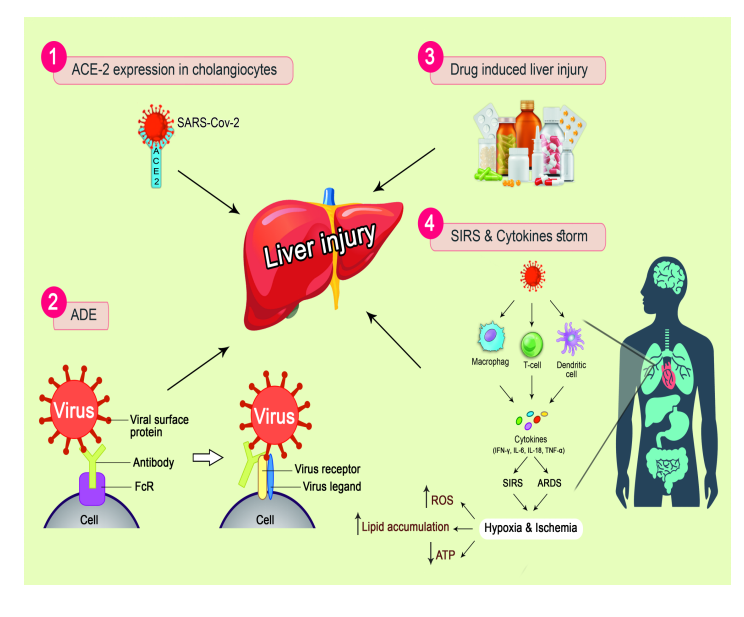
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**Figure 3 Mechanism of gastrointestinal symptoms in patients with coronavirus disease 2019.** (1) Gut-lung axis: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds with angiotensin-converting enzyme 2 (ACE2) to enter the lung, which leads to the accumulation of angiotensin II (ANG II) and the reduction of Angiotensin (1-7). ANG II combined with angiotensin 1 receptor stimulates cytokine release and upsurges C-C chemokine receptor type 9 (CCR9) CD4T cells. Afterward, chemokine (C-C motif) ligand 25 enhances the recruitment of CCR9 CD4T cells into the small intestine. The changing flora then stimulates T helper 17 cells’ polarization, and eventually, interleukin 17A instigates the recruitment of neutrophils. Cytokines and intestinal bacteria also enter the lung through the bloodstream, further affecting lung inflammation; and (2) Gut-liver axis: SARS-CoV-2 binds with ACE2 to enter the intestine, prevents the absorption of the B0AT1/ACE2 transport pathway, and then decreases the stimulation of mammalian target of rapamycin to diminish the expression of antimicrobial peptides which by term resulting in gastrointestinal tract symptoms or enhances ANG II that led to the upregulation of tissue factor VIII, Von Willebrand factor, and plasminogen activator inhibitor-1 expressions by endothelial cells resulting in mesenteric thrombosis. The intestinal flora, through the portal vein, is transferred to the liver, where it binds to toll-like receptors and resulting in hepatitis. Additionally, the liver, through the biliary tract, can transport metabolites to the intestine. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2: ANG II: Angiotensin II; Ang1–7: Angiotensin (1-7); AT1R: Angiotensin 1 receptor; CCR9: C-C chemokine receptor type 9; CCL25: Chemokine (C-C motif) ligand 25; Th17: T helper 17; IL-17: Interleukin 17; PMNS: Polymorph nuclear neutrophils; B0AT1: Sodium-dependent neutral amino acid transporter; mTOR: Mammalian target of rapamycin; AMPs: Antimicrobial peptides; FVIII: Tissue factor VIII; VWF: Von Willebrand factor; PAI-1: Plasminogen activator inhibitor-1; TLR: Toll-like receptor.



**Figure 4 Facial blackness and dull skin after coronavirus disease 2019 recovery.** Three possible mechanisms are shown: (1) Iron in the damaged liver drains into blood vessels. The blood with high iron levels can lead to blackening of the face once it supplies to the facial skin; (2) Estrogen cannot be metabolized in the damaged liver. Finally, the elevation of estrogen in the blood enhances the conversion of tyrosine to melanin; and (3) When liver function is impaired, the adrenocortical function is hypoactive, and melanocyte-stimulating hormone increases resulted in an elevation in the secretion of melanin. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MSH: Melanocyte-stimulating hormone; COVID-19: Coronavirus disease 2019.



**Figure 5 Mechanisms of liver injury in patients with coronavirus disease 2019.** (1) Angiotensin-converting enzyme 2-mediated targeting of cholangiocytes; (2) Antibody-dependent enhancement of infection; (3) Systemic inflammatory response syndrome and cytokine storms; and (4) Drug-induced liver injury. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; ADE: Antibody-dependent enhancement of infection; SIRS: Systemic inflammatory response syndrome; ARDS: Acute respiratory distress syndrome; IFN-γ: Interferon-γ; IL-6: Interlekine-6; IL-18: Interlekine-18; TNF-α; Tumor necrosis factor-α; ROS: Reactive oxygen species; ATP: Adenosine triphosphate.

**Table 1 Incidence of common gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Patient number** | **Anorexia, nausea or vomiting, *n* (%)** | **Diarrhea, *n* (%)** | **Abdominal pain, *n* (%)** |
| Kujawski *et al*[[207](#_ENREF_51)], 2020 | 12 | Nausea: 3 (25) | 4 (33.3) | 2 (16.7) |
| Hajifathalian *et al*[[44](#_ENREF_44)], 2020 | 1059 | Anorexia: 240 (22.7) | 234 (22.1) | 72 (6.8) |
| Nausea: 168 (15.3) |
| Vomiting: 91 (8.6) |
| Young *et al*[[208](#_ENREF_52)], 2020 | 18 | NA | 3 (17) | NA |
| Tabata *et al*[[209](#_ENREF_53)], 2020 | 104 | NA | 8 (9.6) | NA |
| Wölfel *et al*[[210](#_ENREF_54)], 2020 | 9 | NA | 2 (22) | NA |
| Chen *et al*[[26](#_ENREF_26)], 2020 | 99 | Nausea and vomiting: 1 (1) | 2 (2) | NA |
| Xu *et al*[[27](#_ENREF_27)], 2020 | 62 | NA | 3 (8) | NA |
| Gritti *et al*[[211](#_ENREF_55)], 2020 | 21 | NA | 5 (23.8) | NA |
| COVID-19 National Incident Room Surveillance Team[[212](#_ENREF_56)] | 295 | Nausea: 34 (11.5) | 48 (16.3) | 6 (1) |
| COVID-19 National Emergency response Center[[213](#_ENREF_57)] | 28 | NA | 2 (7) | 1 (4) |
| Sierpiński *et al*[[214](#_ENREF_58)], 2020 | 1942 | NA | 470 (24.2) | NA |
| Wu *et al*[[28](#_ENREF_28)], 2020 | 80 | Nausea and vomiting: 1 (1.25) | 1 (1.3) | NA |
| Wang *et al*[[12](#_ENREF_12)], 2020 | 138 | Anorexia: 55 (39.9) | 14 (10.1) | 3 (2.2) |
| Nausea: 14 (10.1) |
| Shi *et al*[[29](#_ENREF_29)], 2020 | 81 | Anorexia: 1 (1) | 3 (4) | NA |
| Vomiting: 4 (5) |
| Yang *et al*[[30](#_ENREF_30)], 2020 | 50 | Vomiting: 2 (4) | NA | NA |
| Mo *et al*[[31](#_ENREF_31)], 2020 | 155 | Anorexia: 26 (31.7) | 7 (4.5) | NA |
| Nausea: 3 (3.7) |
| Vomiting: 3 (3.7) |
| Qi *et al*[[215](#_ENREF_59)], 2020 | 267 | Anorexia: 46 (14.2) | 10 (3.7) | NA |
| Nausea: 6 (2.2) |
| Wen *et al*[[216](#_ENREF_60)], 2020 | 417 | NA | 29 (7) | NA |
| Dan *et al*[[217](#_ENREF_61)], 2020 | 305 | Anorexia: 101(50.2) | 146 (49.5) | 12 (6) |
| Nausea: 59 (29.4) |
| Vomiting: 3 (2) |
| Ma *et al*[[218](#_ENREF_62)], 2020 | 81 | NA | 6(7.41) | NA |
| Luo *et al*[[41](#_ENREF_41)], 2020 | 1141 | Anorexia: NA | 68 (6) | 45 (3.9) |
| Nausea: 134 (11.7) |
| Vomiting: 119 (10.4) |
| Liu *et al*[[219](#_ENREF_63)], 2020 | 238 | Anorexia: 14 (9.2) | 14 (9.2) | 1 (0.7) |
| Nausea: 2 (1.3) |
| Vomiting: 3 (2) |
| Ai *et al*[[220](#_ENREF_64)], 2020 | 102 | Anorexia: NA | 15 (14.3) | 3 (2.9) |
| Nausea: 9 (8.8) |
| Vomiting: 2 (2) |
| Zhao *et al*[[221](#_ENREF_65" \o "Zhao, 2020 #255)], 2020 | 75 | NA | 7 (9.3) | 1 (1.3) |
| Li *et al*[[222](#_ENREF_66)], 2020 | 83 | NA | 7 (8.4) | 7 (8.4) |
| Lin *et al*[[223](#_ENREF_67)], 2020 | 95 | Anorexia: 17 (17.8) | 23 (24.2) | 2 (2.1) |
| Nausea: 17 (17.9) |
| Vomiting: 4 (4.2) |
| Cholankeril *et al*[[224](#_ENREF_68)], 2020 | 207 | Anorexia: NA | 22 (10.8) | 14 (7.1) |
| Nausea: 22 (10.8) |
| Vomiting: NA |
| Ferm *et al*[[43](#_ENREF_43)], 2020 | 892 | Anorexia: 105 (11.8) | 177 (19.8) | 70 (7.8) |
| Nausea: 148 (16.6) |
| Vomiting: 91 (10.2) |
| Redd *et al*[[225](#_ENREF_69)], 2020 | 318 | Anorexia: 110 (34.8) | 107 (33.7) | 46 (14.5) |
| Nausea: 84 (26.4) |
| Vomiting: 49 (15.4) |
| Kluytmans *et al*[[226](#_ENREF_70)], 2020 | 86 | NA | 16 (18.6) | 5 (5.8) |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; NA: Not applicable; COVID-19: Coronavirus disease 2019.

**Table 2 Therapy-specific considerations for inflammatory bowel disease patients**

|  |  |
| --- | --- |
| **Drug** | **Effects** |
| Aminosalicylate acid derivatives (5-ASA) | No proof of increased risk of COVID-19 infection |
| Keep using it even in case of COVID-19 infection |
| Corticosteroids | Their safety during COVID-19 infection is uncertain |
| They can be used in a low dose and short period to treat disease relapses |
| Stopping as soon as possible |
| Ileo-caecal CD patients can be treated with Budesonide; IUC patients can be treated with Budesonide MMX |
| Immunomodulators (Thiopurines and Methotrexate) | No proof of increased risk of COVID-19 infection |
| Accompanied by increased risk of other viral infection |
| It is not recommended to start with monotherapy |
| Combination therapy with biologics should be maintained |
| Recommendations in stopping |
| Stable disease |
| Sustained reduction in case of elderly patients and/or significant comorbidities |
| Symptoms progression of COVID-19 infection |
| Anti-TNF therapy | No proof of increased risk of COVID-19 infection |
| Infusion and dose should be maintained intervally |
| Starting with monotherapy (adalimumab or certolizumab) |
| Stop in case of developing symptoms of COVID-19 |
| Anti-IL-12/23p40 therapy (Ustekinumab) | No proof of increased risk of COVID-19 infection |
| Monotherapy is recommended |
| Stop in case of developing symptoms of COVID-19 |
| Anti-a4b7 integrin therapy (Vedolizumab) | No proof of increased risk of COVID-19 infection |
| Monotherapy is recommended |
| Stop in case of developing symptoms of COVID-19 |
| Janus Kinase inhibitors (tofacitinib) | Although there is no proof of increasing the risk of COVID-19 infection, it may inhibit the immune reaction against viral infections |
| Starting is not recommended |
| Therapy should be maintained without elevating the dose |
| Stop in case of developing symptoms of COVID-19 |

UC: Ulcerative colitis; CD: Crohn’s disease; COVID-19: Coronavirus disease 2019; TNF: Tumor necrosis factor; IL: Interleukin.

**Table 3 Incidence of hepatic abnormalities in patients with severe acute respiratory syndrome coronavirus 2 infection**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Patient number** | **ALT (U/L)** | **AST (U/L)** | **TB (mg/dL)** |
| Zhou *et al*[[32](#_ENREF_32)], 2020 | 191 | ↑59 (31%) | None | NA |
| Shu *et al*[[227](#_ENREF_159)], 2021 | 545 | ↑41 (7.5%) | ↑35 (10.1%) | ↑189 (34.7%) |
| Huang *et al*[[25](#_ENREF_25)], 2020 | 41 | NA | ↑15 (37%) | NA |
| Huang *et al*[[228](#_ENREF_160)], 2020 | 36 | 4 (13.3%) | 18 (58%) | ↑4 (12.9%) |
| Chen *et al*[[26](#_ENREF_26)], 2020 | 99 | ↑28 (28%) | ↑35 (35%) | ↑18 (18%) |
| Ai *et al*[[64](#_ENREF_64)], 2020 | 102 | ↑20 (19.6%) | ↑26 (25.5%) | NA |
| Xu *et al*[[27](#_ENREF_27)], 2020 | 62 | ↑3 (3.75%) | ↑3(3.75%) | NA |
| Yang *et al*[[30](#_ENREF_39)], 2020 | 168 | ↑9 (8%) | ↑18 (17.3%) | ↑7 (6.4%) |
| Wu *et al*[[28](#_ENREF_28)], 2020 | 80 | ↑3 (3.75%) | ↑3 (3.75%) | NA |
| Yao *et al*[[229](#_ENREF_161)], 2020 | 40 | ↑21 (52.5%) | ↑16 (40%) |  |
| Xu *et al*[[230](#_ENREF_162)], 2020 | 355 | ↑91 (25.6%) | ↑102 (28.7%) | ↑10 (25%) |
| Cai *et al*[[231](#_ENREF_163)], 2020 | 298 | ↑39 (13.1%) | ↑25 (8.4%) | ↑66 (18.6) |
| Richardson *et al*[[128](#_ENREF_148)], 2020 | 5700 | ↑2176 (39.0%) | ↑3263 (58.4%) | ↑24 (8.1%) |
| NA |
| Fan *et al*[[134](#_ENREF_154)], 2020 | 40 | ↑27 (18.2%) | ↑32 (21.6%) | ↑9 (6.1%) |
| Guan *et al*[[39](#_ENREF_39)], 2020 | 355 | ↑158 (21.3%) | ↑168 (22.2%) | ↑76 (10.5%) |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin; NA: Not applicable.

**Table 4 Outcome of the patients with severe elevation of aminotransferases in coronavirus disease 2019**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Outcome of patients** | **SARS-CoV-2 patients with hypertransaminasemia (*n* = 20)** | **COVID-19 patients without hypertransaminasemia (*n* = 125)** | ***P* value** |
| Ramachandran *et al*[[169](#_ENREF_169)], 2020 | Shock | 9 (45%) | 38 (30.4%) | 0.207 |
|  | Mechanical ventilation | 10 (50%) | 30 (24%) | 0.028 |
|  | Died | 10 (50%) | 46 (36.8%) | 0.324 |
|  | Length of stay in days, median (IQR) | 7 (4.3, 10.3) | 7 (5, 10) | 0.78 |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IQR: Inter-quartile; COVID-19: Coronavirus disease 2019.

**Table 5 Recommendations of American Association for the Study of Liver Diseases, Asian pacific association for the study of the liver, and European association for the study of the liver for management of liver disease during coronavirus disease 2019**

|  |  |
| --- | --- |
|  | **Selected recommendations** |
| To limit nosocomial spread | (1) Decrease in-person visits via other alternatives like virtual platforms; (2) Symptoms investigation before entering the hospitals to identify COVID-19 patients; (3) Reduce staffing to needed staff only; (4) Reduce the frequent screening and laboratory examinations; (5) Keep adherence to recommended PPE by HCW and patients; (6) Keep proper social distance at hospitals; and (7) Postpone unnecessary or elective operations |
| Management of CLD patients with COVID19 | (1) These patients should be admitted early to hospital; (2) Prioritization of COVID-19 testing for patients with cirrhosis, CLD ones taking immunosuppressive agents and acute decompensated ones; (3) Repeated LFT examining is advisable; (4) Early registration in clinical trials as much as possible; (5) COVID-19 patients with NAFLD should be kept under supervision; (6) It should be taken into consideration the screening of hepatitis B surface antigen; (7) Drugs induced liver injury have to be monitored; (8) These patients can administer 2-3 g/d of acetaminophen, while limiting the use of NSAIDs whenever possible; (9) HBV prophylaxis should be considered before starting immunosuppressive agents; and (10) Stopping Remdesivir in decompensated liver disease patients with ALT more than 5 times the upper limit of normal |
| Management of chronic viral hepatitis (HCV and HBV) | (1) In spite of COVID-19 status, the treatments continuity of chronic HCV and HBV is recommended; (2) In the absence of flare, HBV treatment should be stopped; and (3) For the uninfected people, HCV and HBV treatments should be continued according to guidelines |
| Management of HCC | (1) HCC treatment should be continued according to guidelines, however it can be delayed if possible; (2) In case of COVID-19 patients, delaying of elective transplant and resection surgery and with stopping immunotherapy is advisable; and (3) Early admission to hospital is recommended for HCC patients |
| Management of pre- and post-transplant recipients | (1) It is suggested to screen the donor and recipient for COVID-19 patients; (2) For donors testing positive for COVID-19, transplantation surgeries should be postponed; (3) prioritization of patients with short-term prognosis; (4) For post-transplant patients, the lessen of immunosuppressive dose can be considered for moderate COVID-19 cases, while for mild COVID-19 cases, there is no dose reduction; and (5) For post-transplant recipients, vaccination against pneumonia and influenza is advisable |

PPE: Personal protective equipment; HCWs: Healthcare workers; CLD: Chronic liver disease; COVID-19: Coronavirus disease 2019; LFT: Liver function test; NAFLD: Nonalcoholic fatty liver disease; NSAIDs: Non-steroidal anti-inflammatory drugs; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

**Table 6 Recommendations of American association for the study of liver diseases and European association for the study of the liver for management of auto-immune hepatitis during coronavirus disease 2019**

|  |  |
| --- | --- |
|  | **Selected recommendations** |
| Virtual platforms is recommended to minimize in-person visits should be as much as possible | |
| COVID-19 testing is advised in cases of acute deterioration and liver failure | |
| Patients with low risk of complications (Patients on chronic immunosuppressive therapy) | (1) Frequent patient-provider communications should be closely supervised; (2) Virtual platforms should be used to decrease contact; and (3) Ensure enough drug supply and refills to decrease running out of medications |
| Patients with moderate risk of complications (symptomatic disease without cirrhosis) | (1) Empiric therapy via virtual healthcare platform as much as possible; and (2) Preventing liver biopsy whenever possible |
| Patients with high risk of complications (acute flare, decompensated cirrhosis) | (1) Less invasive procedures as much as possible; (2) In case of COVID-19 patients, if lymphopenia develops, reduction of dose of antimetabolites is recommended; and (3) In case of infection, corticosteroids should be attenuated |

COVID-19: Coronavirus disease 2019.

**Table 7 Recommendations of American association for the study of liver diseases and European association for the study of the liver on use of immunosuppressive therapies in chronic liver disease during coronavirus disease 2019**

|  |  |
| --- | --- |
|  | **Suggestions** |
| (1) Starting with corticosteroids and immunomodulators should be proceeded; and (2) By risk benefit ratio assessment | |
| Patients on immunosuppressive treatment and not infected by COVID-19 | Decreasing or adjustment of doses is not advisable |
| Patients infected with COVID-19 on immunosuppressive drugs | (1) Lessening of corticosteroids dose after specialist physician (consider tapering to prevent adrenal insufficiency); and (2) Decrease doses in case of cyclosporine, mycophenolate, and azathioprine is recommended in severe COVID-19 (especially with patients suffering from lymphopenia) |
| Patients need onset of immunosuppressive agents | Starting treatment is suggested in those patients regardless of COVID-19 status |

COVID-19: Coronavirus disease 2019.