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Patients with cirrhosis during the COVID-19 pandemic: Current evidence and future perspectives

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Abstract

The outbreak of coronavirus disease-2019 (COVID-19) has resulted in a global public health emergency. Patients with cirrhosis were deemed more susceptible to viral infection because of their dysregulated immune response. Similar to the general population, cirrhotic patients exhibit various degrees of COVID-19-related liver injury, which could be attributed to direct virus cytotoxicity, systemic immune system activation, drug-related liver injury, reactivation of pre-existing liver disease, and hypoxic hepatitis. The clinical symptoms in patients with cirrhosis and COVID-19 were similar to those in the general population with COVID-19, with a lower proportion of patients with gastrointestinal symptoms. Although respiratory failure is the predominant cause of mortality in cirrhotic patients with COVID-19, a significant proportion of them lack initial respiratory symptoms. Most evidence has shown that cirrhotic patients have relatively higher rates of morbidity and mortality associated with COVID-19. Advanced cirrhosis was also proposed as an independent factor affecting a poor prognosis and the need to consider COVID-19 palliative care. General measures implemented to prevent the transmission of the virus are also essential for cirrhotic patients, and they should also receive standard cirrhosis care with minimal interruptions. The efficacy of the available COVID-19 vaccines in cirrhotic patients still needs investigation.

Key Words: COVID-19; SARS-CoV-2; Cirrhosis; Acute liver injury; Prognosis; Therapy

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Core Tip: Several studies have addressed the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cirrhosis. The presence and stage of cirrhosis is correlated with the development of severe coronavirus disease-2019 (COVID-19), COVID-19-related adverse outcomes, and mortality. It remains unclear whether SARS-CoV-2 infection is a trigger of acute decompensation or acute-on-chronic liver failure in cirrhotic patients based on the current evidence. There is still no clearly proven effective pharmacological treatment for cirrhotic patients with COVID-19. Clinicians should maintain standard cirrhosis care, defer unnecessary liver-specific procedures and have a low threshold for admission if cirrhotic patients are infected with SARS-CoV-2.

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INTRODUCTION

In December 2019, an outbreak of unexplained pneumonia caused by a novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] occurred in Wuhan, China^[1]. The disease was named coronavirus disease 2019 (COVID-19) and has rapidly spread to other countries, causing a global public health crisis. On March 11, 2020, the World Health Organization (WHO) declared that the outbreak of COVID-19 was a pandemic. COVID-19 is generally a self-limiting disease, but it can progress to acute respiratory distress syndrome (ARDS), septic shock, and death, especially in those with advanced age or underlying comorbidities, including hypertension, diabetes mellitus, and cancer^[2-5]. The estimated case-fatality rate of COVID-19 ranges between 2% and 6%^[2,6,7].

The clinical manifestations in patients with COVID-19 may be nonspecific, but most have fever, cough, followed by dyspnea, fatigue, or sputum production^[2,3,8,9]. It is noteworthy that approximately 14% to 53% of patients experience various degrees of liver damage, although most of these injuries are mild and transient, with a satisfactory prognosis in patients without prior liver disease^[10-13]. In contrast, COVID-19 in patients with pre-existing liver disease has been reported to result in higher hospitalization and mortality rates^[14-22]. Among these preexisting liver diseases, cirrhosis is a chronic liver disease that involves the collapse of the structure of the liver and distortion of the vascular architecture. Cirrhosis is associated with inherent immune dysfunction and an altered gut-liver axis; patients with cirrhosis are particularly at elevated risk of infections and the associated complications^[23]. It remains uncertain whether immunocompromised patients with COVID-19 have a higher risk of adverse outcomes. Patients with cancer or solid organ transplant recipients may have an elevated risk of more severe COVID-19^[24]; whereas patients taking biologic therapies may not have a greater risk of developing severe COVID-19^[24]. No additional risk of death was observed in cancer patients receiving active treatment except in those undergoing chemotherapy^[25]. Whether patients with human immunodeficiency virus infection are at higher risk of mortality due to COVID-19 is unclear^[24,26,27]. In addition to studies involving the aforementioned immunocompromised patients, there have been several studies investigating the clinical and biochemical characteristics related to the prognosis of COVID-19 in cirrhotic patients, yielding some preliminary conclusions^[23,28-33]. In this review, we summarized the current epidemiology, clinical characteristics, liver injury pathophysiology, outcomes, and management strategies in patients with cirrhosis and COVID-19.

EPIDEMIOLOGY

As of late December 2020, there were over 79 million confirmed COVID-19 cases in more than 200 countries and 1.7 million cases of mortality, as reported by the WHO^[34]. Previous studies reported that 2%-11% of COVID-19 patients had pre-existing liver

disease^[10,12], and approximately 0.6% of COVID-19 patients had coexisting liver disease in a recent large-scale population-based United Kingdom cohort study^[35]. In contrast, the literature on the prevalence of cirrhosis in patients with COVID-19 is limited. Two large-scale studies from the United States demonstrated that 0.3% (19/5700) and 1.8% (50/2780) of patients with COVID-19 had underlying cirrhosis^[20,36]. Similarly, two studies from Portugal and China showed that 0.8% (6/756) and 2.4% (3/123) of patients with COVID-19 had pre-existing cirrhosis, respectively^[37,38]. Overall, a low proportion of COVID-19 patients have coexisting liver cirrhosis. Nevertheless, there had been speculated that people with liver cirrhosis are more susceptible to SARS-CoV-2 infection due to their altered immune response^[39-41]. One study from the United States and another from China reported incidences of SARS-CoV-2 infection in hospitalized patients with liver cirrhosis of 6.6% (37/556) and 16.8% (17/101), respectively^[23,42]. Taken together, although they account for a small proportion of patients with COVID-19, patients with underlying cirrhosis are more susceptible to viral infection than the general population.

CLINICAL CHARACTERISTICS

Limited evidence has shown that the clinical manifestations in cirrhotic patients with COVID-19 are similar to those in the general population with COVID-19, with fever and cough remaining the most common symptoms, followed by shortness of breath and sputum production^[21,31,33]. Interestingly, whereas similar proportions of cirrhotic and noncirrhotic patients developed respiratory and cardiovascular symptoms, cirrhotic patients were less likely to develop gastrointestinal symptoms (*e.g.*, diarrhea, nausea, vomiting)^[19,23,31,33]. Possible explanations include the inherently higher proportion of baseline gastrointestinal symptoms in cirrhotic patients, and their use of medications (*e.g.*, lactulose), which could also result in the underestimation of the proportion of patients with gastrointestinal symptoms attributable to COVID-19^[23].

With regard to laboratory test results, the data are scarce; however, the available data showed that patients with cirrhosis and COVID-19 were significantly more likely to have thrombocytopenia than the group of patients with cirrhosis but not COVID-19^[30]. Another Asian multinational study revealed significantly elevated aspartate aminotransferase levels in cirrhotic patients after SARS-CoV-2 infection; meanwhile, the degrees to which the aspartate/alanine transferase and bilirubin levels were elevated in these patients was associated with survival^[14]. Interestingly, the early (usually occurring within the first week of hospitalization) and rapid worsening of these liver biochemicals (*e.g.*, aminotransferase), rather than bile duct enzymes (*e.g.*, alkaline phosphatase, γ -glutamyl transferase), in these cirrhotic patients may indicate that COVID-19-related liver injury is more often caused by drugs or hypoxia in this population. However, further histological and experimental studies are needed to validate this finding^[14]. In summary, although patients with cirrhosis and COVID-19 are presumed to have elevated levels of both liver and bile duct biochemicals (*e.g.*, aminotransferase, bilirubin, alkaline phosphatase, γ -glutamyl transferase) because of the widespread and abundant distribution of angiotensin-converting enzyme 2 (ACE2) receptors in these areas, making them more susceptible to virus-related injury, the mismatch between ACE2 expression in SARS-CoV-2-target organs and ACE2 localization means that ACE2 may not fully explain the liver tropism of SARS-CoV-2, which warrants future larger cohort studies^[43].

Acute decompensation (AD) of liver cirrhosis and acute-on-chronic liver failure (ACLF) are two important complications in patients with cirrhosis, resulting in high mortality and poor outcomes^[44]. It has been proposed that COVID-19 leads to deterioration of hepatic function, leading to AD and ACLF in cirrhotic patients^[17,18,39]. Studies involving patients with cirrhosis and COVID-19 showed that the proportion of patients who developed AD ranged widely from 9.3% to 61.5% (Table 1)^[14,18,19,21,30]. The decompensation events included hepatic encephalopathy (4.5% to 27%)^[14,18,19,21,23,28,31], variceal bleeding (1% to 30.8%)^[14,18,19,21,23,28,30,32,33], worsening ascites (3% to 28%)^[14,18,19,21,28,30,31,33], spontaneous bacterial peritonitis (2.9% to 7%)^[14,18,19], jaundice (23.3%)^[14], and secondary infection (7.1%)^[22]. Moreover, the development of ACLF was reported in 4.8% to 34.6% of patients with cirrhosis and COVID-19^[14,18,23,30-33]. The diversity of the distribution of decompensation events and ACLF development could be attributed to the high heterogeneity among these studies, due to the inclusion of patients with different ethnicities, cirrhosis etiologies and cirrhosis severity levels, and the use of different ACLF definitions (Table 1). Additionally, the relatively small numbers of patients in several studies may complicate the interpretation of these results. Notably,

Table 1 Clinical characteristics of cirrhotic patients infected with SARS-CoV-2

Reference	Patient number (n)	Region	Etiology	Cirrhosis Severity ¹	ACLF ²	Acute decompensation
Qi <i>et al</i> ^[33]	21	China	HCV: 9.5% HBV: 42.9% ALD: 9.5% AIH: 4.8%	CTP-A: 76.2% CTP-B: 14.3% CTP-C: 9.5% MELD: 8 (7-11)	4.8% ³	Variceal bleeding: 19% Ascites: 23.8%
Liu <i>et al</i> ^[32]	17	China	HCV: 11.8% HBV: 70.6%	CTP-A: 88.2% CTP-B: 5.9% CTP-C: 5.9%	APASL: 11.8%	Variceal bleeding: 5.9%
Iavarone <i>et al</i> ^[31]	50	Italy	HCV: 28% HBV: 10% ALD: 24% NAFLD: 6%	CTP-A: 40% CTP-B: 28% CTP-C: 32% MELD: 9 (6-15)	EASL: 28%	HE: 22%
Sarin <i>et al</i> ^[14]	43	Asia	Viral: 60.4% MAFLD: 32.5% ALD: 4.6% AIH: 2.3%	CTP-A: 53.8% CTP-B: 37.2% CTP-C: 9%	APASL: 11.6%	AD event: 9.3% Variceal bleeding: 9.3% HE: 7% Ascites: 23.3% Jaundice: 23.3% SBP: 7%
Moon <i>et al</i> ^[19]	103	International	HCV: 10.5% HBV: 11.8% ALD: 19.7% NAFLD: 22.4%	CTP-A: 44.7% CTP-B: 29.1% CTP-C: 26.2% MELD: 10	N/A	AD event: 25.7% Variceal bleeding: 1% HE: 16.5% Ascites: 27.2% SBP: 2.9%
Lee <i>et al</i> ^[22]	14	Korea	HCV: 14.3% HBV: 35.7% ALD: 35.7% AIH: 7.1%	CTP-A: 64.3% CTP-B: 35.7% MELD: 8 (7-12)	N/A	Secondary infection: 7.1%
Bajaj <i>et al</i> ^[23]	37	United States	HCV: 24.3% ALD: 24.3% NASH: 24.3%	MELD: 17.6 ± 8.6	NACSELD: 30%	Variceal bleeding: 14% HE: 14%
Kimet <i>et al</i> ^[21]	227	United States	N/A	Compensated: 59% Decompensated: 41%	N/A	AD event: 29.5% Variceal bleeding: 3.1% HE: 10.1% Ascites: 4.8%
Shalimar <i>et al</i> ^[30]	26	India	HCV: 7.7% HBV: 11.5% ALD: 34.6% NAFLD: 7.7% AIH: 15.4%	CTP: 8.6 ± 2.3 MELD: 18.1 ± 9.6	EASL: 34.6%	AD event: 61.5% Variceal bleeding: 30.8% Ascites: 7.7%
Marjot <i>et al</i> ^[18]	386	International	HCV: 11% HBV: 21%	CTP-A: 52% CTP-B: 30%	EASL: 23%	AD event: 46% Variceal bleeding: 3%

			ALD: 38%	CTP-C: 17%		HE: 27%
			NAFLD: 26%	MELD: 12 (8-19)		Ascites: 28%
						SBP: 3%
Jeon <i>et al</i> ^[28]	67	Korea	N/A	N/A	N/A	Variceal bleeding: 3%
						Ascites: 3%
						HE: 4.5%

¹Cirrhosis severity based on Child-Turcotte-Pugh classification and model for end-stage liver disease score.

²Definition of acute-on-chronic liver failure (ACLF) based on the The North American Consortium for the Study of End-Stage Liver Disease, Asian Pacific Association for the Study of the Liver, and The European Association for the Study of the Liver guidelines.

³Definition of ACLF was not mentioned in the study.

ACLF: Acute-on-chronic liver failure; AD: Acute decompensation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALD: Alcohol-related liver disease; AIH: Autoimmune hepatitis; CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; APASL: Asian Pacific Association for the Study of the Liver; NAFLD: Nonalcoholic fatty liver disease; EASL: The European Association for the Study of the Liver; SBP: Spontaneous bacterial peritonitis; HE: Hepatic encephalopathy; MAFLD: Metabolic-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis; NACSELD: The North American Consortium for the Study of End-Stage Liver Disease

approximately 20% of patients with cirrhosis and COVID-19 had AD and did not initially present with respiratory symptoms^[18,19]. Therefore, regardless of the presence of respiratory symptoms, the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend that all cirrhotic patients with new or worsening AD or the development of ACLF undergo testing for SARS-CoV-2 during the COVID-19 pandemic^[39,45].

MECHANISMS OF LIVER INJURY IN PATIENTS WITH CIRRHOSIS AND COVID-19

The putative mechanisms underlying liver injury in COVID-19 patients include direct pathogenic virus cytotoxicity, systemic immune system activation and cytokine storms, drug-related liver injury, reactivation of pre-existing liver disease, and hypoxic hepatitis. The major differences between these mechanisms in patients with cirrhotic and noncirrhotic livers are highlighted in [Figure 1](#).

Direct pathogenic virus cytotoxicity

It has been postulated that SARS-CoV-2 uses the same receptor, ACE2, as SARS-CoV to enter host cells, leading to inflammatory responses and cytopathic effects^[46,47]. The expression level and distribution status of the ACE2 receptors in the human body may partially indicate the potential infection targets of SARS-CoV-2^[48]. ACE2 receptors are widespread across the human body and are highly expressed in type II alveolar cells in the lungs, esophageal epithelial cells, absorptive enterocytes in the ileum and colon, myocardial cells, proximal tubule cells in the kidneys, and bladder urothelial cells^[48-50]. In the normal human liver, the expression of ACE2 receptors is particularly high in bile duct epithelial cells (*i.e.*, cholangiocytes) and the vascular endothelium; only a small portion of hepatocytes are positive for ACE2^[10,50,51]. The disruption of cholangiocytes due to the cytopathic effect of SARS-CoV-2 results in bile duct injury and further liver injury^[12,52,53]. In contrast, ACE2 expression was detected in most hepatocytes within cirrhotic nodules, as well as in cholangiocytes and vascular endothelial cells^[51,54]. Patients with cirrhosis also have increased circulating ACE activity and angiotensin II levels, which may facilitate the entry of the virus into host cells, making them more vulnerable to direct virus-related cytotoxicity, leading to a greater severity of hepatic dysfunction and serious clinical consequences^[51,55,56].

Systemic immune system activation

Similar to other viruses, such as cytomegalovirus and Epstein-Barr virus, SARS-CoV-2 can activate excessive innate immune responses and systemic inflammatory reactions, causing rapid disease progression and adverse outcomes^[57,58]. In patients with severe COVID-19, fulminant cytokine storms can occur, involving the release of multiple proinflammatory cytokines and inflammatory markers, including IL-1 β , IL-6, IL-8, IL-17, interferon- γ , granulocyte-colony stimulating factor and tumor necrosis factor-

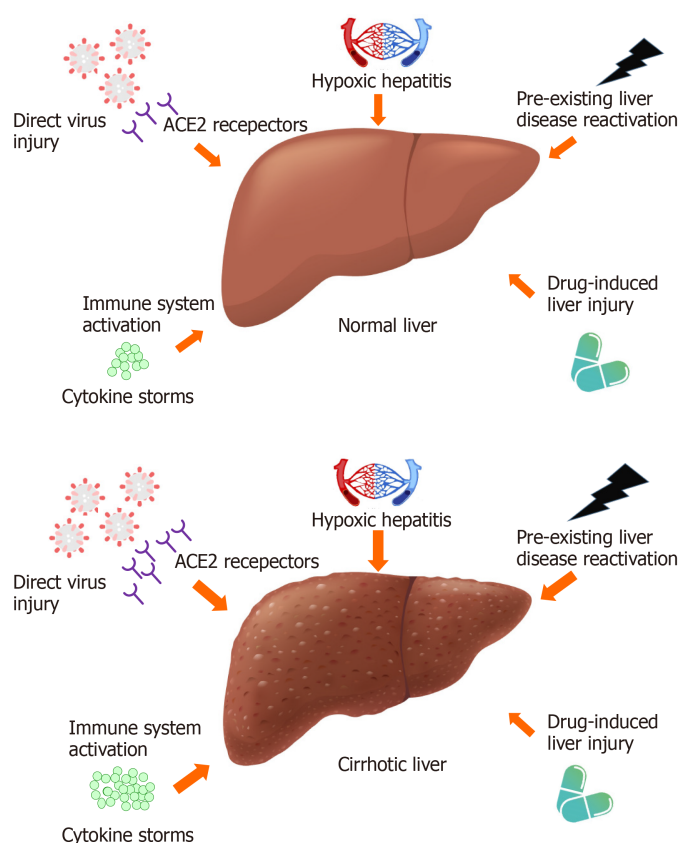


Figure 1 Putative mechanisms of coronavirus disease-2019-related liver injury in the normal liver and the cirrhotic liver. Compared with a normal liver, a cirrhotic liver is more vulnerable to direct injury by the virus because of the widespread ACE2 expression; increased cytokine levels and immune response; similar extent of drug-induced liver injury; more prominent pre-existing liver disease activation; and more severe hypoxic hepatitis. The arrow represents the magnitude of each effect on the liver. The image of SARS-CoV-2 was adapted from an image created by Desiree Ho for the Innovative Genomics Institute. Available from: <https://innovativegenomics.org/free-covid-19-illustrations/>.

α ^[52,59,60]. Hypercytokinemia can damage the tissue of the heart, kidney, lung, and liver, leading to multiple organ failure and mortality^[61]. It is noteworthy that patients with cirrhosis exhibit higher baseline levels of cytokines and are at increased risk of systemic inflammation, which may lead to systemic circulatory and local microcirculatory function impairment, mitochondrial and cell dysfunction, cell death, and organ failure^[62,63].

Lymphocytes, an important type of leukocyte, are responsible for a wide range of immune cell regulation, activation, and proliferative functions necessary for maintaining immune homeostasis^[64]. The degree of lymphopenia, including the numbers of CD4⁺ T cells, CD8⁺ T cells, B cells, and natural killer cells, was associated with disease severity in COVID-19 patients^[61,64-67]. Importantly, cirrhosis disrupts the reticulo-endothelial system, which affects immune surveillance activities, impairs immune protein synthesis, damages circulating immune cells, and compromises immune cells functions, resulting in pancytopenia, including a decreased number of lymphocytes, which is a feature of cirrhosis-associated immune dysfunction^[68,69]. This could partially explain why cirrhotic patients with COVID-19 were at higher risk for severe disease and mortality than noncirrhotic patients^[23,31].

Drug-induced liver injury

During the early phase of the COVID-19 pandemic, multiple drugs, including antiviral agents (*e.g.*, lopinavir/ritonavir, remdesivir, oseltamivir, ribavirin), antibiotics (*e.g.*, macrolides), and corticosteroids, were prescribed. Many of these drugs are metabolized in the liver, and concerns about drug-related hepatotoxicity have been raised, especially when they are used in combination^[70]. Patients who used lopinavir/ritonavir were reported to have a significantly higher proportion with liver function impairment^[71,72], and the administration of systemic corticosteroid or antifungal agents was associated with a risk of elevated aminotransferase levels^[73]. Chloroquine and hydroxychloroquine have been reported to induce acute liver failure, and they should be used with caution in patients with pre-existing liver disease^[70].

Moreover, approximately 15.2% of the patients experienced elevated aminotransferase levels while receiving treatment with remdesivir^[74,75], although two studies revealed similar proportion of patients with elevated levels of aminotransferase in the remdesivir and placebo groups^[76,77]. The EASL suggested that remdesivir should be used with caution in patients with advanced liver disease or severe liver baseline biochemistry derangement^[39]. Overall, the incidence of drug-induced liver injury was estimated to be approximately 25.4% in a meta-analysis^[78]. Nonetheless, concern about SARS-CoV-2 drug-induced liver injury may decrease gradually after the development of vaccines, as vaccine-related hepatotoxicity has rarely been reported^[79-83].

There is a paucity of studies discussing the impact of medications used to treat cirrhosis on patients with cirrhosis and COVID-19. Most guidelines recommend the maintenance of cirrhosis treatment during the COVID-19 pandemic^[39,40,84], although concerns about drug-drug interactions still might exist^[84]. In fact, the more liberal use of nonselective beta-blockers, a standard treatment for lowering portal pressure and the risk of variceal bleeding in patients with cirrhosis, was proposed to reduce unnecessary endoscopic procedures during the COVID-19 pandemic^[45,84,85]. Venous thromboembolism is another emerging clinical problem in patients with cirrhosis due to their hypercoagulable state and coagulation dysregulation^[86]. Evidence from previous studies showed that COVID-19 patients were at increased risk for thromboembolism, which correlated with a worse prognosis^[87]. Therefore, the EASL suggests that patients with cirrhosis and COVID-19 should consider continuing treatment with thromboprophylactic agents^[39], preferably low-molecular-weight heparin, although the actual dose may need further verification by expert consensus^[88,89]. Taken together, after weighing the benefits and risks, resuming treatment for cirrhosis, including with medications intended to prevent the progression or decompensation of liver disease, may be the best strategy in patients with cirrhosis and COVID-19^[18].

Reactivation of pre-existing liver disease

Patients with pre-existing liver disease are presumed to be more vulnerable to COVID-19-related liver damage due to their immune dysregulation and circulatory disturbances, leading to local liver damage and systemic injury^[19,39]. For patients with hepatitis B, the discontinuation of antiviral agents during the COVID-19 pandemic may induce the reactivation of the hepatitis B virus (HBV)^[58], and the administration of tocilizumab, a monoclonal antibody against IL-6 used to control cytokine storms in patients with severe COVID-19, is occasionally reported to cause HBV flare-ups and further hepatic injury^[90,91]. Additionally, systemic corticosteroid administration might cause HBV reactivation and acute liver failure in patients with chronic HBV infection^[84]. Prophylactic antiviral therapy with nucleoside analogues is recommended in patients with known HBV infections undergoing corticosteroid therapy for severe COVID-19^[84].

Cirrhosis is a form of advanced liver disease associated with extensive immune dysfunction and abnormal systemic inflammation^[68]. SARS-CoV-2 infections in patients with cirrhosis is particularly lethal due to the dysregulated immune responses and disordered coagulation^[18]. It is noteworthy that SARS-CoV-2-associated lung injury leading to respiratory failure was the predominant cause of death in patients with cirrhosis, rather than the decompensation of their liver disease^[18,19,29]. This phenomenon could be explained by their altered pulmonary dynamics due to the presence of ascites or encephalopathy, and coexisting lung diseases, including hepatopulmonary syndrome, portopulmonary hypertension, or hepatic hydrothorax, which could exacerbate the risk of respiratory failure in patients with cirrhosis^[18,20]. Despite this, these findings should not contradict the recommendations that standard cirrhosis treatment should be continued with minimal interruptions in these patients, as stated in the guidelines^[39], as their liver dysfunction may also aggravate SARS-CoV-2 induced respiratory failure^[18].

Hypoxic hepatitis

The abundant vascular supply and high metabolic demand in the liver make it vulnerable to circulatory disturbances^[58]. Hypoxic hepatitis, also called ischemic hepatitis, is characterized by a rapid and massive serum aminotransferase elevation resulting from reduced liver oxygen delivery and diminished perfusion in a complication of cardiac, circulatory, or respiratory failure^[92,93]. The ongoing oxygen reduction and lipid accumulation in hepatocytes during shock and hypoxic conditions could lead to mitochondrial damage and cell death, and subsequent reactive oxygen species activation and high levels of oxygen free radicals further amplify the release of proinflammatory cytokines, resulting in liver injury^[40,94]. Given that respiratory failure

and the associated hypoxia are important characteristics of COVID-19^[40], it is reasonable to assume that hypoxia-reperfusion injury is a crucial cause of secondary liver injury in these patients^[40,57,58,94].

Pre-existing liver disease, especially cirrhosis, was also identified as a risk factor for hypoxic hepatitis, leading to a worse prognosis^[20,92]. Cirrhotic livers have abnormal portosystemic shunting and impaired functional flow, dysregulated glutathione synthesis, and increased susceptibility to circulatory failure, all of which could exacerbate hypoxic damage to the liver^[92,95]. Additionally, a hypovolemic state, such as gastrointestinal bleeding, in cirrhotic patients due to coagulopathy could ultimately contribute to the occurrence of hypoxic hepatitis^[96]. The cornerstone of hypoxic hepatitis treatment mostly depends on its early recognition and correction of the underlying disease^[92] (*i.e.*, cirrhosis and COVID-19).

COVID-19 OUTCOMES

It is not surprising that patients with cirrhosis were more likely to have severe COVID-19 than the general population^[7], with proportions ranging from 18.6% to 35.3% (Table 2)^[14,30,32]. Pre-existing cirrhosis was found to be a risk factor for severe COVID-19^[14]. Furthermore, cirrhotic patients are also more likely to develop complications of COVID-19, including ARDS (28.6% to 52%)^[22,31-33], respiratory failure requiring mechanical ventilation (MV) (4% to 38%)^[14,18,19,22,23,31-33], shock (6% to 30%)^[14,22,23,28,31-33], renal failure requiring renal replacement therapy (1.5% to 19%)^[18,19,22,23,28,33], the need for extracorporeal membrane oxygenation (9.5%)^[33], and the need for intensive care unit (ICU) admission (3% to 43%) (Table 2)^[14,18,19,22,23,28,31-33]. It is noteworthy that far greater proportions of COVID-19 patients developed an adverse outcome than receiving the corresponding level of care (*i.e.*, 52% of the patients had ARDS, but only 4% of the patients received MV and were admitted to the ICU) in an Italian study, which reflected the marked scarcity of ICU beds in an area with a high burden of COVID-19^[31]. Therefore, the true number of cirrhotic patients who needed intensive care in these studies may have been underestimated because of the limited availability of healthcare resources during the pandemic^[19].

Compared with the general population with COVID-19, patients with cirrhosis and COVID-19 had higher mortality rates, ranging from 9% to 42.3% (Table 2)^[14,18,19,21-23,28,30-33]. Decompensated liver cirrhosis was identified as an independent risk factor for mortality^[21]; patients with cirrhosis are also at higher risk of COVID-19-related hospitalization and mortality^[20]. Compared with other studies, cirrhosis was not found to be associated with mortality in COVID-19 patients in a Korean nationwide population-based study^[28]. The authors also demonstrated a substantially lower risk of mortality and other complications in patients with cirrhosis and COVID-19^[28]. Nevertheless, the enrollment of all cirrhotic patients (including hospitalized and nonhospitalized patients) and the lack of data on cirrhosis etiology and severity in that study may limit the extrapolation of the results^[28]. Moreover, a North American multicenter study showed that patients with cirrhosis and COVID-19 had a comparable mortality risk to the group of patients with cirrhosis but not COVID-19 (30% *vs* 20%, $P = 0.16$); they also had a similar rate development of ACLF (30% *vs* 23%, $P = 0.11$)^[23]. Whereas the cirrhosis-alone group had worse baseline liver function [*i.e.*, higher Model for End-Stage Liver Disease (MELD) score] in that study, they had more cirrhosis-specific complications (*e.g.*, variceal bleeding, hepatic encephalopathy) during hospitalization. In contrast, the cirrhosis and COVID-19 group had more COVID-19-related complications (*e.g.*, respiratory failure, need for MV, shock), indicating possible different causes of mortality in the two groups^[23]. Taken together, compared with the general population with COVID-19, cirrhotic patients with COVID-19 have a higher risk of in-hospital mortality, but there is still insufficient evidence to support the idea that COVID-19 increases the risk of ACLF or mortality in cirrhotic patients^[39].

The baseline cirrhosis severity in patients correlated with their risk of COVID-19-related morbidity and mortality^[18,19,31]. The MELD score independently predicted mortality in patients with cirrhosis and COVID-19 in an Italian study^[31]. An Asian multinational study concluded that cirrhotic patients with a Child-Turcotte-Pugh (CTP) score of 9 or more at presentation were at higher risk for COVID-19-related mortality^[14]. In line with these findings, a large multinational cirrhosis cohort study revealed that the stage of liver disease (*i.e.*, CTP and MELD score) was associated with a stepwise increased risk of COVID-19-related mortality and the need for admission to the ICU, and CTP-B, CTP-C stage, and baseline MELD score were independent factors

Table 2 Clinical complications and outcomes of cirrhotic patients infected with SARS-CoV-2

Reference	Patient number (n)	COVID-19 severity	COVID-19 complications	Mortality
Qi <i>et al</i> ^[33]	21	N/A	ICU: 23.8% MV: 14.3% Shock: 14.3% ARDS: 28.6% RRT: 9.5% ECMO: 9.5%	23.8%
Liu <i>et al</i> ^[32]	17	Mild ¹ : 64.7% Severe ¹ : 35.3%	ICU: 17.6% MV: 11.8% Shock: 11.8% ARDS: 29.4%	17.6%
Iavarone ^[31] <i>et al</i>	50	N/A	ICU: 4% MV: 4% Shock: 8% ARDS: 52%	34%
Sarin <i>et al</i> ^[14]	43	Severe ² : 18.6%	ICU: 25.6% MV: 23.2% Shock: 14%	16.3%
Moon <i>et al</i> ^[19]	103	N/A	ICU: 23.3% MV: 17.5% RRT: 4.9%	39.8%
Lee <i>et al</i> ^[22]	14	N/A	ICU: 35.7% MV: 21.4% RRT: 7.1% Shock: 28.6% ARDS: 35.7%	28.6%
Bajaj <i>et al</i> ^[23]	37	N/A	ICU: 43% MV: 38% Shock: 30% RRT: 19%	30%
Kim <i>et al</i> ^[21]	227	N/A	Death, hospitalization, oxygen support, ICU, vasopressor support, or MV: 70.5%	25.1%
Shalimar <i>et al</i> ^[30]	26	Mild ³ : 57.7% Moderate ³ : 7.7% Severe ³ : 34.6%	N/A	42.3%
Marjot <i>et al</i> ^[18]	386	N/A	ICU: 28% MV: 18.4% RRT: 5.4%	32%
Jeon <i>et al</i> ^[28]	67	N/A	ICU: 3% Shock: 6% RRT: 1.5%	9%

¹Severe COVID-19 was defined as severe pneumonia (*i.e.*, SpO₂ < 93% despite high-flow nasal cannula O₂ or a respiratory rate (RR) > 30 per minute), features of acute respiratory distress syndrome (ARDS), acute kidney, heart or circulatory failure, altered sensorium or a combination of the above.

²Mild, moderate, and severe coronavirus disease-2019 (COVID-19) were defined as the presence of only upper respiratory tract symptoms without any signs of breathlessness and hypoxia, the presence of pneumonia with a RR between 24 and 30/min and SpO₂ between 90% and 94% on room air, and the presence of pneumonia with a RR > 30/min or SpO₂ < 90% on room air or severe respiratory distress, respectively.

³Severe COVID-19 was defined when patients had 1 of the following criteria: (1) RR ≥ 30/min; (2) Resting SpO₂ < 93%; or (3) Oxygenation index of 300 mm Hg or less. Mild COVID-19 was defined as mild clinical symptoms without pneumonia on imaging.

COVID-19: Coronavirus disease-2019; ICU: Intensive care unit; MV: Mechanical ventilator; ARDS: Acute respiratory distress syndrome; RRT: Renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

associated with the risk of mortality^[18]. These findings have significant prognostic implications and could help clinicians perform risk stratification and make decisions while treating cirrhotic patients with COVID-19, increasing the level of care earlier in those with advanced liver disease^[18]. Furthermore, clinicians could also consider the implementation of palliative care in COVID-19 patients with decompensated cirrhosis who experience rapid clinical deterioration because of their extremely poor prognosis, to ensure appropriate healthcare resource allocation in areas where there is a high burden of COVID-19^[18,39,84].

MANAGEMENT STRATEGIES

Current recommendations for cirrhotic patient management during the COVID-19 pandemic proposed by the EASL, AASLD, and Asian Pacific Association for the Study of the Liver (APASL) are summarized in [Table 3](#).

General consideration

Various methods described to reduce SARS-CoV-2 transmission and infection in the WHO protocol for the general public are also vital to cirrhotic patients, including maintaining a social distance at least one meter, wearing a mask, avoiding closed or crowded places, regularly cleaning hands with alcohol-based hand rub, and washing hands thoroughly with soap and water^[97]. For cirrhotic patients who need outpatient follow-up, several alternative ways to reduce in-person visits could be considered, including telemedicine, video conference or phone tracking^[15,39,40,42,45]. Integrated telehealth provides remote monitoring, focused education, caregiver support, and early intervention to ensure medical compliance^[85]. The continuation of antiviral therapy for viral hepatitis was proposed by all three associations^[15,39,40,45]. The guidelines regarding prophylaxis for decompensation events (e.g., spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy) should be followed to avoid non-COVID-19 cirrhotic-related admission^[15,39]. Moreover, the threshold for hospital admission should be low in patients with cirrhosis and COVID-19 because they are at greater risk of developing adverse outcomes^[15,39]. It is noteworthy that approximately 40% of SARS-CoV-2 infections in cirrhotic patients were healthcare-related in one study^[31]. Therefore, for cirrhotic patients who need inpatient treatment, the designation of non-COVID wards is essential, and limiting patient visitors and minimizing inpatient interaction and transport are also crucial to reduce the possibility of virus transmission^[39,45].

Pharmacological management

Currently, remdesivir is the only United States Food and Drug Administration-approved therapy for hospitalized COVID-19 patients^[98], although several recent large-scale randomized controlled trials revealed conflicting results in the general population with COVID-19^[76,99,100]. There have been no studies on the pharmacokinetics and outcomes of remdesivir use in cirrhotic patients^[45]; only limited data showed that remdesivir did not confer a significant survival benefit on COVID-19 patients with pre-existing chronic liver disease^[21].

Dexamethasone, a potent corticosteroid agent, was shown to reduce the risk of mortality in COVID-19 patients requiring MV^[101]. The National Institutes of Health and Infectious Disease Society of America recommended the use of dexamethasone in hospitalized critically ill COVID-19 patients or those who need supplemental oxygen, noninvasive ventilation, or MV^[102,103]. Similarly, there have been no studies on the use of dexamethasone or alternative corticosteroids in patients with cirrhosis during the pandemic. No statements have been made in favor of or against the routine use of corticosteroids in patients with cirrhosis and COVID-19 in the current guidelines^[39,45].

Table 3 Guidelines recommended for the management of cirrhosis patients during the COVID-19 pandemic

	EASL	AASLD	APASL
Outpatient	Common rules of physical distancing	Limited outpatient visitsWearing mask and keeping appropriate distancing	Phone or telemedicine
	Early admission for patient infected with SARS-CoV-2	Limited family or friend accompanied	Limited travel
	Prevent decompensation (<i>e.g.</i> , variceal bleeding, HE, SBP) and avoid admission	Video conference, phone or telemedicine	Continue hepatitis B and C treatment
	Telemedicine or remote monitor	Provide prescriptions for 90 d instead of 30 dLimited travel	
	Continue hepatitis B and C treatment	Continue hepatitis B and C treatment	
	Receive vaccination for <i>Streptococcus pneumoniae</i> and influenza		
Inpatient	Designate non-COVID-19 ward	Designate non-COVID-19 ward	Option of palliative treatment for advanced liver disease with COVID-19 disease
	Perform SARS-CoV-2 testing in patient with new or worsening decompensation or ACLF	Perform SARS-CoV-2 testing in patient with new or worsening decompensation or ACLF	
	Option of palliative treatment for patient with advanced liver disease with COVID-19	Minimize interaction and transport for patient Telemedicine equipmentLimit patient visitors	
Endoscopy	Limit to emergency (<i>e.g.</i> , GI bleeding or bacterial cholangitis) in patient with COVID-19	Limit to emergency (<i>e.g.</i> , GI bleeding or bacterial cholangitis) in patient with COVID-19	Limit to emergency (<i>e.g.</i> , GI bleeding or bacterial cholangitis) in patient with COVID-19
	SARS-CoV-2 testing prior to endoscopic procedureNo delay in endoscopy in areas with low COVID-19 burden	SARS-CoV-2 testing prior to endoscopic procedure	PPE used in endoscopy for patient and staff
	Noninvasive tool for variceal surveying	PPE used in endoscopy for patient and staff Clean and disinfect the operation room	Variceal survey can be arbitrary postponed 3 mo depend on COVID-19 outbreak. Noninvasive tool for variceal survey
		Prophylaxis with beta-blocker instead of endoscopic screening	Prophylaxis with beta-blocker instead of endoscopic screening
HCC surveillance	Deferred in patients with COVID-19 until recovery	Deferred in patients with COVID-19 until recovery	Prioritized for patients at high risk
	Prioritized for patients at high risk (<i>e.g.</i> , elevated alpha-fetoprotein level or advanced cirrhosis)	Continued radiological surveillance, but an arbitrary delay of 2 mo is reasonable	Continued radiological surveillance, but an arbitrary delay of 3 mo is reasonable

EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Disease; APASL: Asian Pacific Association for the Study of the Liver; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HE: Hepatic encephalopathy; SBP: Spontaneous bacterial peritonitis; ACLF: Acute on chronic liver failure; GI: Gastrointestinal; PPE: Personal protective equipment; HCC: Hepatocellular carcinoma

As previously mentioned, tocilizumab, is a humanized monoclonal antibody targeting IL-6, which is a key driver of cytokine storms in severe COVID-19. Tocilizumab was postulated to counter dysregulated inflammation and reduce the need for organ support in patients with severe COVID-19^[39]; however, it failed to confer any clinical or survival benefit on patients with severe COVID-19 in a recent randomized controlled trial^[104]. The National Institutes of Health and Infectious Disease Society of America warned against the routine use of tocilizumab in hospitalized patients, including cirrhotic patients^[102,103].

Liver-specific procedures

Routine screening for esophageal varices (EVs) and hepatocellular carcinoma (HCC) is essential for patients with cirrhosis^[39,105]. Esophagogastroduodenoscopy is an effective method of assessing bleeding severity and stopping bleeding in cirrhotic patients with

EVs. However, as endoscopy is considered an aerosol-generating procedure, its performance is associated with the risk of SARS-CoV-2 transmission^[40,45,106]. Current guidelines recommend the postponement of nonurgent or elective endoscopies during the pandemic^[107,108], depending on the local prevalence of COVID-19, patient risk factors, and treatment center resources^[105]. Urgent or emergent endoscopies should only be performed in cases of active gastrointestinal bleeding or bacterial cholangitis^[39,40,84]. If they must be performed, all patients should first be tested for SARS-CoV-2^[39,45], and healthcare workers involved in the endoscopy should wear a full set of personal protection equipment, including double gloves and N95 masks^[45,84,108]. Regarding deferring HCC screening in patients with COVID-19 until recovery^[39,40], a multidisciplinary approach to individual risk evaluation should be implemented based on local resources^[39,40,105]. Patients at a high risk of HCC (*e.g.*, active viral hepatitis, advanced cirrhosis, elevated α -fetoprotein level) should be prioritized^[39,105]; otherwise, most patients can be monitored at prolonged intervals reaching up to eight months^[105]; or delayed follow-up for two to three months^[40,45].

CONCLUSION

In this unprecedented COVID-19 pandemic, although patients with cirrhosis account for a small portion of the total population, they are more vulnerable to viral infection, resulting in both hepatic and extrahepatic complications, which are further associated with a higher risk of mortality and greater healthcare resource utilization. Because of their immune dysfunction, cirrhotic patients have distinct features of COVID-19-related liver injury. Data focusing on their clinical manifestations and laboratory results after SARS-CoV-2 infection are scarce, and more importantly, whether COVID-19 is a trigger of AD or ACLF in patients with cirrhosis is still unknown. As there is no pharmacological therapy proven to be effective in cirrhotic patients with COVID-19, the maintenance of standard care for cirrhosis and the avoidance of virus transmission are the cornerstones of management. As the COVID-19 vaccines become available, their safety and efficacy in cirrhotic patients need further investigation. We hope that both healthcare providers and patients can stand together to be strong enough to weather the storm.

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