

Coronavirus Disease-2019 and Implications on the Liver



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KEYWORDS

• Cirrhosis • Immunosuppression • SARS-CoV-2 • Transplant • Vaccination

KEY POINTS

- The coronavirus disease-2019 (COVID-19) pandemic has had a substantial impact on patients with chronic liver disease (CLD) and liver transplantation (LT) recipients.
- The management of many CLD has been significantly altered by the COVID-19 pandemic.
- Vaccination against COVID-19 protects patients with CLD and LT recipients from adverse outcomes and is safe in these patients.
- Vaccine efficacy may be reduced in LT recipients and other immunosuppressed patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is responsible for causing coronavirus disease-2019 (COVID-19). SARS-CoV-2 was first detected in humans in late 2019 and spread to become a worldwide pandemic. This virus is most similar to the beta-coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), that were responsible for the SARS outbreak in 2002 to 2003 and the MERS outbreak in 2012, respectively. SARS-CoV-2 primarily causes upper respiratory tract infections and pneumonia. Severe cases can lead to acute respiratory distress syndrome and death. Although the lung manifestations are the most common and most severe, SARS-CoV-2 has effects on other organs including the liver and gastrointestinal tract. The aim of this article is to review the effects of SARS-CoV-2 on the liver and how COVID-19 and the resulting pandemic have altered the outcomes and management of chronic liver diseases (CLDs) and liver transplantation (LT).

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EFFECTS OF CORONAVIRUS DISEASE-2019 ON THE LIVER

Coronavirus Disease-2019 and Abnormal Liver Biochemistries

Abnormalities in liver biochemistries are common in patients with COVID-19, with a highly variable prevalence of 14% to 83% in hospitalized patients and occurring more frequently in severe COVID-19.^{1–5} Liver biochemical abnormalities are most commonly characterized as mild elevations of alanine transaminase (ALT) and aspartate transaminase (AST) (<5 times the upper limit of normal [xULN]). Bilirubin is usually normal or only slightly elevated and alkaline phosphatase/gamma-glutamyl transferase elevations are uncommon (occurring in 6% and 21% of patients, respectively).⁶ AST levels do not correlate with markers of muscle breakdown (creatinine kinase) or systemic inflammation (C-reactive protein and ferritin), suggesting that elevations seen in the setting of COVID-19 may be due to direct liver injury.⁷ However, the incidence of liver biochemical abnormalities in patients with COVID-19 does not seem to be associated with the presence of preexisting CLD.⁸ The aminotransferase elevation in COVID-19 is often AST-predominant, which is similar to alcohol-related liver disease and ischemic hepatitis.⁷ The pattern of AST-predominant aminotransferase elevation has also been associated with COVID-19 disease severity.⁴ The reason for AST predominance is unclear but could be related to hepatic hypoperfusion from COVID-19-induced microthrombotic disease⁹ or systemic hypoxia. The fact that similar AST-predominant elevations were reported during the 2009 influenza H1N1 outbreak could support the hypothesis that systemic hypoxia is the underlying driver of this liver enzyme pattern.¹⁰ Low albumin levels in the setting of COVID-19 can also be seen and correlate with more severe COVID-19.¹¹ Severe liver injury, defined as elevations in total bilirubin and/or evidence of synthetic dysfunction, is uncommon but associated with poorer clinical outcomes.⁵ Given the frequency of elevated liver biochemistries in patients hospitalized with COVID-19, it is recommended that liver biochemistries be monitored regularly in this patient population.¹²

There can be many reasons for elevated liver biochemistries in patients with COVID-19, including muscle breakdown in the setting of myositis or cardiac injury, direct hepatic infection with SARS-CoV-2, hepatic ischemia caused by hypotension or thrombosis, cytokine release syndrome/immune-mediated injury, post-COVID cholangiopathy, and drug-induced liver injury (DILI) (Fig. 1). Given the broad differential, determining the exact cause of the elevated liver biochemistries in a patient with COVID-19 can be challenging and the cause is often multifactorial. Fig. 2 offers a proposed algorithm for the evaluation of abnormal liver tests in the patient with COVID-19.

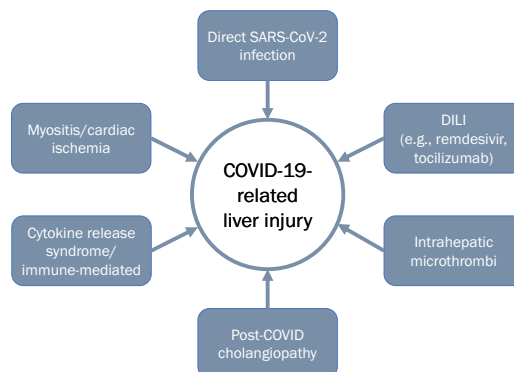


Fig. 1. Potential causes of COVID-19-related liver injury. DILI, drug-induced liver injury.

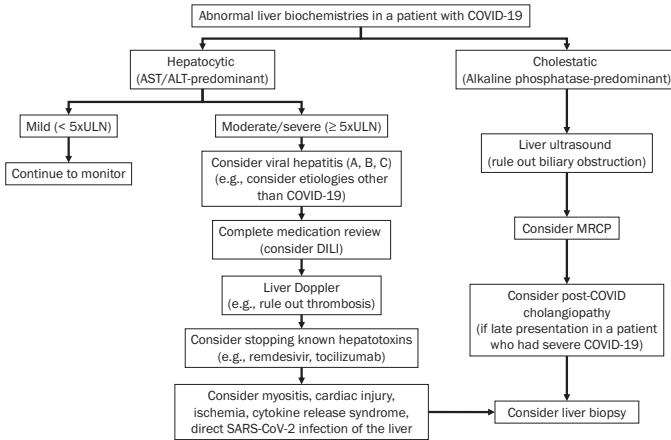


Fig. 2. Algorithm for the evaluation of abnormal liver biochemistries in the patient with COVID-19. DILI, drug-induced liver injury; MRCP, magnetic resonance cholangiopancreatography; ULN, upper limit of normal.

Direct Hepatic Infection via Angiotensin-Converting Enzyme 2 and/or Dipeptidyl Peptidase 4

SARS-CoV-2 binds to cells using angiotensin-converting enzyme 2 (ACE2) as a receptor and is subsequently internalized.¹³ In the liver, ACE2 is found on cholangiocytes, sinusoidal epithelial cells, and hepatocytes. Direct viral infection of hepatocytes and cholangiocytes is one potential mechanism for COVID-19-induced hepatic injury because of the presence of ACE2 on these cells. Gene expression of ACE2 is greatest in cholangiocytes with levels that are comparable to alveolar type 2 cells in the lung.¹⁴ Autopsy results from patients with COVID-19 have shown the presence of SARS-CoV-2 within hepatocytes confirming that hepatic infection by SARS-CoV-2 does occur,¹⁵ likely via ACE2. Hepatic ACE2 levels are significantly upregulated in several CLDs including hepatitis C virus (HCV) (30-fold increase)¹⁶ and nonalcoholic steatohepatitis (NASH) (compared with those with simple steatosis),¹⁷ potentially predisposing these patients to more frequent and/or significant liver injury caused by COVID-19.

Another enzyme that may be responsible for direct hepatic insult from COVID-19 is dipeptidyl peptidase-4 (DPP-4). MERS-CoV is known to use DPP-4 as a receptor for cell entry and SARS-CoV-2 can also use DPP-4 as a receptor.¹⁸ DPP-4 is found in most organs but is present in particularly high levels in the liver. It is often upregulated in diabetes and the metabolic syndrome,¹⁹ which are frequently present in NASH. DPP-4 may also play a role in hepatic fibrosis.²⁰ Although these findings may suggest a possible mechanism of direct COVID-19-related liver injury, whether DPP-4 is truly responsible for elevated liver biochemistries in patients with COVID-19 is still unproven.

Thrombosis and Ischemia

Another possible mechanism of liver injury during COVID-19 is due to a pro-thrombotic state leading to microthrombi and resulting ischemia. It has been well documented that COVID-19 produces a hypercoagulable state that increases the risk of thrombosis and microvascular thrombosis.²¹ Autopsy studies of patients who died from COVID-19 have discovered the presence of microthrombi in several organs including the liver. In one study, liver biopsy samples from 48 patients who died from

severe COVID-19 revealed portal venous and sinusoidal microthrombi in all patients.⁹ A meta-analysis of several autopsy studies found a lower, but still significant, prevalence of hepatic vascular thrombosis (29%).²² This study also reported cases of hepatic venous outflow obstruction and phlebosclerosis of the portal vein.

Immune-Mediated Injury

COVID-19 is known to cause a significant pro-inflammatory response and cytokine release syndrome; therefore, an immune-mediated injury may be contributing to elevated liver biochemistries in patients with COVID-19. Patients with COVID-19 with elevated liver biochemistries are more likely to have fever, higher levels of pro-inflammatory markers (C-reactive protein and procalcitonin), and higher lactate dehydrogenase.²³ However, further study is needed to determine if COVID-19 truly causes an immune-mediated liver injury.

Post-Coronavirus Disease Cholangiopathy

Cholangiopathy has been described as a rare, late liver-related complication of severe COVID-19.^{24–26} In one study of 2047 patients who were hospitalized with COVID-19, 12 patients with severe COVID-19 developed cholangiopathy.²⁵ The imaging and histologic findings in these patients were similar to the previously described secondary sclerosing cholangitis in critically ill patients (SSC-CIP).²⁷ Typical magnetic resonance cholangiopancreatography findings in these patients included beading of intrahepatic bile ducts and bile duct wall thickening with enhancement. Several patients underwent liver biopsy that showed large bile duct obstruction without bile duct loss. The average time to cholangiopathy diagnosis was 118 days after initial COVID-19 diagnosis. Five of these patients were eventually evaluated for LT because of persistent jaundice, hepatic dysfunction, and/or recurrent episodes of bacterial cholangitis, and one did eventually undergo LT.²⁵ The underlying pathogenesis explaining why post-COVID cholangiopathy occurs is not currently understood and further study in this area is needed.

Effect of Coronavirus Disease-2019-Directed Therapies on the Liver

DILI is a frequent cause of elevated liver biochemistries in hospitalized patients with COVID-19, including two COVID-19-directed therapies, remdesivir, and tocilizumab, that have been implicated as possible causes of DILI in patients with COVID-19.

Remdesivir, a viral RNA polymerase inhibitor, was one of the first drugs to show efficacy against COVID-19. The earliest studies of compassionate-use remdesivir showed that elevated liver biochemistries were the most frequently reported adverse event. Compared with placebo, patients receiving remdesivir more frequently had treatment discontinued for elevated transaminases or bilirubin. However, these studies were not adequately powered to determine if a significant difference existed.²⁸ Subsequently, a large randomized controlled trial of remdesivir use in COVID-19 showed no difference in liver biochemistries between treatment and control groups.²⁹ Nonetheless, it is still recommended to avoid remdesivir in patients with ALT greater than 5 xULN and it should be discontinued if ALT increases above this level while on treatment.

Tocilizumab, an IL-6 antagonist that inhibits the pro-inflammatory cytokine cascade, has been used to treat COVID-19. Tocilizumab-induced liver injury has previously been documented in patients receiving it for rheumatoid arthritis, although these events are very rare.³⁰ There have also been several case reports of apparent tocilizumab-DILI in patients with COVID-19, with one patient having aminotransferase elevations greater than 40 xULN³¹; however, these cases are also very rare.

Tocilizumab is not recommended in patients with aminotransferase elevations greater than 5 xULN.

ALCOHOL-RELATED LIVER DISEASE AND THE CORONAVIRUS DISEASE-2019 PANDEMIC

In the years before the start of the COVID-19 pandemic, alcohol consumption and mortality from alcohol-associated liver disease were already on the rise.³² During the COVID-19 pandemic this rise has continued and even accelerated. Stay-at-home orders early in the pandemic led to social isolation, loss of support systems including addiction treatment programs, disruptions in work and education, and easier access to alcohol (eg, online, takeout), all factors that likely contributed to a significant increase in alcohol consumption and alcohol-associated liver disease during the pandemic.³³ This manifested in drastic increases in listings for LT (7% increase) and LT (10% increase) for alcohol-associated liver disease.³⁴ Transplant listing and LT for severe alcohol-associated hepatitis alone have also rapidly increased by over 50%, likely because of an increased burden of alcohol-related liver disease during the pandemic but also due to an unrelated nationwide shift away from strict policies requiring at least 6 months of alcohol abstinence before consideration of LT.

CORONAVIRUS DISEASE-2019 OUTCOMES IN LIVER DISEASE

Chronic Liver Disease and Cirrhosis

Several studies have shown that patients with CLD are not more likely to be diagnosed with COVID-19^{2,35} and one study indicated that patients with cirrhosis might actually have a lower risk of testing positive for SARS-CoV-2.³⁶ This is likely due to increased patient adherence to public health measures such as social distancing because it is unlikely that cirrhosis provides a protective effect. However, once patients with pre-existing liver disease of any etiology are diagnosed with COVID-19, they have higher rates of mortality than those without liver disease. Respiratory failure is the leading cause of death in patients with CLD and COVID-19, followed by liver-related causes.^{8,37}

The same has been shown in patients with cirrhosis even after adjusting for covariates (eg, etiology of liver disease, race, comorbidities, geographic region).³⁸ Outcomes seem to be correlated with severity of pre-existing cirrhosis, with odds ratio (OR) of death for Child-Pugh (CP)-A 1.90, CP-B 4.14 and CP-C 9.32.³⁷ Outcomes for patients with decompensated cirrhosis and COVID-19 are extremely poor, with mortality rates as high as 80% for patients who require intensive care unit (ICU) admission.³⁷ Although early mortality rates in patients with cirrhosis and COVID-19 are high, the rates of death and readmission at 90 days for patients who survive the acute insult return to baseline risk.³⁹ Therefore, COVID-19 does not seem to result in long-term progression of liver disease outside of the acute infection period.

Viral Hepatitis

In 2017, the World Health Organization released the first Global Hepatitis Report and set a goal of eliminating viral hepatitis by 2030.⁴⁰ Unfortunately, the necessary diversion of limited health care resources toward COVID-19 efforts limited the identification of new hepatitis B virus (HBV) and HCV infections and also limited access to treatment. This delay in viral hepatitis elimination and treatment because of the COVID-19 pandemic will certainly result in worse long-term viral hepatitis outcomes, with many patients progressing to cirrhosis and developing its accompanying complications such as hepatocellular carcinoma (HCC). A modeling study of 100 countries

predicted that a 1-year delay in the diagnosis of HCV could lead to an additional 44,800 cases of HCC and 72,300 deaths from HCV worldwide by 2030.⁴¹ Fortunately, the presence of HBV or HCV alone is not associated with COVID-19 mortality.⁴² In addition, antiviral therapy for HBV or HCV has not been associated with worsened COVID-19 outcomes.

Nonalcoholic Steatohepatitis

It has been well documented that older age, obesity and diabetes are associated with worsened COVID-19 outcomes.³⁵ Given obesity and diabetes are often comorbid with NASH, there has been concern that patients with NASH are at increased risk of poor COVID-19-related outcomes. However, whether NASH independent of comorbidities increases the risk of severe COVID-19 and death is unclear. Several studies have suggested this might be true: nonalcoholic fatty liver disease (NAFLD) has been associated with worsened COVID-19 outcomes independent of obesity and other comorbidities.^{43,44} However, a large international cohort of 745 patients with cirrhosis and/or CLD failed to show an increased risk of mortality for NAFLD patients with COVID-19 (HR 1.01, 95% CI 0.57–1.79).³⁷

Autoimmune Hepatitis

There has also been concern that patients with autoimmune hepatitis (AIH) would be at increased risk of COVID-19-related morbidity and mortality. Interestingly, despite the use of immunosuppression, patients with AIH seem to have similar outcomes compared with patients with other CLD.⁴⁵ Furthermore, AIH patients seem to have equivalent rates of COVID-19-related mortality when compared with the general population, and immunosuppression was not shown to be an independent risk factor for mortality or severe COVID-19.^{45,46}

Liver Transplant Recipients

Given their immunosuppressed state, it was feared that LT recipients would be at increased risk for severe COVID-19 and death. LT recipients are diagnosed with COVID-19 more frequently than non-transplant recipients.^{47,48} However, this is likely because of closer monitoring and a lower threshold for testing in this patient population as opposed to an increased risk of SARS-CoV-2 infection per se. LT recipients do seem to report more frequent gastrointestinal symptoms, with diarrhea occurring in 30% to 40%,^{49,50} but rates of elevated liver biochemistries are similar between LT and non-LT recipients.^{49,51} LT recipients are also more likely to have chronic kidney disease, type 2 diabetes mellitus, and obesity, which are well known risk factors for worse COVID-19-related outcomes. Yet, the studies to date have been conflicting. Several studies have reported high mortality rates in solid organ transplant recipients with COVID-19.^{50,52} However, after controlling for covariates including comorbidities, several other studies have suggested that LT recipients may not be at an increased risk of severe COVID-19 or death compared with non-LT recipients.^{47,49} This would be consistent with studies from the prior novel coronavirus outbreaks (SARS and MERS) that showed LT recipients were not at increased risk of morbidity and mortality compared with the general population.⁵³ The suggestion of similar clinical outcomes between LT recipients and non-transplant recipients could be explained by the theorized protective effects of immunosuppression against a SARS-CoV-2-induced severe inflammatory host response, which is thought to be a primary driver in severe COVID-19.⁵⁴ This is supported by data showing that high dose dexamethasone improves mortality in patients with severe COVID-19.⁵⁵

MANAGEMENT OF CHRONIC LIVER DISEASE DURING THE CORONAVIRUS DISEASE-2019 PANDEMIC

The optimal management of CLD during the COVID-19 pandemic is continually evolving as new data become available. In addition, management varies based on the presence or absence of active SAR-CoV-2 infection and on the underlying liver disease etiology (Table 1).

Autoimmune Hepatitis

Without coronavirus disease-2019

Given the risk of a flare/relapse with reduction or discontinuation of immunosuppression,⁵⁶ providers should not adjust baseline immunosuppression for AIH in hopes of preventing COVID-19-related morbidity and mortality. A new diagnosis of AIH or a flare of existing AIH should be treated as clinically appropriate despite the risk of SARS-CoV-2 infection.

Table 1 Management of CLD during the COVID-19 pandemic		
Etiology	Without COVID-19	With COVID-19
Autoimmune hepatitis	<ul style="list-style-type: none"> Do not preemptively reduce immunosuppression Treat new diagnosis or flare as clinically appropriate 	Mild COVID-19: <ul style="list-style-type: none"> Do not reduce immunosuppression Moderate/severe COVID-19: <ul style="list-style-type: none"> Consider reducing immunosuppression by 25%-50% Consider reducing or stopping antimetabolite (eg, azathioprine, mycophenolate)
Chronic viral hepatitis	No change (ie, start or continue antiviral therapy as clinically appropriate)	HBV: <ul style="list-style-type: none"> Initiate or continue treatment if indicated based on current HBV treatment guidelines Consider HBV prophylaxis if treating COVID-19 with immunosuppression (eg, dexamethasone, tocilizumab) HCV: <ul style="list-style-type: none"> Continue HCV therapy if already started Postpone initiation of HCV therapy until after recovery from COVID-19
NASH	No change	No change
PBC	No change	No change
PSC	No change	No change
ALD	No change	No change

Abbreviations: ALD, alcohol-associated liver disease; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

With coronavirus disease-2019

Given similar COVID-19-related outcomes in patients with AIH on immunosuppression compared with the general population,⁴⁵ providers should not routinely reduce immunosuppression in the setting of a new COVID-19 diagnosis. The severity of COVID-19 should first be considered to determine the best next steps. For outpatients with asymptomatic or mild COVID-19, immunosuppression should not be adjusted. For patients with moderate to severe COVID-19 (ie, hospitalized and/or ICU admission), the patient's AIH disease history (such as frequency of prior relapses) and fibrosis stage should be considered. For instance, a flare of AIH in a patient with cirrhosis/advanced fibrosis could result in hepatic decompensation; therefore, the threshold for reducing immunosuppression in these patients should be higher. If the decision is made to reduce immunosuppression, baseline doses may be reduced by 25% to 50%. The patient should subsequently be monitored closely for a AIH flare by checking liver enzymes daily in the hospitalized patient and every 1 to 2 weeks once the patient is discharged. For patients on antimetabolites such as azathioprine or mycophenolate with neutropenia and/or lymphopenia associated with COVID-19, the antimetabolite dose should be reduced or stopped and a white blood cell count with differential should be monitored every 1 to 2 weeks.

Chronic Viral Hepatitis

Without coronavirus disease-2019

Antiviral therapies have not been shown to increase the risk of severe COVID-19. Therefore, antiviral therapy can be safely started and continued in HBV and HCV patients without COVID-19.

With coronavirus disease-2019

Given antiviral therapy does not worsen COVID-19 outcomes, continuation of antiviral therapy for patients with HBV and HCV is also recommended for those with SARS-CoV-2 infection. As initiation of therapy for HCV is not urgent, initiation of HCV therapy for patients with COVID-19 should be postponed until the patient has recovered from COVID-19.¹² HBV therapy should be initiated despite active SARS-CoV-2 infection if indicated based on current HBV treatment guidelines. Given the risk of reactivation of HBV with immunosuppression, patients started on immunosuppression for COVID-19 with medications such as glucocorticoids or tocilizumab should be considered for HBV prophylaxis.^{12,57,58}

Other Chronic Liver Diseases (Nonalcoholic Steatohepatitis, Alcohol-Associated Liver Disease, Primary Biliary Cholangitis, and Primary Sclerosing Cholangitis)

The management strategies for many CLDs including NASH, alcohol-associated liver disease, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) have not been significantly altered by the COVID-19 pandemic. Patients with NASH should continue to be advised on risk factor control (diabetes, hyperlipidemia, and hypertension) and lifestyle changes to promote weight loss, although it should be acknowledged that the pandemic has made exercise and healthy eating habits more challenging for many. Patients with severe alcohol-associated hepatitis can be considered for corticosteroid treatment if indicated. Routine screening for colorectal cancer, gallbladder carcinoma and cholangiocarcinoma for patients with PSC should continue. Patients with PBC on treatment (such as ursodiol) should continue on this even if they develop SARS-CoV-2 infection.

Telemedicine/Delivery of Care

Telemedicine, which is the delivery of health care from afar using technology, previously had slow uptake because of restrictive regulations, lack of reimbursement, lack of widespread Internet infrastructure, and resistance to change.⁵⁹ However, shortly after the pandemic began there was a drastic increase in telemedicine use to help with mitigation efforts to slow the spread of COVID-19.⁶⁰ Many restrictions on telemedicine services were lifted along with changes in reimbursement. As the pandemic progresses, it remains unseen how the delivery and use of telemedicine will continue to evolve. For liver-related care, telemedicine offers particular promise in the delivery of subspecialty hepatology care to patients in rural areas, those with limited transportation and financial means, and incarcerated persons. For example, the effort to eliminate viral hepatitis will likely need to rely heavily on telemedicine to reach these populations.⁶¹ However, there are many patients with CLD with socioeconomic disparities that may limit their access to high-speed Internet resulting in inadequate access to telemedicine.⁶² There will need to be a specific focus on improving Internet infrastructure, expanding access to computers and mobile devices, and education to improve technological competence, to ensure that these populations have equitable access to telemedicine.

CORONAVIRUS DISEASE-2019 VACCINATION

Patients with CLD have an increased risk of COVID-19 morbidity and mortality and should be prioritized for COVID-19 vaccination and booster doses.⁶³ All of the available SARS-CoV-2 vaccines, including the messenger ribonucleic acid (mRNA) (Pfizer-BioNTech, Moderna) and adenoviral vector vaccines (Johnson & Johnson [J&J], AstraZeneca, Sputnik), are safe for patients with CLD and there are no contraindications for their use in this patient population.^{64–66} Thus, patients should be vaccinated as soon as they are eligible and a vaccine is available to them.⁶⁴ COVID-19 vaccination does not require delaying or discontinuing therapy for any CLD such as antiviral therapy for HBV/HCV or immunosuppression for AIH. Routine non-COVID-19 vaccines (such as vaccination against hepatitis A or HBV) also do not need to be delayed while patients are receiving the COVID-19 vaccine series and can be given as scheduled. For further guidance regarding COVID-19 vaccination in patients with liver disease, AASLD has created an expert panel consensus statement that will be continually updated as new data arise.⁶³

Cirrhosis/Chronic Liver Disease

Patients with cirrhosis have been shown to have impaired responses to non-COVID-19 vaccines such as pneumococcus and HBV, likely due to immune dysfunction seen in cirrhosis.^{67,68} Although there are limited data currently on the efficacy of COVID-19 vaccines in patients with CLD, the available data suggest a similar impaired but still significantly protective response to COVID-19 vaccines. A large study from the Veterans Affairs system propensity matched 20,037 patients with CLD who had received one dose of an mRNA vaccine (Moderna or Pfizer-BioNTech) with 20,037 control patients who had not been vaccinated. At 28 days after one dose, there was a 64% reduction in SARS-CoV-2 infections and 100% reduction in hospitalization and death in patients with CLD. A second dose provided additional protection with a 78% reduction in SARS-CoV-2 infections and 100% protection against hospitalization and death. This contrasts with a 94%–95% reduction in SARS-CoV-2 infections after two doses of an mRNA vaccine in the general population.^{65,66} The severity of liver disease is also associated with impaired response to vaccination. Vaccinated patients with decompensated cirrhosis

had only a 50% reduction in new SARS-CoV-2 infections compared with 66% in patients with compensated cirrhosis.⁶⁹

Liver Transplantation Recipients

Data on COVID-19 immunization in LT recipients have shown the vaccines to be safe and effective at preventing hospitalization and death.⁶³ Available data do not show an increased risk of alloimmunity and graft rejection.⁷⁰ It is important to note that none of the available vaccines contain live SARS-CoV-2; therefore, replication of SARS-CoV-2 after vaccination is not possible even in immunocompromised patients. However, compared with immunocompetent individuals, LT recipients have lower levels of anti-spike antibody production after COVID-19 vaccination and a quicker decline in antibody levels over time.⁷¹ This is similar to prior studies that have shown LT recipients have a poor response to non-COVID-19 vaccinations.⁷⁰ Risk factors for poor antibody formation after COVID-19 vaccination in this population include older age, chronic kidney disease, use of high dose steroids and use of mycophenolate mofetil.⁷² Despite this, it is not recommended to reduce immunosuppression to improve immune response to COVID-19 vaccination given the risk of acute cellular rejection.⁶³ The antibody response from mRNA COVID-19 vaccination can be improved with additional doses.^{73,74} As a result, current guidelines recommend a primary series of three doses for the mRNA vaccines in immunocompromised patients including LT recipients followed by one or more booster doses (Table 2).⁶³ For patients who received the J&J vaccine, the primary series should consist of a second dose of the J&J vaccine or a dose of an mRNA vaccine followed by one or more booster doses. Given that antibody formation after vaccination is greater for patients with cirrhosis compared with post LT patients, candidates for LT should be vaccinated before transplant whenever possible.^{63,75} Potential live liver donors should also be encouraged to undergo

Table 2
General guidelines for COVID-19 vaccination for adults in the United States with CLD and LT recipients

	Number/Manufacturer of Primary Series	Booster
CLD	2 Pfizer-BioNTech mRNAor2 Moderna mRNAor2 Novavax adjuvantedor1 J&J/Janssen adenoviral vector ^a	Bivalent Pfizer-BioNTech or Moderna mRNA ≥2 months after primary series
AIH on immunosuppression	3 Pfizer-BioNTech mRNAor3 Moderna mRNAor2 Novavax adjuvantedor1 J&J/Janssen adenoviral vector followed by any mRNA vaccine ^a	Bivalent Pfizer-BioNTech or Moderna mRNA ≥2 months after primary series
LT recipients	3 Pfizer-BioNTech mRNAor3 Moderna mRNAor2 Novavax adjuvantedor1 J&J/Janssen adenoviral vector followed by any mRNA vaccine ^a	Bivalent Pfizer-BioNTech or Moderna mRNA ≥2 months after primary series

Abbreviations: AIH, autoimmune hepatitis; CLD, chronic liver disease; LT, liver transplant

See CDC website for additional details, including dose intervals and pediatric recommendations: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html>.

^a Janssen COVID-19 vaccine should only be used in certain limited situations; mRNA primary vaccine series preferred whenever possible

vaccination before donation. Even if LT is likely to happen before completion of the vaccine series, COVID-19 vaccination should continue after transplantation. Any additional vaccine doses that need to be completed post-LT can be given at the earliest appropriate interval following transplant (around 4 weeks' post-LT). If COVID-19 vaccination cannot be started before transplant, the optimal timing for vaccination is likely at least 3 months post-LT when immunosuppression is lower to allow for better antibody formation; however, it is possible to begin vaccination as early as 4 weeks post-LT.⁶³

Table 2 shows general guidelines for COVID-19 vaccination in adults with CLD and LT recipients. Recommendations for vaccination in LT recipients are likely to change as new data become available. Additional booster doses may be recommended for both transplant recipients and the general population as immunity naturally wanes and new viral variants emerge. Check the CDC website for the latest available recommendations: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised>.

Liver Transplantation Candidates

COVID-19 vaccines have been proven to be safe and effective at preventing hospitalization and death in patients with cirrhosis and in LT recipients.⁶³ When possible, vaccination should occur before transplant due to better antibody formation and protection against poor outcomes after vaccination in patients with cirrhosis compared with LT recipients.⁷⁵ Many transplant centers have required COVID-19 and other vaccinations before listing for liver transplant. These policies are clinically and ethically justified but remain at the discretion of each transplant center.⁷⁶

Autoimmune Hepatitis

Patients with AIH on immunosuppression have also been shown to have a poor response to vaccinations against non-COVID-19 diseases.⁷⁰ Early data on COVID-19 vaccination for patients on immunosuppression also indicate an impaired immune response in this population.⁷⁷ Therefore, it is currently recommended that immunosuppressed patients, including patients with AIH on immunosuppression, receive a three-dose primary series of an mRNA vaccine plus one or more booster doses (see **Table 2**).⁷⁸

There have been several case reports of a rare AIH-like liver injury following COVID-19 vaccination.^{79–81} A systematic review by Chow and colleagues summarized the existing case reports and series that included 32 patients with an AIH-like syndrome following an mRNA or Oxford-AstraZeneca COVID-19 vaccine.⁸² Several of these patients did not meet criteria for AIH and likely just had hepatocellular or cholestatic DILI to the vaccine without autoimmune features. There was also a small subset of patients (n = 4) who had a prior diagnosis of AIH that was in remission before receiving the vaccine and then developed a flare following COVID-19 vaccination.⁸³ Given the low incidence, it has not been determined whether these rare events are simply coincidental or causally related to the vaccine. This rare potential risk should not discourage COVID-19 vaccination, even in those with preexisting AIH or CLD.

LIVER TRANSPLANTATION AND CORONAVIRUS DISEASE-2019

Severe Acute Respiratory Syndrome Coronavirus 2-Positive Liver Transplantation Recipient

LT recipients require high doses of immunosuppression immediately post-transplant to prevent rejection and there is significant concern for worsened post-LT outcomes if a transplant recipient were to become infected with SARS-CoV-2 at the time of

transplant. As a result it is recommended that all recipients be tested for SARS-CoV-2 before transplant.¹² There have been several reports of successful living donor LT in SARS-CoV-2-positive recipients after a minimum of 14 days from positive SARS-CoV-2 PCR.¹² However, available data suggest that the risk of postoperative morbidity and mortality related to recent COVID-19 can remain high for much longer than 14 days after acute infection and seems to remain particularly elevated for up to 7 weeks post-infection.^{12,84} Therefore, except in extreme circumstances, patients with active/recent COVID-19 should not undergo LT.¹² The specific circumstances and urgency of the recipient should be considered when deciding whether to proceed with LT.

Severe Acute Respiratory Syndrome Coronavirus 2-Positive Donor

If an organ from a SARS-CoV-2-positive donor is transplanted into a SARS-CoV-2-negative recipient, there is a theoretic risk of SARS-CoV-2 transmission from the donor to recipient. To date, all of the reported cases of SARS-CoV-2 transmission from a COVID-19-positive donor have occurred in lung transplantation⁸⁵ and there have been no proven or suspected cases of donor-to-recipient SARS-CoV-2 transmission in non-lung transplants.⁸⁶ In fact, several case reports have described the successful use of SARS-CoV-2 positive donors without documented transmission to the transplant recipient in non-lung solid organ transplant.^{87–91} Given the limited data that exist, no recommendation regarding the risk of SARS-CoV-2 transmission to the recipient can be made.¹²

Given the concerns about possible donor-to-recipient transmission, it is recommended that all potential donors be tested for SARS-CoV-2 before LT.¹² However, SARS-CoV-2 PCR may remain positive for months after resolution of infection despite a patient no longer being infectious. Although a lack of infiltrates on chest imaging or a SARS-CoV-2 diagnosis greater than 10 days earlier may indicate inactive infection, it can often be hard to differentiate between active and inactive infection.¹² The cycle time (number of amplification cycles needed to produce a positive PCR test) may be helpful to differentiate active from inactive infection.⁹² Low cycle times reflect higher viral load, whereas high cycle times reflect lower viral load, possibly indicating inactive infection.

The decision to proceed with transplantation using a SARS-CoV-2-positive donor should consider the severity and timing of COVID-19 in the potential donor and the urgency of the potential recipient. Donor organ quality should also be considered independently from the risk of donor-to-recipient viral transmission.

Management of the Liver Transplantation Recipient without Coronavirus Disease-2019

Given the risk of acute cellular rejection, maintenance immunosuppression should be continued and the doses should not be lowered. Patients who develop acute rejection should also continue to receive the standard of care with high dose immunosuppression to preserve graft function.⁹³

Management of the Liver Transplantation Recipient with Coronavirus Disease-2019

For LT recipients with an active SARS-CoV-2 infection, the decision to modify immunosuppression and dosing should be individualized based on history of rejection, the risk of future rejection, length of time post-LT and the severity of COVID-19. Tacrolimus has been associated with better survival in transplant recipients with COVID-19 and generally should not be decreased or stopped.⁹⁴ Mycophenolate, however, has been found to be an independent risk factor for severe COVID-19 in LT recipients

and decreasing or stopping it is a reasonable approach to managing LT recipients with moderate/severe COVID-19.⁴⁷

Outpatient/Mild Coronavirus Disease-2019 Management

Immunosuppression should not be adjusted for LT recipients with mild COVID-19. There are several treatment options available for patients who are diagnosed with COVID-19 including nirmatrelvir-ritonavir (Paxlovid), molnupiravir, monoclonal antibodies and remdesivir. Nirmatrelvir-ritonavir is a combination of oral protease inhibitors that blocks SARS-CoV-2 protease activity. In a randomized controlled trial, it was shown to be highly effective at reducing rates of hospitalization or death (89% reduction compared with placebo).⁹⁵ Nirmatrelvir-ritonavir is not recommended in patients with severe renal (eGFR 30 mL/min) or severe liver (CP-C) impairment. There are significant drug interactions with nirmatrelvir-ritonavir, especially calcineurin inhibitors, which may lead to dangerously high levels of these drugs in some transplant recipients. For patients who are not candidates for nirmatrelvir-ritonavir, other therapies that can be considered are monoclonal antibodies, remdesivir and molnupiravir.

Inpatient/Moderate–Severe Coronavirus Disease-2019 Management

Given the association of antimetabolite medications and worsened COVID-19 outcomes, it is recommended that doses of azathioprine or mycophenolate should be lowered in moderate to severe COVID-19, including patients hospitalized for COVID-19.¹² Glucocorticoids may be beneficial in severe COVID-19 and have not been shown to worsen outcomes; therefore, immunosuppression consisting of glucocorticoids should not be routinely adjusted.⁹⁶ In patients who develop neutropenia and/or lymphopenia (absolute lymphocyte count <1000 cells/microL for adults) due to COVID-19, the dose of azathioprine or mycophenolate should be reduced and labs (white blood cell count with differential and liver biochemistries) should be checked every 1 to 2 weeks to monitor for rejection and improvement in neutropenia and/or lymphopenia.

SUMMARY

The COVID-19 pandemic has had a substantial impact on patients with CLD and LT recipients and has significantly altered the care of these patients. Vaccination against COVID-19 is effective at protecting patients with CLD and LT recipients from adverse outcomes and is safe in these patients; however, vaccine efficacy may be reduced in LT recipients and other immunosuppressed patients. COVID-19 has challenged the transplant community and the decisions about the use of potential donors with recent or current SARS-CoV-2 infection and when it is safe to proceed with LT in potential recipients with SARS-CoV-2 infection.

CLINICAL CARE POINTS

- Compared to the general population, patients with chronic liver disease and liver transplant recipients are at a significantly increased risk of poor outcomes due to COVID-19.
- For patients without active COVID-19 infection who are on immunosuppression for autoimmune hepatitis or after liver transplantation, the doses of immunosuppressive medications should not be routinely altered in an attempt to prevent COVID-19 complications.
- In addition, flares of autoimmune hepatitis or episodes of post liver transplant rejection should be treated as clinically appropriate.

- Although patients with chronic liver disease and liver transplant recipients may have an impaired response to COVID-19 vaccination, vaccination in these patients has still been proven to be safe and effective at preventing morbidity and mortality due to COVID-19.
- Antibody formation after vaccination has been shown to be greater in patients with chronic liver disease as compared to liver transplant recipients, therefore COVID-19 vaccination prior to transplant should be prioritized.

DISCLOSURE

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