

## COVID-19 and comorbidities of hepatic diseases in a global perspective

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### Abstract

The worldwide outbreak of coronavirus disease 2019 (COVID-19) has challenged the priorities of healthcare system in terms of different clinical management and infection transmission, particularly those related to hepatic-disease comorbidities. Epidemiological data evidenced that COVID-19 patients with altered liver function because of hepatitis infection and cholestasis have an adverse prognosis and experience worse health outcomes. COVID-19-associated liver injury is correlated with various liver diseases following a severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) infection that can progress during the treatment of COVID-19 patients with or without pre-existing liver disease. SARS-CoV-2 can induce liver injury in a number of ways including direct cytopathic effect of the virus on cholangiocytes/hepatocytes, immune-mediated damage, hypoxia, and sepsis. Indeed, immediate cytopathogenic effects of SARS-CoV-2 *via* its potential target, the angiotensin-converting enzyme-2 receptor, which is highly expressed in hepatocytes and cholangiocytes, renders the liver as an extra-respiratory organ with increased susceptibility to pathological outcomes. But, underlying COVID-19-linked liver disease pathogenesis with abnormal liver function tests (LFTs) is incompletely understood. Hence, we collated COVID-19-associated liver injuries with increased LFTs at the nexus of pre-existing liver diseases and COVID-19, and defining a plausible pathophysiological triad of COVID-19, hepatocellular damage, and liver disease. This review summarizes recent findings of the exacerbating role of COVID-19 in pre-existing liver disease and vice versa as well as international guidelines of clinical care, management, and treatment recommendations for COVID-19 patients with liver disease.

**Key Words:** Liver disease; COVID-19; Pathophysiology; Epidemiology; Prophylaxis

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**Core Tip:** The clinical menace of coronavirus disease 2019 (COVID-19)-related comorbidities of hepatic diseases and severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) tropism for the liver result in liver impairment with increased liver injury markers and cytokine storm. SARS-CoV-2 aggravates liver injury *via* coagulative and fibrinolytic pathways, cytokine-mediated liver injury, ischemia-hypoxia, and immune-mediated cell death pathways owing to adverse outcomes of liver disease such as nonalcoholic steatohepatitis, drug-induced liver injury, nonalcoholic fatty liver disease, metabolic associated fatty liver disease, and hepatocellular carcinoma. This review summarizes diagnostic approaches, therapeutics, clinical guidelines, and vaccines for COVID-19 and liver disease comorbidities.

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## INTRODUCTION

Coronavirus belongs to family *Coronaviridae*, subfamily *Orthocoronavirinae*, and order *Nidovirales*<sup>[1]</sup>. All over the world, coronaviruses are responsible for causing enteric, neurologic, and hepatic diseases in humans, animals, and other mammals<sup>[2]</sup>. On the basis of genome and phylogenetic analysis, the subfamily contains four genera named *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*<sup>[3]</sup>. Coronaviruses caused epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012<sup>[4]</sup>. The novel coronavirus 2019 (SARS-CoV-2)- belongs to genus *Betacoronavirus*. It is an enveloped virus with a positive-sense, single-stranded RNA genome. SARS-CoV-2 has affected more than 65.8 million people with 1.5 million deaths globally.

In early December 2019, the first documented pneumonia case of unknown origin in Wuhan city of China was confirmed by high-throughput sequencing analysis as a novel *Betacoronavirus* that is currently named SARS-CoV-2. A sudden worldwide outbreak of this virus was declared as health emergency and pandemic of international concern by the World Health Organization (WHO)<sup>[4]</sup>. In previous epidemics of SARS-CoV and MERS-CoV, bats were considered as the natural host and potential reservoir. Different studies evidenced bats as a reservoir of SARS-CoV-2, however, pangolin species were also considered as natural reservoir of SARS-CoV-2<sup>[5]</sup>.

In the SARS pandemic, the virus was found in patient's stool sample<sup>[6]</sup>, which indicates that fecal samples could be a possible source of transmission of SARS-CoV-2<sup>[7]</sup>. After clinical recovery, prolonged shedding of SARS-CoV-2 in feces highlighted the possibility of fecal-oral transmission<sup>[8]</sup>. Positive semen samples containing SARS-CoV-2 have also been observed in two patients who were in recovery and in four who were in the acute stage of infection<sup>[9]</sup>. Recently, an ocular route of transmission has also been identified in SARS-CoV-2<sup>[10]</sup>.

Symptoms of coronavirus disease 2019 (COVID-19) vary from mild respiratory symptoms to acute respiratory distress syndrome along with multiple organ failure<sup>[11]</sup> and death, mainly in elderly patients having several comorbidities. The WHO provided timely, effective, and safe supportive management guidelines for COVID-19 patients, which revealed that clinical syndromes associated with SARS-CoV-2 include uncomplicated illness, mild-to-severe pneumonia, acute respiratory distress syndrome, sepsis, and septic shock<sup>[12]</sup>. However, gastrointestinal symptoms<sup>[13]</sup> and several extra-pulmonary signs such as liver injury have also been associated with COVID-19<sup>[14]</sup>.

In COVID-19 patients, markers of liver injury may be abnormal<sup>[15]</sup>. As shown in **Table 1**, disturbed alanine transaminase (ALT), aspartate transaminase (AST) levels and increased bilirubin have been seen in 14%-53% of COVID-19 patients<sup>[16]</sup>. A recent study of 1100 patients reported that 18% patients with nonsevere and 56% with severe COVID-19 had elevated serum AST levels. Increased ALT levels were observed in 20% of patients with nonsevere and 28% with severe COVID-19 infection<sup>[17]</sup>. Moreover, it has been noted that COVID-19 patients with gastrointestinal symptoms showed a high

**Table 1** Prevalence of coronavirus disease 2019 patients with altered manifestations of hepatic injury markers

Salient findings	Country	Ref.
Of 417 COVID-19 patients, 76.3% had altered values of liver function tests and 21.5% had liver injury during hospitalization. The use of lopinavir/ritonavir increased the risks of liver injury by 4-fold.	China	Cai <i>et al</i> <sup>[32]</sup> , 2020
The prevalence of patients with GI symptoms and elevated level of liver enzymes was 18.6%. The severity of disease increased in patients with digestive symptoms.	China	Pan <i>et al</i> <sup>[81]</sup> , 2020
Abnormal liver function tests are common in COVID-19 patients. Of 115 patients, 9.57% had increased ALT levels and 14.78% had increased AST levels.	China	Zhang <i>et al</i> <sup>[82]</sup> , 2020
Liver dysfunction at an early stage increases the mortality risk in COVID-19 patients. A total of 151 patients (42.5%) were reported with cholestasis and 101 (28.5%) had hepatocellular injury. Liver dysfunction was more common in critically ill patients.	China	Fu <i>et al</i> <sup>[83]</sup> , 2020
About 48.4% of patients with normal liver function had abnormal liver function tests after receiving lopinavir/ritonavir. Liver injury biomarkers (LDH, ALP, GGT, TBiL, prealbumin, and albumin) were dysregulated in a cohort of 288 COVID-19 patients, suggestive of potential as markers of liver injury and a prognosis of severe of COVID-19 disease.	China	Fan <i>et al</i> <sup>[37]</sup> , 2020 and Fan <i>et al</i> <sup>[84]</sup> , 2020
The presence of acute liver injury was linked with high risk of COVID-19 morbidities and admission to an ICU.	United States	Hajifathalian <i>et al</i> <sup>[85]</sup> , 2020
Serum liver enzymes were increased in from 14% to 53% of hospitalized COVID-19 patients.	United States	Fix <i>et al</i> <sup>[68]</sup> , 2020
Increased bilirubin level was seen in 16.7% and increased ALT and AST were seen in 15% of COVID-19 patients.	United States	Sultan <i>et al</i> <sup>[86]</sup> , 2020

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID-19: Coronavirus disease 2019; GGT: Gamma-glutamyl transferase; GI: Gastrointestinal; ICU: Intensive care unit. LDH: Lactate dehydrogenase; TBiL: Total bilirubin.

prevalence of liver injury compared with patients with no gastrointestinal symptoms. Correspondingly, the prevalence of chronic liver disease (CLD) was high in patients with gastrointestinal symptoms of COVID-19<sup>[18]</sup>.

Liver cancer is the fourth most common cause of cancer-associated death worldwide<sup>[19]</sup>. The most common type is hepatocellular carcinoma (HCC), and patients with HCC have underlying CLD, which includes alcoholic liver injury, nonalcoholic fatty liver disease (NAFLD), and chronic hepatitis B or C virus infection<sup>[19]</sup>. It has been reported that cancer patients are at high risk of COVID-19. A study of three hospitals in Wuhan reported 1276 confirmed cases of COVID-19, among which 28 patients had different types of cancer and two of them had HCC<sup>[20]</sup>. NAFLD, also called metabolic associated fatty liver disease (MAFLD), is highly prevalent globally<sup>[21]</sup>. A study reported that patients with NAFLD had increased ALT levels following COVID-19 infection<sup>[22]</sup>. A study from China showed that patients with NAFLD had an increased risk of COVID-19 compared with patients without it<sup>[23]</sup>. However, more studies are required to understand the mechanism of liver injury caused by NAFLD and COVID-19. It has been observed that use of immunosuppressant drugs in post liver transplant patients more prone them to SARS-CoV-2 infection. Additionally, the use of these drugs were found to enhance the cytokine storm in COVID-19 patients<sup>[18,24]</sup>.

COVID-19-associated liver injury is manifested by entry of SARS-CoV-2 into the liver that can progress during COVID-19 treatment in patients with or without pre-existing liver disease<sup>[25]</sup>. SARS-CoV-2-related liver injury can occur by multiple factors, including direct cytopathic effect of the virus on cholangiocytes/hepatocytes, immune-mediated damage, hypoxia<sup>[19]</sup>, sepsis<sup>[26]</sup>, and drugs (*e.g.*, acetaminophen, ritonavir/lopinavir, interferon, Chinese herbs, and antibacterial agents) used in treating COVID-19<sup>[27]</sup>. However, there is no proof that patients with chronic hepatitis are at risk of COVID-19 unless other comorbidities (*e.g.*, cardiovascular disease, diabetes, and hypertension) that can increase the risk of liver disease are present<sup>[26]</sup>. The angiotensin-converting enzyme 2 (ACE2) receptor is associated with entry of SARS-CoV-2 and is highly expressed (about 80%) in alveolar cells of the lungs<sup>[28]</sup>, the gut, and the kidneys<sup>[29]</sup>. The expression of ACE2 receptor has also been observed in myocardial cells, nephron proximal tubule cells, absorptive enterocytes of the ileum and colon, bladder urothelial cells; and the oral, nasal and nasopharyngeal mucosal epithelia<sup>[30]</sup>. It has been reported that ACE2 cell surface receptors are highly expressed in cholangiocytes and hepatocytes, which indicates tropism of SARS-CoV-2 in the liver<sup>[31]</sup>.

## COVID-19-ASSOCIATED LIVER INJURY AND ITS CLINICAL IMPLICATIONS IN A GLOBAL SCENARIO

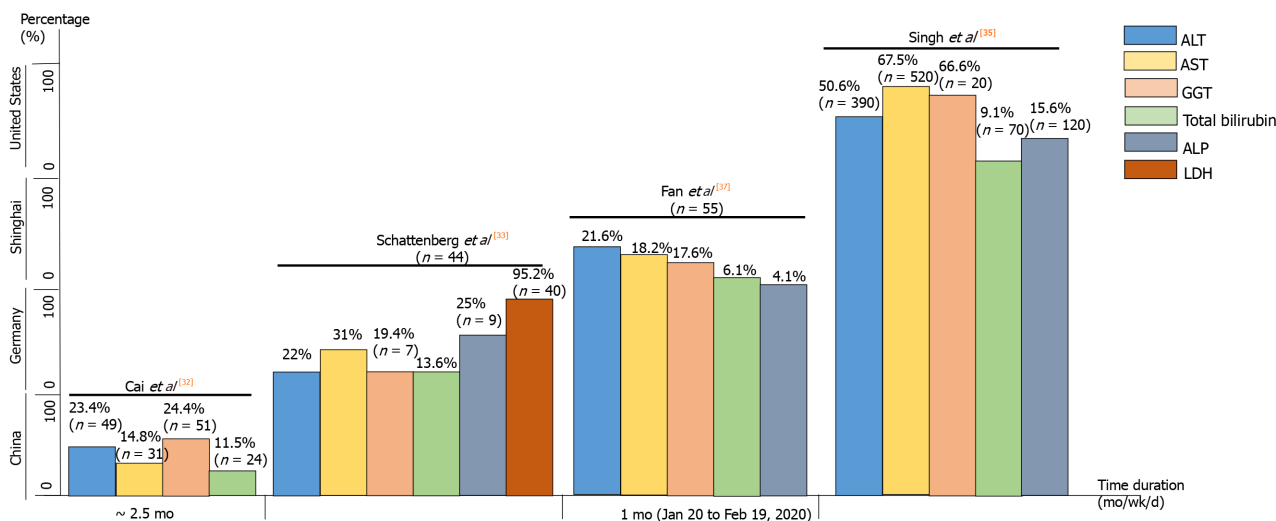
Abnormal levels of liver injury markers such as AST and ALT or abnormal liver function tests (LFTs) in COVID-19 patients place an additional disease burden on clinicians as well as to scientists in terms of treatment regimens and defining the association of COVID-19-linked hepatic diseases. The data that document liver impairment in COVID-19 patients reveal variable levels of liver injury markers across the globe, as shown in [Figure 1](#)<sup>[32-36]</sup>. In this context, the preliminary data were reported by Cai *et al.*<sup>[32]</sup> from Shenzhen, China from January 11 to February 21, 2020 and followed-up to March 7, 2020. The data in the report was from a local hospital that found 318 of 417 COVID-19 patients (76.3%) with abnormal LFT values and 90 of 417 (21.5%) with liver injury during hospitalization. The incidence of liver injuries in Asia was further evaluated by Vespa *et al.*<sup>[34]</sup> in a cohort of 292 COVID-19 patients until March 30, 2020. Compared with Cai *et al.*<sup>[32]</sup>, a cholestatic pattern of liver injury with an increased level of alkaline phosphatase (ALP) > 150 U/L was observed in 9.6% of the selected population. Another study of cholestatic liver injury conducted from January 20 to 31, 2020 at the Shanghai Public Health Clinical Center reported abnormal liver functions as increased levels of ALT and AST, gamma-glutamyl transferase (GGT), ALP, and total bilirubin<sup>[37]</sup>. Thus, the documented reports describe data related to predictive markers of COVID-19 and associated liver injury, but the underlying causes of liver injury associated with worse outcomes are still elusive.

The clinical significance of COVID-19-associated liver disease needs to be described. Some studies have addressed the clinical challenges. Of relevance is a report by Vespa *et al.*<sup>[34]</sup> of an increase in ALP values because of SARS-CoV-2 liver tropism *via* the ACE2 receptor on hepatocytes and cholangiocytes. Furthermore, they correlated the ALP elevation as a marker of patient frailty or as representing an increased systemic inflammatory response to SARS-CoV-2 infection<sup>[34]</sup>. The prevalence of altered liver injury markers is highly associated with drug-induced liver injury (DILI) during the COVID-19 pandemic. Several studies<sup>[32,38-40]</sup> have reported potential harms related to pharmacotherapy with lopinavir/ritonavir in COVID-19 patients and the vulnerability of patients in developing severe pneumonia *via* increased LFTs. Moreover, the pathological characteristics of liver injury *via* autopsy analysis of COVID-19 patients provides evidence in support of DILI. A study revealed moderate microvesicular steatosis with mild hepatic inflammation, indicating the possibility of hepatic injury. However, this pattern of histological injury could be correlated with either DILI or SARS-CoV-2 infection<sup>[41]</sup>.

Several risk factors can be linked to the incidence of COVID-19-associated liver injury. A retrospective study in a French population found a marked prevalence of obesity in confirmed COVID-19 patients. The study included 340 COVID-19 patients, 230 (68%) with noncritical COVID-19 and 110 (32%) with critical COVID-19. It was found that 85 of 340 patients with severe COVID-19 (25%) were obese compared with 15.3% of the general French population. Following standardization by age and sex, the prevalence rates of obesity were 1.35% and 1.89% times higher in patients with severe COVID-19 and in those admitted to intensive care units, respectively, than in the general French population<sup>[42]</sup>. Likewise, Zheng *et al.*<sup>[43]</sup> reported the key association of obesity with the severity of COVID-19 in MAFLD patients, which provides a rationale for the likelihood of the importance of obesity-related comorbidities of liver diseases<sup>[44,45]</sup>.

## PRE-EXISTING LIVER DISEASE AND COVID-19: AN INTERLINKED SETUP AND ITS RELATED CONSEQUENCES

CLDs are an existing threat that accounts for the leading causes of liver-related mortality worldwide<sup>[46-48]</sup>. The major CLDs, including hepatitis B virus or C virus infection, alcohol-induced liver damage (ALD), and NAFLD, lead to prolonged liver damage and increased incidence of CLD-associated cancers, particularly, HCC<sup>[49,50]</sup>. Underlying liver diseases were one of the crucial causative factors in the previous SARS outbreak, with high mortality rates in adults and elders<sup>[51]</sup>. The Centers for Disease Control and Prevention recently included liver diseases as a comorbidity and predisposing factor for contracting SARS-CoV-2 infection. Moreover, the American Association for the Study of Liver Diseases (AASLD) endorses COVID-19 testing on a priority basis for patients who manifest symptoms of liver disease<sup>[52]</sup>. The COVID-19



**Figure 1 Overview of a global perspective related to incidence of coronavirus disease 2019-associated alterations in liver function tests.** The figure presents only data published in peer-reviewed journals. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; LDH: Lactate dehydrogenase.

pandemic together with the global prevailing menace of CLD further complicates the care of pre-existing liver disease patients as a result of failure of screening, and follow-up. Therefore, the intricate link between pre-existing liver disease and COVID-19 requires additional study and specific disease management. It has to be expected that patients with underlying liver diseases are more vulnerable to exacerbating COVID-19-related effects and vice versa<sup>[53]</sup> that may account for the high morbidity and mortality rates in the current COVID-19 pandemic.

Relevant to pre-existing liver diseases, alcohol use disorder or ALD is the CLD with the highest hospitalization burden and has seen a more than 2-fold increase in China. The effect is likely to be repeated in the United States, with 12.7% estimated hospitalization rate associated with COVID-19. A gradual increase in the incidence of ALD was accompanied by an increase in patients indicated for liver transplantation prior to COVID-19 pandemic. The direct clinical implications of COVID-19 on ALD are still unknown, but it can be suspected that SARS-CoV-2 infection can serve as a major host-compromising factor with underlying ALD and subsequently results in acute-on-chronic liver failure. The high proportion of ALD among CLD patients is reflected in the number of patients with decompensated ALD during COVID-19 pandemic<sup>[52]</sup>.

Growing evidence of COVID-19-related liver disease comorbidities suggests that MAFLD patients are at higher risk of COVID-19 disease progression<sup>[43,54,55]</sup>. A retrospective study conducted by Fondevila *et al*<sup>[56]</sup> described a mechanistic approach in the context of a higher risk of SARS-CoV-2 infection in obese patients. They assessed the hepatic mRNA expression of SARS-CoV-2 cell entry molecules, ACE2 and the cellular transmembrane protease serine 2 (*TMPRSS2*) in obese patients with NAFLD and/or diabetes mellitus type-2. Based on liver mRNA expression of both ACE2 and *TMPRSS2* in obese patients, the results revealed that SARS-CoV-2 entry factors are differently affected in diabetes and NAFLD. Moreover, major alterations in the expression of SARS-CoV-2 entry molecules in men and women suggest a lower susceptibility of women to liver injury. While obese women with diabetes have unexpectedly lower levels of ACE2 and *TMPRSS2* than obese normoglycemic women, obese patients with nonalcoholic steatohepatitis had a higher expression of those genes, suggesting that advanced stages of NAFLD might predispose to COVID-19.

COVID-19 patients with comorbidities of advanced hepatic complications are generally at an increased risk of infection because of cirrhosis-associated immune dysfunction<sup>[57]</sup>. A retrospective study by Iavarone *et al*<sup>[58]</sup> documented a substantial 30-d mortality rate of 34% in a cohort of 50 cirrhotic patients with COVID-19, which was higher than the rate in cirrhotic patients with bacterial infections. Overall COVID-19 mortality from the medical consequences of respiratory failure was correlated with the worsening of liver dysfunction. Other categories of COVID-19 patients with hepatic diseases that are of great concern are liver transplant recipients and patients with autoimmune liver diseases receiving immunosuppressant drugs<sup>[57]</sup>. However, COVID-19-associated effects in recipients of living donor allografts are still unclear<sup>[59]</sup>. A case reported by The American Society of Transplantation and the American Society of

Transplant Surgeons described the impact of COVID-19-associated hepatitis during liver transplantation. A patient underwent ABO-incompatible living donor liver transplantation without knowing that the liver donor was infected with COVID-19 during the donation procedure. In that case, donor-derived transmission to the recipient was not identified, and the liver donor was found to be recovering from COVID-19 infection. Donor-derived transmission was not identified<sup>[60]</sup>.

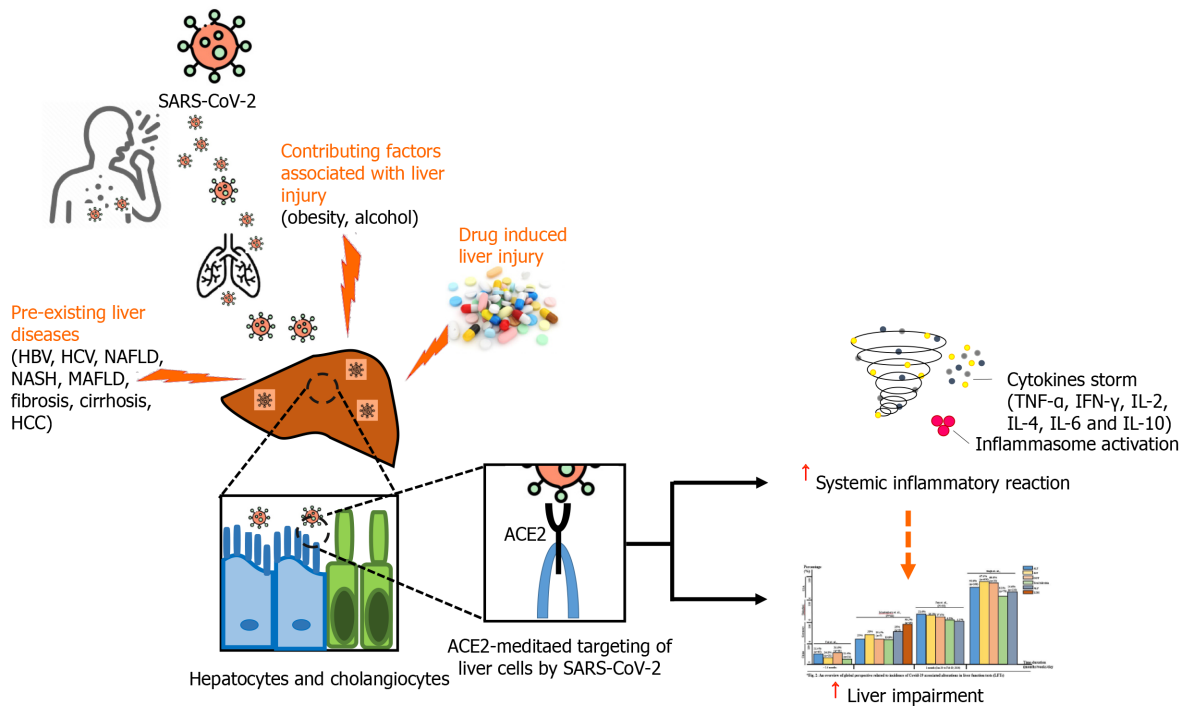
## A PLAUSIBLE PATHOPHYSIOLOGICAL TRIAD OF COVID-19, HEPATOCELLULAR DAMAGE AND LIVER DISEASES

Epidemiological studies have described liver dysfunction and the effects of SARS-CoV-2 infection on the liver cells in COVID-19 patients by elevated levels of liver injury markers such as ALT, AST, and bilirubin<sup>[32,33,57,61,62]</sup>. It has been stated previously that the SARS-CoV and MERS-CoV viruses primarily affect the upper respiratory tract but also affect the liver<sup>[62,63]</sup>. Despite the immediate and direct action of SARS-CoV-2 *via* potential targets on the epithelial cells of lung alveoli as well as the respiratory tract, emerging evidence suggests that the high expression of ACE2 receptors in the liver renders it susceptible to the pathogenicity of SARS-CoV-2<sup>[36,64]</sup>. Pathological examination of COVID-19 patients has confirmed cytopathic injury in the lungs<sup>[41]</sup> and has recently confirmed SARS-CoV-2 infection as an etiology of liver disease. The proposed mechanisms associated with COVID-19-induced liver injury include direct viral insult-linked hepatic derangements, cytokine storm-prompted liver injury, and ischemia related to COVID-19-induced hypoxia as shown in [Figure 2](#)<sup>[52,65-68]</sup>.

Liver impairment in COVID-19 might be directly correlated with SARS-CoV-2 infection of liver cells. Approximately 2%-10% COVID-19 patients with diarrhea have confirmed SARS-CoV-2 RNA in stool and blood samples, which implies the possibility of viral exposure in the liver. The affinity of SARS-CoV-2 and SARS-CoV for the ACE2 receptor indicates respective target sites, mainly the upper respiratory tract, lung tissue, and cholangiocytes of the liver, where the virus replicates and manifests COVID-19 associated symptoms<sup>[61]</sup>. In that context, Zhao *et al*<sup>[69]</sup> studied a SARS-CoV-2 infection model in human liver ductal organoids. They reported genomic evidence that SARS-CoV-2 virus infection resulted in dysregulation of barrier and bile-acid transporting functions of the cholangiocytes. The study found that altered cholangiocyte functions could have been the result of a direct SARS-CoV-2 cytopathogenic effect on target cell that expressed ACE2 and *TM6SS2*.

Cytokine storm is one of the hallmarks of infectious and noninfectious diseases that are capable of causing severe multiple organ injuries. Establishment of the cytokine environment is a multifactorial network that involves an immunological response to an invading antigen along with interplay of activated host immune and inflammatory cells. In line with the concept of cytokine storm in COVID-19 patients, Han *et al*<sup>[65]</sup> performed a prospective cohort study at a local hospital in Wuhan, China that enrolled 102 COVID-19 confirmed patients and 45 healthy control volunteers. They analyzed the serum profiles of inflammatory cytokines, including tumor necrosis factor-, interferon-, interleukin (IL)-2, IL-4, IL-6, IL-10, and C-reactive protein (CRP) by immunoassays. Significant increases in the levels of the inflammatory markers and CRP were seen in COVID-19 patients compared with the healthy volunteers. Moreover, the levels of IL-6 and IL-10 were significantly higher in critical than severe or moderate COVID-19 patients, suggesting that increased IL-6 and IL-10 may allow rapid diagnosis of patients with increased risk of lethal disease. Furthermore, Wang *et al*<sup>[70]</sup> reported COVID-19-associated conspicuous cytopathy. The severity of SARS-CoV-2 infection is associated with disturbed levels of liver enzymes, increased alveolar-arterial oxygen gradient and GGT level, and decreased albumin and circulating CD4<sup>+</sup> T cells and B lymphocytes. The predominant histological features of COVID-19 liver infection are substantial apoptosis and binuclear hepatocytes<sup>[71]</sup>.

Hepatic dysfunction in severe COVID-19 is accompanied by aberrant activation of the coagulative and fibrinolytic pathways<sup>[71]</sup>, moderately decreased platelet counts, increased neutrophil counts and neutrophil-to-lymphocyte ratios, and high ferritin levels. Such laboratory findings are perceived as nonspecific inflammatory markers, but the altered levels can coincide with a failure of innate immune regulation during progression of severe COVID-19. Indeed, alteration of immune balance activates coagulation and NETosis, and subsequently affects systemic iron metabolism secondary to macrophage activation<sup>[38]</sup>.



**Figure 2 Severe acute respiratory syndrome-coronavirus type 2-associated pathogenesis and immunological response in the liver.** ACE2: Angiotensin-converting enzyme 2; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IFN: Interferon; IL: Interleukin; MAFLD: Metabolic associated fatty liver disease; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus type 2; TNF: Tumor necrosis factor.

## DIAGNOSTIC APPROACHES FOR COVID-19

SARS-CoV-2 infection is confirmed by serologic tests that measure the antibody response or antibody titer in the patient. In COVID-19 patients, antibodies are produced in the days to weeks after SARS-CoV-2 infection. Thus, the presence of antibodies indicates that a person was infected with SARS-CoV-2, irrespective of whether the infection caused severe or mild disease or even an asymptomatic infection. Surveillance of antibody seropositivity allows inferences to be made about the extent of infection and the cumulative incidence of infection in the population. Serologic Enzyme-linked immunosorbent assays can be used for COVID-19 serosurveillance and to determine the extent of infection in the population. A confirmed case of SARS-CoV-2 infection is declared by a positive result from nasal and pharyngeal swab specimens by high-throughput sequencing or real-time reverse transcriptase polymerase chain reaction (RT-PCR)<sup>[17]</sup>. Molecular testing (RT-PCR) confirms infection, often in patients with severe disease, as they are individuals who seek and require health care. A percentage of patients with mild or asymptomatic infections who do not require medical attention may not be tested, and as a result, the full spectrum of the disease will not be known<sup>[72]</sup>. SARS-CoV-2 infection is associated with epidemiological characteristics, clinical signs, and symptoms of COVID-19 that can be accessed from electronic medical records and laboratory findings. Radiological assessments of COVID-19 patients include chest X-rays or computed tomography. Whereas, laboratory assessments that help to indicate the prognosis of COVID-19 include complete blood counts, blood chemistry, coagulation tests, assays of liver and renal function markers, electrolytes, CRP, procalcitonin, lactate dehydrogenase, and creatine kinase<sup>[17]</sup>.

## RECOMMENDATIONS OF THERAPEUTICS FOR COVID-19: VACCINES, LABEL AND OFF-LABEL MEDICATIONS FOR PATIENT CARE

The COVID-19 pandemic has prompted the scientific community and clinicians to develop COVID-19-related therapeutics and vaccines to mitigate as well as control the pathogenicity of SARS-CoV-2. Previous investigations on genomic sequencing of

SARS-CoV and MERS have contributed to vaccination strategies in developing current vaccines against SARS-CoV-2<sup>[73]</sup>. The characteristics of vaccines in clinical testing are based upon inactivated or live-attenuated viruses, protein subunits, virus-like particles, replicating and nonreplicating viral vectors, and DNA and RNA that may provoke protective immunity to SARS-CoV-2 infection<sup>[74,75]</sup>. Since July 2, 2020, the global landscape of SARS-CoV-2 vaccine development reported 163 vaccine candidates, 135 of the 163 are in preclinical or exploratory stages of development. Currently, mRNA-1273 (Moderna), Ad5-nCoV (CanSino Biologicals), INO-4800 (Inovio, Inc.), LV-SMENP-DC, a Pathogen-specific aAPC (ShinzenGeno-Immune Medical Institute), ChAdOx1 (Oxford University) BioNtech (Pfizer), Sputnik V (Gamaleya, Russia), and Sinovac (China) have been approved by the WHO under emergency use authorization<sup>[76]</sup>. India has started mass vaccination with its locally produced Covaxin vaccine. A prolonged time period for approval of vaccines is needed for validation of efficacy and adverse effects in target populations before post-market surveillance. However, adverse reactions to vaccines including fatigue, chills, aches, skin rashes, muscle pain, fever, and joint pain could be a barrier in the global rollout of COVID-19 vaccines<sup>[77]</sup>. In April, 2020, the Access to COVID-19 Tools accelerator was launched by the WHO and its partners to cooperate in fighting against the COVID-19 pandemic. Moreover, a global collaboration aims to accelerate development, production, and equitable access to COVID-19 tests, treatments, and vaccines among countries, particularly low-to-middle income countries (SAGE; <http://www.who.int/>).

In terms of therapeutics, COVID-19 medications fall into two categories: Those that target the viral replication cycle and those that aim to control the symptoms of the disease. The aminoquinolines chloroquine and hydroxychloroquine are polymerase inhibitors classically used as antimalarial medications. In malaria, it inhibits heme polymerase, causing the accumulation of toxic heme in the parasite that leads to its death. In COVID-19, it is thought that the drugs keep the virus out of host cells by blocking glycosylation of host receptors and blocking the production of viral proteins by inhibiting endosomal acidification. The WHO recommends the off-label use of hydroxychloroquine or chloroquine and lopinavir/ritonavir for treatment of COVID-19 with any disease severity and any duration of symptoms. Remdesivir and systemic corticosteroids are potential candidates for conditional recommendation of use in hospitalized COVID-19 patients for usual care regardless of disease severity (WHO/2019-nCoV/therapeutics/2020.1). The WHO considers off-label use of medication as country-specific. In many countries, doctors are giving COVID-19 patients medicines that have not been approved for this disease (MEURI; <http://www.who.int/>). Thus, COVID-19 patients have received off-label and compassionate-use therapies, such as interferon- combined with the repurposed drug Kaletra, an approved combination of the human immunodeficiency virus protease inhibitors ritonavir and lopinavir, chloroquine, azithromycin, favipiravir, remdesivir, steroids, and anti-IL-6 inhibitors, based on either *in vitro* antiviral or anti-inflammatory properties<sup>[78]</sup>. It is unclear if COVID-19 therapeutics protect against liver injury or disease. It would be interesting to look into protective effects in future.

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## RECOMMENDATIONS FOR MANAGEMENT OF COVID-19 PATIENTS WITH PRE-EXISTING LIVER DISEASES

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The WHO has approved comprehensive guidelines to strengthen the care and management of COVID-19 patients and to provide up-to-date guidance to clinicians and physicians. That report addresses the best practices to manage severe acute respiratory infection (SARI), including infection prevention and control measures and supportive care for COVID-19 patients. Furthermore, the prime considerations focus on recognizing and treating patients with SARI through appropriate diagnosis, early supportive therapy, management of acute respiratory distress and septic shock, prevention of complications, and use of specific COVID-19 treatments<sup>[79]</sup>. Indeed, patients with CLD do not appear to be over-represented in cohorts of patients with COVID-19, where they make up less than 1% of reported cases. These observations suggest that patients with CLD may have a decreased risk of contracting severe SARS-CoV-2. However, the risk of infection and/or the risk of a severe course of COVID-19 may be different depending on the nature of the CLD and the presence or absence of advanced fibrosis or cirrhosis. In that context, the European Association for the Study of the Liver, European Society of Clinical Microbiology and Infectious Diseases and AASLD provided comprehensive guidance for physicians and clinicians for the care of



patients with CLD during the early stages of the COVID-19 pandemic<sup>[68,80]</sup>. The salient guidelines are summarized in [Table 2](#) for clinical relevance and management of COVID-19 and liver patients.

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## CONCLUSION

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The chaotic conditions of the global spread of COVID-19 necessitate clinical care and management of patients with pre-existing morbidities, especially highly prevalent liver diseases in developed and developing countries to decrease the economic and health losses globally. Understanding the pathophysiological mechanisms of COVID-19 and its associated adverse effects in hepatic diseases is indispensable for the development of therapeutics and vaccines as well as mitigation of risks factors of disease. The WHO guidelines and associations for the study of liver diseases are timely and helpful in decreasing burden of disease and health education. The WHO needs to play a vital role in equitable and global availability (rollout) of COVID-19 vaccines to low-to-middle income countries to prevent COVID-19 pandemic and associated comorbidities.

**Table 2 Summary of specific European Association for the Study of the Liver, European Society of Clinical Microbiology and Infectious Diseases and American Association for the Study of Liver Diseases guidelines and recommendations for the clinical care and management of patients with liver diseases during coronavirus disease 2019 pandemic**

	Hospitalization and severe COVID-19	Alterations to standard treatment strategies		Progression of liver disease
	Early administration, laboratory findings and risk of SARS-CoV-2 infection	Treatment of higher risk groups	Resumption of targeted treatment and surveillance	Patient education and intensive lifestyle advice
NAFLD	High prevalence risk of SARS-CoV-2 infection in NAFLD patients with COVID-19 suggest an early admission to the hospital	No side effects related to ACE inhibitors or AR blockers to date, thus, arterial hypertension treatment should continue in accordance to prescribed guidelines	Not well known	Intensive lifestyle interventions including nutritional guidance, weight loss and diabetes management may prevent the risk of severe COVID-19 complications
Chronic Viral Hepatitis	Patients on chronic HBV or HCV medications with poor compliance should observed treatment protocols, directly	(1) In HBV and COVID-19 patients, an alternative agent should be considered rather than interferon- $\alpha$ therapy; (2) COVID-19 patients with high risk of severe acute HCV should consider for an appropriate antiviral therapy on case-by-case basis under the full consultation; and (3) COVID-19 patients with resolved HBV infection, receiving corticosteroids, tocilizumab, or other immunosuppressant agents should be considered for appropriate antiviral therapy to prevent viral reactivation under full consultation	(1) Without COVID-19, the patients should continue the HBV or HCV medications in accordance to general guidelines; and (2) in COVID-19 patients, initiation of HBV or HCV medication should be deferred until full recovery from COVID-19 or on case-by-case basis under the full consultation	Use of telemedicine for patients of on-going chronic HBV or HCV treatment without COVID-19
Autoimmune hepatitis	(1) Immunocompromised patients on corticosteroid treatment during COVID-19 requires respiratory support; And (2) patients on respiratory support may be considered for addition of, or conversion to, dexamethasone treatment	(1) Patients on high doses of corticosteroid may show more susceptibility to SARS-CoV-2 infection or severe COVID-19; (2) Low doses may be considered under special circumstances ( <i>e.g.</i> , drug-induced lymphopenia, or bacterial/fungal superinfection with severe COVID-19) under consultation with specialist; (3) or may consider budesonide as an alternative first line agent in patient without cirrhosis to induce remission who have a flare of autoimmune hepatitis	Immunocompromised patients with COVID-19 may be considered for dosing of corticosteroid, sufficient for adrenal insufficiency	All patients should receive vaccination of <i>Streptococcus pneumoniae</i> and influenza
Alcohol-related liver hepatitis	Alcohol-induced severe hepatitis patients on corticosteroid treatment with COVID-19 require respiratory support	Not well known	Not well known	Increased probability of higher alcohol consumption during social distancing, so, preemptive strategies including patient outreach and telephone alcohol liaison, should be considered
Cirrhosis	(1) Cirrhotic patients with COVID-19 should be considered for early hospitalization; and (2) to avoid admission and to prevent decompensation, guidelines on prophylaxis of spontaneous bacterial peritonitis, gastrointestinal hemorrhage and hepatic encephalopathy should be followed	Vasoconstriction therapy should be considered with great caution for critically ill cirrhotic patients with COVID-19	Cirrhotic patients are vulnerable to both SARS-CoV-2 infection and altered standards of patient care during pandemic. Thus, the best efforts should be made for care of cirrhotic patients according to general guidelines	All patients should receive vaccination of <i>Streptococcus pneumoniae</i> and influenza
Hepatocellular carcinoma	Specific risk of HCC patients with COVID-19 remains undefined	In COVID-19 patients, initiation of HBV or HCV medication should be deferred until full recovery from COVID-19 or on case-by-case basis under the full consultation	Full HCC surveillance should resume under specific circumstances	Consider virtual patient visits to discuss diagnosis and management of HCC and other liver tumors
Liver	Patients on the liver transplant	Precautions should be followed to make	Not well known	Patients should

transplant candidates	waiting list with decompensated cirrhosis are at high risk of severe COVID-19 and death following SARS-CoV-2 infection	COVID-19 free liver transplantation process		avoid attending in-person community recovery support meetings, such as Alcoholics Anonymous, and provide alternative telephone or online resources
Liver transplant recipients	Early admission should be considered for all liver transplant recipients who develop COVID-19	Drug levels of calcineurin inhibitors and mechanistic target of rapamycin inhibitors should be closely monitored on administration with COVID-19 medications, particularly hydroxychloroquine, protease inhibitors or new trial drugs for COVID-19	Reduction of immunosuppressant dosing may be considered under special circumstances ( <i>e.g.</i> , drug-induced lymphopenia, or bacterial/fungal superinfection with severe COVID-19) under consultation with specialist	All patients should receive vaccination of <i>Streptococcus pneumoniae</i> and influenza

ACE: Angiotensin-converting enzyme; AR: Adrenoreceptor; COVID-19: Coronavirus disease 2019; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma. HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus type 2.

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