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Review

COVID-19-associated liver injury: Clinical characteristics, pathophysiological mechanisms and treatment management

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become a global epidemic and poses a major threat to public health. In addition to COVID-19 manifesting as a respiratory disease, patients with severe disease also have complications in extrapulmonary organs, including liver damage. Abnormal liver function is relatively common in COVID-19 patients; its clinical manifestations can range from an asymptomatic elevation of liver enzymes to decompensated hepatic function, and liver injury is more prevalent in severe and critical patients. Liver injury in COVID-19 patients is a comprehensive effect mediated by multiple factors, including liver damage directly caused by SARS-CoV-2, drug-induced liver damage, hypoxia reperfusion dysfunction, immune stress and inflammatory factor storms. Patients with chronic liver disease (especially alcohol-related liver disease, nonalcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma) are at increased risk of severe disease and death after infection with SARS-CoV-2, and COVID-19 aggravates liver damage in patients with chronic liver disease. This article reviews the latest SARS-CoV-2 reports, focusing on the liver damage caused by COVID-19 and the underlying mechanism, and expounds on the risk, treatment and vaccine safety of SARS-CoV-2 in patients with chronic liver disease and liver transplantation.

1. Introduction

COVID-19 was first reported in Wuhan, China (December 2019) and was officially declared a pandemic by the World Health Organization in March 2020 [1]. As of Aug 14th, 2022, according to the COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University, USA, 589 million people worldwide have been diagnosed with COVID-19, and more than 6.4 million of them have died from its complications. Most patients infected with SARS-CoV-2 are asymptomatic or have mild symptoms, but there are still a considerable number of severe COVID-19 patients who can develop acute respiratory distress syndrome (ARDS) within 10 days, accompanied by multiorgan failure and coagulopathy, which can eventually lead to death [2]. Thus, the global COVID-19 pandemic poses a serious threat to public health in various countries.

Although SARS-CoV-2 is mostly known for causing substantial respiratory pathology, it can also result in several extrapulmonary manifestations. These conditions include liver injury [3], acute cardiac injury [2], gastrointestinal symptoms [4], neurologic illnesses [5], and acute kidney injury [6]. These complications seriously interfere with the treatment for COVID-19 and damage patient's health; even after recovery, COVID-19 can still affect the normal life of patients due to its sequelae [7,8]. Among these extrapulmonary manifestations, liver involvement is relatively common during COVID-19, and the clinical manifestations can range from asymptomatic liver enzymes elevation to decompensated hepatic function. Existing studies have shown that 2–11% of patients with SARS-CoV-2 infection have chronic liver disease (CLD), and 14–53% of patients have abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during disease progression [9]. Meanwhile, patients with severe COVID-19 have a

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higher rate of liver dysfunction.

Do patients with existing chronic liver diseases (such as alcohol-related liver disease, nonalcoholic fatty liver disease, viral hepatitis, and liver cirrhosis) have a higher rate of infection, severe illness and mortality from the SARS-CoV-2 virus? Because patients with cirrhosis or liver cancer are immunocompromised, they may be more susceptible to SARS-CoV-2. Is there a conflict between the ongoing medications for these patients with CLD and their treatment for COVID-19? What is the safety of COVID-19 vaccination in these patients, and what are the potential risks of liver transplantation (LT) during the COVID-19 pandemic? This review summarizes these important issues based on recent developments in the field and briefly addresses the risk of infection and vaccine safety in liver transplant patients to optimize the therapeutic management of patients with COVID-19-associated liver injury and to draw lessons for the prevention, diagnosis and treatment of COVID-19-associated liver injury.

2. Clinical features of COVID-19-associated liver functional abnormalities

The clinical symptoms of COVID-19 patients mainly manifest as respiratory system damage. Most patients are admitted to the hospital due to fever, dry cough, chest tightness, and dyspnea. A few of these patients also have nonspecific symptoms, such as fatigue, diarrhea, nausea, and vomiting [10]. The early stage of liver injury may also have similar manifestations; thus, it is difficult to assess correlation between the two. There are also rare reports of skin darkening due to COVID-19, which may be caused by abnormal liver function that hinders the inactivation of estrogen and leads to adrenocortical hypofunction, causing increased melanin secretion. At the same time, abnormal liver function increases the level of iron in the blood, and the increase in iron in the blood supply to the face can causes a blackening face [4]. In population terms, older patients with COVID-19 have a higher risk of liver injury [11]. The incidence of liver injury is much higher in males (63.4%) than in females (36.6%), and liver injury is more common in patients with severe/critical disease than in those with mild disease [12]. Patients with abnormal liver function have longer mean hospital stays than patients with normal liver function (15.09 ± 4.79 days vs. 12.76 ± 4.14 days) [13]. Even after the patient is cured and discharged from the hospital, abnormal liver function can long persist [14]. Doctors should pay attentions to the liver injury response when virus infection becomes severe and conduct long-term dynamic monitoring of liver function after the discharge of patients with liver injury.

Overall, the proportion of COVID-19 patients with abnormal liver function on admission has been found to range from 37.2 % to 76.3 % [13,15], and the proportion with liver injury ranges from 21.5 % to 45.7 % [15,16]. Most of these patients showed mild AST and ALT elevation, which can be accompanied by a slight elevation in the total bilirubin (TBIL) level [17]. The elevation in the TBIL level was found to be more significant in severe/critical patients [12,18], but no obvious jaundice symptoms were seen [19]. A mild decrease in albumin levels has been observed, with no significant change in prothrombin time [20,21]. Levels of the cholestatic liver enzymes [gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP)] have been shown to be increased by 21.1 % and 6.1 %, respectively [22]. The abnormal increase in ALP in patients with severe COVID-19-associated liver injury was not obvious during hospitalization, but the proportion of patients with GGT levels exceeding 3 times the upper limit of normal could be as high as 58.1 % [15]. Hypoalbuminemia combined with an abnormal GGT or AST level at hospital admission was found to be a highly significant independent risk factor for intensive care unit (ICU) admission and for the composite endpoint of ICU admission and/or COVID-19-related death [23]. The higher proportion of male patients with abnormal liver function compared to female patients may be due to higher levels of C-reactive protein (CRP) and procalcitonin in the liver [13].

Patients with abnormal liver tests on admission have a significantly lower survival probability 25 days after admission than patients with normal liver tests [24], but there is no correlation between COVID-19-associated liver injury and patient mortality [25,26]. Autopsy results for deceased COVID-19 patients have shown moderate microvascular steatosis and mild lobular and portal activity in the liver [21,27]. Reductions in the numbers of CD4 + and CD8 + T cells, but no viral inclusions were observed in the liver. Other reports have indicated hepatomegaly with dark red, congestion of the hepatic sinuses with microthrombosis, and hepatocyte degeneration accompanied by lobular focal necrosis and neutrophil infiltration [28,29]. However, neither the histological features of liver failure nor bile duct injuries were observed in these deceased patients.

Given that the liver plays an important role in the production of coagulation factors, acute phase reactants and albumin, hepatic dysfunction may impact the multisystem manifestations of COVID-19, such as multiorgan failure, coagulopathy and ARDS [2,5,9]. In addition, the liver is the primary metabolic and detoxification organ in the human body, and even a moderate loss of hepatic function may alter the therapeutic effects and safety of antiviral drugs due to the decrease in liver metabolism. Therefore, a more detailed understanding of the causes of COVID-19-associated liver injury is essential.

3. Mechanism of COVID-19-associated liver injury

Abnormal liver function in COVID-19 patients is mainly caused by direct damage to the liver induced by SARS-CoV-2, drug-induced liver injury, hypoxia reperfusion dysfunction, immune imbalance and cytokine storms (Fig. 1), while the activation/exacerbation of preexisting liver disease can exacerbate COVID-19-associated liver injury. These mechanisms will be briefly described below.

3.1. Direct damage to the liver caused by SARS-CoV-2

SARS-CoV-2 has broad organotropism, and SARS-CoV-2 RNA expression has been detected in the liver and in many other extrapulmonary organs [30,31]. In situ hybridization has shown that SARS-CoV-2 virions are enriched in vessel lumens and portal endothelial cells [28]. Transmission electron microscopy identified typical SARS-CoV-2 virus particles in the cytoplasm of hepatocytes, and hepatocytes infected by the coronavirus showed obvious cell membrane dysfunction, mitochondrial swelling and endoplasmic reticulum dilatation [21]. These finding indicates that SARS-CoV-2 may directly cause hepatocellular lesions.

Angiotensin-converting enzyme 2 (ACE2), a host cell receptor of the SARS virus, was recently confirmed to mediate SARS-CoV-2 infection [32,33]. ACE2 is mainly expressed in lung alveolar epithelial cells and small intestine enterocytes and is also expressed in arterial smooth muscle cells and venous, artery endothelial cells in all organs [32]. Single-cell RNA sequencing analysis of the liver showed that the expression level of ACE2 was highest in cholangiocytes (compared to type 2 alveolar cells), followed by liver sinusoidal endothelial cells (LSECs) and hepatocytes [34]. The expression of ACE2 is lower in hepatocytes (20-fold less than the expression level in cholangiocytes), but it is still detectable [35]. Liver ductal organoid culture revealed that a portion of the liver injury caused by COVID-19 may be due to direct cholangiocyte damage and consequent accumulation of bile acid caused by SARS-CoV-2 infection [36]. These data indicate that the liver is a potential target for SARS-CoV-2, and the direct binding of SARS-CoV-2 to cholangiocytes, which causes damage to cholangiocytes and bile duct dysfunction, is a suspected mechanism of liver injury.

Notably, under the condition of CLD (liver fibrosis/cirrhosis), the expression of ACE2 increases [37,38], indicating that preexisting liver damage may exacerbate the hepatic tropism of SARS-CoV-2. Cholangiocytes play a key role in liver regeneration and the immune response when liver injury occurs [39]. Elevated GGT and ALP levels are sensitive indicators of cholangiocyte damage and are widely detected

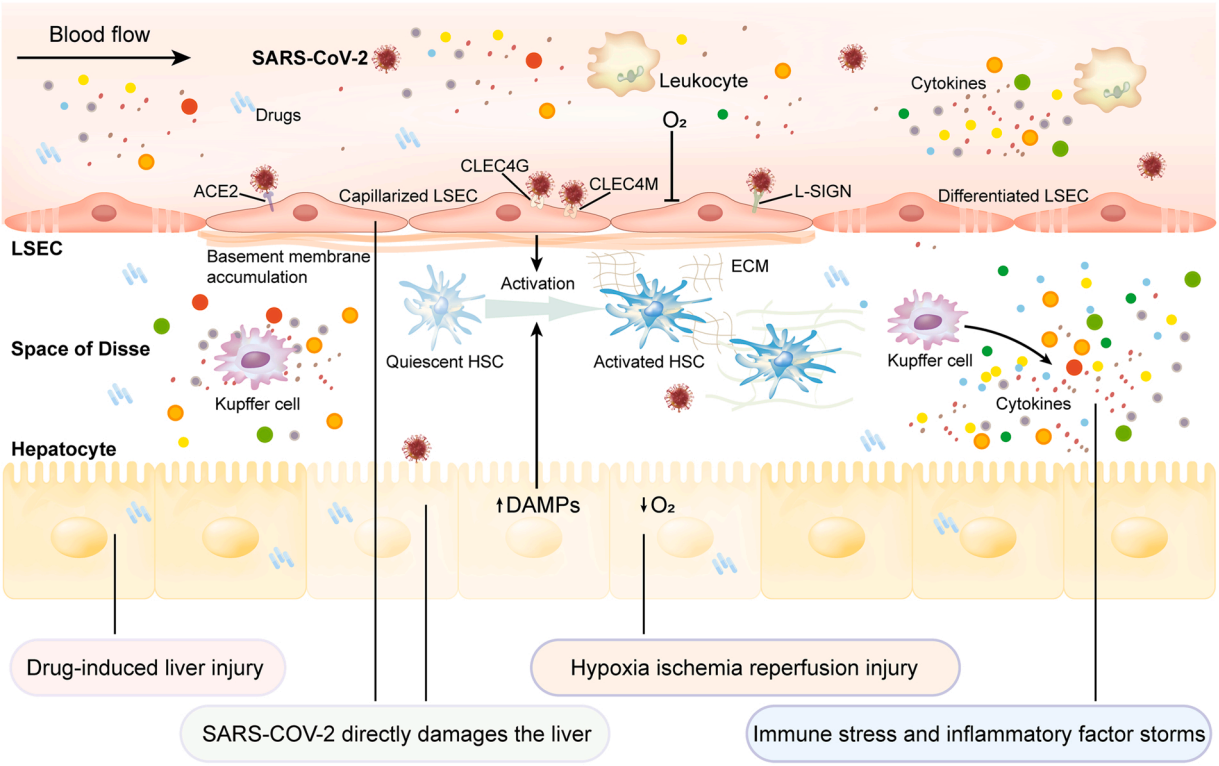

Fig. 1. Mechanisms of COVID-19-associated liver injury. (1) Drug-induced liver injury; (2) SARS-CoV-2 directly damages the liver; (3) hypoxia ischemia reperfusion injury; and (4) immune stress and inflammatory factor storms.

and applied in clinical practice. Considering that the patients with COVID-19-associated liver injury mainly have elevated transaminases, their ALP levels are not significantly elevated, and viral inclusions have not observed in their livers. Given the use of multiple drugs and multi-organ complications, such as systemic inflammatory status, renal impairment, and cardiopulmonary insufficiency, it is less likely that SARS-CoV-2 will affect cholangiocytes through ACE2 and cause liver cell damage, and liver damage directly caused by the virus is not considered a key factor.

3.2. *Drug-induced liver injury*

As there is no specific antiviral drug for SARS-CoV-2, the antipyretics, antiviral drugs, antibacterial drugs, herbal medications, immunosuppressants and other drugs that patients try during clinical treatment (especially during the early stage of the COVID-19 outbreak) can directly or indirectly lead to drug-induced liver injury. Meanwhile, interactions between multiple drugs types taken at the same time, as well as the discontinuation of drugs in patients with underlying liver diseases (viral hepatitis, alcoholic liver, nonalcoholic fatty liver, liver cancer, etc.), or the potential interaction of medications with the abovementioned COVID-19 treatment drugs may aggravate the risk of liver injury. Most of the antipyretic drugs taken by COVID-19 patients contain paracetamol, which is a general drug that can cause abnormal liver function in patients. The latest position paper from the European Association for the Study of Liver (EASL) indicates that lopinavir/ritonavir, colchicine, azithromycin, hydroxychloroquine, and ivermectin are no longer recommended for the treatment of SARS-CoV-2 infection [40]. Lopinavir/ritonavir, as an anti-HIV virus protease inhibitor, has shown in vitro anti-SARS-CoV activity but has been confirmed as an independent risk factor for severe liver injury during drug therapy against SARS-CoV-2 [41–43]. In a retrospective study encompassing 417 COVID-19 patients, lopinavir increased the risk of liver injury fourfold, while the proportion of patients with severe COVID-19 taking antibiotics, interferon, nonsteroidal anti-inflammatory drugs, ribavirin or herbal medications, which can cause liver damage, was significantly higher than that of patients with nonsevere disease [15]. By comparing the use of all drugs after admission, it was found that patients with abnormal liver function had a higher rate of lopinavir, glucocorticoids and thymopeptides use [44]. Chronic use of moderate or high doses of glucocorticoids (≥10 mg/day prednisolone or equivalent) is also associated with hospitalization for severe COVID-19 [45].

Long-term infusion of the anaesthetic ketamine in hospitalized patients results in marked elevation of TBIL and exacerbates cholestatic liver injury in patients, whereas even high-dose, long-term infusions of propofol and sufentanil do not result in increased TBIL in patients [46]. This suggests that high doses of ketamine for analgesia should be avoided in patients with COVID-19. Recent case study reports have also recommended that P-gp inhibitors should be used with caution when patients are taking remdesivir due to the potential for hepatotoxicity because the drug–drug interaction between remdesivir and P-gp inhibitors can aggravate liver damage in patients [47]. Furthermore, patients should be alert to liver injury and hepatitis virus reactivation caused by corticosteroids and tocilizumab. This is because corticosteroids can activate hepatitis B virus (HBV) replication suppressing the function of cytotoxic T cells and by directly stimulating HBV genomic sequences [48,49]. However, tocilizumab, an inhibitor of interleukin-6 (IL-6), can not only directly cause liver injury but can also induce reactivation of hepatotropic viruses [50]. Therefore, there should be a concern for patient safety in the use of this drug in the treatment of COVID-19. It is recommended that the benefits of these drugs with the potential for liver injury be evaluated that caution should be exercised prior to clinical use; moreover, if liver enzyme abnormalities develop in a patient who is taking a hepatotoxic drug, drug-induced liver injury should first be confirmed or ruled out.

3.3. Hypoxia reperfusion dysfunction

SARS-CoV-2 has been reported to bind directly to numerous receptors present in LSECs, such as ACE2, L-SIGN, CLEC4G and CLEC4M [51,52]. A distinctive feature of SARS-CoV-2 infection is vascular injury, with severe endothelial damage, microangiopathy, widespread thrombosis and neoangiogenesis being the responses to endothelial injury [53,54]. Therefore, some researchers have considered that COVID-19 is a vascular disease. Vascular damage and coagulopathy can cause respiratory failure and even ARDS. More than 40% of COVID-19 patients with various degrees of hypoxemia require mechanical ventilation, and the proportion of severe patients needing oxygen therapy can be as high as 71.1% [1]. The high metabolic activity and complex vascular supply in the liver make it particularly vulnerable to circulatory disturbances, and prolonged hypoxia and reperfusion injury can cause liver damage. SARS-CoV-2 can lead to an increased number of portal vein branches, intrahepatic vascular network disorder associated with massive luminal dilatation, partial or complete luminal thrombosis of the hepatic sinusoidal and portal veins, and fibrosis of the portal tract [28,55].

Compared with patients without significant liver injury, tocilizumab use and ischemia were found to be independent predictors of severe liver injury and played a major role in the pathogenesis of liver injury [26]. Under situations of systemic stress, the compensatory decrease in visceral and peripheral blood flow results in a decrease in hepatic blood flow, leading to hepatocellular hypoxia. The hallmark of ischemic liver injury is centrilobular necrosis, which usually manifests as an acute and marked elevation in serum transaminase levels [56,57]. Under shock and hypoxic conditions, the reduction in oxygen and lipid accumulation in hepatocytes can lead to cell death. Subsequent mitochondrial damage, and significant elevation of reactive oxygen species and their peroxidation products can lead to liver injury by activating redox-sensitive transcription factors and further amplifying the release of multiple proinflammatory factors [58]. Meanwhile, Kupffer cells can produce cytokines in response to ischemia and can trigger the recruitment and activation of neutrophils [59]. In addition, the microcirculation dysfunction caused by LSEC damage can further aggravate coagulopathy and the development of thrombosis in patients [51]. This phenomenon usually progresses rapidly, with a severe increase in the level of transaminase (20 times the upper limit of normal), accompanied by a lactate dehydrogenase (LDH) level elevation, which can be restored to normal after hypoxia is corrected [60]. Although liver damage is a typical feature of macrophage activation syndrome and may lead to coagulation dysfunction, the liver damage associated with COVID-19 is usually mild and transient, without the development of overt acute liver injury [21,61]. The reintroduction of oxygen to ischemic hepatocytes generates reactive oxygen species that cause reperfusion injury via lipid peroxidation [59].

Hypoxic hepatitis (also known as ischemic hepatitis) has typical clinical manifestations. Patients with respiratory failure, heart failure or shock suddenly have a dramatic but transient increase in serum transaminase levels to more than 20 times the upper limit of normal, and hypoxic hepatitis can be diagnosed after excluding other causes (especially drug-induced or viral hepatitis) of liver cell necrosis [57]. Although its typical histopathological manifestations are centrilobular necrosis, such patients are often not suitable candidates for liver biopsy in clinical practice. The severity of disease in COVID-19 patients is correlated with endothelial damage, and soluble thrombomodulin, angiopoietin-2 and E-selectin were only found to be elevated in severely ill patients [62]. However, von Willebrand factor antigen (VWF), a marker of endothelial damage, progressively increased with progression of the disease; when the VWF antigen exceeded 423%, a higher mortality rate was observed [62]. In patients with COVID-19, IL-6 and its circulating receptors can be detected, and these complexes can cause damaging changes in LSECs and may promote coagulation, leading to liver injury [63].

3.4. Immune stress and inflammatory factor storms

As an infectious disease that causes immune-mediated inflammatory injury, COVID-19 can cause not only pulmonary inflammatory injury but also multiorgan and multisystem dysfunction, and COVID-19-associated liver injury is a manifestation of systemic inflammatory response syndrome (SIRS). Some patients with COVID-19 do not have severe clinical symptoms in the early stages but then suddenly deteriorate and present with multiorgan failure [2,27]. An inflammatory cytokine storm caused by hyperimmunity may be the primary cause. Elevated levels of monocyte chemoattractant protein 1, interferon-inducible protein-10, IL-2, IL-6, IL-8, IL-10, and IL-17 expression have been found in the sera of SARS-CoV-2-infected patients [2,64]. However, COVID-19 patients with liver injury have higher levels of inflammatory cytokines, and elevated IL-6 and decreased CD4 + T cells have been identified as independent risk factors for severe liver injury [42,43]. In a study of liver proteomics in COVID-19 patients, RIG-I, TNF and IL1R were shown to be highly expressed in liver tissues, and these signals are ultimately integrated into the NF-κB-mediated inflammatory pathway [65]. The massive release of inflammatory cytokines can cause cytokine storms and can lead to SIRS, ARDS and multiple organ dysfunction, such as dysfunction of the liver and intestines. In patients with severe COVID-19, this exacerbated systemic inflammatory response can cause circulatory dysfunction and inadequate blood oxygen perfusion, leading to hypotension, hypoxia and coagulation disorders [66]. Histopathological examinations have shown hepatocyte necrosis, mononuclear infiltration, vascular congestion and thrombosis in the livers of patients with severe COVID-19 [66].

4. Chronic liver disease complicated by SARS-CoV-2 infection

Mild liver damage is common in patients with COVID-19, and 2–11% of SARS-CoV-2-infected patients have CLD [9]. The existence of CLD increases the risk of SARS-CoV-2 infection and death. However, the infection, severity and mortality rates of SARS-CoV-2 are different for each type of liver disease. Collectively, patients with alcohol-related liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma (HCC) have significantly increased SARS-CoV-2 infection rates and mortality. In contrast, patients with viral hepatitis (HBV, HCV) and autoimmune liver disease (AILD) show essentially no difference in SARS-CoV-2 infection and mortality rates compared with patients without this type of liver disease (Fig. 2).

4.1. Alcohol-related liver disease

Affected by the epidemic lockdown and home isolation, alcohol consumption has increased significantly in China, the USA, Belgium and other countries [67–69]. The increase in alcohol consumption is often accompanied by an increase in emergency hospital admissions. Mortality associated with ALD increased across age, race, and sex during the US epidemic [70,71]. According to statistics from 257 hospitals in Japan during the epidemic, the admission rate per 1000 people admitted for ALD or pancreatitis was 1.22 times that in the preepidemic period [72]. Meanwhile, the increase in the admission rate has increased the risk of patients being exposed to SARS-CoV-2. In a machine-learning big data analysis involving 155 countries, increased alcohol intake was found to be associated with an increased risk of COVID-19 [73]. Although current studies rarely include accurate data on the infection, severity, and mortality of SARS-CoV-2 in patients with ALD, there is no doubt that patients with ALD are at an increased risk of SARS-CoV-2 infection. A multicenter study in the USA indicated that ALD, decompensated cirrhosis and HCC were independent risk factors for higher overall mortality in COVID-19 patients [74]. The mortality of ALD patients after being infected with COVID-19 is particularly high, reaching 35.8% [75]. Although the study did not disclose the classification of liver fibrosis or complications in ALD patients, the high mortality rate is enough to

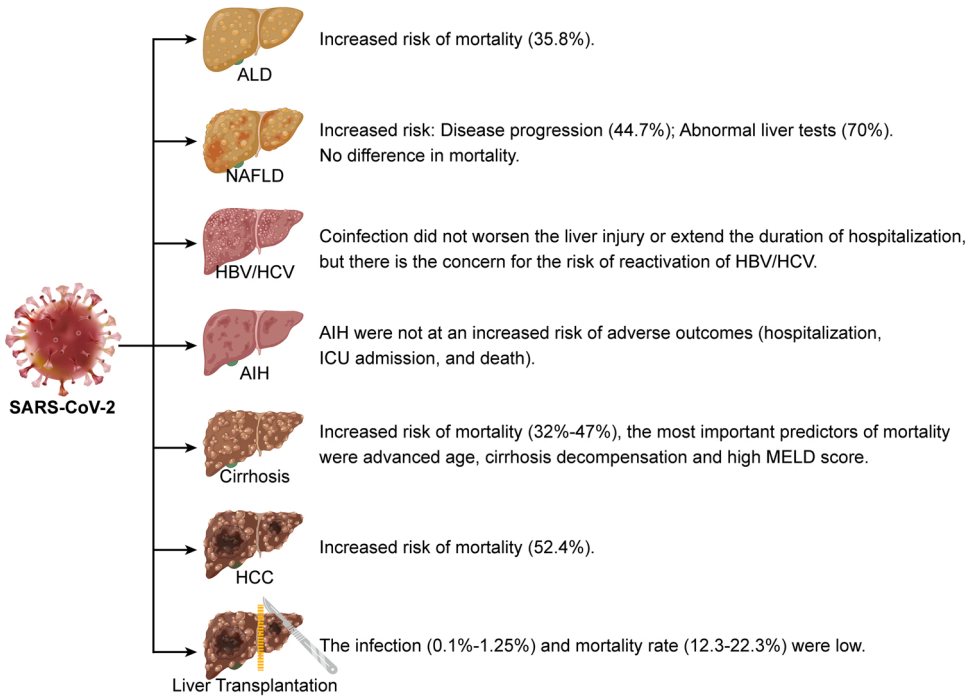

Fig. 2. Outcomes of COVID-19 in patients with chronic liver disease.

attract the attention of doctors and patients. Recent studies have suggested that chloroquine and hydroxychloroquine should be used with caution in ALD patients with COVID-19, as the combination of these two drugs can induce hepatotoxicity [76].

There are four main reasons why alcohol use and ALD may cause adverse consequences in patients with COVID-19. 1) Alcohol disrupts both the innate and adaptive immune systems by affecting the function and survival of immune cells, significantly weakening the body's defense against infection and likely making patients vulnerable to SARS-CoV-2 infection and subsequent secondary bacterial infections [77]. 2) Chronic alcohol consumption increases susceptibility to ARDS [78]. This may be related to the direct effects of alcohol on immune function, as well as reduced antioxidant concentrations and alveolar epithelial dysfunction in the lungs in people with chronic alcohol abuse. 3) Patients with a history of alcohol abuse often have other comorbidities including metabolic syndrome, which is independently associated with severe COVID-19 outcomes [79]. 4) Affected by the lockdown during the epidemic and the scheduling and transfer of hospital resources, ALD patients cannot return for regular medical visits, and ALD recurrence is caused by increased drinking during home isolation.

4.2. Nonalcoholic fatty liver disease

After being infected with SARS-CoV-2, patients with NAFLD (also called metabolic-associated fatty liver disease/MAFLD) were found to have a higher likelihood of abnormal liver function (70 % vs. 11.1 %), a higher risk of disease progression (44.7 % vs. 6.6 %), and a longer viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days) than patients without NAFLD [80]. A study of 280 COVID-19 patients in a multicenter cohort in Jiangsu Province, China, revealed that patients with NAFLD at the time of admission had significantly higher ALT and AST levels than non-NAFLD patients [81], indicating that NAFLD patients were more prone to develop liver injury after infection with SARS-CoV-2. Preexisting MAFLD can increase the severity of COVID-19 [82]. Progressive cholestasis and associated sclerosing cholangitis are common complications following SARS-CoV-2 infection in patients with chronic NAFLD [83]. In general, the prognosis of MALFD patients is determined by the severity of liver fibrosis, not by the presence of steatosis or steatohepatitis, even after the patient is infected with SARS-CoV-2 [84,85]. In NAFLD patients with COVID-19, an increase in the Fibrosis-4 (FIB-4) index preinfection was associated with worse clinical outcomes, and age was the strongest predictor of hospitalization and mortality [86]. Compared to patients without or with a low FIB-4 score, MAFLD patients with intermediate or high FIB-4 scores are more likely to be obese, elderly, have diabetes and have higher CRP levels, liver enzyme levels, and NAFLD fibrosis scores and lower platelet and lymphocyte counts, triglyceride levels and high-density lipoprotein cholesterol levels [87].

Overall, the risk of severe COVID-19 in patients with MAFLD is 2.6–5 times that in patients without MAFLD [88,89]. After adjusting for confounders, the risk of severe COVID-19 in patients with MAFLD under 60 was found to be 4-fold that in patients without MAFLD [90]. Patients with MAFLD on admission and who have elevated serum IL-6 levels are at a higher risk of severe COVID-19 [89]. Interestingly, greater accumulation of visceral adipose tissue in COVID-19 patients was associated with a higher risk of admission to the ICU. That is, for each centimeter increase in the patient's upper abdominal circumference, the possibility of ICU treatment increases by 1.13-fold, and the possibility of mechanical ventilation increases by 1.25-fold [91]. However, there is no difference in COVID-19-associated mortality between non-NAFLD and NAFLD patients [92].

In terms of the mechanism, genetic predisposition to MAFLD and hepatic fat accumulation does not increase susceptibility to severe COVID-19 [93]. The expression levels of four SARS-CoV-2-related mRNAs and proteins (ACE2, CTSL, TMPRSS2, PIKFYVE) were not found to be increased in MAFLD mice or in human livers [94]. This finding indicates that MAFLD does not increase the uptake of SARS-CoV-2 by the liver. Therefore, the cytokine storm caused by the inflammatory state and immune system imbalance associated with MAFLD may be the reason for the greatly increased risk of severe COVID-19 and ICU admission in patients with MAFLD. Recent studies have shown that SARS-CoV-2 can exacerbate cellular and tissue metabolic disorders in obese/diabetic patients, elderly individuals, and males by impairing the insulin/IGF signaling pathway in the liver, lung, adipose tissue and pancreatic cells [95]. Overall, NAFLD increases the risk of patients developing severe COVID-19 and requiring admission to the

ICU; thus, NAFLD patients infected with SARS-CoV-2 need better intensive care and monitoring.

4.3. Chronic viral hepatitis

Viral hepatitis is an infectious disease caused by different viruses (such as HBV and HCV), with liver inflammation and necrotic lesions as the main manifestations. In the case of persistent infection, this liver inflammation will progress to liver cirrhosis and liver cancer, causing great damage to human health. Given the high burden of HBV and HCV worldwide, it is necessary to discuss whether SARS-CoV-2 infection will worsen liver damage in patients with chronic hepatitis. HBV and SARS-CoV-2 coinfected patients have been shown to have elevated liver function indicators (AST, ALT, ALP, GGT, LDH, TBIL) to varying degrees compared to monoinfected SARS-CoV-2 patients, but there was no significant difference in liver injury [96,97]. HBV-positive patients show more severe monocytopenia and thrombocytopenia than HBV-negative patients infected with SARS-CoV-2, as well as worse hepatic function, with regard to lipid metabolism and albumin production [98]. Coinfected patients have more severe disease, a poorer prognosis for liver injury, greater complications and higher mortality [99]. Age and the CRP level were independent risk factors for the recovery of patients with coinfections [100]. Moreover, both D-dimer and IL-6 levels were higher in coinfected patients than in patients with SARS-CoV-2 monoinfection [101], indicating that the inflammatory response may contribute to injury following SARS-CoV-2 coinfection.

In contrast to the above results, in two large retrospective cohort studies that included 2073 and 5936 COVID-19 patients, neither current nor previous HBV infection was associated with a higher incidence of liver injury and death, whereas abnormal direct bilirubin and AST levels at admission were independent predictors of COVID-19 mortality [102,103]. These results indicate that HBV infection does not lead to induced serious adverse prognoses for patients with COVID-19, but most studies have not examined the expression levels of HBV-associated markers during infection and clearance of SARS-CoV-2. Testing of HBV-related markers in coinfected patients has revealed no extensive fluctuations in the quantitative levels of HBeAg/Ab, HBsAg/Ab, and HBV-DNA during SARS-CoV-2 infection, indicating that coinfection does not trigger seroconversion or reactivation of chronic hepatitis B, nor does it increase the disease severity or duration of hospitalization [104]. These results appear to suggest that, in most cases, chronic HBV infection does not increase the severity of COVID-19, nor does it cause a worse prognosis.

A previous study described three patients with hepatitis B reactivation after being cured of COVID-19 [97]. Two of these patients were prescribed methylprednisolone, a drug reported to activate HBV, during hospitalization [48]. However, one patient only took interferon and lopinavir/ritonavir and did not take methylprednisolone, but reactivation of hepatitis B virus still occurred. Liver needle biopsy results demonstrated a certain degree of diffuse swelling (ballooning degeneration) and necrosis of hepatocytes, periportal fibrosis, and infiltration of portal tracts with a few inflammatory cells, but no canalicular bile duct or interface hepatitis was seen. Immunohistochemical analysis was positive for HBsAg and negative for HBcAg [97]. These findings suggest that chronic HBV patients who are infected with SARS-CoV-2 could have a risk of hepatitis B reactivation with or without the use of corticosteroids. One prospective study evaluated the risk of HBV reactivation in 61 immunotherapy-treated patients with HBV and severe COVID-19 [105]. A follow-up of at least one month demonstrated no cases of HBsAg seroconversion, and only 2 patients (3%) had detectable serum HBV-DNA (< 15 IU/ml). All these results indicate that although there is a risk of hepatitis B virus reactivation in SARS-CoV-2-infected patients, the overall risk is low.

The infection rate of HCV combined with SARS-CoV-2 is low (6.2%). Older age, black ethnicity, and the presence of diabetes or a history of stroke increase the rate of infection with SARS-CoV-2 in HCV patients, but the degree of liver fibrosis in HCV-positive patients has little effect on the rate of SARS-CoV-2 infection [106]. Whether HCV infection is present has no effect on the rate of ICU admission and mortality in COVID-19 patients, and the use of corticosteroids did not increase mortality in HCV-positive patients, whereas the rate of hospitalization of coinfected patients increased with increasing FIB-4 scores [107].

Considering the risk of reactivation, the guidelines of the American Association for the Study of Liver Disease (AASLD) and the EASL strongly recommend that anti-HBV/HCV therapy should be continued once a diagnosis of COVID-19 is confirmed [108,109]. In addition, it is necessary to monitor the HBV/HCV-DNA levels and liver function in these patients and to take appropriate measures to prevent HBV/HCV reactivation.

4.4. Autoimmune liver disease

Autoimmune liver disease (AILD) refers to inflammatory liver lesions that are mediated by autoimmunity, including primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and overlapping syndromes with the main features of any two of the above diseases. Most AILD patients require lifelong immunosuppressive therapy to delay the progression to cirrhosis and liver failure.

The proportion of AILD patients infected with COVID-19 is not high. Zecher et al. reported that the positive rate of AILD patients infected with COVID-19 was 2.2% (39/1779) [110]. A larger cohort study revealed that the infection rate of AIH patients with COVID-19 was 0.66 % (20/3043), and the infection rates of patients with PBC (0.36 %; 12/3314) and PSC (0.45 %; 9/1982) were slightly lower [111]. In terms of the clinical features, among patients infected with COVID-19, AIH patients have a higher incidence of gastrointestinal symptoms than patients with other CLDs (ALD, NAFLD, HBV, etc.), but there is no difference in the incidence of asymptomatic and respiratory symptoms [111]. In two large retrospective analyses of AIH patients infected with SARS-CoV-2, the presence or absence of AIH had no effect on the severity of COVID-19, ICU admission, or mortality [111,112]. Maintaining immunosuppression in AIH patients reduced the risk of new-onset liver injury during COVID-19 and was not associated with an increased risk of severe COVID-19, while older age and cirrhosis were independent predictors of the development of severe COVID-19 in AIH patients [111,112]. COVID-19 was also found to cause recurrence of AIH, but the proportion of these patients was small (3.6%), and the AIH recurrence may be associated with a reduced dosage of immunosuppressive drugs [112]. Other studies have also reported that reducing the use of immunosuppressive medications during COVID-19 in AIH patients may increase the risk of disease recurrence [113,114]. In addition, COVID-19 can be a trigger of severe AIH even after the resolution of infection [115]. Thus, during the epidemic, immunosuppressive treatment should not be stopped for AIH patients, and it is necessary to carry out continuous and regular follow-up of patients recovering from COVID-19.

4.5. Cirrhosis

Liver fibrosis refers to diffuse overdeposition and an abnormal distribution of extracellular matrix in the liver, which is a pathological repair response of the liver to chronic injury and is a key step in the progression of various CLDs to cirrhosis. If not treated in time, fibrosis may progress to decompensated cirrhosis, liver cancer, and various complications of end-stage liver disease. During the COVID-19 epidemic, multiple reports indicated that the rates of SARS-CoV-2 infection in patients with liver cirrhosis were lower than those in patients without liver cirrhosis [116,117]. Nevertheless, the mortality rate of SARS-CoV-2 infection in cirrhotic patients (8.9 %, 12.7 %) was higher than that of SARS-CoV-2 infection in noncirrhotic patients (3.9 %, 7.0 %), both in terms of 30-day mortality and 90-day mortality [117]. Other

studies reported similar results, but the mortality rate was higher (32 % vs. 8 %) [75], (34 % vs. 18 %) [118], (47 % vs. 16 %) [119], which is related to the severity of the disease in patients with liver cirrhosis (Fig. 3). In a survey of veterans in the US suffering from liver cirrhosis and SARS-CoV-2 infection, the patients with liver cirrhosis who were positive for SARS-CoV-2 were 4.1 times more likely to be treated with mechanical ventilation and had a 3.5 times higher 30-day mortality than patients without SARS-CoV-2 infection, and advanced age, a high Model for End-Stage Liver Disease (MELD) score (≥12), and decompensated liver cirrhosis were independent predictors of death in patients with cirrhosis-SARS-CoV-2 [116].

Patients with cirrhosis have been found to exhibit significantly lower serum albumin levels and a significantly higher prothrombin time and creatinine and bilirubin levels at the time of COVID-19 diagnosis than recorded in the previous admission diagnosis data [118]. The proportion of patients with a Child–Pugh score ≥ 10 increased from 12 % before admission to 33 % after discharge (the proportion of patients with a MELD score ≥15 also rose from 13 % to 26 %), indicating that COVID-19 exacerbated the patients' liver injury [118]. The development of hepatic decompensation after SARS-CoV-2 infection in patients with cirrhosis is also common and is significantly associated with an increased risk of death. In a study that included 152 patients with cirrhosis and SARS-CoV-2, 39 (25 %) of the patients developed decompensation symptoms, and 24 died, accounting for 51.1 % of the total number of deaths [120]. Moreover, among patients with decompensated cirrhosis, those with a higher Chalson Complication Index had a higher incidence of ascites, jaundice, diarrhea, and gastrointestinal bleeding and more comorbidities [121]. Several systems that are associated with liver function ratings, an elevated Child–Pugh classification and MELD scores were strongly associated with an increased risk of patient death (Fig. 3). For example, the mortality in patients with cirrhosis and SARS-CoV-2 infection increased from 23.9% in Child–Pugh class A patients to 63.0 % in Child–Pugh class C patients [120]. Elevated FIB-4 scores were also associated with a poor prognosis in hospitalized patients [122–124]. In a comparative trial of the liver function rating system, the chronic liver failure consortium (CLIF-C) definition allowed more patients to be diagnosed with acute-on-chronic liver failure (ACLF); thus, the CLIF-C was superior to the North American Consortium for the Study of End-Stage Liver Disease, the Child–Pugh, and the MELD scores in predicting mortality in patients with cirrhosis and SARS-CoV-2 infection [119].

Patients with cirrhosis have elevated ACE2 and angiotensin II expression, and infection with SARS-CoV-2 in this pathological state will promote more viral influx into cells [37]. ACE2 cleaves angiotensin II into angiotensin 1–7 (Ang1–7), which leads to cytokine activation and cytokine-induced hepatocyte necrosis or apoptosis, thereby worsening liver damage in patients [125]. Overall, cirrhosis increases the risk of severe illness and death from COVID-19, and conversely, COVID-19 exacerbates liver injury in patients with cirrhosis. Therefore, more careful clinical testing and treatment of patients with cirrhosis who are infected with COVID-19 is needed, while patients with cirrhosis who are SARS-CoV-2 negative should not stop taking their medication to prevent worsening of their liver cirrhosis.

4.6. Hepatocellular carcinoma

Cancer patients have a higher risk of SARS-CoV-2 infection and a worse prognosis than noncancer patients, and patients with high-risk tumors, especially those with an NRS2002 score ≥ 3 and advanced tumor stages, may have higher mortality [126,127]. The risk of death in cancer patients infected with COVID-19 is mainly influenced by age, sex and comorbidities and is independent of whether they have had radiotherapy, targeted therapy, immunotherapy, or hormonal therapy within the past 4 weeks [128].

COVID-19 infection in patients with HCC was less reported during the epidemic, and a multicenter, observational cohort study showed that HCC patients with COVID-19 could have an all-cause mortality rate of up to 52.4 %, which is almost 7-fold higher than that in patients without HCC [74]. However, the trial had a small number of patients with HCC. In a large study of liver cancer patients infected with SARS-CoV-2, 52 patients died within 30 days of infection, and 43 (82.7 %) of these deaths were related to SARS-CoV-2 infection [127]. In a follow-up study of patients with HCC, the COVID-19 pandemic led to a longer follow-up interval for patients, which may reduce the overall response rate of patients, and the prognosis of patients was worse when the follow-up interval was > 95 days [129]. This should remind liver cancer patients, especially those with early-stage liver cancer, of the importance of timely follow-up examinations and not to delay testing due to the risk of SARS-CoV-2 infection, which can lead to a large tumor outbreak.

Patients with advanced liver disease, especially those who are older and have other comorbidities, are more likely to be immunocompromised. Intensive monitoring of clinical indicators after SARS-CoV-2 infection is needed and therapeutic approaches should be individually tailored to the patient's condition. Follow-up studies should be conducted to further evaluate the causes of liver injury due to SARS-CoV-2 infection and the impact of underlying liver diseases on the efficacy of COVID-19 treatment and outcome.

5. Liver transplantation during the COVID-19 pandemic

Liver transplantation remains the only definitive therapy for patients with decompensated cirrhosis, but the epidemic has had a great impact on the implementation and postoperative management of LT. Data from 22 countries have shown that the number of living donor LTs and deceased donor LTs decreased in 2020 compared with 2019 by 32.5 % and 9.3 %, respectively [130]. Liver transplant candidates have a high prevalence of COVID-19 (6.05 %) and a high risk of early death (32.7 %) [131]. In patients with decompensated liver cirrhosis and a

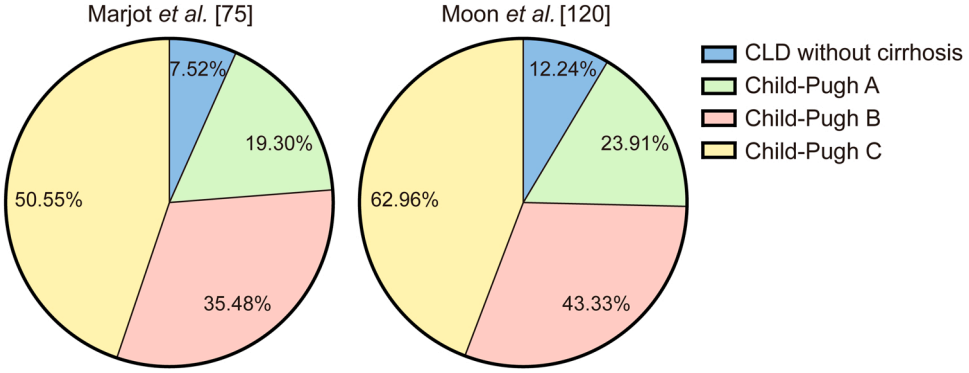

Fig. 3. Mortality after SARS-CoV-2 infection in patients with cirrhosis (by the Child–Pugh score).

laboratory-MELD score ≥ 15, the mortality rate has been shown to reach 49.2 %, which is a 3-fold increase in mortality compared to patients with the same MELD score but without SARS-CoV-2 infection, and COVID-19-related respiratory failure was the predominant cause of death in such patients (89.2 %) [131].

Interestingly, patients are relatively less likely to be infected with SARS-CoV-2 after LT. A large survey of 9 European countries revealed that 258 of 29,981 (0.9 %) LT recipients were infected with SARS-CoV-2 [132]. The infection rate in the UK was 0.1% (8/4500) [133]. Italy had a slightly higher rate of infection, but it was only 1.25 % (8/640) [134]. In terms of the clinical symptoms, the incidence of gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) in patients with LT after being infected with SARS-CoV-2 is higher than that of patients without LT [135]. The mean creatinine, TBIL and ALP levels were also higher than in patients with LT than in patients without LT, and the hospitalization and ICU admission rates of LT patients were 40 % and 8 %, respectively [136]. The mortality rate of LT patients after being infected with SARS-CoV-2 ranged from 12.3 % to 22.3 % [137–140], which was lower than that of COVID-19 patients who did not undergo LT [135,137]. A single-center study in the US showed that the shortest time for patients to contract COVID-19 after LT is 7 days (both donor and recipient SARS-CoV-2 tests are negative pretransplantation), and the median time from symptom onset to death is 19 days (9–24 days) [139]. Previous infection with SARS-CoV-2 was not associated with a risk of death from LT [131], and a prior LT was not associated with a risk of death from SARS-CoV-2 infection [135]. However, the immunosuppressive drugs (tacrolimus) that are used in LT patients were associated with better survival in the treatment of COVID-19 [132]. Advanced age, cancer and complications (such as diabetes) are associated with a high risk of death [132,135,140]. In view of this, clinicians are encouraged to keep tacrolimus at normal doses, risk stratification of liver transplant recipients should consider other coexisting conditions as well, and LT should not be delayed in patients due to the epidemic.

Reduced immunosuppression during COVID-19 did not increase the risk of recipient death or graft failure, while the severity of liver injury in patients who were positive for SARS-CoV-2 after LT was positively associated with the rate of ICU admission and the risk of death [138]. Hence, close monitoring of liver enzyme changes can help in the early identification of patients who are at risk for adverse outcomes. When a donor is diagnosed with COVID-19 and his liver is transplanted into a SARS-CoV-2-negative recipient, the LT recipient presents with moderate acute hepatitis with prominent clusters of apoptotic hepatocytes [141]. Although it is feasible for donors and/or recipients to undergo LT during a SARS-CoV-2 infection, this is the only treatment option for patients with liver decompensation in end-stage liver disease [142,143]. The majority of programs recommend screening deceased donors for SARS-CoV-2 to prevent inadvertent transplants from these donors.

6. Management of liver diseases during COVID-19

Most patients with COVID-19 have mild and transient symptoms of liver injury and return to normal without therapy. Nevertheless, when patients exhibit symptoms of liver injury or when they are taking medications that are associated with liver injury or have a preexisting CLD, liver function tests should be performed and carefully monitored, and the patient should be given liver protection drugs at the same time. Therefore, the focus should be on patients with CLD, especially those with SARS-CoV-2 positivity, who are at a greater risk of severe disease and death.

6.1. Chronic liver disease

During the epidemic, the risk of contracting COVID-19 should be minimized in CLD patients who still need to be hospitalized. Both the AASLD and EASL recommend isolating COVID-19 inpatients from uninfected patients with CLD while maximizing the use of telemedicine to reduce patient–physician contact [108,109]. If a patient develops moderate/severe liver injury during treatment for COVID-19, it is reasonable to discontinue the drug to identify the cause of liver injury [76].

NAFLD patients may have diabetes, hypertension or obesity, leading to a greater risk of severe disease and death after infection with SARS-CoV-2. In addition to monitoring liver function indicators during hospitalization, changes in blood glucose and blood pressure should be closely monitored in NAFLD-COVID-19 comorbidity patients. For HBV/HCV patients, both the AASLD and EASL recommend continuing antiviral therapy. If the patient has not been treated with anti-HBV/HCV agents while infected with SARS-CoV-2, the AASLD recommends postponing the initiation of antiviral treatment. In patients with chronic HBV who develop liver injury while coinfected with SARS-CoV-2, whether the patient is taking tocilizumab or corticosteroids should be determined, and HBsAg testing should be performed to determine or rule out HBV reactivation leading to hepatitis exacerbation [76]. Given that the discontinuation of nucleoside analogs may lead to HBV reactivation and relapse [144], discontinuation of antiviral therapy for HBV patients is not recommended. Most COVID-19 drugs have few drug–drug interactions with direct HCV antivirals, except protease inhibitors, which have drug–drug interactions with lopinavir/ritonavir and must be used with caution [76]. Thus, patients with HCV should also be on continuous antiviral medication. However, at the same time, the interaction between the new drugs targeting COVID-19 and anti-hepatitis virus drugs should also be monitored to prevent worsening of the disease or an outbreak of hepatitis virus. AIH patients should continue immunosuppressive therapy because AIH episodes caused by unnecessary drug reduction/discontinuation will require higher doses of steroids, thus potentially increasing the risk of SARS-CoV-2 infection [114].

As mentioned above, patients with cirrhosis, especially those with high-grade liver fibrosis, decompensated cirrhosis, or ACLF, are at a dramatically increased risk of severe disease and death after infection with SARS-CoV-2, and in such patients, treatment for cirrhosis and its complications (ascites, portal hypertension, hepatic encephalopathy, etc.) should be continued [109]. Patients with compensated cirrhosis should also have an HCC ultrasound and alpha-fetoprotein (AFP) testing every 6 months, while a 2-month delay in testing due to the epidemic is acceptable to prevent COVID-19 [108]. However, a balance should be maintained between the risk of delayed HCC detection and the risk of spreading COVID-19 so that the delay due to the pandemic does not lead to a more serious diagnosis and delayed treatment of liver disease. Postponing elective transplant, radiotherapy or resection surgery for newly diagnosed HCC patients should be considered [145]. Patients with advanced HCC treated with tyrosine kinase inhibitors should be able to continue therapy uninterrupted, while any immunotherapy may need to be temporarily suspended to avoid exposure to SARS-CoV-2 at the infusion center [146]. The epidemic has severely affected the dispatch of medical resources, and the resource-intensive management of patients with cirrhosis and HCC is particularly vulnerable to this decrease in medical resources during the pandemic. The surveillance of HCC and the monitoring of patients already treated for HCC should be guided by the principle of maximizing the risk-benefit ratio. The priority may be to allocate the medical resources to patients who have end-stage or recurrent HCC and to patients eligible for an immediate LT, for whom a risk-benefit assessment would be a judicious strategy.

6.2. Liver transplantation

The COVID-19 pandemic adds complexity to the care of pretransplant and posttransplant patients. At the same time, the shortage of health care workers, inadequate medical resources (ICU beds, blood products, and personal protective equipment), and the risk of cross-infection from outbreaks limit LT. When screening candidates for LT, the assessment can be made on the basis of specific circumstances, with the prioritization of LT for patients with ACLF, a high MELD score, acute

liver failure or HCC at the upper limits of the Milan criteria [147]. In contrast, liver transplantation may be suspended for patients within the lower limit of the Milan criteria to minimize the risk of infection in recipients and donors. Given that the risk of donor transmission is unknown, most societies recommend avoiding organs from SARS-CoV-2-positive donors [108,109]. In SARS-CoV-2-positive transplants, transplantation should be considered in candidates at least 2–3 weeks after symptom resolution and after 1 or 2 negative SARS-CoV-2 diagnostic tests.

For patients without COVID-19 after LT, there is no need to adjust the dose of immunosuppressive drugs in the transplant recipient; for patients with mild to moderate COVID-19, the current immunosuppressive dose should be maintained, and the patient's condition should be monitored closely. For patients with rapidly progressing or severe COVID-19, the dose of calcineurin inhibitors should be reduced, and the discontinuation of antimetabolites should be considered [148]. In patients who are 6 months or more posttransplant and develop fever, lymphopenia and/or worsening pneumonia, it is recommended to reduce or stop mycophenolate and azathioprine and to consider reducing but not stopping calcineurin inhibitors [108,109].

7. SARS-CoV-2 vaccination in patients with liver disease

COVID-19 has become a major public health threat in humans. Performing regular epidemic prevention and control, accelerating the speed of vaccination against SARS-CoV-2, and expanding the vaccination rate in the population have become the consensus approach of the international community to effectively prevent and control SARS-CoV-2 infection. Patients with CLD, especially cirrhosis and HCC, are at increased risk of severe illness and death from COVID-19. Thus, vaccination of CLD patients against SARS-CoV-2 as soon as possible is an important protective measure. In Fig. 4, we summarized the AASLD and EASL expert panel consensus on COVID-19 vaccination for patients with liver disease [40,149,150].

COVID-19 vaccine clinical trials excluded immunocompromised patients and oncology patients. Although some patients with liver disease, such as those with compensated liver disease or HBV, were included in the Pfizer-BioNTech and Moderna vaccine phase III clinical trials, the patient population was small, and the trial reports did not publish the vaccine effectiveness and safety in patients with liver disease [151,152]. As a result, there are few effective data on COVID-19 vaccines in patients with CLD or LT. In 381 patients with NAFLD who received the Beijing Institute of Biological Products inactivated SARS-CoV-2 vaccine, the most common adverse reactions were headache (5.2 %), muscle pain (5.5 %) and injection site pain (18.4 %), and all adverse reactions were self-limiting and mild, with no grade 3 adverse reactions recorded [153]. The presence of SARS-CoV-2 neutralizing antibodies was detected in 95.5 % (364 cases) of NAFLD patients 14 days after the entire vaccination course, with a median neutralizing antibody titer of 32 [153]. This shows that the inactivated COVID-19 vaccine has good immunogenicity and safety in patients with NAFLD. In 80 LT recipients receiving the Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine, only 47.5 % had positive neutralizing antibody titers, and their average antibody levels were 2-fold lower than those of healthy controls after vaccination (95.41 AU/ml vs. 200.5 AU/ml), indicating poor immunogenicity in LT recipients [154].

In prospective studies of the Moderna, Pfizer or Johnson & Johnson vaccinations in patients with liver disease, 61.3 % of LT recipients and 24 % of patients with CLD had a poor antibody response (suboptimal or undetectable), and among patients with CLD, 22.8 % of those with cirrhosis and 25% of those without cirrhosis had a poor antibody response [155]. The median antibody levels were 95.5, 41.3 and 17.6 for patients without cirrhosis, with cirrhosis and with a history of LT, respectively, with a decreasing trend with the severity of the disease [155]. However, based on the seroconversion rate, there were no differences in the humoral and cellular immune responses between the patients with varying Child–Pugh classes [156]. Compared with immunocompetent patients, LT recipients had lower persistence of anti-nucleocapsid IgG antibodies and a more pronounced decrease in antibody levels within 6 months after SARS-CoV-2 infection [157]. Increasing the number of vaccinations can improve the immune response of LT recipients; a recent study showed that the immune

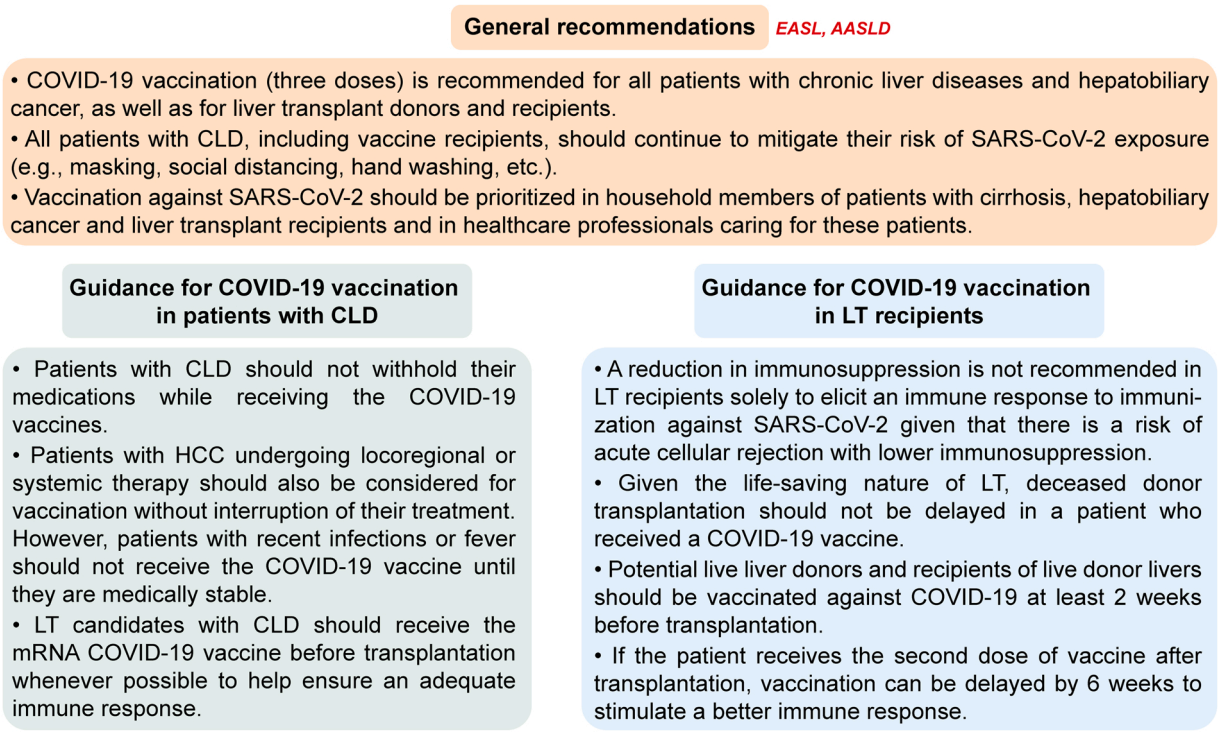

Fig. 4. Recommendations for COVID-19 vaccination in patients with liver disease.

response rate after the third dose of the vaccine was significantly higher than that before the third dose of the vaccine (98 % vs. 57 %) [158]. In contrast, median antibody levels and seroconversion rates increased 9-fold in 60% of non-responders after four doses of vaccine [159]. Although immunocompromised patients have a lower humoral response triggered by vaccination, the risk of infection, severe disease, and death is greatly reduced in vaccinated organ transplant recipients compared with unvaccinated organ transplant recipients [160,161]. In addition, older age, short-term liver transplantation and use of antimetabolites (e.g., mycophenolate mofetil) are related factors that lead to ineffective vaccination of LT recipients [162,163]. Therefore, timely vaccination with the SARS-CoV-2 vaccine is recommended for patients with CLD who are stable and for recipients awaiting LT.

8. Conclusion

COVID-19-associated liver injury is caused by the cumulative effects of multiple factors, including hepatotropic SARS-CoV-2, drug-induced liver injury, hypoxic reperfusion, immune stress and inflammatory factor storms. Although liver damage is relatively common in patients with COVID-19, most patients predominantly have transient and mild liver enzyme (AST, ALT) elevations, and rarely, there are cases of COVID-19-associated ACLF. When COVID-19 patients also have ALD, NAFLD, cirrhosis or HCC, they are at a higher risk of severe disease and death. Interestingly, the current study showed no significant correlation between patients with viral hepatitis or AILD and the risk of SARS-CoV-2 infection, severe disease, or death, but continued medication is still needed to prevent the recurrence of liver disease in patients with this comorbidity. Meanwhile, CLD patients with COVID-19 should be closely monitored for liver enzyme abnormalities, especially in the elderly and/or those with comorbidities, who are often at a greater risk of death. Although the number of liver transplantations performed during the epidemic has decreased, LTs still need to be performed with caution and should be performed as conditions permit for patients with ACLF, acute liver failure, a high MELD score or HCC at the upper limits of the Milan criteria. The new increase in the use of telemedicine provides effective protection to reduce cross-infection between doctors and patients, but patients with CLD still need regular follow-up examinations to prevent deterioration of their condition. Vaccination, as an effective measure to prevent COVID-19 in patients with liver disease, should be administered as soon as possible to patients with stable CLD and those waiting to receive LT to reduce the risk of SARS-CoV-2 infection and severe disease.

The global outbreak of SARS-CoV-2 has posed severe challenges to the public health and safety in various countries and has had a serious negative impact on the health of a large number of patients with CLD. Affected by the lockdown instigated by the epidemic, many CLD patients may reduce or delay liver function testing, which may lead to an explosive increase in the number of liver disease patients after the epidemic. Therefore, we hope to learn from the current epidemic and call for a comprehensive plan to enhance preparedness for future patient surges.

Ethics approval

Not Applicable.

CRediT authorship contribution statement

Penghui Li designed the study and drafted the manuscript. **Ying Liu**, **Ziqi Cheng** and **Xiaorui Yu** participated in the literature search and discussion. **Penghui Li** and **Yinxiong Li** revised the manuscript. All the authors approved the final version of the manuscript.

Conflict of interest statement

All authors declare that they have no competing interests.

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