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**Hepatic manifestations of coronavirus disease 2019 infection: Clinical and laboratory perspective**

Hanif FM *et al*. Liver in COVID-19 disease

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**Abstract**

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become a global challenge of unprecedented nature since December 2019. Although most patients with COVID-19 exhibit mild clinical manifestations and upper respiratory tract involvement, in approximately 5%-10% of patients, the disease is severe and involves multiple organs, leading to multi-organ dysfunction and failure. The liver and gastrointestinal tract are also frequently involved in COVID-19. In the context of liver involvement in patients with COVID-19, many key aspects need to be addressed in both native and transplanted organs. This review focuses on the clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 with no prior liver disease, patients with pre-existing liver diseases and liver transplant recipients. A brief overview of the history of COVID-19 and etiopathogenesis of the liver injury will also be described as a prelude to better understanding the above aspects.

**Key Words:** COVID-19; Liver injury; SARS-CoV-2; Clinical manifestations; Liver function tests; Cirrhosis

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**Core Tip:** Thenovel coronavirus disease 2019 (COVID-19) has affected the entire globe with devastating consequences on the health and economy of all countries. Primarily a disease of the upper respiratory tract, it may involve multiple organs in severe cases, which are fortunately rare. The liver and gastrointestinal tract are also frequently involved in COVID-19. Involvement of the liver is multifaceted and may be asymptomatic or may lead to acute liver failure. This review article focused on various clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 This will help in creating awareness among the general physicians, gastroenterologists, hepatologists and infectious disease consultants regarding this important complication.

**INTRODUCTION**

During the past 20 years, three major outbreaks by coronaviruses have occurred. These include severe acute respiratory distress syndrome (SARS), Middle East respiratory syndrome and coronavirus disease 2019 (COVID-19)[1]. Among these, COVID-19, caused by SARS coronavirus 2 (SARS-CoV-2) was reported for the first time in Wuhan, China in December 2019, which later spread in pandemic form throughout the world[2]. In patients with COVID-19 infection, upper and lower respiratory tract involvement, *e.g.,* common cold, bronchiolitis, and pneumonia, are the dominant manifestations. Primary clinical symptoms of COVID-19 patients are fever, dry cough, fatigue and myalgia. However, in many cases, SARS-CoV-2 affects other organs such as the heart, gastrointestinal tract, liver and kidneys with organ-specific symptoms (Table 1). Many patients with severe disease may die from multiorgan failure. In this review, we described liver involvement in COVID-19, which can be studied from many aspects. The focus of this review, however, was on clinical and laboratory manifestations of liver disease in COVID-19 patients, in the native healthy liver, native diseased liver and in the transplanted liver.

For this narrative review, we searched the electronic databases of Web of Science, Scopus, Embase, PubMed and Google Scholar. The search terms used were: COVID-19, combined with the following terms; acute liver injury (ALI), acute-on-chronic liver failure (ACLF), chronic liver disease (CLD), cirrhosis of liver, hepatitis, deranged liver function tests (LFTs), liver failure, SARS-CoV-2, angiotensin-converting enzyme 2, hepatocellular carcinoma (HCC), liver transplantation, autoimmune liver disease, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV). The search was carried out within the time frame of January 1, 2020 to May 2022. We found 4758 records and used 85 (mainly original articles or guidelines) for extracting information to be presented in this review.

**PATHOGENESIS OF LIVER INJURY**

COVID-19 causes liver damage that is mostly hepatocellular in nature as demonstrated by increased transaminase levels. It is often asymptomatic and manifests with derangement in liver functions on laboratory testing. COVID-19-induced liver injury is due to a multitude of reasons, which possibly differ from case to case according to various clinical scenarios[1]. Various mechanisms have been proposed including the direct cytopathic effect of the virus itself, immune dysfunction, systemic inflammatory response syndrome, cytokine storm, sepsis, vascular thrombosis, hypoxia and ischemia-reperfusion injury, as shown in Figure 1. Additionally, drug-induced liver injury has also been implicated as a possible secondary mechanism of liver impairment in patients with COVID-19[3].

The entry of SARS-CoV-2 into human host cells with resultant injury is primarily mediated *via* a metalloproteinase enzyme, called angiotensin-converting enzyme 2 (ACE2) receptor, located in various tissues, including the lungs, liver and gastrointestinal tract[4]. The previous RNA-seq data in the Human Protein Atlas database ([www.proteinatlas.org](http://www.proteinatlas.org/)) has demonstrated relatively low expression of ACE2 in the liver that, in all respects, could be considered a potential target. In particular, ACE2 expression is limited to the cholangiocytes of normal hepatic tissue and, to a minimal extent, in the hepatocytes[4]. A low throughput study of ACE2 protein expression in selected cell types of multiple organs showed a low frequency of ACE2 occurrence in cholangiocytes but not in hepatocytes, Kupffer cells and endothelial cells[5]. However, the antibody detection might be subjected to nonspecificity and sensitivity issues. Neither data sources could provide a definitive conclusion of cell type specific expression of the *ACE2* gene in the liver.

Recent advances of single cell technologies allow unbiased profiling of all cell types in given tissues at an unparalleled scale. Chai *et al*[5] performed an unbiased evaluation of cell type specific expression of ACE2 in healthy hepatic tissues employing scRNA-seq data of two independent cohorts. This study revealed significant enrichment of ACE2 expression in cholangiocyte clusters (59.7% of cells) compared to hepatocytes (2.6% of cells) suggesting that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes, and the liver abnormalities of COVID-19 patients may not be due to a direct hepatocyte damage but, probably, to cholangiocyte dysfunction. It is well established that cholangiocytes play an essential role in liver regeneration and immune response; hence, their dysfunction may contribute to liver damage (Figure 2). Overexpression of the ACE2 receptor on hepatocytes has been observed in patients with liver fibrosis/cirrhosis and in cases of hypoxia. This might explain the high probability of liver injury in these populations[6]. Since liver biopsies of COVID-19 patients show focal hepatic necrosis without significant surrounding inflammatory infiltration, this points toward direct viral injury. However, considering high receptor levels in cholangiocytes rather than hepatocytes and as most of the COVID-19 patients manifest with elevated transaminases, the possibility of direct viral attack is less likely[7]. Other possible pathways of virus entry in hepatocytes have also been suggested to play a role in liver involvement in COVID-19 (Figure 3).

Another mechanism potentially associated with hepatic injury is the cytokine storm generated by the coronavirus infection. Excess inflammatory burden and potential immune-mediated damage lead to increased vascular permeability, multiorgan failure and death[1,3]. Similarly, studies have documented a correlation between high levels of interleukins, a group of cytokines, and severity of COVID-19[8].

In addition, COVID-19-related vascular thrombotic complications with consequent hypoxia and shock can lead to liver injury mediated by the ischemia-reperfusion injury mechanism. Ischemia-reperfusion injury involves a biphasic process of ischemia-induced cell injury and reperfusion-induced inflammatory response. Thus, an activated proinflammatory immune cascade due to the aforementioned processes can be a possible mechanism of liver injury in COVID-19 patients[3,6,9].

Finally, studies have also reported variable degrees of hepatotoxicity with medications used in the treatment of COVID-19[10,11]. Hundt *et al*[12] reported the use of medications needed to treat COVID-19 virus (remdesivir, hydroxychloroquine, lopinavir/ritonavir and tocilizumab) as a significant predictor of raised transaminases [> 5 × upper limit of normal (ULN)] during hospitalization for COVID-19. Cai *et al*[13] described lopinavir/ritonavir as a risk factor for liver injury in COVID-19 patients [odds ratio (OR): 4.44; 95% confidence interval: 1.50-13.17]. However, these authors did not report significant risk with the use of antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, herbal medications and interferon.

Muhović *et al*[14] reported severe drug-induced liver injury with tocilizumab in patients previously treated with chloroquine and lopinavir/ritonavir. As interleukin-6 is known to be associated with liver regeneration and metabolism, it is postulated that inhibition of interleukin-6 by tocilizumab may be the potential cause of liver enzyme derangement[11,15]. Hepatotoxicity can be expected in COVID-19 patients as the liver metabolizes nearly all medications used in COVID-19. Several mechanisms, like upregulation of ACE2 receptors and downregulation of cytochrome p450, sensitize the hepatocytes to the SARS-CoV-2 virus or therapeutic agents. While on the other hand, the pharmacological features of medications may increase susceptibility to liver injury[11].

In summary, the progression of COVID-19 from a mild to severe form is associated with a dysregulated immune response, which leads to uncontrolled viral replication and cellular damage, thus further exacerbating the immune-mediated damage, which includes liver damage[16].

**CLINICAL MANIFESTATIONS**

The SARS-CoV-2 genomic sequence has shown similarity with the SARS coronavirus and Middle East respiratory syndrome coronavirus. Like these viruses, respiratory symptoms along with gastrointestinal and liver involvement have been reported in SARS-CoV-2[17]. Clinical manifestations in COVID-19 infected patients with no previous liver comorbidities may range from asymptomatic liver function abnormalities to liver failure, as shown in Table 1[1,18].

**ABNORMAL LIVER FUNCTIONS**

The reported prevalence of liver injury in COVID-19 varies widely from 10.5% to 58.0% depending on many factors[4,19]. Various studies have reported a slight derangement of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin levels[19,20]. The reported figures of complications in COVID-19 are slightly lower as compared to SARS-CoV and Middle East respiratory syndrome-CoV infections, as shown in Table 2. A systemic review reported a 15.0% elevation of AST and ALT, while a 16.7% elevation of bilirubin was reported[21]. Similarly, a meta-analysis pooled 13251 COVID-19 patients and reported a mild decrease in albumin in 39.8% cases, with a mild increase in AST in 22.8% and ALT levels in 20.6%[19]. Parohan *et al*[22] reported older age, male sex, obesity and underlying liver disease as commonly associated risk factors for deranged LFTs.

Furthermore, the extent of liver enzyme derangement has been associated with the severity of COVID-19 infection and its prognosis. Marjot *et al*[23] and Wang *et al*[24] reported higher levels of AST in intensive care unit (ICU) admitted COVID-19 patients. Similarly, Guan *et al*[25] reported 18.2% liver enzyme derangement in non-severe disease as compared to 39.4% with severe disease in 1099 Chinese patients affected by COVID-19 infection. The authors also described higher bilirubin, ALT and AST levels in COVID-19 patients that had either passed away or required ICU admission and/or the need for mechanical ventilation as compared to those patients who did not[25].

Different studies have reported different prognoses of deranged LFTs in COVID-19 patients. Moreover, different studies have used different definitions of liver injury. Ding *et al*[26] labeled liver injury as a 3 × ULN increase in ALT or AST or 2 × ULN increase in total bilirubin, direct bilirubin or alkaline phosphatase. The authors documented ALI in 0.5% of the COVID-19 patients without underlying liver disease. In addition, all patients had concomitant debilitating conditions like acute respiratory distress syndrome, septic shock, kidney injury, *etc*. Hajifathalian *et al*[27] defined ALI as elevation of any parameter of a liver biochemistry panel and demonstrated a higher risk of ICU admission and death in patients with ALI. Phipps *et al*[28] retrospectively studied a large cohort of in-hospital patients based on raised ALT levels, graded liver injury into no/mild (< 2 × ULN), moderate (2-5 × ULN) or severe (> 5 × ULN) forms. Although only 6.4% of the study population developed severe injury, it was significantly associated with severe clinical outcomes including death. The authors also proposed that severe liver injury can be used as a prognostic factor in hospitalized patients. Considering the association of deranged LFTs with disease severity and prognosis, Tian and Ye[17] suggested that changes in LFTs should be vigilantly monitored for early identification and management.

Although, the majority of studies have reported higher levels of liver enzymes with the severity of COVID-19, a few case reports also documented liver failure in patients without underlying liver disease. Gurala *et al*[18] and Weber *et al*[29] documented acute liver failure in patients without comorbidities and presenting with worsening pulmonary symptoms. However, Orandi *et al*[30] reported acute liver failure documented by replicating SARS-COV-2 RNA in hepatocytes in a young female with COVID-19 presenting with non-respiratory symptoms. Moreover, Busani *et al*[31] reported two fatal cases of acute liver failure in patients with COVID-19 secondary to herpes simplex virus 1 infection. Both patients were treated with tocilizumab.

The resolution of liver injury post-COVID-19 hospitalization is not well studied. A large retrospective study demonstrated persistent deranged LFTs post-discharge in 31.7% of the study population. Thus, it was suggested that recovery from liver injury after resolution of COVID-19 symptoms could be delayed[26]. Hence, the European Association for the Study of the Liver (EASL) position paper recommends monitoring LFTs not only during hospitalization but also post-discharge in COVID-19 patients with persistent deranged laboratory parameters[32].

**CHRONIC LIVER DISEASE**

CLD, an immunocompromised state, makes the patient susceptible to various diseases including COVID-19 virus[4]. The reported prevalence of CLD amongst COVID-19 patients ranges between 2%-11%[23]. Studies have reported contradictory outcomes for CLD patients with COVID-19. Some have documented higher mortality rates while others negated these findings.

An international registry study between March 2020 and July 2020 documented 745 CLD patients from 29 countries infected with COVID-19 virus. Of the total study population, 386 (51.8%) had cirrhosis, 345 were hospitalized, 108 required ICU admission, and 71 required mechanical ventilation. Among these, 123 (32%) cirrhotic patients died mainly due to pulmonary complications (64%). Moreover, in comparison with non-cirrhotic CLD patients, multivariate analysis documented age, higher Child-Turcotte-Pugh (CTP) score and ALD as significant prognostic factors. Additionally, increased morbidity and mortality were observed with an incremental increase in CTP score[33]. Similarly, a preliminary report of 152 CLD patients documented 39.8% mortality in patients with cirrhosis with CTP B and CTP C scores serving as significant predictors of mortality (*P* = 0.03 and < 0.001, respectively)[34].

A large National COVID Cohort Collaborative dataset study reported 220727 COVID-19 patients with CLD. Among which, 8941 were patients with cirrhosis, out of which, 8.8% required mechanical ventilation, while 8.9% of patients died at 30 d. In contrast, amongst 29446 non-cirrhotic patients, 2.0% required mechanical ventilation while 30 d mortality was documented in 1.7% of patients. The multivariate analysis documented higher odds of mortality among patients with cirrhosis compared to patients without cirrhosis with COVID-19 (adjusted hazard ratio: 3.31)[35]. However, a pooled analysis of six studies documented no significant association between the severity of COVID-19 and death in patients with CLD[36].

Similarly, in a nationwide Swedish cohort, a nonsignificant association was documented between mortality and COVID-19 in CLD patients. In addition, the presence or absence of cirrhosis did not have an impact on this association. However, the authors did document a slightly higher risk of hospitalization and development of severe COVID-19 in CLD patients as compared to matched controls (adjusted hazard ratio: 1.08 and 1.23, respectively)[37].

ALI at the admission of COVID-19-affected patients was documented in 14 (32.6%) patients, while (39.5%) developed ALI during the hospital stay. Acute decompensation was reported in 9.1%, while 11.6% developed acute-on-chronic liver failure. Further analysis documented higher mortality and complications (liver-related and overall) in decompensated cirrhotic patients with COVID-19. In non-cirrhotic patients with liver injury there was a higher propensity of ICU admission, but the recovery, hospital stay and mortality were comparable to those without liver injury[38]. In another study of 179 patients with cirrhosis with acute decompensation, 50% developed acute-on-chronic liver failure, and this complication was associated with a higher rate of mortality (*P <* 0.001)[33]. Thus, it may be concluded that not only the underlying liver disease but also the existing liver reserve may predict a patient’s outcomes with COVID-19 infection. Hence, active and dynamic management of these patients should be done considering their high associated risk of morbidity and mortality.

Recognizing high-risk groups and those predisposed to the severe clinical courses are of utmost importance to plan preventive strategies and management. A limited number of studies have documented the variable impact of etiology on the severity of COVID-19 infection[37].

In a nationwide cohort of 42320 CLD patients, underlying etiology was not associated with a significant risk of hospitalization or development of severe COVID-19. In this study, 32.7% had viral hepatitis, 15.0% had NAFLD, 2.1% had ALD, and 44.0% had other etiologies. However, an international registry of 745 CLD patients with COVID-19 documented ALD as a predictor of mortality (*P* = 0.04). However, no significant association was documented with NAFLD, hepatitis B and C[33]. Similarly, a United States multicenter study also documented ALD along with decompensated cirrhosis and HCC as a liver-specific predictor of mortality in COVID-19 patients[39]. The authors suggested that the added cytokine storm of the SARS-CoV-2 virus to the already heightened inflammatory state in alcoholics could be the cause of the detrimental outcomes. Moreover, increased use of alcohol due to economic and social burdens during the COVID-19 era could be a contributing factor[39,40]. Wang *et al*[41], in a large case-control study, documented that patients with CLD secondary to alcohol-related liver damage and alcoholic liver cirrhosis have odds of 7.05 and 7.00, respectively, of developing COVID-19.

Viral hepatitides, mainly hepatitis B and C, have infected millions of people worldwide. A case-control study of electronic health records documented that adjusted odds of developing COVID-19 were 8.93 and 4.37 with chronic hepatitis C and chronic hepatitis B, respectively[41].

A higher prevalence of hepatitis B has been reported in COVID-19 patients in Asian studies, ranging from 0.8%-6.3%, while a lower prevalence rate of 0.1% has been reported in a United States-based study[41-43]. Although, the pathogenesis is unclear, studies have documented the variable associations of HBV on clinical outcomes of patients with COVID-19. In 105 COVID-19 and HBV co-infected patients, Zhang *et al*[44] reported 23 cases of HBV-related CLD patients with COVID-19. Among which, two patients with cirrhosis (8.7%) became critically ill. Yet, no mortality was reported.

Chen *et al*[45] retrospectively analyzed 20 HBV-positive patients amongst 326 COVID-19 patients. Authors reported three deaths in hepatitis B surface antigen-negative patients, while no patients in the hepatitis B surface antigen-positive group died. Moreover, no statistically significant difference was noted in LFTs, hospital stay and disease severity[45]. In another retrospective analysis of 5639 chronic hepatitis B patients with COVID-19, the authors concluded that current or past hepatitis B infection is not associated with increased mortality[46]. However, another Chinese study documented higher COVID-19 severity and mortality in HBV-infected patients[47]. Zou *et al*[48] observed liver injury as a significant cause of disease severity and mortality in chronic hepatitis B patients with COVID-19.

A chronic immunosuppressed state potentiates the risk of HBV reactivation in patients with chronic or resolved hepatitis B. Moreover, HBV reactivation is associated with high morbidity and mortality[49]. Few case reports have documented HBV reactivation in patients with COVID-19. Aldhaleei *et al*[50] reported a case of HBV reactivation in a patient with COVID-19 presenting with an altered level of consciousness and deranged LFTs. However, high HBV DNA levels were interpreted as reactivation without prior DNA levels.

It is postulated that the immunosuppressive therapy used in COVID-19 can attenuate the host immunity against HBV, thus leading to increased HBV replication. Moreover, with the later withdrawal of immunosuppressants, the reconstituted immune system might mount a heightened immune response against HBV antigen-laden hepatocytes, thus leading to liver injury[51]. Sagnelli *et al*[52] reported HBV reactivation in a patient with COVID-19 pneumonia 7 d after stopping corticosteroid therapy. Wu *et al*[53] also documented HBV reactivation in a COVID-19 patient on entecavir treated with recombinant interferon-alpha-2b, lopinavir/ritonavir and subsequently with methylprednisolone. However, Yip *et al*[46] did not document HBV reactivation in 10 patients on no treatment treated with corticosteroids for severe COVID-19. Nevertheless, the detrimental risk of hepatitis B reactivation persists with COVID-19 treatment. Thus, the Asian Pacific Association for the Study of the Liver (APASL) COVID-19 Taskforce recommends screening all COVID-19 patients for hepatitis B surface antigen. Moreover, antiviral treatment should be prescribed to hepatitis B-positive patients especially treated with interleukin-6 monoclonal antibodies or other immunosuppressive therapy[3].

The prevalence of HCV in COVID-19 is not well reported. A case series from the United States of 5700 hospitalized patients with COVID-19 reported < 0.1% incidence of HCV infection[54]. However, a retrospective single-center study reported a higher incidence of 4.1%. In the latter study, the authors also reported HCV, age, D-dimers and serum ferritin as predictors of in-hospital mortality[55]. The authors suggested that vascular endothelial dysfunction, elevated cytokine levels and the role of overexpressed transmembrane protease serine 2 could be the potential cause of morbidity and mortality of COVID-19 in HCV-infected patients.

Lensen *et al*[56] reported reactivation of HCV leading to patient mortality in an elderly patient following COVID-19 vaccination. However, the patient had multiple comorbidities along with HBV and HCV co-infection-related cirrhosis[56]. Although, a large veteran database study of HCV-positive patients documented a higher rate of hospitalization, the rates of ICU admission and mortality were similar to negative patients. Moreover, the rate of hospitalization increased with higher fibrosis[57]. The American Association for the Study of Liver Diseases recommends continuing therapy for HBV and HCV if patients are already on treatment when infected with COVID-19. In addition, HBV treatment should be considered in patients with a risk of HBV flare[58].

With the increasing prevalence of NAFLD, it is not surprising that a higher incidence of NAFLD is noted among COVID-19 patients. The prevalence varies from 30% to 55%. The range may be an overestimate, as most of the studies were concentrated on hospitalized patients[59]. NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease) is associated with factors like diabetes and obesity, which are known to aggravate COVID-19 severity[60]. An electronic health records-based study reported that CLD patients have an increased risk of acquiring COVID-19 with the highest odds in patients with NAFLD (adjusted OR: 13.11), nonalcoholic cirrhosis (adjusted OR: 11.5) and chronic hepatitis C (adjusted OR: 8.7)[41]. A systemic review and meta-analysis of 14 studies reported an increased risk of COVID-19 severity and ICU admission in patients with NAFLD. However, no difference in mortality was observed in comparison to non-NAFLD patients[61]. Similar findings have also been reported in other studies[60,62,63]. However, a single-center study from India reported a nonsignificant difference in hospital stay and mortality in COVID-19 patients with or without NAFLD[64]. Similarly, Madan *et al*[65] also documented no association of fatty liver with COVID-19 morbidity and mortality.

Thromboembolism risk is high in COVID-19 patients and is associated with high mortality[66]. A prospective cohort documented a statistically significant association of NAFLD with the development of pulmonary thrombosis in COVID-19 patients. Increased levels of proinflammatory proteins and cytokines may be the contributing factor in this debilitating disease process[59].

Like hepatitis B and C, the underlying liver fibrosis plays an important role in COVID-19 outcomes. Targher *et al*[67] determined the impact of non-invasive fibrosis scores, FIB-4 or NAFLD fibrosis score on COVID-19 severity. After adjustment for sex, obesity and diabetes, the authors documented a significant association of severe COVID-19 with high/intermediate FIB-4 or NAFLD fibrosis score[67].

Regarding autoimmune hepatitis (AIH), a database study of three large registries with 70 AIH patients documented no differences in rates of hospitalization, ICU admission and death between patients with and without AIH-related CLD. However, a higher risk of mortality was observed in the AIH cohort with CTP B and C. Interestingly, the use of immunosuppression was not associated with mortality[68]. Another case series reported uneventful clinical course of 10 AIH patients on immunosuppression[69].

Thus, liver disease etiology may play a role, but the underlying liver fibrosis is the cornerstone to determining susceptibility to COVID-19 and its outcomes. Furthermore, no studies have documented increased predisposition to COVID-19 infection or adverse outcomes in patients with CLD secondary to AIH, primary biliary cholangitis or primary sclerosing cholangitis[70].

**HEPATOCELLULAR CARCINOMA**

Studies amongst oncological patients have reported a higher risk of acquiring COVID-19 infection along with a greater risk of morbidity and mortality. Moreover, recent cancer treatment may also worsen the outcomes[71,72]. The reported mortality in cancer patients with COVID-19 ranges from 11% to 28%. Nevertheless, concomitant comorbidities, functional class and cancer activity status are associated with a poorer prognosis. Hence, the immunodeficient status of cancer patients determines clinical outcomes[72].

It is estimated that more than 70% of HCC patients have underlying CLD or cirrhosis[73]. It has been shown that the SARS-CoV-2 virus can aggravate liver damage in patients with underlying disease, thus making patients with HCC more susceptible to COVID-19-related morbid complications[74]. Yet, data on the outcomes of HCC with COVID-19 is scarce. A large United States-based multicenter study involving CLD patients infected with COVID-19 reported 52% mortality among patients with HCC (*n* = 22). Additionally, the authors concluded that decompensated cirrhosis, ALD and HCC were independent liver-related risk factors of mortality[75].

HCC is an aggressive tumor with a tumor volume doubling time of nearly 70 to 120 d[76]. A monthly ultrasound for 6 mo for HCC surveillance is thus recommended under normal circumstances. However, during the pandemic, the delay of 2-3 mo in surveillance has been considered acceptable[58,77]. Inchingolo *et al*[78] suggested prioritizing patients who are at high risk of incidence and/or recurrence of HCC and patients eligible for liver transplantation.

Since the majority of resources were diverted in managing and treating COVID-19 patients during the COVID-19 pandemic, various hepatological associations and societies drafted recommendations for the management of patients with HCC in these times[58,77,79].

Regarding the treatment of HCC, hepatology societies have recommended tailoring the treatment on a case-by-case basis. The American Association for the Study of Liver Diseases proposes that during the COVID-19 pandemic, HCC treatment with curative intent should not be delayed[58]. In addition, APASL recommends postponing surgical treatment and suspending vascular intervention if there is high risk of decompensation or comorbidities since it increases the risk of severe COVID-19. Moreover, ablation therapy could be considered an alternative therapy during this time[77]. Like APASL, EASL guidelines recommend postponing locoregional therapies as these are mostly for the purpose of cytoreduction[77,79]. Similarly, radiation therapy should only be considered in case of functional or life-threatening situations[77].

Although, APASL suggests a preference for oral tyrosine kinase inhibitors over intravenous therapy, EASL proposes dose reduction based on the individual patients[77,79]. Moreover, EASL recommends temporary withdrawal of immune-checkpoint inhibitor therapy in patients with HCC[79].

In general, in all patients with HCC, it is of utmost importance to screen patients for the SARS-CoV-2 virus prior to diagnosis or intervention. Assessment and/or treatment should be postponed until noninfective status is achieved in COVID-19-positive patients. Limited staff with protective gear along with hygienic measures should always be followed during each intervention to curtail the spread of the novel viruses[77].

**SOLID ORGAN TRANSPLANTS**

Globally, solid organ transplantation has been profoundly affected by the COVID-19 pandemic, resulting in decreased rates of organ procurement and transplantation[80,81]. Liver is the second most common solid organ transplanted in the world after kidney[82]. Although prolonged immunocompromised status and post-transplant associated comorbidities theoretically increase the susceptibility to COVID-19 severity, the data on liver transplant recipients is scarce. Contradictory to the initial reports, a recent multicenter and large database studies have reported similar outcomes in transplanted and non-transplanted COVID-19 populations[80,83,84]. The studies were performed on only hospitalized patients, so it could not be concluded that transplanted patients are prone to be hospitalized due to COVID-19[80]. Centers for Medicare and Medicaid Services has labelled transplant surgery in Tier 3b that is not to be postponed[85]. Owing to diverted and limited resources amidst the pandemic, hepatology societies have restricted liver transplants to urgent transplants only. Table 3 describes a summary of recommendations from various societies regarding liver transplantation activities during the COVID-19 pandemic.

**LIMITATIONS**

There are certain limitations to this study. We addressed the clinical presentation and laboratory abnormalities primarily, and pathogenesis and particularly pathology were not described. We also did not cover management and prognostic aspects of this infection in detail. New variants of COVID-19 virus were also not discussed nor the vaccination of patients with liver diseases.

**FUTURE DIRECTIONS**

There is a need for international collaboration for carrying out basic research for better understanding the pathogenesis of hepatobiliary injury in COVID-19 as it can pave the path for the development of targeted therapy and personalized medicine. The role of direct virus infection of the liver with consequent cytopathic effects *vs* indirect liver injury needs to be explored further. Expression profiles of various SARS-CoV-2 entry receptors vary across different *in* *vitro* and *in* *vivo* liver models; however, evidence of specific viral hepatotropism of SARS-CoV-2 is inadequate. Abnormal LFT values are common in patients with COVID-19; both the prognostic significance of these derangements and whether they are directly attributable to hepatic SARS-CoV-2 infection remain to be explored in future focused research.

**CONCLUSION**

In conclusion, liver involvement is common in patients with COVID-19 infection, particularly in those with moderate to severe disease. It is mostly asymptomatic or mild in nature. Conversely, patients with pre-existing liver disease are prone to serious COVID-19. Data on the impact of COVID-19 infection on patients with pre-existing diseases or liver transplants is either conflicting or scarce. Hence, large collaborative studies with prolonged follow-up are needed to fully comprehend the impact of this challenging infection on patients with liver diseases.

**REFERENCES**

1 **Perisetti A**, Gajendran M, Mann R, Elhanafi S, Goyal H. COVID-19 extrapulmonary illness-special gastrointestinal and hepatic considerations. *Dis Mon* 2020; **66**: 101064 [PMID: 32807535 DOI: 10.1016/j.disamonth.2020.101064]

2 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

3 **APASL Covid-19 Task Force.**, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int* 2020; **14**: 415-428 [PMID: 32447721 DOI: 10.1007/s12072-020-10054-w]

4 **Napodano C**, Pocino K, Stefanile A, Marino M, Miele L, Gulli F, Basile V, Pandolfi F, Gasbarrini A, Rapaccini GL, Basile U. COVID-19 and hepatic involvement: The liver as a main actor of the pandemic novel. *Scand J Immunol* 2021; **93**: e12977 [PMID: 32931622 DOI: 10.1111/sji.12977]

5 **Xiaoqiang Chai,** Longfei Hu, Yan Zhang, Weiyu Han, Zhou Lu, Aiwu Ke, Jian Zhou, Guoming Shi, Nan Fang, Jia Fan, Jiabin Cai, Jue Fan, Fei Lan. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. BioRxiv, 2020 [DOI: 10.1101/2020.02.03.931766]

6 **Ye Q**, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020; **319**: G245-G252 [PMID: 32639848 DOI: 10.1152/ajpgi.00148.2020]

7 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

8 **Zhan K**, Liao S, Li J, Bai Y, Lv L, Yu K, Qiu L, Li C, Yuan G, Zhang A, Mei Z. Risk factors in patients with COVID-19 developing severe liver injury during hospitalisation. *Gut* 2021; **70**: 628-629 [PMID: 32571973 DOI: 10.1136/gutjnl-2020-321913]

9 **Li D**, Ding X, Xie M, Tian D, Xia L. COVID-19-associated liver injury: from bedside to bench. *J Gastroenterol* 2021; **56**: 218-230 [PMID: 33527211 DOI: 10.1007/s00535-021-01760-9]

10 **Licata A**, Minissale MG, Distefano M, Montalto G. Liver injury, SARS-COV-2 infection and COVID-19: What physicians should really know? *GastroHep* 2021; **3**: 121-130 [PMID: 34149320 DOI: 10.1002/ygh2.455]

11 **Sodeifian F**, Seyedalhosseini ZS, Kian N, Eftekhari M, Najari S, Mirsaeidi M, Farsi Y, Nasiri MJ. Drug-Induced Liver Injury in COVID-19 Patients: A Systematic Review. *Front Med (Lausanne)* 2021; **8**: 731436 [PMID: 34616757 DOI: 10.3389/fmed.2021.731436]

12 **Hundt MA**, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology* 2020; **72**: 1169-1176 [PMID: 32725890 DOI: 10.1002/hep.31487]

13 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]

14 **Muhović D**, Bojović J, Bulatović A, Vukčević B, Ratković M, Lazović R, Smolović B. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int* 2020; **40**: 1901-1905 [PMID: 32478465 DOI: 10.1111/Liv.14516]

15 **Schmidt-Arras D**, Rose-John S. IL-6 pathway in the liver: From physiopathology to therapy. *J Hepatol* 2016; **64**: 1403-1415 [PMID: 26867490 DOI: 10.1016/j.jhep.2016.02.004]

16 **Saviano A**, Wrensch F, Ghany MG, Baumert TF. Liver Disease and Coronavirus Disease 2019: From Pathogenesis to Clinical Care. *Hepatology* 2021; **74**: 1088-1100 [PMID: 33332624 DOI: 10.1002/hep.31684]

17 **Tian D**, Ye Q. Hepatic complications of COVID-19 and its treatment. *J Med Virol* 2020; **92**: 1818-1824 [PMID: 32437004 DOI: 10.1002/jmv.26036]

18 **Gurala D**, Al Moussawi H, Philipose J, Abergel JR. Acute Liver Failure in a COVID-19 Patient Without any Preexisting Liver Disease. *Cureus* 2020; **12**: e10045 [PMID: 32983735 DOI: 10.7759/cureus.10045]

19 **Zarifian A**, Zamiri Bidary M, Arekhi S, Rafiee M, Gholamalizadeh H, Amiriani A, Ghaderi MS, Khadem-Rezaiyan M, Amini M, Ganji A. Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis. *J Med Virol* 2021; **93**: 336-350 [PMID: 32681674 DOI: 10.1002/jmv.26314]

20 **Musa S**. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab J Gastroenterol* 2020; **21**: 3-8 [PMID: 32253172 DOI: 10.1016/j.ajg.2020.03.002]

21 **Wang X**, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liver: An Update. *Front Med (Lausanne)* 2021; **8**: 651658 [PMID: 34646834 DOI: 10.3389/fmed.2021.651658]

22 **Parohan M**, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. *Hepatol Res* 2020; **50**: 924-935 [PMID: 32386449 DOI: 10.1111/hepr.13510]

23 **Marjot T**, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: 33692570 DOI: 10.1038/s41575-021-00426-4]

24 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

25 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

26 **Ding ZY**, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B; Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol* 2021; **74**: 1295-1302 [PMID: 33347952 DOI: 10.1016/j.jhep.2020.12.012]

27 **Hajifathalian K**, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, Sharaiha RZ; WCM-GI research group∗. Gastrointestinal and Hepatic Manifestations of 2019 Novel Coronavirus Disease in a Large Cohort of Infected Patients From New York: Clinical Implications. *Gastroenterology* 2020; **159**: 1137-1140.e2 [PMID: 32389667 DOI: 10.1053/j.gastro.2020.05.010]

28 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]

29 **Weber S**, Mayerle J, Irlbeck M, Gerbes AL. Severe liver failure during SARS-CoV-2 infection. *Gut* 2020; **69**: 1365-1367 [PMID: 32327526 DOI: 10.1136/gutjnl-2020-321350]

30 **Orandi BJ,** Li G, Dhall D, Bajpai P, Manne U, Arora N, Lu A, Coronado AC, Kassel R, Pinninti S, Lewis CE, Chapleau C, Locke JE, Gutierrez S, Luz H. Acute Liver Failure in a Healthy Young Female With COVID-19. *JPGN Reports* 2021; **2**: e108 [DOI: 10.1097/PG9.0000000000000108]

31 **Busani S**, Bedini A, Biagioni E, Serio L, Tonelli R, Meschiari M, Franceschini E, Guaraldi G, Cossarizza A, Clini E, Maiorana A, Gennari W, De Maria N, Luppi M, Mussini C, Girardis M; Modena Covid-19 Working Group (MoCo19). Two Fatal Cases of Acute Liver Failure Due to HSV-1 Infection in COVID-19 Patients Following Immunomodulatory Therapies. *Clin Infect Dis* 2021; **73**: e252-e255 [PMID: 32840571 DOI: 10.1093/cid/ciaa1246]

32 **Marjot T**, Eberhardt CS, Boettler T, Belli LS, Berenguer M, Buti M, Jalan R, Mondelli MU, Moreau R, Shouval D, Berg T, Cornberg M. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper. *J Hepatol* 2022; **77**: 1161-1197 [PMID: 35868584 DOI: 10.1016/j.jhep.2022.07.008]

33 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]

34 **Moon AM**, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, Genescà J, Gill US, James TW, Jones PD, Marshall A, Mells G, Perumalswami PV, Qi X, Su F, Ufere NN, Barnes E, Barritt AS, Marjot T. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. *J Hepatol* 2020; **73**: 705-708 [PMID: 32446714 DOI: 10.1016/j.jhep.2020.05.013]

35 **Ge J**, Pletcher MJ, Lai JC; N3C Consortium. Outcomes of SARS-CoV-2 Infection in Patients With Chronic Liver Disease and Cirrhosis: A National COVID Cohort Collaborative Study. *Gastroenterology* 2021; **161**: 1487-1501.e5 [PMID: 34284037 DOI: 10.1053/j.gastro.2021.07.010]

36 **Lippi G**, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 114-115 [PMID: 32282549 DOI: 10.1097/MEG.0000000000001742]

37 **Simon TG**, Hagström H, Sharma R, Söderling J, Roelstraete B, Larsson E, Ludvigsson JF. Risk of severe COVID-19 and mortality in patients with established chronic liver disease: a nationwide matched cohort study. *BMC Gastroenterol* 2021; **21**: 439 [PMID: 34814851 DOI: 10.1186/s12876-021-02017-8]

38 **Sarin SK**, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, Hwang J, Qi X, Cua IH, Suh JI, Park JG, Putcharoen O, Kaewdech A, Piratvisuth T, Treeprasertsuk S, Park S, Wejnaruemarn S, Payawal DA, Baatarkhuu O, Ahn SH, Yeo CD, Alonzo UR, Chinbayar T, Loho IM, Yokosuka O, Jafri W, Tan S, Soo LI, Tanwandee T, Gani R, Anand L, Esmail ES, Khalaf M, Alam S, Lin CY, Chuang WL, Soin AS, Garg HK, Kalista K, Batsukh B, Purnomo HD, Dara VP, Rathi P, Al Mahtab M, Shukla A, Sharma MK, Omata M; APASL COVID Task Force, APASL COVID Liver Injury Spectrum Study (APCOLIS Study-NCT 04345640). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int* 2020; **14**: 690-700 [PMID: 32623632 DOI: 10.1007/s12072-020-10072-8]

39 **Kim D**, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, Perumalswami P, Roytman M, Li M, Vogel AS, Catana AM, Wegermann K, Carr RM, Aloman C, Chen VL, Rabiee A, Sadowski B, Nguyen V, Dunn W, Chavin KD, Zhou K, Lizaola-Mayo B, Moghe A, Debes J, Lee TH, Branch AD, Viveiros K, Chan W, Chascsa DM, Kwo P, Dhanasekaran R. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021; **19**: 1469-1479.e19 [PMID: 32950749 DOI: 10.1016/j.cgh.2020.09.027]

40 **Moon AM**, Curtis B, Mandrekar P, Singal AK, Verna EC, Fix OK. Alcohol-Associated Liver Disease Before and After COVID-19-An Overview and Call for Ongoing Investigation. *Hepatol Commun* 2021; **5**: 1616-1621 [PMID: 34510833 DOI: 10.1002/hep4.1747]

41 **Wang Q**, Davis PB, Xu R. COVID-19 risk, disparities and outcomes in patients with chronic liver disease in the United States. *EClinicalMedicine* 2021; **31**: 100688 [PMID: 33521611 DOI: 10.1016/j.eclinm.2020.100688]

42 **Yip TC**, Gill M, Wong GL, Liu K. Management of hepatitis B virus reactivation due to treatment of COVID-19. *Hepatol Int* 2022; **16**: 257-268 [PMID: 35235148 DOI: 10.1007/s12072-022-10306-x]

43 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

44 **Zhang B**, Huang W, Zhang S. Clinical Features and Outcomes of Coronavirus Disease 2019 (COVID-19) Patients With Chronic Hepatitis B Virus Infection. *Clin Gastroenterol Hepatol* 2020; **18**: 2633-2637 [PMID: 32553905 DOI: 10.1016/j.cgh.2020.06.011]

45 **Chen L**, Huang S, Yang J, Cheng X, Shang Z, Lu H, Cheng J. Clinical characteristics in patients with SARS-CoV-2/HBV co-infection. *J Viral Hepat* 2020; **27**: 1504-1507 [PMID: 32668494 DOI: 10.1111/jvh.13362]

46 **Yip TC**, Wong VW, Lui GC, Chow VC, Tse YK, Hui VW, Liang LY, Chan HL, Hui DS, Wong GL. Current and Past Infections of HBV Do Not Increase Mortality in Patients With COVID-19. *Hepatology* 2021; **74**: 1750-1765 [PMID: 33961298 DOI: 10.1002/hep.31890]

47 **Chen X**, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, Mo P, Yao L, Yang R, Gao S, Gui X, Hou W, Xiong Y, Li J, Zhang Y. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B Virus Co-infection. *Virol Sin* 2020; **35**: 842-845 [PMID: 32839868 DOI: 10.1007/s12250-020-00276-5]

48 **Zou X**, Fang M, Li S, Wu L, Gao B, Gao H, Ran X, Bian Y, Li R, ShanshanYu, Ling J, Li D, Tian D, Huang J. Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. *Clin Gastroenterol Hepatol* 2021; **19**: 597-603 [PMID: 32553907 DOI: 10.1016/j.cgh.2020.06.017]

49 **Myint A**, Tong MJ, Beaven SW. Reactivation of Hepatitis B Virus: A Review of Clinical Guidelines. *Clin Liver Dis (Hoboken)* 2020; **15**: 162-167 [PMID: 32395244 DOI: 10.1002/cld.883]

50 **Aldhaleei WA**, Alnuaimi A, Bhagavathula AS. COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates. *Cureus* 2020; **12**: e8645 [PMID: 32550096 DOI: 10.7759/cureus.8645]

51 **Lau G**, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, Piratvisuth T, Jia JD, Mizokami M, Cheng G, Chen GF, Liu ZW, Baatarkhuu O, Cheng AL, Ng WL, Lau P, Mok T, Chang JM, Hamid S, Dokmeci AK, Gani RA, Payawal DA, Chow P, Park JW, Strasser SI, Mohamed R, Win KM, Tawesak T, Sarin SK, Omata M. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatol Int* 2021; **15**: 1031-1048 [PMID: 34427860 DOI: 10.1007/s12072-021-10239-x]

52 **Sagnelli C**, Montella L, Grimaldi P, Pisaturo M, Alessio L, De Pascalis S, Sagnelli E, Coppola N. COVID-19 as Another Trigger for HBV Reactivation: Clinical Case and Review of Literature. *Pathogens* 2022; **11** [PMID: 35890060 DOI: 10.3390/pathogens11070816]

53 **Wu YF**, Yu WJ, Jiang YH, Chen Y, Zhang B, Zhen RB, Zhang JT, Wang YP, Li Q, Xu F, Shi YJ, Li XP. COVID-19 or treatment associated immunosuppression may trigger hepatitis B virus reactivation: A case report. *World J Clin Cases* 2021; **9**: 5266-5269 [PMID: 34307577 DOI: 10.12998/wjcc.v9.i19.5266]

54 **Dufour JF**, Marjot T, Becchetti C, Tilg H. COVID-19 and liver disease. *Gut* 2022; **71**: 2350-2362 [PMID: 35701093 DOI: 10.1136/gutjnl-2021-326792]

55 **Ronderos D**, Omar AMS, Abbas H, Makker J, Baiomi A, Sun H, Mantri N, Choi Y, Fortuzi K, Shin D, Patel H, Chilimuri S. Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality. *World J Clin Cases* 2021; **9**: 8749-8762 [PMID: 34734053 DOI: 10.12998/wjcc.v9.i29.8749]

56 **Lensen R**, Netea MG, Rosendaal FR. Hepatitis C Virus Reactivation Following COVID-19 Vaccination-A Case Report. *Int Med Case Rep J* 2021; **14**: 573-576 [PMID: 34512037 DOI: 10.2147/IMCRJ.S328482]

57 **Butt AA**, Yan P, Chotani RA, Shaikh OS. Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection. *Liver Int* 2021; **41**: 1824-1831 [PMID: 33534931 DOI: 10.1111/Liv.14804]

58 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]

59 **Vrsaljko N**, Samadan L, Viskovic K, Mehmedović A, Budimir J, Vince A, Papic N. Association of Nonalcoholic Fatty Liver Disease With COVID-19 Severity and Pulmonary Thrombosis: CovidFAT, a Prospective, Observational Cohort Study. *Open Forum Infect Dis* 2022; **9**: ofac073 [PMID: 35287335 DOI: 10.1093/ofid/ofac073]

60 **Asemota J**, Aduli F. The Impact of Nonalcoholic Fatty Liver Disease on the Outcomes of Coronavirus Disease 2019 Infection. *Clin Liver Dis (Hoboken)* 2022; **19**: 29-31 [PMID: 35106147 DOI: 10.1002/cld.1169]

61 **Singh A**, Hussain S, Antony B. Non-alcoholic fatty liver disease and clinical outcomes in patients with COVID-19: A comprehensive systematic review and meta-analysis. *Diabetes Metab Syndr* 2021; **15**: 813-822 [PMID: 33862417 DOI: 10.1016/j.dsx.2021.03.019]

62 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Detrimental effects of metabolic dysfunction-associated fatty liver disease and increased neutrophil-to-lymphocyte ratio on severity of COVID-19. *Diabetes Metab* 2020; **46**: 505-507 [PMID: 32505652 DOI: 10.1016/j.diabet.2020.06.001]

63 **Ghoneim S**, Butt MU, Hamid O, Shah A, Asaad I. The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study. *Metabol Open* 2020; **8**: 100057 [PMID: 32924000 DOI: 10.1016/j.metop.2020.100057]

64 **Nath P**, Kumar R, Mallick B, Das S, Anand A, Panigrahi SC, Duseja A, Acharya SK, Chawla YK, Praharaj DL. Effect of Nonalcoholic Fatty Liver Disease (NAFLD) on COVID-19: A Single-Center Study of 3983 Patients With Review of Literature. *Cureus* 2022; **14**: e26683 [PMID: 35949776 DOI: 10.7759/cureus.26683]

65 **Madan K**, Rastogi R, Bhargava R, Dagar V, Singla V, Sahu A, Singh P, Garg P, Aggarwal B, Singh RK. Is Fatty Liver Associated with Increased Mortality and Morbidity in Coronavirus Disease 2019 (COVID-19) Pneumonia? *J Clin Exp Hepatol* 2022; **12**: 1320-1327 [PMID: 35469129 DOI: 10.1016/j.jceh.2022.04.013]

66 **Malas MB**, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* 2020; **29**: 100639 [PMID: 33251499 DOI: 10.1016/j.eclinm.2020.100639]

67 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut* 2020; **69**: 1545-1547 [PMID: 32414813 DOI: 10.1136/gutjnl-2020-321611]

68 **Marjot T**, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, Baldelli L, Kennedy J, Mercer C, Ozga AK, Casar C, Schramm C; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis, Moon AM, Webb GJ, Lohse AW. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol* 2021; **74**: 1335-1343 [PMID: 33508378 DOI: 10.1016/j.jhep.2021.01.021]

69 **Gerussi A**, Rigamonti C, Elia C, Cazzagon N, Floreani A, Pozzi R, Pozzoni P, Claar E, Pasulo L, Fagiuoli S, Cristoferi L, Carbone M, Invernizzi P. Coronavirus Disease 2019 in Autoimmune Hepatitis: A Lesson From Immunosuppressed Patients. *Hepatol Commun* 2020; **4**: 1257-1262 [PMID: 32838102 DOI: 10.1002/hep4.1557]

70 **Ekpanyapong S**, Bunchorntavakul C, Reddy KR. COVID-19 and the Liver: Lessons Learnt from the EAST and the WEST, A Year Later. *J Viral Hepat* 2022; **29**: 4-20 [PMID: 34352133 DOI: 10.1111/jvh.13590]

71 **Chan SL**, Kudo M. Impacts of COVID-19 on Liver Cancers: During and after the Pandemic. *Liver Cancer* 2020; **9**: 491-502 [PMID: 33078127 DOI: 10.1159/000510765]

72 **Pomej K**, Scheiner B, Hartl L, Balcar L, Meischl T, Mandorfer M, Reiberger T, Müller C, Trauner M, Pinter M. COVID-19 pandemic: Impact on the management of patients with hepatocellular carcinoma at a tertiary care hospital. *PLoS One* 2021; **16**: e0256544 [PMID: 34437610 DOI: 10.1371/journal.pone.0256544]

73 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]

74 **Gupta T**. COVID-19 and liver disease: Are we missing something? *World J Hepatol* 2022; **14**: 479-481 [PMID: 35317182 DOI: 10.4254/wjh.v14.i2.479]

75 **Kukla M,** Skonieczna-Żydecka K, Kotfis K, Maciejewska D, Łoniewski I, Lara LF, Pazgan-Simon M, Stachowska E, Kaczmarczyk M, Koulaouzidis A, Marlicz W. COVID-19, MERS and SARS with Concomitant Liver Injury-Systematic Review of the Existing Literature. *J Clin Med* 2020; **9**: 1420 [PMID: 32403255 DOI: 10.3390/jcm9051420]

76 **Nathani P**, Gopal P, Rich N, Yopp A, Yokoo T, John B, Marrero J, Parikh N, Singal AG. Hepatocellular carcinoma tumour volume doubling time: a systematic review and meta-analysis. *Gut* 2021; **70**: 401-407 [PMID: 32398224 DOI: 10.1136/gutjnl-2020-321040]

77 **Shiina S**, Gani RA, Yokosuka O, Maruyama H, Nagamatsu H, Payawal DA, Dokmeci AK, Lesmana LA, Tanwandee T, Lau G, Sarin SK, Omata M. APASL practical recommendations for the management of hepatocellular carcinoma in the era of COVID-19. *Hepatol Int* 2020; **14**: 920-929 [PMID: 33174159 DOI: 10.1007/s12072-020-10103-4]

78 **Inchingolo R**, Acquafredda F, Tedeschi M, Laera L, Surico G, Surgo A, Fiorentino A, Spiliopoulos S, de'Angelis N, Memeo R. Worldwide management of hepatocellular carcinoma during the COVID-19 pandemic. *World J Gastroenterol* 2021; **27**: 3780-3789 [PMID: 34321843 DOI: 10.3748/wjg.v27.i25.3780]

79 **Boettler T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: 32289115 DOI: 10.1016/j.jhepr.2020.100113]

80 **Pereira MR**, Arcasoy S, Farr MA, Mohan S, Emond JC, Tsapepas DS, Shi Q, Purpura L, Uhlemann AC, Zucker J, Verna EC. Outcomes of COVID-19 in solid organ transplant recipients: A matched cohort study. *Transpl Infect Dis* 2021; **23**: e13637 [PMID: 33993630 DOI: 10.1111/tid.13637]

81 **Bhatti ABH**, Nazish M, Khan NY, Manan F, Zia HH, Ilyas A, Ishtiaq W, Khan NA. Living Donor Liver Transplantation During the COVID-19 Pandemic: an Evolving Challenge. *J Gastrointest Surg* 2021; **25**: 3092-3098 [PMID: 34131867 DOI: 10.1007/s11605-021-05057-3]

82 **El Kassas M**, Alboraie M, Al Balakosy A, Abdeen N, Afify S, Abdalgaber M, Sherief AF, Madkour A, Abdellah Ahmed M, Eltabbakh M, Salaheldin M, Wifi MN. Liver transplantation in the era of COVID-19. *Arab J Gastroenterol* 2020; **21**: 69-75 [PMID: 32439237 DOI: 10.1016/j.ajg.2020.04.019]

83 **Chaudhry ZS**, Williams JD, Vahia A, Fadel R, Parraga Acosta T, Prashar R, Shrivastava P, Khoury N, Pinto Corrales J, Williams C, Nagai S, Abouljoud M, Samaniego-Picota M, Abreu-Lanfranco O, Del Busto R, Ramesh MS, Patel A, Alangaden GJ. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A cohort study. *Am J Transplant* 2020; **20**: 3051-3060 [PMID: 32654332 DOI: 10.1111/ajt.16188]

84 **Molnar MZ**, Bhalla A, Azhar A, Tsujita M, Talwar M, Balaraman V, Sodhi A, Kadaria D, Eason JD, Hayek SS, Coca SG, Shaefi S, Neyra JA, Gupta S, Leaf DE, Kovesdy CP; STOP-COVID Investigators. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am J Transplant* 2020; **20**: 3061-3071 [PMID: 32844546 DOI: 10.1111/ajt.16280]

85 **CMS Adult Elective Surgery and Procedures Recommendations**. [cited 20 September 2022]. Available from: https://www.cms.gov/files/document/covid-elective-surgery-recommendations.pdf

**Footnotes**

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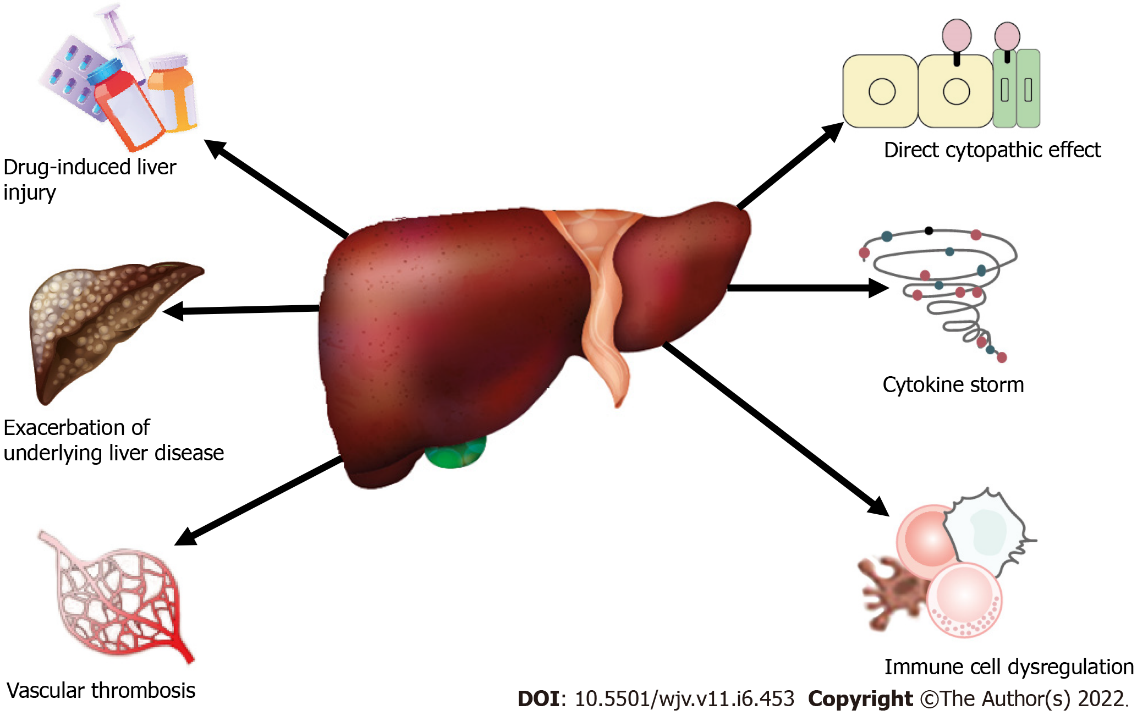
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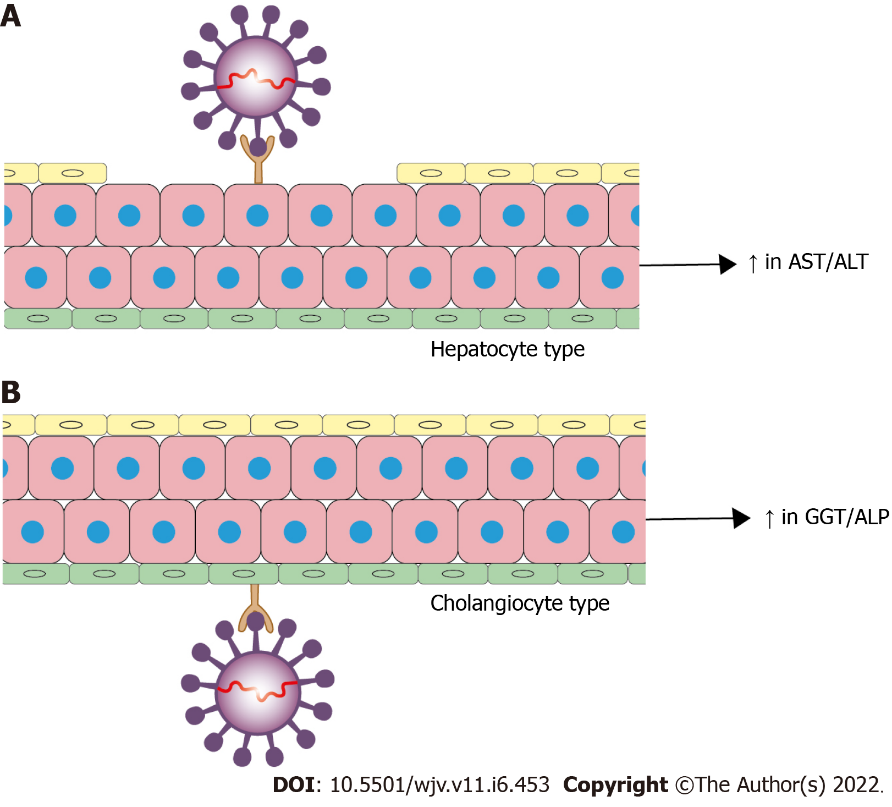
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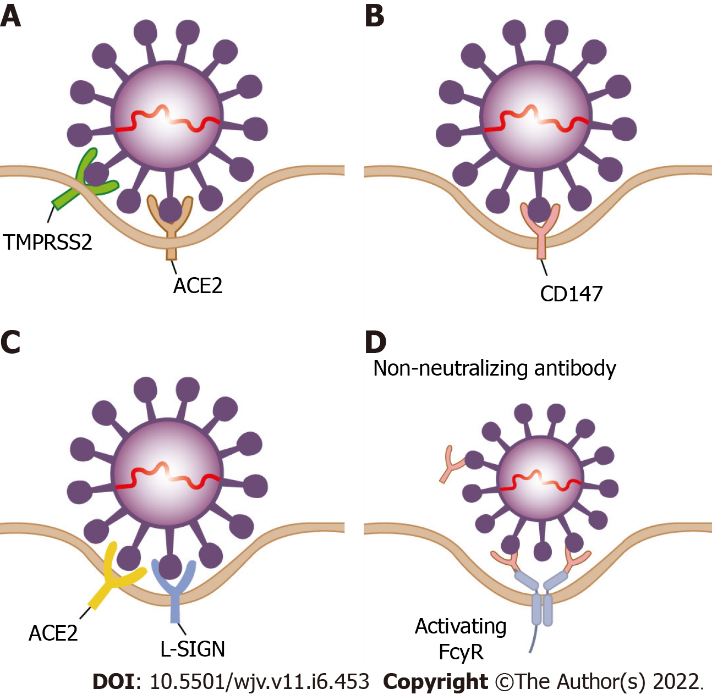
**Figure Legends**



**Figure 1 Schematic illustration of possible mechanisms of liver injury in coronavirus disease 2019.** Other mechanisms (not shown) may be involved.



**Figure 2 Two principal types of severe acute respiratory syndrome coronavirus 2 infection of the liver parenchyma.** A: Direct severe acute respiratory syndrome coronavirus 2 infection targeted to hepatocytes is designated as hepatocellular type; B: Direct viral entry into biliary epithelial cells is known as the cholangiocyte type. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-Glutamyltransferase; ALP: Alkaline phosphatase.



**Figure 3 Possible pathways of virus entry in hepatocytes.** A: The angiotensin converting enzyme-2 in conjunction with transmembrane protease serine protease 2 is considered the predominant receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells; B: CD147 is another possible receptor for SARS-CoV-2 entry into hepatocytes. CD147 is highly expressed in tumor tissues, inflamed tissues and pathogen-infected cells including hepatocytes; C: L-SIGN (CD209L) may serve as a liver-specific cell receptor for SARS-CoV-2 infection of hepatocytes; D: Antibody-dependent enhancement may also facilitate SARS-CoV-2 infection of hepatocytes. During antibody-dependent enhancement of infection, suboptimal non-neutralizing antibodies cannot completely neutralize the virus; instead, they bind with the Fc receptors expressed on hepatocytes, leading to virus entry and infection. ACE2: Angiotensin-converting enzyme 2.

**Table 1 Major clinical manifestations and laboratory abnormalities in coronavirus disease 2019**

|  |
| --- |
| **Signs/symptoms** |
| Systemic and respiratory system manifestations |
| Fever, cough, malaise, dyspnea, fatigue, sputum |
| Cardiovascular system manifestations |
| Heart failure, arrhythmia, shock, tight chest, acute myocarditis |
| Gastrointestinal manifestations |
| Anorexia, diarrhea, loss of appetite, loss of taste, gastrointestinal bleeding, nausea and vomiting, abdominal pain, mild pancreatitis, mild colitis |
| Hepatobiliary manifestations |
| Abnormal liver function tests, jaundice, hypoalbuminemia, new-onset decompensation, acute-on-chronic liver failure, cholangiopathy, acalculous cholecystitis |
| Kidney manifestations |
| Acute kidney injury, proteinuria, hematuria |
| Neurological manifestations |
| Dizziness, headache, skeletal muscle injury, acute cerebrovascular disease, seizures |

**Table 2 Rates of hepatic complications in different clinically significant human coronavirus infectious diseases**

|  |  |  |  |
| --- | --- | --- | --- |
| **Hepatic complications** | **SARS-CoV-2, %** | **SARS-CoV, %** | **MERS-CoV, %** |
| IncreaseinALT | 13.3-28.0 | 52.5-8.07 | 11.0-56.3 |
| IncreaseinAST | 22.0-58.0 | 37.1-86.9 | 15.0-86.8 |
| IncreaseinTB | 10.5-18.0 | 30.0 | NA |
| Decreaseinserumalbumin | 36.8 | 40.4-72.0 | NA |
| Co-morbiditywithliverdisease | HBV-positive patients were more prone to develop severe disease (32.9%) *vs* HBV-negative patients (15.3%) | HBV infection was not associated with worse clinical outcomes | NA |

ALT: Alanine transaminase; AST: Aspartate transaminase; HBV: Hepatitis B virus; MERS: Middle east respiratory syndrome; NA: Not applicable; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SARS-CoV: Severe acute respiratory distress syndrome; TB: Total bilirubin.

**Table 3 Summary of recommendations from various hepatology societies regarding liver transplantation during the coronavirus disease 2019 pandemic**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Step** | **AASLD** | **EASL** | **APASL** | **Indian Transplant Society** |
| Indications | Develop a hospital-specific policy for organ acceptance in consideration to community incidence of COVID-19 infection | Restrict transplant with poor short-term prognosis like ALF, ACLF, high MELD score and HCC at upper limit of Milan criteria | Can limit transplant to urgent cases (ALF, high MELD, high risk of HCC progression) according to resources and infection status of country | Until April 2020, elective transplants were withheld. However, in ALF and ACLF transplant could proceed |
| Pre- transplant evaluation | Test all recipients and donors for SARS-CoV-2 before transplantation. In case of COVID-19 infection in potential recipient, transplant can be considered after at least 14-21 d if symptoms are resolved and repeat SARS-CoV-2 test is negative. Vaccination of potential recipient is encouraged | All recipients and donors should be tested for SARS-CoV-2 before transplantation. Reduction of hospital stay for transplant evaluation and consultation | All recipients and donors should be tested for SARS-CoV-2 before transplantation. Donor should also be evaluated for evidence of COVID-19 infection on chest CT | All recipients and donors should be tested for SARS-CoV-2 before transplantation |
| Post-transplant management without COVID-19 | Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage COVID-19 vaccination at least 6 wk post-transplant if partially vaccinated pretransplant than vaccination can be completed 1 mo after transplant | Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza | Standard immunosuppression protocols should be followed in new transplant recipient. In cases of long-term transplant dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza | Standard immunosuppression protocols should be followed in post-transplant period |
| Post-transplant management with COVID-19 | Consider lowering immunosuppression levels especially anti-metabolite drugs (*e.g.*, azathioprine or MMF). Dose adjustment of immunosuppression should be based on severity of COVID-19. Monitor kidney function and calcineurin inhibitor levels | Dose adjustment of calcineurin- and/or mTOR- inhibitors may be required to avoid drug interactions with anti-viral therapy | Consider lowering immunosuppression levels in patients with moderate COVID-19 infection. Immunosuppression should be reduced in recipients with lymphopenia, fever or worsening pneumonia. Severe COVID-19 should be treated as per local protocol. Drug-to-drug interaction should be considered with anti-viral therapy |  |

AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on chronic liver failure; ALF: Acute liver failure; APASL: Asian Pacific Association for the Study of the Liver; COVID-19: Coronavirus disease 2019; CT: Computed tomography; EASL: European Association for the Study of the Liver; MELD: Model For End-Stage Liver Disease; HCC: Hepatocellular carcinoma; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.



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