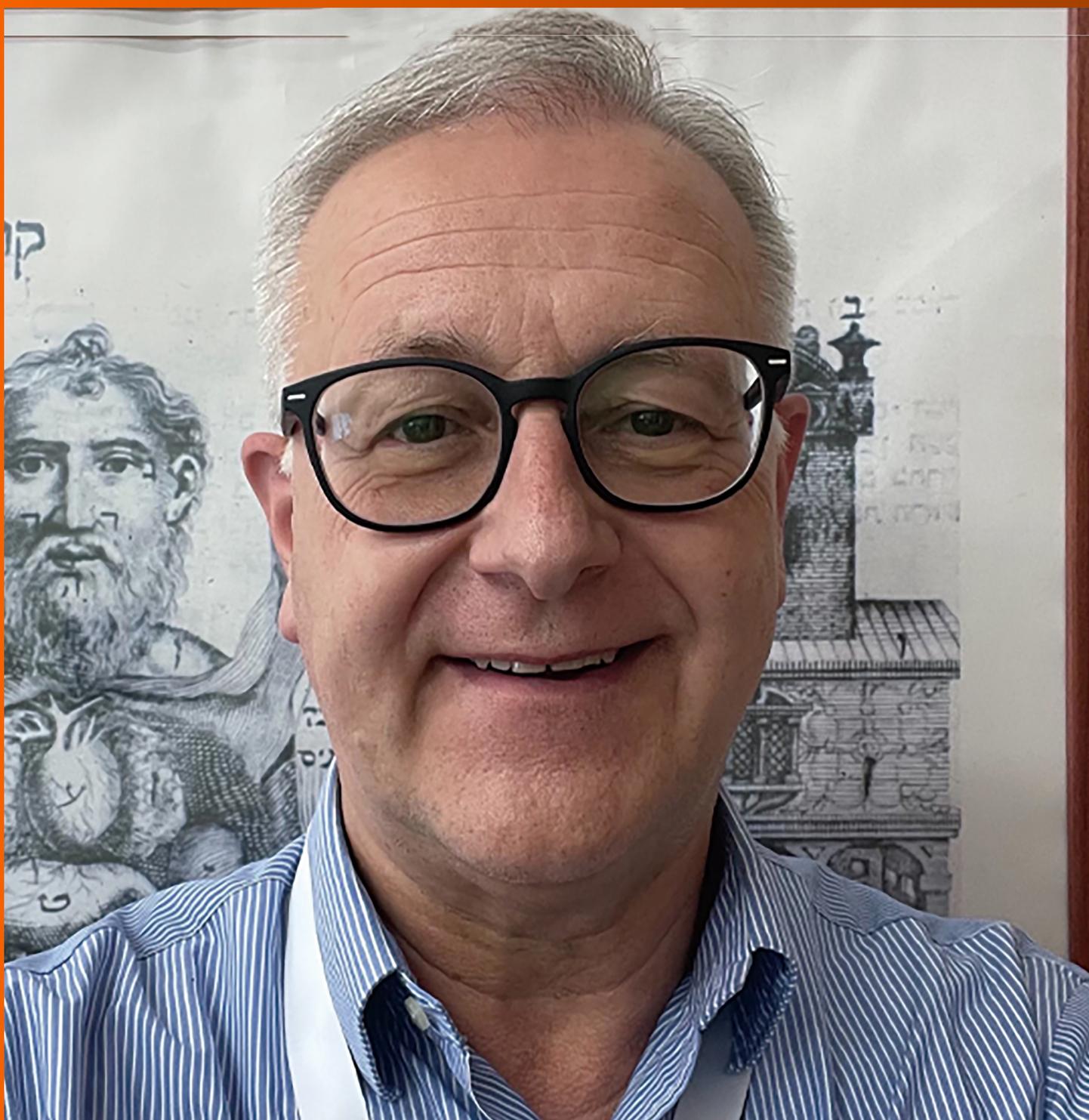


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COVID-19 and the liver: What do we know so far?

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has caused unprecedented pressure on public health and healthcare. The pandemic surge and resultant lockdown have affected the standard-of-care of many medical conditions and diseases. The initial uncertainty and fear of cross transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have changed the routine management of patients with pre-existing liver diseases, hepatocellular carcinoma, and patients either listed for or received a liver transplant. COVID-19 is best described as a multisystem disease caused by SARS-CoV-2, and it can cause acute liver injury or decompensation of the pre-existing liver disease. There has been considerable research on the pathophysiology, infection transmission, and treatment of COVID-19 in the last few months. The pathogenesis of liver involvement in COVID-19 includes viral cytotoxicity, the secondary effect of immune dysregulation, hypoxia resulting from respiratory failure, ischemic damage caused by vascular endotheliitis, congestion because of right heart failure, or drug-induced liver injury. Patients with chronic liver diseases, cirrhosis, and hepatocellular carcinoma are at high risk for severe COVID-19 and mortality. The phase III trials of recently approved vaccines for SARS-CoV-2 did not include enough patients with pre-existing liver diseases and excluded immunocompromised patients or those on immunomodulators. This article reviews the currently published research on the effect of COVID-19 on the liver and the management of patients with pre-existing liver disease, including SARS-CoV-2 vaccines.

Key Words: COVID-19; Chronic liver disease; SARS-CoV-2; Severe acute respiratory syndrome coronavirus; Liver transplant; Liver and SARS-CoV-2 vaccines; SARS-CoV-2 induced liver injury

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Core Tip: Liver involvement in coronavirus disease 2019 (COVID-19) is caused by either viral cytotoxicity or secondary to systemic immune dysregulation. Patients with pre-existing liver disease are at high risk of disease progression, morbidity, and mortality. Chronic liver disease with COVID-19 should be managed as per the standard guidelines, with education on hand hygiene, social distancing, and face masks to reduce hospital admissions. There is no evidence that currently available vaccines for severe acute respiratory syndrome coronavirus 2 will have any complications different from other inactivated vaccines and are recommended for patients with pre-existing liver disease, hepatocellular carcinoma, or liver transplant recipients.

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INTRODUCTION

Coronavirus is an enveloped single-stranded RNA virus belonging to the Coronaviridae family and Orthocoronavirinae subfamily. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) respectively caused epidemics in 2003 and 2012. The pandemic of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 was first reported from Wuhan, China on December 31, 2019 in patients with atypical pneumonia[1]. While symptoms are mild in most patients, severe and critical symptoms (in 10%-15% of patients) like hypoxemia ($SpO_2 < 94\%$), acute respiratory distress syndrome, multiorgan failure, or shock; may need hospitalization and respiratory support[2,3]. Older patients, especially those with comorbidities like hypertension, diabetes, chronic liver disease (CLD), and heart disease, are at risk of severe disease and mortality[2,3]. With the rapid spread of COVID-19, there has been significant concern regarding the safe management of patients with pre-existing liver disease (CLD), hepatocellular carcinoma (HCC), and candidates for a liver transplant. This review discusses the current evidence on liver involvement in COVID-19 and its impact on managing patients with CLD, including current recommendations for SARS-CoV-2 vaccines.

LIVER DYSFUNCTION IN COVID-19

Based on the published literature, 14%-53% of patients with COVID-19 developed hepatic dysfunction, and 2%-11% of the patients were reported to have underlying CLD[4-9]. Hepatic dysfunction characterized by elevated liver enzymes was significantly higher in severe and critical COVID-19 and was associated with poor outcomes[4]. In a meta-analysis of 45 studies, the most common biochemical abnormality of the liver in COVID-19 was hypoalbuminemia (39.8%), followed by elevation of gamma-glutamyl transferase (GGT 35.8%), or aminotransferases [aspartate aminotransferase (AST 21.8%) and alanine aminotransferase (ALT 20.4%)] [10]. The incidence of elevated hepatic enzymes was also higher in COVID-19 patients requiring intensive care unit (ICU) admission as compared to non-ICU patients (62% vs 23%) [4]. In another meta-analysis of 128 studies, the most common hepatic abnormality was hypoalbuminemia (61.3%), followed by elevation of GGT (27.9%), ALT (23.3%), and AST (23.4%) in the patients with COVID-19. The degree of the hepatic abnormalities was directly proportional to the severity of the disease[11].

MECHANISM OF LIVER INJURY

The pathogenic properties of SARS-CoV-2 depend on the binding of viral spike proteins to the host angiotensin-converting enzyme 2 (ACE-2) receptors, which allows the virus to enter the target cells along with priming by the host transmembrane serine protease 2 (TMPRSS2)[12-14]. The ACE-2-TMPRSS2 is expressed in the ileum, liver, lung, nasal mucosa, bladder, testis, prostate, and kidney (in that order)[14-17]. SARS-CoV-2 binding to ACE-2 receptors in the upper respiratory tract is the primary site of replication and entry to the body[14]. ACE-2-TMPRSS2-positive cells in the gastrointestinal tract include enterocytes in the biliary duct or pancreatic duct epithelium and hepatocytes[14,17].

The mechanism of liver injury in COVID-19 is possibly multifactorial. SARS-CoV-2 might induce direct hepatotoxicity (SARS-CoV-2 enters into the liver *via* cholangiocytes or translocation from gut to the liver) or indirect hepatic injury (from systemic inflammation with immune dysregulation, hypoxia from respiratory failure, ischemic damage due to coagulopathy or endotheliitis, right heart failure due to myocarditis, deterioration of pre-existing liver diseases, or drug-induced liver injury)[15] (Figure 1). The liver function abnormalities like increased GGT are consistent with a direct cytotoxic effect of SARS-CoV-2 on cholangiocytes[15,18]. However, the expression of ACE-2 receptors is minimal on hepatocytes suggesting a significant contribution of indirect causes of liver damage rather than direct hepatotoxicity[16,18]. The treatment of severe COVID-19 with antiviral agents, immunomodulators, antibiotics, or supportive agents, may also cause hepatotoxicity. Among those agents, remdesivir, favipiravir, lopinavir/ritonavir combination, corticosteroids, and tocilizumab could increase liver enzyme levels[18-20]. Adjuvant drugs like acetaminophen and antibiotics may also cause hepatotoxicity[20] (Table 1).

IMPACT OF COVID-19 ON PRE-EXISTING LIVER DISEASE

COVID-19 with CLD

In a systematic review and meta-analysis of 73 studies, the prevalence of CLD was 3% in 24299 COVID-19 patients[21]. Other studies reported a 3%-11% prevalence of underlying CLD with COVID-19[4-9,22]. The patients with CLD may also be more susceptible to contract SARS-CoV-2 infection[23]. Besides, the presence of CLD increased the risk of severe COVID-19 [pooled odds ratio (OR) 1.48] and overall mortality (pooled OR 1.78)[21,24]. Two other meta-analyses found that pre-existing liver diseases increase the risk of severe COVID-19, decompensation, and mortality[24,25]. From an extensive registry of over 17 million patients from the United Kingdom, COVID-19 was associated with a 2.34 (95% confidence interval: 1.94-2.83) times increased risk of mortality with liver disease[26]. The evidence is conflicting on the increased risk of severe COVID-19 in patients with chronic viral hepatitis[4,27]. However, SARS-CoV-2 infection in patients with chronic hepatitis B could have an increased risk of reactivation. A study of 21 patients with known chronic hepatitis B, SARS-CoV-2 infection was associated with hepatitis B reactivation in three patients[28].

Fatty liver disease with COVID-19

In a multicenter retrospective study from the United States, CLD and nonalcoholic fatty liver disease (NAFLD) were independent risk factors for ICU admission and invasive mechanical ventilation[29]. NAFLD was also associated with the progression of COVID-19 to severe disease in other studies[30-32]. The Asian Pacific Association for the Study of the Liver COVID-19 Liver Injury Spectrum Study (APCOLIS) study included 228 confirmed COVID-19 patients from 13 Asian countries with pre-existing liver disease. Metabolism associated fatty liver disease (MAFLD) was the commonest (61%) etiology[33]. In a retrospective study, a history of NAFLD/MAFLD was associated with increased odds of admission for COVID-19[34]. Obesity is common in patients with NAFLD and is an independent risk factor for severe COVID-19, invasive mechanical ventilation, and increased mortality[31,35]. However, in a study by Hashemi *et al*[29], the clinical severity of COVID-19 in patients of NAFLD was observed to be independent of obesity. The deleterious interplay of chronic inflammation observed in NAFLD with an acute inflammatory response to SARS-CoV-2 could explain the higher hepatic injury and a worse outcome in metabolically compromised NAFLD patients[36]. In another study, the extent of liver fat was correlated with serum markers of inflammation and oxidative stress[37]. It explains

Table 1 Impact of drugs currently used for the management of coronavirus disease 2019 on the liver

Drug	Mechanism of action	Impact on CLD management
Remdesivir	Viral RNA-dependent RNA polymerase inhibitor	Liver toxicity possible; No liver relevant drug-drug interactions
Lopinavir/ritonavir	Protease inhibitors	mTOR inhibitors (sirolimus, everolimus) should not be co-administered; Close monitoring of drug level is required for calcineurin inhibitors (cyclosporine, tacrolimus); The risk of lopinavir-associated hepatotoxicity in patients with very advanced liver disease is low; Patients with decompensated cirrhosis should not be treated
Tocilizumab	Humanized monoclonal antibody targeting interleukin-6 receptor	Patients with decompensated cirrhosis should not be treated Consider risk of HBV reactivation
Methylprednisolone (steroids)	Bind nuclear receptors to dampen proinflammatory cytokines	The risk of other infections (e.g., spontaneous bacterial peritonitis) and viral shedding may increase in patients with decompensated liver cirrhosis; Consider antimicrobial prophylaxis; Consider risk of HBV reactivation
Favipiravir	Guanine analogue, RNA-dependent RNA polymerase	Elevation of ALT and AST possible; No data in cirrhosis available

ACE-2: Angiotensin-converting enzyme; CLD: Chronic liver disease; G6PD: Glucose-6-phosphate dehydrogenase; HBV: Hepatitis B virus; mTOR: Mammalian target of rapamycin; SBP: Spontaneous bacterial peritonitis.

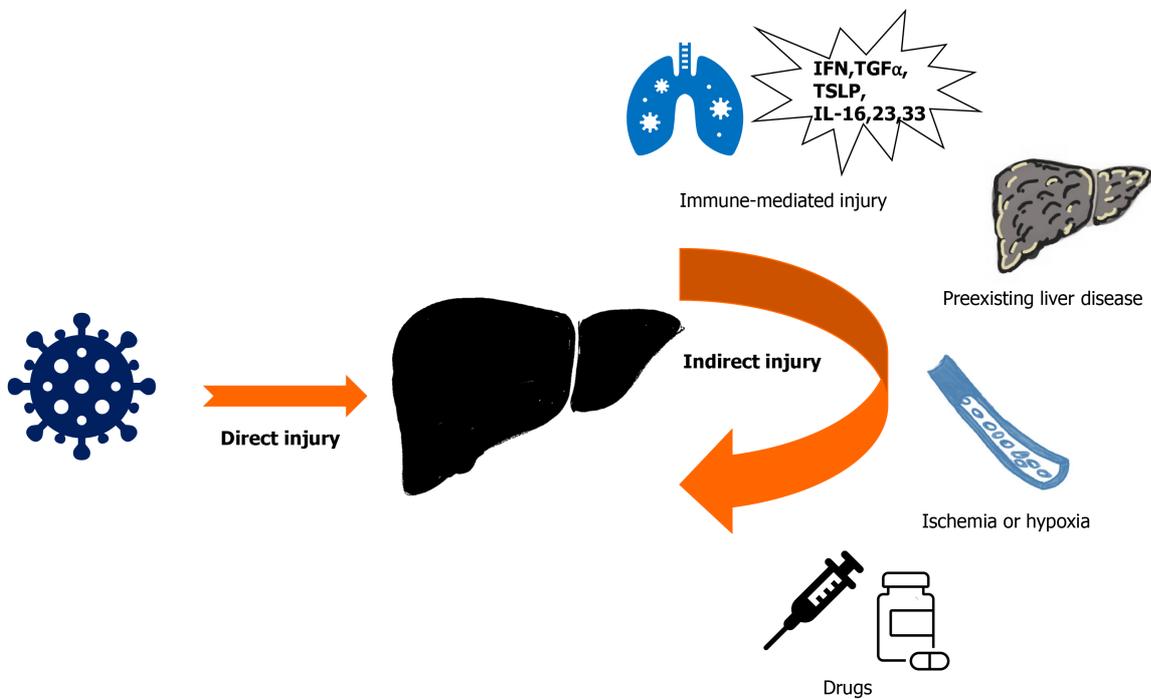


Figure 1 Mechanism of liver injury in coronavirus disease 2019.

the multifaceted impact of NAFLD on the pathophysiology and clinical course of COVID-19. However, effective treatment for metabolic disease can mitigate the increased risk from NAFLD[29,36].

COVID-19 and cirrhosis

Patients with cirrhosis are also at increased risk of decompensation with SARS-CoV-2 infection[38]. The presence of cirrhosis was also found to be an independent predictor of mortality in COVID-19[29,31]. In a study from the United States, the risk factors related to higher mortality in COVID-19 and CLD were alcoholic liver disease, decompensated cirrhosis, and HCC[39]. The worse outcomes in patients with cirrhosis can be multifactorial and likely due to cirrhosis-associated immune and inflammation modulation, limited physiological reserves, and increased risk of severe COVID-19[39]. Other large registries of patients with cirrhosis and COVID-19, like SECURE-cirrhosis and COVID-Hep.net, reported a case fatality rate of 38%, which may be as

high as 70% in the Child-Pugh C category[40].

Hepatocellular carcinoma

Patients with malignancy are vulnerable during the COVID-19 pandemic, with an increased risk of SARS-CoV-2 infection[41,42]. The overall prognosis of COVID-19 in cancer patients is poor, with high ICU admissions and mortality[41-43]. A small retrospective study of 28 cancer patients with COVID-19, including 2 HCC patients, had worse outcomes than the general population[43]. The increased risk may be attributed to age, multiple comorbidities, and the presence of cirrhosis. In patients with HCC, COVID-19 may exacerbate existing CLD and complicate the management of cancer.

PRESENTATION OF COVID-19 WITH PRE-EXISTING LIVER DISEASE

The SARS-CoV-2 infection in patients with pre-existing liver pathology may increase the risk of decompensation, acute liver injury, or a combination of both. Acute liver injury was the most observed presentation (43%) in CLD patients without cirrhosis, while acute-on-chronic liver failure (11.6%) and decompensation (9%) were more common in patients with cirrhosis[34]. The risk factors for decompensation include comorbid illnesses like diabetes or obesity. The AST/ALT ratio, total bilirubin, and R-value (ALT/ALP ratio) can predict survival in cirrhotic patients[34]. The residual hepatic synthetic function in CLD patients is inversely proportional to liver-related complications with COVID-19. Liver injury has been seen in the third week in CLD patients without cirrhosis and in the first week in cirrhotic patients[34].

COVID-19 AND LIVER TRANSPLANT RECIPIENT

Being an immunocompromised host, liver transplant recipients have an increased risk of acquiring SARS-CoV-2 infection and progression to severe disease. The outcome of COVID-19 in liver transplant patients was evaluated in a prospective study of 111 patients in Spain. Of 96 patients (86.5%) who were diagnosed with COVID-19 requiring hospital admission, 22 patients (19.8%) needed respiratory support, 12 (10.8%) required ICU admission, and the case fatality rate was 18% which was relatively lower than the matched general population despite higher severity of disease[44]. Similar results were found in another multicenter study of 112 patients from the United States. The hospital and ICU mortality rates were 22.3% and 26.8%, respectively, which was lower than the rates in matched patients of CLD without liver transplant[45]. The postulated hypothesis for better outcomes was ongoing immunomodulatory therapies that may ameliorate a harmful immune response (*i.e.* cytokine storm), reducing mortality[45,46]. However, immunosuppressants may delay viral clearance, explaining the severe disease[44]. The factors associated with mortality in liver transplant recipients were new liver injury, younger age, hispanic ethnicity, metabolic syndrome, vasopressor requirement, and antibiotic usage. Moderate liver injury [ALT 2-5 times the upper limit of normal (ULN)] and severe liver injury (ALT more than five times the ULN) was significantly associated ($P = 0.007$) with mortality and ICU admission[45].

MANAGEMENT OF CHRONIC LIVER DISEASE DURING COVID-19 PANDEMIC

The COVID-19 pandemic had a considerable impact on the management of CLD. Various factors must be considered and monitored while managing this group of patients. There is a potential threat of cross transmission of SARS-CoV-2 among patients and health care workers (HCWs) during physical assessment and treatment. However, it is imperative to maintain the continuity of care of patients with CLD to reduce the risk of decompensation and hospital admission. The measures recommended for safe and effective management of CLD patients can be divided into general and specific (Figure 2).

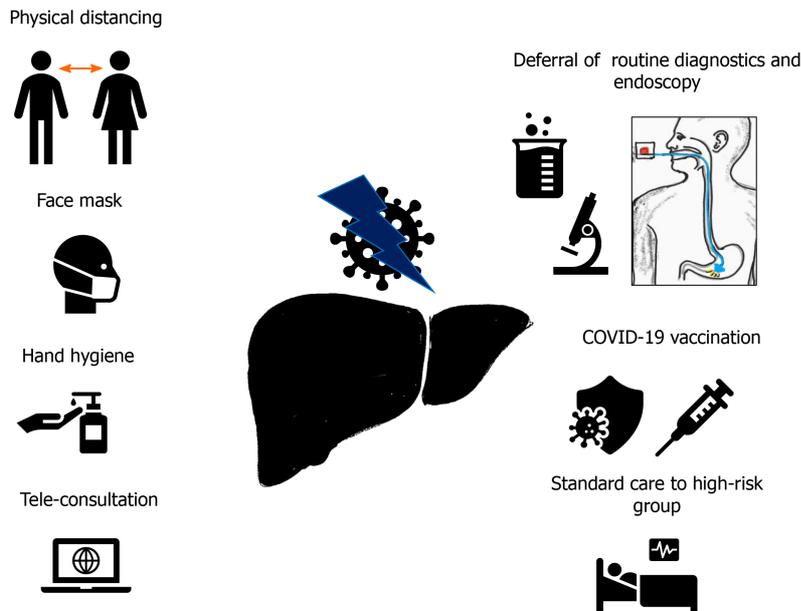


Figure 2 General measures for the safe management of patients with pre-existing liver disease during coronavirus disease 2019 pandemic. COVID-19: Coronavirus disease 2019.

General measures for all patients

Physical distancing, avoiding closed spaces without a face mask, and hand hygiene are vital pillars of SARS-CoV-2 infection prevention. Education on infection prevention measures should be included with other social measures like abstinence from alcohol and medication compliance. The screening of fever or respiratory symptoms should be performed on all patients and HCWs at the entrance of the hospital premises. Telemedicine, postponing routine outpatient visits, or periodic laboratory testing are other strategies that can be considered, depending on the available resources and patient condition[1]. The patient education must include prophylactic vaccination for streptococcus pneumonia or influenza.

Specific measures

Compensated liver disease: There is no evidence that initial clinical symptoms of SARS-CoV-2 are different in patients with CLD. Patients with NAFLD/MAFLD may suffer from other metabolic comorbidities like diabetes mellitus, hypertension, hyperlipidemia, and obesity, which need optimization and regular monitoring. Experts recommend against the alteration of immunosuppression in autoimmune hepatitis and liver transplant patients to reduce the risk of severe COVID-19[47]. The risk of aerosolization of SARS-CoV-2 during endoscopy must be considered during routine management of esophageal varices. Experts recommended non-endoscopic pathways to assess esophageal varices, especially during periods of high community transmission[47]. Any acute decompensation in patients with known CLD needs exclusion of SARS-CoV-2 coinfection. The potential reactivation of hepatitis B in patients with COVID-19 and chronic hepatitis B mandates monitoring of liver function tests and hepatitis B virus -DNA levels[28].

Decompensated liver disease: The care of the patients should follow standard guidelines while reducing direct visits to the healthcare facility (*e.g.*, using telemedicine or telephone consultation) wherever feasible. The standard management of these patients, like prophylaxis for variceal bleeding, spontaneous bacterial peritonitis, or hepatic encephalopathy, should be continued unaltered to prevent further worsening and reduce admissions[47].

Liver transplantation: The liver transplant recipients are at increased risk of contracting COVID-19, like patients with CLD. The general measures can include teleconsultation to shorten in-hospital stay and interactions with other HCWs. There were attempts to generate international consensus on treatment protocols of liver transplant recipients during this pandemic to reduce the risk of cross-transmission of SARS-CoV-2 and optimize healthcare resources[47]. The immunosuppression in liver transplant recipients may interfere with the immune response against the virus, while

any alteration in the treatment may cause acute graft rejection. Also, the use of various therapeutics to treat COVID-19 and drug-drug interactions with immunomodulators raises concerns of hepatotoxicity. In a prospective cohort study by Colmenero *et al*[44], mycophenolate at doses higher than 1000 mg/d was an independent predictor of severe COVID-19 in 111 liver transplant patients diagnosed with COVID-19. The synergistic effect of mycophenolate and SARS-CoV-2 may deplete peripheral lymphocytes responsible for an aberrant immune reconstitution to SARS-CoV-2[11,48]. In a multicenter study from the United States of COVID-19 in 112 liver transplant patients, new liver injury was associated increased mortality and ICU admission[45].

The close monitoring of liver enzymes in liver transplant patients and COVID-19 is suggested to watch for new liver injury or graft rejection. The immunosuppression regimen preferably should not be altered, except in the case of a mycophenolate-based regimen. Hypothermia is associated with worsening liver functions in severe COVID-19 and should be corrected with appropriate interventions[45].

Candidates for liver transplant: SARS-CoV-2 routine testing should be performed for both the recipient and donor before transplantation. However, a single negative RT-PCR test cannot exclude an asymptomatic infection[47]. During high community transmission or inundated healthcare resources, the transplantation should be offered only to select patients with poor short-term prognosis. It includes acute or acute-on-chronic liver failure, a high Model for End-stage Liver Disease score, or HCC with upper limits of the Milan criteria[45,49]. The diagnostic workup and procedure for the transplant program must be performed rapidly, with a short hospital stay[49].

Hepatocellular Carcinoma: Although the number of patients with HCC in the published COVID-19 studies is minimal, similar infection risk mitigation should be implemented in patients with CLD. The clinical services of cancer patients have been significantly affected by the current coronavirus pandemic, with decreased referral of the patients to the multidisciplinary tumor board (MTB), and treatment delays[50]. The evaluation, treatment and monitoring of HCC should be personalized based on the availability of medical resources and level of infection risk of SARS-CoV-2. Guidelines on the management of liver disease and HCC have been published by various academic societies[47,51]. The recommendations include virtual MTB meetings, prioritizing surgery on a case-to-case basis with preference to patients with low disease burdens and alternative therapies like radiofrequency and microwave ablation in selected patients. Treatment deferral or modification should be based on the best available evidence and availability of resources[52].

SARS-COV-2 VACCINES

Scientists developed vaccines against SARS-CoV-2 with unprecedented speed. The vaccines have been found effective in reducing the incidence of severe disease, hospitalization, and mortality. Vaccines based on various platforms, like mRNA, nonhuman viral vectors, and inactivated whole SARS-CoV-2 were developed. Despite more than 200000 participants in phase III trials, there is minimal data on efficacy in patients with pre-existing liver diseases. In the BNT162b2 (Pfizer/BioNTech) vaccination study, 217 participants (0.6%) had CLD and only 3 (< 0.1%) had moderate to severe liver disease[53]. Similarly, only 196 liver disease patients (0.6%) were included in the mRNA-1273 (Moderna) trial[54]. Data on patients with pre-existing liver disease is not available from the ChAdOx1-nCoV-19 (Oxford–AstraZeneca) vaccine trial[55]. Patients on systemic immunosuppression were excluded in all phase III trials, undermining the role of vaccines in the liver transplant recipients or patients with autoimmune liver disease on immunosuppressants. However, in the real world, millions are already vaccinated, including patients with liver disease; thus, data on safety and effectiveness are expected to be available soon. The deficiencies of innate or adaptive immune responses and an attenuated response to others vaccines are well recognized in CLD patients. A similar altered response to SARS-CoV-2 vaccines is also suspected. Nevertheless, based on an increased risk of severe disease, and in the absence of any data suggesting harm, the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and British Association for the Study of Liver currently recommend the available SARS-CoV-2 vaccines for patients with CLD, and liver transplant recipients[56-58]. Although the vaccines may be less effective in patients with CLD and liver transplant recipients, they still provide protection[58].

CONCLUSION

Emerging research suggests that liver injury is common in COVID-19 patients and associated with worse outcomes. Patients with CLD and post liver transplant patients are at risk of SARS-CoV-2 infection, with an increased risk of complications and mortality. The management of this vulnerable group of patients should be prioritized based on their clinical condition, strategies to reduce cross transmission, and optimizing limited resources. Liver transplant and HCC management programs should be modified depending on the prevalence of community transmission of SARS-CoV-2. Specific management issues should be considered during the treatment of COVID-19 in patients with pre-existing liver diseases.

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