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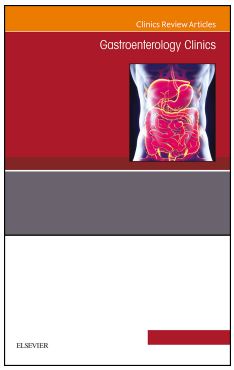

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Liver and Biliary Tract Disease in Patients with COVID-19 Infection

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Keywords: COVID-19, SARS-CoV-2, cirrhosis, chronic liver disease, acute liver disease, abnormal liver biochemistries, liver transplantation, vaccination

Key points:

- Hepatic biochemical test abnormalities in patients with Coronavirus disease-2019 (COVID-19) can be encountered in up to 50% of infected individuals; the pattern of liver injury is mostly

hepatocellular, while the mechanism of liver injury is thought to be multifactorial. Chronic hepatobiliary manifestation of cholangiopathy is being increasingly recognized.

- Underlying chronic liver disease is not uncommon in patients with COVID-19 infection, and such patients with cirrhosis have higher and increasing mortality with liver disease severity as assessed by Child-Pugh class.
- Because of the high rate of hepatic decompensation in patients with cirrhosis following COVID-19 infection, early diagnosis and early admission should be emphasized.
- While response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination may be suboptimal in immunosuppressed and immunocompromised patients, patients with cirrhosis receiving SARS-CoV-2 vaccination can result in a reduction of COVID-19 infection, COVID-19 related hospitalization, and mortality; thus, patients with chronic liver disease and particularly patients with cirrhosis, liver-transplant candidates and liver transplant recipients are strongly recommended for COVID-19 vaccination.

Abstract

Coronavirus disease-2019 (COVID-19) had become a global pandemic since March 2020. Although, the most common presentation is of pulmonary involvement, hepatic abnormalities can be encountered in up to 50% of infected individuals, which may be associated with disease severity, and the mechanism of liver injury is believed to be multifactorial. A unique entity of cholangiopathy is being increasingly recognized following COVID-19 infection. Chronic liver disease is not uncommon in patients with COVID-19, and patients with cirrhosis have higher mortality when stratified according to Child-Pugh class; therefore, early diagnosis and early management should be emphasized in patients with cirrhosis to prevent further hepatic decompensation. Guidelines for management in patients with chronic liver

disease during COVID-19 era are being regularly updated. Patients with chronic liver disease and cirrhosis, including liver transplant candidates and liver transplant recipients are strongly recommended to receive SARS-CoV-2 vaccination because it can reduce COVID-19 infection, COVID-19 related hospitalization, and mortality.

Introduction

Coronavirus disease-2019 (COVID-19), the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019, and has become a global pandemic since March 2020, leading to significant morbidity and mortality in humans. Although, it most commonly presents with pulmonary manifestations, hepatic abnormalities can be encountered in up to 50% of infected individuals, which can vary in severity from asymptomatic to severe liver injury.[1] Chronic liver disease (CLD) is not uncommon in the background of patients hospitalized with COVID-19 infection, which is, in itself, associated with more severe COVID-19 disease and higher mortality,[2] especially in patients with cirrhosis.[3] This review summarizes hepatic manifestations in patients with COVID-19 infection and outcome in those with chronic liver disease (CLD), and addresses vaccination and management of patients with CLD during the ongoing COVID-19 pandemic.

Prevalence of liver dysfunction and hepatobiliary manifestation in SARS-CoV-2-infected patients

The incidence of elevated liver biochemistries in hospitalized COVID-19 infected patients ranges from 14-83%.[2] More commonly, an elevation of aspartate transaminase (AST) has been reported in 8-83%, and an elevation of alanine transaminase (ALT) in 10-61%; however, mild elevation of bilirubin has been reported in 3-23%, of alkaline phosphatase (ALP) in 1-22%, and of gamma-glutamyl transferase (GGT) in 13-54% of patients with COVID-19 infection.[4-25] Abnormalities in liver biochemistries are reported with similar frequencies regardless of the presence of pre-existing liver disease.[26] The pattern of liver

injury is mostly hepatocellular rather than cholestatic.[1] Mild AST and ALT elevations of 1-2 times the upper limit of normal (ULN) are commonly observed early in the disease course. AST is usually higher than ALT, and this may increase with COVID-19-associated-disease severity and mortality, which could possibly reflect non-hepatic injury.[2,27] One retrospective cohort of patients with COVID-19 infection from the United States (n=3,381) noted mild liver injury in 45%, moderate in 21%, and severe acute liver injury in 6.4% of hospitalized patients with COVID-19.[28] Usually the hepatic biochemical test abnormalities return to normal values within 2-3 weeks without specific treatment.[18] Liver injury is more commonly observed in severe COVID-19 cases than in mild cases, and COVID-19 infection in patients with elevated liver biochemistries (especially with AST and ALT elevation > 5 times ULN) was associated with higher mortality.[29] Hypoalbuminemia at hospital admission has also been a marker of COVID-19 severity.[30-32] When assessing COVID-19 patients with elevated hepatic biochemical tests, other etiologies unrelated to COVID-19 such as viral hepatitis should be considered.[2] Further, pregnant patients with COVID-19 infection have also been reported to have AST or ALT elevation in up to 21-22%, suggesting that appropriate monitoring of hepatic biochemical tests is needed in this population.[33] Notably, a recent study reported that patients with COVID-19 had underlying chronic liver disease in around 2-11%.[14] Patients with more advanced liver disease had higher mortality after COVID-19 infection, with the highest mortality among patients with cirrhosis and with the rate increasing with more severe liver disease, as assessed by Child-Pugh class.[2,34]

Mechanisms of liver injury from COVID-19 infection

SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally-encoded RNA dependent RNA polymerase.[2] There are several potential mechanisms and causes of liver injury in patients with COVID-19 infection, some of which may be virus specific and others non-specific. Liver histologic findings at autopsy[35] have noted one or more features of microvesicular/macrovesicular steatosis, mixed

lobular necroinflammation and portal inflammation, focal necrosis, and porto-venous/sinusoidal micro-thrombosis **(Figure 1)**.

1) Direct hepatic infection by SARS-CoV-2

SARS-CoV-2 binds to target cells through angiotensin-converting enzyme 2 (ACE2) entry receptors. ACE2 is present in both hepatocytes and cholangiocytes; therefore, liver is a potential target for infection and may be the pathogenesis of SARS-COV-2-related liver injury**.** ACE2 expression in healthy liver is found in the cholangiocytes (59.7%) and this rate is much higher than in the hepatocytes (2.6%),[36] thus, liver injury may result from direct viral damage to bile duct epithelial cells which have been known to be significant in liver regeneration and immune response,[37] although the exact mechanism is still unclear. Multiple levels of evidence, using autopsy samples, suggest SARS-CoV-2 liver tropism, including detection of SARS-CoV-2 viral RNA by PCR in up to 55-69% of liver samples,[38,39] successful isolation of infectious SARS-CoV-2 particles, and identification of transcription-, proteomic- and transcription factor-based activity profiles in hepatic autopsy samples.[39] For example, transcriptomic profiling confirmed the expression of known SARS-CoV-2 entry receptors and proteins that included ACE2, transmembrane protease serine 2 (TMPRSS2), procathepsin L (CTSL), Ras-related protein Rab-7a (RAB7A), and the high-density lipoprotein scavenger receptor B type 1 (SR-B1)[39] and with relative upregulation of type-I,-II and -III interferons, JAK/STAT (Janus kinase/ signal transducer and activator of transcription) and metabolic signaling in the RT-PCR-positive livers.[40]

2) Host inflammatory response to SARS-CoV-2

Following SARS-CoV-2 infection, the host immune response can be triggered which can cause excessive release of inflammatory mediators such as IL-6, IL-10, IL-2 and interferon gamma in parallel with disease severity and which in turn may lead to a cytokine storm.[41] To support this hypothesis, studies have noted that COVID-19 patients in an ICU setting with multi-organ failure have features of severe hepatic

dysfunction associated with higher inflammatory markers.[6,18] Global proteomic profiling in hepatic tissues has noted significant upregulation of type I and II interferon (IFN) responses after SARS-CoV-2 infection.[39]

3) Drug-induced liver injury (DILI)

Medications used during treatment of COVID-19 include antibiotics, antiviral agents, corticosteroids, and immunomodulators which can variably cause liver injury. Cai Q reported that the use of lopinavir/ritonavir increased the risk of liver injury by four-fold.[17] Remdesivir (a nucleoside analog inhibitor of viral RNA polymerase) has been associated with a 23% increase in hepatic biochemical levels.[42] Transaminase elevations have been observed in patients treated with tocilizumab (IL-6 inhibitors).[43] A systematic review reported the pooled incidence of drug-induced liver injury in patients with COVID-19 at 25.4% (95%CI 14.2-41.4).[29] Further, some drugs used in combination such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and Chinese herbal medicines may also account for hepatotoxicity. A large global series noted that transaminase elevation was preferentially caused by antiviral drugs administered empirically due to their known therapeutic efficacy for other viral infections. Often a hepatocellular pattern has been encountered as opposed to cholestatic or mixed injury. Outcome was favorable in most patients and fatality attributable to a drug was rare.[2,14]

4) Pre-existing liver diseases

About 2-11% of patients with COVID-19 have underlying CLD.[14] Data on pre-existing liver diseases in COVID-19 from two international registries (SECURE-Cirrhosis and COVID-Hep)(n=745) reported etiologies including non-alcoholic fatty liver disease (NAFLD) 43%, alcohol-related liver disease (ALD) 24%, chronic hepatitis B (HBV) infection 12%, and chronic hepatitis C (HCV) infection 13%. In this cohort, 48% had CLD without cirrhosis and 52% had cirrhosis.[3] Corticosteroids or other immunosuppressive agents for COVID-19 treatment may facilitate HBV reactivation in patients with occult or chronic HBV infection.[35] Further, patients with more advanced liver disease may be at increased risk of infection due to cirrhosis-associated immune dysfunction.[44]

5) Cholangiopathy / secondary sclerosing cholangitis

Several case series have reported delayed-onset and progressive cholestasis as a unique clinical entity in patients following severe COVID-19 infection.[45-48] Cholestasis is present early in the disease course and cholangiopathy occurs later. A retrospective study from a single US center[45] reported 12 patients who experienced progressive biliary injury after recovering from severe COVID-19, characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by evidence of biliary tree abnormalities on imaging. Median time from COVID-19 diagnosis to onset of cholangiopathy was 118 days. Magnetic resonance cholangiopancreatography (MRCP) findings included beading of intrahepatic ducts, multifocal strictures, and dilation of the biliary tree. Liver biopsy has noted features of acute and/or chronic bile duct obstruction without ductopenia. The pathogenesis is still unclear. These manifestations may represent changes due to biliary tree ischemia, that may reflect a continuum of secondary sclerosing cholangitis in critically ill patients (SSC-CIP), and/or may also be a consequence of direct infection of SARS-CoV-2 of the liver and biliary tract.[46,49] Furthermore, this complication may be more frequently encountered in patients with pre-existing CLD.[48]

6) Hypoxic-ischemic liver injury

In critically ill patients, hemodynamic instability may cause liver injury from a hypoxic-ischemic process which causes a rise in aminotransferases in the setting of shock or cardiac failure.[41] Ischemic hepatitis and hepatic congestion related to cardiomyopathy is a common consequence of COVID-19 infection, occurring in 33% of individuals in one US series.[22] Further, venous and arterial thromboses are currently recognized as a feature of COVID-19, including hepatic involvement.[50]

COVID-19 and patients with chronic liver diseases

In a cohort of 2,780 multicenter US patients with COVID-19 (CLD 9%), CLD was associated with significantly higher mortality (RR=2.8, 95%CI 1.9-4.0). Mortality was higher in patients with cirrhosis (RR=4.6, 95%CI 2.6-8.3). Fatty liver disease and non-alcoholic steatohepatitis (NASH) were the most common etiologies among the patients with CLD and the mortality was independent of risk factors of body mass index, hypertension, and diabetes.[26] Another large cohort from an International Registry (SECURE-Cirrhosis and COVID-Hep) in patients with CLD and cirrhosis (n=745) noted 32% mortality in patients with cirrhosis versus 8% in those without cirrhosis (p<0.001); and mortality in patients with cirrhosis increased according to liver disease severity based on Child-Pugh classification.[3] Studies on COVID-19 outcome and mortality in patients with CLD and cirrhosis are described in **Table 1**.

Viral hepatitis

A retrospective cohort from Hong Kong (n=5,639, 6.3% current HBV infection, 6.4% past HBV infection) demonstrated that current or past HBV infection was not associated with more severe liver injury or mortality from COVID-19.[51] Similarly, a large retrospective cohort from China (n=2,073 patients with COVID-19) found that HBV infection was not associated with the risk of poor COVID-19 outcomes.[52] Notably appropriate use of antiviral therapy for HBV during corticosteroid therapy for COVID-19 should be considered to minimize the risk of HBV reactivation. In parallel, data from the Electronically Retrieved Cohort of HCV infected Veterans (ERCHIVES) (including 975 HCV-positive and 975 propensity score matched HCV-negative persons with SARS-CoV-2 infection) demonstrated similar mortality in patients with versus without HCV infection.[53]

Autoimmune liver diseases

De novo autoimmune hepatitis may rarely occur following SARS-CoV-2 infection.[49] Data on patients with autoimmune hepatitis (AIH) and SARS-CoV-2 infection from 3 international registries (ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis)(n=932 CLD with SARS-CoV-2, including 70 with AIH) demonstrated that patients with AIH were not at increased risk of adverse outcomes and mortality despite receiving

immunosuppressants.[54] Another retrospective study on patients with AIH and COVID-19 from an international multicenter study (110 patients with AIH) revealed that patients with AIH were not at risk for worse outcomes following COVID-19. Cirrhosis was an independent predictor of severe COVID-19 in patients with AIH (OR=17.46; 95%CI 4.22-72.13, p< 0.001), and maintenance of immunosuppression during COVID-19 was not associated with an increased risk of severe COVID-19 but could lower the risk of new-onset liver injury.[55] This finding should reassure clinicians not to routinely reduce immunosuppression in such patients following COVID-19 infection.

NAFLD

Patients with NAFLD are at increased overall risk of developing severe COVID-19 which may be contributed by the presence of other high-risk co-morbidities such as obesity, diabetes mellitus, and hypertension.[49] A retrospective study from China (202 patients with COVID-19, including 37.6% with NAFLD, demonstrated that NAFLD was associated with COVID-19 progression (OR=6.4, 95%CI 1.5-31.2), and patients with NAFLD had a longer viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days, p<0.0001) compared to patients without NAFLD.[56] Patients with NAFLD are more likely to develop liver injury when having COVID-19 infection, but no patient developed severe liver-related complications during hospitalization in one cohort from China (280 COVID-19 patients including 30% with NAFLD).[57] Moreover, patients with NAFLD, with non-invasive fibrosis scores [fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS)] appeared to correlate with a higher likelihood of developing severe COVID-19, irrespective of metabolic comorbidities.[58] A large US multicenter study (n=363, NAFLD 15.2%) demonstrated that NAFLD was independently associated with ICU admission (OR=2.30, 95%CI 1.27-4.17) and mechanical ventilation (OR=2.15, 95%CI 1.18-3.91); and presence of cirrhosis was an independent predictor of mortality (OR=12.5, 95%CI 2.16-72.5).[59] Additionally, a systematic review and meta-analysis on clinical outcomes in NAFLD patients with COVID-19 (14 studies including 1,851 NAFLD patients) found an increased risk of

severe COVID-19 and admission to ICU due to COVID-19 in patients with underlying NAFLD; however, no difference in mortality was observed between NAFLD versus non-NAFLD patients.[60]

Alcohol-related liver disease (ALD)

Alcohol-related liver disease (ALD) has been reported as an independent risk factor for mortality (OR=1.79, 95%CI 1.03-3.13) in CLD patients with COVID-19.[3] The frequency of ALD has rapidly increased since the beginning of COVID-19 pandemic. Data from United Network for Organ Sharing (UNOS) demonstrated a significant increase in ALD listing (+7.26%; p<0.001) during the COVID-19 pandemic, and ALD (40.1%) accounted for more listings than those due to HCV (12.4%) and NASH (23.4%) combined.[61] The greatest increase in ALD listing has been among young adults aged 18-34 years and aged 35-50 years (plus 35%) and among patients with severe alcohol-associated hepatitis (plus 50%). This rise in alcoholism may be due to COVID-19 related stressors, such as unemployment or increased health risks due to the pandemic.

Cirrhosis

Patient with cirrhosis have high rates of hepatic decompensation, acute-on-chronic liver failure (ACLF), and death from respiratory failure following SARS-CoV-2 infection.[50] Data from an International Registry (SECURE-Cirrhosis and COVID-Hep) on COVID-19-infected patients with CLD and cirrhosis (n=745, including 386 patients with cirrhosis, 359 with non-cirrhotic CLD from 21 countries in 4 continents reported mortality in COVID-19-infected patients with cirrhosis at 32% versus mortality in CLD without cirrhosis at 8% (p< 0.001). Mortality increased according to Child-Pugh class (mortality in classes A [19%], B [35%], and C [51%]) in patients with cirrhosis with respiratory failure being the main cause of death (71%). In this study, there was also an increase in mortality following hospitalization, admission to ICU, and invasive ventilation, with Child-Pugh class C patients having 90% mortality in those requiring mechanical ventilation **(Figure 2)**.[3] Acute hepatic decompensation occurred in 46% and half of these patients had ACLF, and around 21% of patients with cirrhosis infected with SARS-CoV-2 lacked respiratory symptoms; hence, patients with new onset of hepatic decompensation or ACLF should be tested for SARS-

CoV-2 even in the absence of respiratory symptoms. This large cohort also demonstrated that age, baseline liver disease stage (especially Child-Pugh classes B and C), and ALD were independent risk factors for mortality from COVID-19.[3] The possible pathogenesis linking cirrhosis and severe COVID-19 lung disease is likely multifactorial and likely related to factors such as increased systemic inflammation, cirrhosis-associated immune dysfunction, coagulopathy, and intestinal dysbiosis.[50] A multicenter-matched cohort study from North America compared mortality in those with cirrhosis and COVID-19 (n=37) vs. cirrhosis alone (n=127) vs. COVID-19 alone (n=108) and reported that patients with cirrhosis and COVID-19 had higher mortality compared to COVID-19 alone (30% vs 13%, *p*=0.03), but comparable to cirrhosis alone (30% vs 20%, *p*=0.16); in those with ACLF, the mortality was similar regardless of COVID-19 (55% vs 36%, *p*=0.25).[62] Recent meta-analysis of 63 studies revealed a pooled odds ratio for all-cause mortality of 2.48 (95% CI: 2.02-3.04) in patients with cirrhosis and COVID-19.[63] Accordingly, patients with cirrhosis infected with SARS-CoV-2, should have their COVID-19 vaccination prioritized due to their high mortality.

Post-liver transplant

As opposed to patients with cirrhosis, liver-transplant recipients do not appear to have an increased mortality following SARS-CoV-2 infection compared with the matched general population.[50] A prospective nationwide study conducted by the Spanish Society of Liver Transplantation (SETH) reported the incidence of COVID-19 to be higher in LT patients, but mortality (around 18%) was lower than in the matched general population; in this cohort, mycophenolate was associated with a risk of developing severe COVID-19 in a dose-dependent manner.[64] Another large multicenter study from two international registries (COVID-Hep and SECURE-Cirrhosis), including 151 LT recipients with COVID-19 infection, found that LT was not associated with increased mortality (rate=18.5%) **(Figure 2)**, whereas increased age and presence of comorbidities (such as elevated creatinine level and non-liver cancer) were associated with mortality among LT-recipients.[65] Such data is consistent with data from the European Liver and Intestine

Transplantation Association (ELITA)/the European Liver Transplant Registry (ELTR) multicenter COVID-19 registry (149 LT centers, 243 COVID-19-infected LT recipients) where the mortality was 20%, with mortality being higher in patients > 70 years old, and with comorbidities (such as impaired renal function or diabetes mellitus); contrariwise, tacrolimus use was associated with improved survival.[66] Studies on COVID-19 outcomes in patients with post-liver transplantation are reported in **Table 2**.

Hepatocellular carcinoma (HCC)

In a US multi-center study of adult patients with CLD and COVID-19 (n=867), HCC was found to be a factor associated with higher overall mortality (HR=3.31, 95%CI 1.53-7.16) independent of ALD and decompensated cirrhosis.[67] Concomitantly, in another study from France on COVID-19 patients with CLD (15,476 CLD patients with COVID-19), 30-day mortality was associated with primary liver cancer (OR=1.38, 95%CI 1.17-1.62, p<0.001), chronic liver disease (OR=1.79, 95%CI 1.71-1.87, p<0.001), decompensated cirrhosis (OR=2.21, 95%CI 1.94-2.51, p<0.001) and alcohol use disorders (OR=1.11, 95%CI 1.05-1.17, p<0.001).[68] HCC is often associated with liver cirrhosis, suggesting that impaired immunity may increase the risk of developing severe COVID-19.[69]

Notably, COVID-19 may exacerbate pre-existing liver disease and thus complicate HCC management.[70] An experience from a multicenter study from France in patients with HCC (n=670, 293 with SARS-CoV-2 infection and 377 without infection) demonstrated fewer patients with HCC presenting to the multidisciplinary tumor board, especially with their initial HCC diagnosis. Treatment strategy was modified in 13.1% of patients, and patients experienced significant treatment delay (≥ 1 month) in 2020 compared with 2019 (21.5% vs 9.5%, p<0.001). Around 7.1% of HCC patients had a diagnosis of active COVID-19 infection (52.4% hospitalized, 19.1% mortality).[71] Summaries of recommendations from the AASLD Expert Panel Consensus Statement[1] and the EASL-ESCMID position paper[34,72] on the management of patients with chronic liver diseases during COVID-19 era are reported in **Table 3**.

COVID-19 vaccination in patients with chronic liver disease and liver-transplant recipients

Adult CLD patients, particularly those with cirrhosis, are strongly recommended to receive COVID-19 vaccination.[73] A large cohort study of patients with cirrhosis from the Veterans Administration (VA) on the clinical outcome of mRNA vaccines compared with unvaccinated patients reported that patients with CLD who received at least one dose of an mRNA vaccine (n=20,037) had a 64.8% reduction in SARS-CoV-2 infections and 100% protection against hospitalization or death at 28 days after the initial dose.[74] The rate of reduction of SARS-CoV-2 infection after the first dose in those with decompensated cirrhosis was 50.3% and in those with compensated cirrhosis was 66.8%. Receiving a second dose of the vaccine was associated with a 78.6% reduction in COVID-19 infection and 100% reduction in COVID-19-related hospitalization or death after 7 days.[74] Another retrospective study among US veterans demonstrated that some patients with cirrhosis developed breakthrough COVID-19 infection after full or partial vaccination; however, these infections were associated with reduced mortality compared to those without vaccination.[75]

A case series (n=40, including 21 with CLD and 19 with LT) from the SECURE-Cirrhosis and COVID-Hep international registries reported that vaccination against SARS-CoV-2 appears to result in favorable outcomes, as demonstrated by the absence of the need for mechanical ventilation, the need for ICU care, or death among fully-vaccinated patients.[76] Risk factors for lower serological response to immunization included older age, use of antimetabolite drugs, time from transplantation, and use of B cell-depleting therapies.[73] A study on immunogenicity of the first and second dose of the mRNA SARS-CoV-2 vaccine among solid organ transplant recipients demonstrated low levels of detectable antibody around 17% at 20 days after the first dose[77] and 54% at a median of 29 days after the second dose.[78] The French National Authority for Health recommends administration of a third dose of vaccine in immunosuppressed patients based on the data on three doses of the BNT162b2 mRNA COVID-19 vaccine (manufactured by Pfizer-

BioNTech) in solid organ transplant recipients (n=101) that reports significant improvement in anti-SARS-CoV-2 antibody response (up to 68% at 4 weeks after the third dose).[79] A fourth dose of SARS-CoV-2 vaccine was associated with slightly improved humoral response among patients with a weak response after 3 doses but no improvement among those with no response after 3 doses, although, no breakthrough infections were observed during follow-up.[80]

Additionally, a prospective cohort study that compared the SARS-CoV2-specific humoral and T-cell immune response after the second mRNA vaccination in patients with cirrhosis and in LT recipients (n=194 including 141 LT and 53 cirrhosis Child-Pugh classes A-C) demonstrated that after the second dose, seroconversion was achieved in 63% of LT recipients and 100% of patients with cirrhosis and controls using the anti-S trimer assay (p<0.001).[81] Spike-specific T-cell response rates were 36.6%, 65.4%, and 100% in LT recipients, cirrhosis, and controls, respectively. Around 28% of LT recipients did not develop both humoral and T-cell response after the second vaccination. These data, therefore, support the potential role for a third vaccine dose, especially in LT recipients with low or absent prior vaccine responses. In this cohort, predictors of absent or low humoral response were age > 65 years (OR=4.57, 95%CI 1.48-14.05) and arterial hypertension (OR=2.50, 95%CI 1.10-5.68). In contrast, failure was less likely with calcineurin inhibitor monotherapy versus other immunosuppressive regimens (OR=0.36, 95%CI 0.13-0.99).[81] Guideline recommendations for COVID-19 vaccination in chronic liver disease and liver-transplant recipients[73,82,83] are described in **Table 4**. The Centers for Disease Control (CDC) recommendations on vaccinations are periodically updated and can be accessed by the link of https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html.

Acute liver injury after COVID-19 vaccination

A large epidemiological study from Europe reported no increment in new AIH cases diagnosed during the widespread use of COVID-19 vaccination; and these data do not support the assumption that

COVID-19 vaccination induces AIH.[84] However, *de novo* AIH-liked liver injury occurring after COVID-19 vaccination has been reported in case series in which data from 18 countries demonstrated liver injury after SARS-CoV-2 vaccination (n=87, 63% female).[85] Liver injury was diagnosed at a median of 15 (range 3-65) days after vaccination, attributed to the Pfizer-BioNTech (BNT162b2) vaccine in 59%, the Oxford-AstraZeneca (ChAdOX1 nCoV-19) vaccine in 23%, and the Moderna (mRNA-1273) vaccine in 18%. The liver injury was predominantly hepatocellular (84%) and 57% of patients had features of immune-mediated hepatitis (positive autoantibodies and elevated immunoglobulin G levels). Corticosteroids were administered to 53% of patients and resulted in complete biochemical resolution without a relapse after corticosteroid withdrawal. Outcome was generally favorable, except for one patient who developed fulminant liver failure.[85] Of note, the mechanisms leading to acute liver injury after COVID-19 vaccination have not been fully elucidated and it is difficult to establish a definite causal relationship between COVID-19 vaccination and hepatitis. Furthermore, these events are extremely rare and respond well to corticosteroid treatment, and the overall benefits of vaccination outweigh the risks of liver injury; thus, this side effect should not represent a barrier to SARS-CoV-2 vaccination.[49]

Conclusion

COVID-19 infection has had a major impact on people across the world since December 2019, causing up to 6.5 million deaths globally until now in 2022. Patients with chronic liver disease, especially cirrhosis, and liver-transplant recipients are particularly vulnerable to severe COVID-19. These populations are, therefore, strongly recommended to receive COVID-19 vaccination to reduce their morbidity and mortality. Data on vaccine safety and efficacy is emerging, but several issues remain unresolved, such as prevalence of breakthrough infection after vaccinations, adequate doses and timing of vaccination in those receiving immunosuppressants or in transplant recipients. Management of immunosuppressive agents in post-LT patients with severe COVID-19 infection requires further study. As the COVID-19

pandemic rapidly evolves in different regions due to the emergence of mutant strains, early diagnosis and treatment of COVID-19 in patients with advanced liver disease deserves a special focus to minimize the risk of hepatic decompensation. The pandemic has been further associated with increased alcohol consumption, unhealthy eating behaviours, and interruptions of hepatology care which may lead to an increase in severity of liver disease; therefore, clinicians should strongly recommend alcohol cessation and provide health education to their patients with liver diseases.

FIGURE LEGENDS AND TABLES

Figure 1. Proposed mechanisms of liver injury from SARS-CoV-2 infection.

Figure 2. Mortality in patients with COVID-19 infection in chronic liver disease, cirrhosis (Child-Turcotte-Pugh classes A, B, and C) and liver-transplant recipients, and stepwise increment of mortality in patients with chronic liver disease and cirrhosis following hospitalization, admission to ICU and invasive ventilation. *(Data from Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. Journal of hepatology. 2021;74(3):567-577; and Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. The Lancet Gastroenterology & Hepatology. 2020;5(11):1008-1016)*

Table 1. Studies on COVID-19 outcome and mortality in patients with chronic liver disease and cirrhosis.

Study	Number	Country	Pre-existing liver diseases	Findings
Yadav DK, et al.[86] (meta-analysis)	2,115	China	4% (mostly cirrhosis and HBV)	- High prevalence of liver injury (27%). - Patients with liver injury had more severe COVID infection (OR=2.57, *p*=0.01), and higher mortality (OR=1.66, *p*=0.03). - Overall mortality in patients with COVID-19 infection with liver injury is 23.5%.
Sarin SK, et al.[87] (The APCOLIS study	228	13 Asian countries	185 CLD patients including 43 with cirrhosis (NAFLD in 55%, and viral hepatitis in 30%)	- Mortality in CLD patients with COVID-19 vs. cirrhosis with COVID-19 (2.7% vs. 16.3%, *p*=0.002). - 43% of CLD presented with acute liver injury, 20% of patients with cirrhosis presented with either ACLF (11.6%) or acute decompensation (9%). - A Child-Turcotte Pugh score ≥ 9 at presentation predicted high mortality [HR=19.2 (95% CI 2.3-163.3), *p*<0.001].
Mallet V, et al.[68]	15,476 COVID-19 patients with chronic liver disease	France	Chronic liver disease (alcohol-induced 23%, HBV 5%, HCV 4.6%, HCC 4.6%, LT 2.1%)	- 30-day post-COVID mortality with chronic liver disease 19%. - Chronic liver disease increased risk of COVID-19-related death. - Patients with alcohol use disorders, decompensated cirrhosis, or primary liver cancer had an increased risk of COVID-19-related mortality.
Butt AA, et al.[53] (ERCHIVES database)	SARS-CoV-2 with HCV=975, SARS-CoV-2 without HCV=975	USA	HCV	- HCV infected persons with SARS-CoV-2 are more likely to be admitted to a hospital. - Mortality was not different between those with vs. without HCV infection.
Verhelst X, et al.[88]	110	Belgium	Autoimmune hepatitis	- Low COVID-19 infection rate (1.2%), survival 100%, liver decompensation 0%, hospitalization 3.5%. - Supports not stopping immunosuppressive treatment during COVID-19 infection.
Di Giorgio A, et al.[89]	148	Italy	Autoimmune liver diseases (AILD)	- Confirmed cases of COVID-19 3%, survival 99%, mortality 1%. - Patients with AILD were not more susceptible to COVID-19 than the general population. Tapering or withdrawal of immunosuppression was not required.
Marjot T, et al.[54] (ERN RARE-LIVER/COVID-	932 patients with CLD and COVID-19 (70 with AIH)	International registry	Autoimmune hepatitis	- No differences in major outcomes between patients with AIH and non-AIH CLD, including hospitalization (76% vs. 85%; *p*=0.06), ICU admission (29% vs. 23%; *p*=0.240), and death (23% vs. 20%; *p*=0.64). - Factors associated with mortality within the AIH cohort included old age,

Hep/SECURE-Cirrhosis)				and Child-Pugh class B and C cirrhosis, but not use of immunosuppression.
Younossi ZM, et al.[90]	4,835 patients with COVID-19 (NAFLD=553)	USA	NAFLD	- 3.9% of patients with NAFLD and COVID-19 infection experienced acute liver injury. - Crude inpatient mortality in the NAFLD group was 11%. - Independent predictors of mortality included higher FIB-4 and multimorbidity scores, morbid obesity, older age, and hypoxemia on admission.
Kim D, et al.[67] (The COLD study)	867 CLD=620 (71.5%) Cirrhosis=227 (26.2%) ALD=94 NAFLD=456 HBV=62 HCV=190 HCC=22	US multicenter	Chronic liver disease and cirrhosis	- The overall all-cause mortality was 14%. - Independent risk factors for overall mortality were ALD (HR=2.42, 95%CI 1.29-4.55), decompensated cirrhosis (HR=2.91, 95%CI 1.70-5.00) and HCC (HR=3.31, 95%CI 1.53-7.16).
Jin Ge, et al.[91] (The National COVID Cohort Collaborative (N3C) study)	220,727 patients with CLD and known SARS-CoV-2 test status: 58% non-cirrhosis/negative, 13% non-cirrhosis/positive, 24% cirrhosis/negative, 4% cirrhosis/positive SARS-CoV-2 test	USA	Chronic liver disease and cirrhosis	- SARS-CoV-2 infection was associated with 2.38 times hazard ratio of all-cause mortality within 30 days among patients with cirrhosis.
Marjot T, et al.[3] (SECURE - cirrhosis and COVID-Hep)	745 ALD=179 NAFLD=322 HBV=96 HCV=92 HCC=48	International registry	Chronic liver disease and cirrhosis	- Mortality in patients with cirrhosis 32% vs. mortality in chronic liver disease 8%. - Mortality according to Child-Pugh classes was class A (19%), B (35%), and C (51%). - ALD was an independent risk factor for death (OR=1.79, 95%CI 1.03-3.13). - In the CLD cohort, mortality increased following hospitalization, admission to ICU, and invasive ventilation. - After adjusting for baseline characteristics, NAFLD, viral hepatitis, and HCC were not independently associated with death.
Lavarone M, et al.[92]	50	Italy	Cirrhosis	- Overall 30-day mortality was 34%. - COVID-19 was associated with liver function deterioration and mortality in cirrhosis. - Severity of lung and liver diseases (according to CLIF-C ACLF, CLIF-OF

				and MELD scores) independently predicted mortality. - No major adverse events were related to thromboprophylaxis (heparin administered to 80% of patients) or antiviral treatments.
Clift AK, et al.[93] (population-based cohort study)	11,865 patients with cirrhosis (0.2% of total cohort)	UK	Cirrhosis	- Increased hazard ratio for COVID-19-related mortality in patients with cirrhosis. - Male cirrhosis (HR=1.29, 95%CI 0.83-2.02), Female cirrhosis (HR=1.85, 95%CI 1.15-2.99).
Bajaj JS, et al.[62]	- Patients with cirrhosis & COVID-19 (n= 37) - Patients with COVID-19 (n=108) - Patients with cirrhosis (n=127)	North America and Canada	Cirrhosis	-Patients with cirrhosis & COVID-19 had higher mortality compared with patients with COVID-19 (30% vs. 13%, *p*=0.03) but not between patients with COVID-19 and those with cirrhosis alone (30% vs. 20%, *p*=0.16).
Ioannou GN, et al.[94] (Veterans Affairs national healthcare system)	305 cirrhosis with SARS-CoV-2	USA	Cirrhosis	- SARS-CoV-2 infection was associated with a 3.5-fold increase in mortality in patients with cirrhosis. - 30-day mortality for patients with cirrhosis and SARS-CoV-2 infection was 18%. - The most important predictors of mortality were advanced age, decompensated cirrhosis, and high MELD score.

COVID-19: Coronavirus disease-2019; SARS-CoV-2: The severe acute respiratory syndrome coronavirus 2; CLD: chronic liver disease; ALD: alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; AIH: autoimmune hepatitis; HCC: hepatocellular carcinoma; LT: liver transplant; ACLF: acute-on-chronic liver failure; FIB-4: fibrosis-4; HR: hazard ratio; OR: odds ratio; MELD: Model for End-Stage Liver Disease.

Table 2. Studies on COVID-19 outcome and mortality in liver transplant recipients.

Study	Numbers of LT recipients with SARS-CoV-2 infection	Country	Findings
Rabiee A, et al.[95]	112	USA	- Mortality 22.3%. - Moderate liver injury (ALT 2-5x ULN) 22.2%, severe liver injury (ALT > 5x ULN) 12.3%. - Liver injury in LT recipients was associated with mortality (p=0.007; OR=6.91) and ICU admission (p=0.007; OR=7.93). - Reduction of immunosuppression during COVID-19 was not associated with mortality (p=0.084).
Colmenero J, et al.[64] (SETH registry)	111	Spain	- Mortality 18%, severe COVID-19 31.5%. - LT patients had an increased risk of acquiring COVID-19 but their mortality was lower than the matched general population. - Mycophenolate may increase the risk of severe COVID-19 in a dose-dependent manner.
Kates OS, et al.[96]	73	USA	- The 28-day mortality among solid organ transplant cohort (n=482 hospitalized with COVID-19) was 20.5%. - LT was not associated with increased 28-day mortality (p=0.36).
Ravanan R, et al.[97] (UK National Health Service Blood and Transplant registry)	64	England	- SOT recipients with SARS-CoV-2 infection had a higher all-cause mortality compared to wait-listed patients (25.8% vs. 10.2%). - LT recipients had a lower SARS-CoV-2 infection rate than other SOT recipients (OR=0.53, 95%CI 0.40-0.70).
Webb GJ, et al.[65] (SECURE-cirrhosis and COVID-Hep)	151	International registry	- Overall mortality was 18.5%. - LT did not significantly increase the risk of death. - Age, high creatinine level, and non-liver cancer were associated with mortality among LT recipients.
Belli LS, et al.[66] (ELITA/ELTR COVID-19 registry)	243	Europe	- Mortality 20.2%, respiratory failure was the major cause of death. - Older age, diabetes, and chronic kidney disease were associated with mortality. - Tacrolimus use (HR=0.55, 95%CI 0.31-0.99) had a positive independent effect on survival.

Polak WG, et al.[98] (ELITA/ELTR COVID-19 registry)	57 SARS-CoV-2-infected LT candidates, 272 SARS-CoV-2-infected LT recipients	Europe	- Incidence of COVID-19 among LT candidates was 1.05% and LT recipients 0.34%. - Mortality was 18% among LT candidates and 15% among LT recipients.

COVID-19: Coronavirus disease-2019; SARS-CoV-2: The severe acute respiratory syndrome coronavirus 2; LT: liver transplant; ALT: alanine transaminase; ULN: upper limit of normal; HR: hazard ratio; OR: odds ratio; N: number of patients; SOT: solid organ transplant.

Table 3. Guideline recommendations for patients with chronic liver diseases during COVID-19 pandemic.

Chronic liver diseases	AASLD recommendation[1] and EASL-ESCMID position paper[34,49,72]
Chronic viral hepatitis (HBV and HCV)	- Continue treatment for hepatitis B or C if patient already receiving treatment. - HBsAg and anti-HBc should be tested prior to initiating corticosteroid therapy, JAK 1/2 inhibitor, and tocilizumab therapy. - Initiating hepatitis B treatment should be considered if hepatitis B flare is clinically suspected or when initiating immunosuppressive therapy, corticosteroids, or IL-6 monoclonal antibody therapy. - Initiating hepatitis C treatment should be delayed until after resolution of COVID-19 infection.
Autoimmune liver diseases	*Without COVID-19 infection* - Continue the same dosage of immunosuppressive agents to prevent a disease flare. - Vaccination for *Streptococcus pneumoniae* and influenza should be emphasized. *With COVID-19 infection* -In case of worsening pneumonia attributed to COVID-19 infection, lowering the overall level of immunosuppressive therapy should be considered (individualized adjustment). - If active AIH, initiating immunosuppressive therapy is recommended despite COVID-19 infection. - In AIH patients with active COVID-19 infection and elevated liver biochemistries, do not presume flare of AIH without biopsy confirmation.
NAFLD	- Preventing liver disease progression by intensive lifestyle modifications, including weight loss advice and diabetes control. - Early admission should be considered for all patients with NAFLD who become infected with SARS-CoV-2.
Alcohol-related liver disease (ALD)	- Encourage alcohol cessation. - Clinicians should weigh the risk of susceptibility for severe COVID-19 when initiating corticosteroids in patients with severe alcoholic hepatitis.
Cirrhosis	- Prophylaxis for spontaneous bacterial peritonitis (SBP), gastrointestinal hemorrhage, and hepatic encephalopathy

	should be maintained to prevent hospitalization due to portal hypertension-related complications. - Patients with new onset of hepatic decompensation or ACLF should be tested for SARS-CoV-2 even in the absence of respiratory symptoms. - Early admission is recommended if COVID-19 is diagnosed. - All patients should receive vaccination for *Streptococcus pneumoniae* and influenza.
Liver transplant recipients	*Without COVID-19 infection* - No reduction of immunosuppression to prevent acute rejection. - Emphasize importance of vaccination for *Streptococcus pneumoniae* and influenza. *With COVID-19 infection* - Early admission is recommended. - Do not assume acute cellular rejection without biopsy confirmation in LT recipients in the presence of active COVID-19 infection and elevated liver biochemistries. - Minimizing dosage of immunosuppressive therapy should be considered case-by-case under specialist consultation based on severity of COVID-19 and risk of graft rejection. - Lower the overall level of immunosuppression (e.g., azathioprine or mycophenolate) to decrease the risks of superinfection, especially with anti-metabolite therapies. - Closely monitor calcineurin inhibitor levels, for features of acute kidney injury, and potential drug-drug interactions. - Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection.
HCC	*Without COVID-19 infection* - Continue to perform surveillance in patients at risk for HCC as close to schedule as possible. Delay of schedule for two months is reasonable. - For HCC patients, care should be maintained according to guidelines, including continuing systemic treatments and evaluation for LT. *With COVID-19 infection* - HCC surveillance can be deferred until after recovery.

	- For HCC patients, early admission is recommended. Locoregional therapies should be postponed and immune-checkpoint inhibitors should be temporarily withdrawn.

COVID-19: Coronavirus disease-2019; SARS-CoV-2: The severe acute respiratory syndrome coronavirus 2; HBV: hepatitis B virus; HCV: hepatitis C virus; JAK: Janus kinase; AIH: autoimmune hepatitis; NAFLD: non-alcoholic fatty liver disease; LT: liver transplant; HCC: hepatocellular carcinoma; IL: interleukin; ACLF: acute-on-chronic liver failure.

Table 4. Guideline recommendations for COVID-19 vaccination in chronic liver disease and liver transplant recipients *(Data from Refs [73,82,83])*

Guideline recommendations for COVID-19 vaccination in chronic liver disease
▪ Patients with CLD who are receiving antiviral treatment for HBV or HCV or medical treatment for PBC or AIH should continue their medications while receiving the COVID-19 vaccines. ▪ Patients with HCC undergoing locoregional or systemic therapy should be considered for vaccination without treatment interruption. ▪ An additional third dose of an mRNA vaccine is recommended at least 28 days after the second dose of an mRNA COVID-19 vaccine in all immunosuppressed patients, HCC, and CLD patients receiving prednisone, anti-metabolites, or biological therapies with a booster three months after the third dose. ▪ It is not recommended to withhold immunosuppression prior to or after COVID-19 vaccine.
Guideline recommendations for COVID-19 vaccination in liver-transplant recipients
▪ COVID-19 vaccination is recommended for all LT recipients. ▪ LT candidates should receive a COVID-19 vaccine prior to transplantation whenever possible, if not, the optimal time to administer the COVID-19 vaccine is ≥ 3 months post-LT. However, immunization may be initiated as early as 4 weeks post-transplant, especially for high-risk individuals. ▪ A reduction in immunosuppression is not recommended in LT recipients when receiving COVID-19 vaccine due to the risk of ACR. ▪ COVID-19 vaccination should be avoided in LT recipients with active ACR. ▪ Potential live liver donors and recipients should be vaccinated ≥ 2 weeks before transplantation if feasible. ▪ Family members and caregivers of LT recipients should also be vaccinated against SARS-CoV-2. ▪ LT recipients who recover from COVID-19 infection should still complete COVID-19 vaccine series.

COVID-19: Coronavirus disease-2019; SARS-CoV-2: The severe acute respiratory syndrome coronavirus 2; CLD: chronic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; PBC: primary biliary cholangitis; AIH: autoimmune hepatitis; HCC: hepatocellular carcinoma; LT: liver transplant; ACR: acute cellular rejection.

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