COVID-19 and Effect on Liver Transplant

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Abstract

Purpose of review The Coronavirus disease-2019 (COVID-19) pandemic has significantly impacted all aspects of liver transplantation. We reviewed the literature regarding COVID-19 clinical outcomes, treatment, and vaccination of liver transplant candidates and recipients.

Recent findings Patients with chronic liver disease, especially with cirrhosis, have higher morbidity and mortality from COVID-19 than patients without liver disease. Increased mortality has not been consistently seen in liver transplant recipients, in whom severe disease is more strongly associated advanced age and medical comorbidities, rather than with transplant-specific factors. While several targeted COVID-19 therapies have reported hepatotoxicity, these therapies may be safe and effective in patients with liver disease and liver transplant recipients. Questions remain regarding whether SARS-CoV-2 can be transmitted via the donor liver and whether transplant is safe in patients and/or donors with recent or active COVID-19.

Summary COVID-19 has significantly affected the care of liver transplant candidates and recipients. Guidelines for the safe practice of liver transplantation are rapidly evolving, and current recommendations are discussed.

Introduction

Coronavirus disease-2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had an enormous impact on healthcare systems worldwide, not only via morbidity and mortality but also through major disruption of healthcare practices and procedures. As of April
2021, there have been over 500,000 COVID-related deaths in the U.S. and over 2.9 million deaths worldwide [1]. Patients with chronic diseases and immunosuppression, including those with chronic liver disease and recipients of liver transplant, may have increased risk for severe disease [2•, 3•, 4•, 5]. A number of treatment options are available for use in patients with liver disease, although concerns about hepatotoxicity with many of these agents may limit use in some cases [6]. More recently, vaccination against COVID-19 has offered an important preventive strategy for patients with liver disease [7, 8•].

In addition to individual patient considerations, policies and practice of liver transplantation have been deeply impacted by the pandemic. After initial declines, numbers of liver transplants performed in the U.S. rebounded in the second half of 2020, with new policies and society recommendations in place guiding SARS-CoV-2 testing in transplant recipients and donors [9•, 10•]. However, multiple questions remain regarding timing and safety of liver transplant in recipients or donors with positive SARS-CoV-2 test.

Clinical outcomes of COVID-19 in patients with chronic liver disease and cirrhosis

A number of studies have evaluated clinical outcomes of COVID-19 in patients with preexisting advanced liver disease, including patients with and without cirrhosis (summarized in Table 1). Compared to patients without preexisting liver disease, patients with chronic liver disease or cirrhosis have a higher rate of mortality and other severe clinical outcomes (admission to an intensive care unit [ICU] and need for mechanical ventilation), though specific rates have varied. Patients with chronic liver disease—especially nonalcoholic fatty liver disease (NAFLD)—are overrepresented among those hospitalized for COVID-19, accounting for up to 10–20% of admitted patients [2•, 11, 12••]. Compared to patients without chronic liver disease, those with chronic liver disease have higher rates of ICU admission, need for mechanical ventilation, and mortality [11]. Specific predictors of mortality include alcohol-related liver disease, especially among patients with noncirrhotic chronic liver disease; presence of hepatic decompensation; and presence of medical comorbidities such as hypertension, diabetes, or cardiovascular disease [2•, 12••, 13••].

Increasing severity of preexisting liver disease—including cirrhosis compared to noncirrhosis, or increasing Child-Pugh Class indicating more decompensated underlying disease—has been consistently associated with higher rates of mortality [2•, 12••, 13••, 14]. When looking specifically at patients with cirrhosis and COVID-19, several multicenter studies in the U.S., Europe, and China have found a mortality rate over 20–30%, significantly higher than among patients with COVID-19 without cirrhosis [2•, 11, 12••, 15–17]. In a study based on two international registries that included 745 patients with chronic liver disease and COVID-19 infection, for example, there was 32% mortality in patients with cirrhosis compared to 8% in those without cirrhosis (p<0.001) [13••]. Among patients with cirrhosis, in whom morbidity and mortality is often tied to infection, COVID-19 may produce more severe clinical outcomes than other infections. In a retrospective multicenter study in Italy, for example, patients with cirrhosis with COVID-19 had 34% 30-day mortality rate, significantly higher than among patients with cirrhosis hospitalized for bacterial infections [11]. However, in a multicenter U.S. study, there was a trend toward higher mortality among patients with cirrhosis and COVID-19
| Study (date, region, number of sites) | Patient cohort and comparator(s) | Main outcomes | Other findings |
|-------------------------------------|----------------------------------|---------------|----------------|
| Qi et al. • May 2020 • China • 16 centers | Primary cohort: 21 patients with cirrhosis No comparator group | 23.8% mortality rate among primary cohort | Laboratory findings associated with higher mortality: lower total lymphocyte count, lower platelet count, and higher direct bilirubin |
| Singh and Khan • May 2020 • United States • 34 centers | Primary cohort: 250 patients with CLD, including 50 patients with cirrhosis Comparator group: liver disease vs. no liver disease using propensity score matching for BMI, HTN, DM, age, race, and nicotine use | Higher risk of mortality in liver disease vs. no liver disease (RR 2.8, 95% CI 1.9–4.0) Highest risk of mortality in cirrhosis vs. no liver disease (RR 4.6, 95% CI 2.6–8.3) | ALT elevations (>50 U/L) seen in 46.1% of patients with liver disease and 50.6% of patients without liver disease |
| Iavarone et al. • June 2020 • Italy • 9 centers | Primary cohort: 50 patients with cirrhosis Comparator group: patients hospitalized for hepatic decompensation due to bacterial infection over preceding year | 30-day mortality rate of 34% among primary cohort, significantly higher than in comparator group | Respiratory failure and worsening liver function during SARS-CoV-2 infection associated with higher mortality |
| Bajaj et al. • July 2020 • United States • 7 centers | Primary cohort: 37 patients with cirrhosis Comparator groups (age and gender-matched): (1) 108 patients with COVID-19 without cirrhosis and (2) 127 patients with cirrhosis without COVID-19 | Higher mortality in cirrhosis + COVID-19 vs. COVID-19 alone (30% vs. 13%); similar mortality in cirrhosis + COVID-19 vs. cirrhosis alone (30% vs. 20%) | Higher CCI was only predictor of mortality across entire cohort |
| Hashemi et al. • July 2020 • United States • 9 centers | Primary cohort: 69 patients with CLD and 9 patients with cirrhosis Comparator group: hospitalized patients without CLD | Cirrhosis was associated with higher mortality (aOR 12.5, 95% CI 2.16–72.5) | CLD and NAFLD were associated with ICU admission, need for mechanical ventilation, and increased length of stay |
| Sarin et al. • July 2020 • Asia • 13 countries | Primary cohort: 228 patients, including 185 patients with CLD and 43 patients with cirrhosis No comparator group | 20% of patients with cirrhosis presented with ACLF or decompensation from baseline Higher CTP class was associated with increased risk of liver-related complications | 43% of patients with CLD presented with acute liver injury Higher bilirubin and AST/ALT ratio were associated with higher mortality among patients with cirrhosis |
| Kim and Adeniji et al. | Primary cohort: 867 patients with CLD, including 227 patients with cirrhosis | 14% mortality rate among all patients | Hispanic ethnicity and decompensated cirrhosis |
| Study (date, region, number of sites) | Patient cohort and comparator(s) | Main outcomes | Other findings |
|-------------------------------------|---------------------------------|---------------|---------------|
| • September 2020<br> • United States<br> • 21 centers<br> • October 2020<br> • International registry<br> • 29 countries<br> • Marjot et al.<br> • October 2020<br> • Primary cohort: 745 patients with CLD, including 386 patients with cirrhosis<br> • Comparator group: 620 patients without CLD using propensity score matching<br> | • ALD, CTP class C, and HCC associated with higher mortality | • Advanced age and ALD associated with higher mortality |  |
| • Pereira et al.<br> • May 2020<br> • New York City, United States<br> • 2 centers<br> • Bechetti et al.<br> • June 2020<br> • Europe<br> • 12 centers<br> • Belli et al.<br> • June 2020<br> • Europe (mainly Italy, Spain, France)<br> • 56 centers<br> • Colmenero et al.<br> • August 2020<br> • Spain<br> • 25 centers<br> | • Primary cohort: 90 SOT recipients, including 14 liver transplant recipients (13 liver and 1 liver–kidney)<br> • No comparator group<br> • Primary cohort: 57 liver transplant recipients<br> • No comparator group<br> • Primary cohort: 103 liver transplant recipients<br> • No comparator group<br> • Primary cohort: 111 liver transplant recipients<br> • Comparator group: matched patients from general population using SIR and SMR<br> | • Mortality rate of 18% among all patients<br> • Higher mortality in cirrhosis vs. CLD without cirrhosis (32% vs. 8%)<br> • Mortality risk increased with higher CTP class<br> • Mortality rate of 12%, only observed in hospitalized patients<br> • Mortality rate of 16%, only seen in patients 60 years of age or older<br> • Higher mortality in LT recipients vs. general population (18% vs. 14.9%, SMR 95.5)<br> • Higher mortality in LT recipients vs. general population (18% vs. 14.9%, SMR 95.5)<br> • No patient deaths reported in LT recipients under the age of 60<br> • Mycophenolate use associated with risk of severe COVID-19 (RR 3.94, 95% CI 1.59–9.74), in particular with doses higher than 1 g/day<br> | • Most common COVID-19 directed treatment was HCQ (91% of patients)<br> • No difference in outcomes among patients with IS reduction (37%) or IS discontinuation (7%)<br> • Higher mortality in patients at least 2 years from date of transplant vs. within 2 years (18% vs. 5%, not statistically significant)<br> • Mycophenolate use associated with risk of severe COVID-19 (RR 3.94, 95% CI 1.59–9.74), in particular with doses higher than 1 g/day<br> • CNIs and everolimus not associated with increased risk of severe COVID-19<br> • Increased mortality associated with older age, higher creatinine, and nonliver cancer<br> |  |
| • Webb et al.<br> • August 2020<br> • International registry<br> | • Primary cohort: 151 liver transplant recipients<br> • Comparator group: 627 non-LT recipients with COVID-19<br> | • Lower mortality in LT recipients vs. non-LT recipients (19% vs. 27%)<br> |  |
compared to age- and gender-matched patients with cirrhosis without COVID-19, but the difference was not statistically significant (30% versus 20%, respectively; \( p = 0.16 \))—highlighting the impact of underlying cirrhosis itself upon inpatient mortality rates [15].

Mortality from COVID-19 among patients with chronic liver disease, as in patients without chronic liver disease, is driven largely by cardiopulmonary complications including respiratory failure, sepsis, and shock. However, liver injury and acute-on-chronic liver failure may also contribute to morbidity and mortality in these patients. Hepatic dysfunction and abnormal liver function
tests are common in patients with COVID-19, especially those with severe
disease [18–22]. More severe and even chronic hepatic complications, in-
cluding progressive cholangiopathy or fulminant liver failure, have also
now been reported [23–25]. In patients with preexisting liver disease, liver
injury may be more prevalent. In an international multicenter study from
13 Asian countries of patients with preexisting liver disease with COVID-
19, 43% of patients with chronic liver disease presented with acute liver
injury, 9% of patients with cirrhosis presented with acute decompensation,
and 12% of patients with cirrhosis presented with acute-on-chronic liver
failure [14]. In addition, in an international multicenter study of patients
with autoimmune hepatitis (AIH), acute liver injury was observed in 37%
of patients [26].

COVID-19 and the practice of liver transplantation

The impact of the COVID-19 pandemic on rates of liver transplantation

As with all aspects of healthcare systems internationally, the practice of liver
transplantation has been significantly impacted by the COVID-19 pandemic.
Initial severe limitations in the ability to conduct liver transplant, especially in
the early phases of the pandemic in 2020, are now giving way to resumption of
practice with new policies and considerations in place.

In the early phases of the pandemic in the U.S. in winter-spring of 2020,
there was an acute decline in the number of liver transplants performed across
the country, as many centers either limited the number of transplants or
temporarily ceased performing transplants altogether (Fig. 1). Compared to
expected numbers based on prior years, in March–May 2020 there were mark-
edly fewer patients added to the liver transplant waitlist and substantially more
patients inactivated from the waitlist (Fig. 2); in states with the highest rates of
COVID-19, for example, there was over 30% reduction in new listings, over
30% reduction in deceased donor liver transplant, and nearly 60% increase in
mortality of patients on the waitlist in the early phase of the pandemic [27].
There was significant variability in practice among specific transplant centers,
even within the same geographic region, especially in regions with high rates of
COVID-19.

Patterns in liver transplantation during the early months of the COVID-
19 pandemic reflected a combination of safety and logistical considerations.
There were significant concerns about the risk to transplant recipients of
SARS-CoV-2 acquisition at medical appointments or in the hospital, as well as
either in the hospital or in the community after initiation of immuno-
suppressive medications posttransplant. Family and caregiver visitation con-
tinue to face restrictions both in hospitals and once patients are discharged
home. SARS-CoV-2 testing abilities were limited, restricting the ability to test
potential recipients or donors in a timely manner. In parallel, transplant
teams—along with the entire medical community—faced severe shortages of
personal protective equipment needed for surgery and other patient care,
restricted operating room space and staffing, restricted postoperative inten-
sive care unit or inpatient ward space and staffing, and state- or institution-
guided limitations on group meetings. Some hepatologists and surgeons
were “redployed” to care for the influx of COVID-19 patients. Additional
national considerations also impacted transplant practice—for example, the
major disruption in airline travel led to reduced ability to recover and transport organs to transplant centers [28].

Later in 2020, as centers mobilized to resume organ transplantation practice nearer to usual, rates of waitlist registration and deceased donor liver transplant increased to match or exceed expected levels, and the overall numbers of deceased donor liver transplants in 2020 actually exceeded those in 2019, reflecting increases in deceased organ donation in 38 of the 58 national organ procurement organizations [27, 29]. Rates of living donor liver transplantation, on the other hand, faced more lasting reductions throughout the year than were seen with deceased donor liver transplantation. Although rates in the second half of the year began to approach expected prepandemic levels, by the end of the year in 2020 overall, there were fewer living donor liver transplants than in 2019 [27, 29]. However, changes in transplant rates throughout 2020 were likely also impacted by the changes in liver allocation that went into effect immediately prior to the onset of the pandemic.

Fig. 1. Liver transplants performed and wait list additions in the US in 2020
SARS-CoV-2 testing prior to liver transplantation

Society guidelines recommend testing for SARS-CoV-2 for both liver transplant donors and recipients [9•, 10•, 30]. All transplant recipients undergo nasopharyngeal PCR testing prior to surgery, and all Organ Procurement Organizations (OPOs) now use RNA testing from nasopharyngeal and/or bronchoalveolar lavage specimens for organ donors, ideally within 72 h of organ recovery. Because there is a substantial rate of false-negative SARS-CoV-2 testing, imaging with chest X-ray or chest CT should be considered in potential recipients or donors who have negative RNA testing but concerning symptoms, in order to more definitively exclude active COVID-19. Recommended practice for recipient and donor SARS-CoV-2 testing according to the American Society of Transplantation (AST) is shown in Fig. 3.

SARS-CoV-2 positivity in liver transplant recipients

Ideally, all liver transplant donors and recipients would test negative for SARS-CoV-2 at the time of transplantation, and outside of rare circumstances, transplantation is not routinely recommended for patients with active COVID-19. In patients who have recovered from COVID-19, it is unknown whether SARS-CoV-2 may reactivate to cause illness—including hepatic injury—after transplant and initiation of immunosuppression. Furthermore, it is unknown whether risk and severity of long-term complications of COVID-19—such as kidney injury, fatigue, myopathy, and autonomic dysregulation—may be increased in patients receiving immunosuppression [31, 32]. As such, society guidelines currently recommend that transplant take place at least 14–21 days after clinical recovery, and after one or two negative SARS-CoV-2 tests [9•, 10•]. Multiple case reports documented successful liver transplant after the recipient has recovered from COVID-19, with most occurring at least 30 days after last
positive test [33–35]. More recently, multiple centers have reported transplantation as early as two weeks after positive SARS-CoV-2 test, without subsequent complications related to COVID-19 [36, 37].

For patients with chronic liver disease, there may be prolonged SARS-CoV-2 viral shedding for weeks or even months after clinical recovery from the acute illness [38, 39]. As such, it may be impractical or unduly restrictive to require negative SARS-CoV-2 testing for patients with high risk of morbidity and mortality while awaiting transplant, such as patients with high Model for End-stage Liver Disease (MELD) score or those with acute liver failure. Initial reports of liver transplantation in SARS-CoV-2 positive patients, while rare, suggest that transplant in this context may be safe: in a case of a SARS-CoV-2-positive patient with Hepatitis B-/Hepatitis D-associated chronic liver disease, liver transplantation from a SARS-CoV-2-positive donor was successful, with good graft function and no evidence of viral hepatitis by two months posttransplant [40]. In patients who are recovered from active COVID-19, therefore, liver transplantation may still be considered, even in the presence of prolonged viral shedding.

An even more challenging situation is that in which patients meet indications for urgent or emergent liver transplantation while acutely ill from COVID-19. This may arise in the context of acute-on-chronic liver failure and/or acute liver failure among patients who have symptomatic COVID-19 but cannot wait the weeks required to clear the infection. While this complication is rare, liver transplantation may be the only potential life-saving intervention for those patients. To our knowledge, there is only one case currently published of a liver transplant in this context, in which a patient with active COVID-19 with respiratory impairment developed acute liver failure—thought to be from acute Wilsonian crisis, possibly precipitated by COVID-19 infection—successfully underwent liver transplantation [41]. This patient ultimately converted to have

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**Fig. 3.** Donor and recipient testing after COVID-19

| Donor testing after COVID-19: | Recipient testing after COVID-19: |
|-------------------------------|----------------------------------|
| **Repeat NAT testing is negative** | **Repeat NAT testing is negative** |
| OR | **AND** |
| **Initial COVID infection was 21-90 days prior** | **Symptoms have resolved** |
| **AND** | **AND** |
| **Symptoms have resolved** | **Symptoms have resolved** |

*Repeat +NAT after 90 days is considered a new infection

*Some experts recommend 2 negative tests
negative RNA testing on day 27 posttransplant, after treatment with remdesivir, and had excellent graft function at time of hospital discharge. This case importantly demonstrates that liver transplantation for patients with acute liver failure may be a viable therapeutic option, but the safety of this approach is unknown. Important considerations may include the extent of lung injury that is present at the time of transplant, as respiratory failure remains the main cause of death even among patients with advanced liver disease.

**SARS-CoV-2 positivity in liver transplant donors and considerations around hepatic infection**

Organ recovery from donors with history of resolved COVID-19 who now have negative SARS-CoV-2 RNA testing is considered safe, and this practice has been widely adopted [9•, 10••, 42]. The risk of SARS-CoV-2 transmission from a liver donor to a recipient is also considered low if the donor has resolved COVID-19 with persistent positive RNA testing 21–90 days after disease onset, and use of these organs is often appropriate. In donors with a history of mild COVID-19 with disease onset more than 10 but fewer than 21 days prior, the risk of SARS-CoV-2 transmission is unknown. More than 90 days after disease onset, SARS-CoV-2 positivity could reflect reinfection, and the risk of viral transmission is similarly unknown.

The risk associated with liver donation from SARS-CoV-2-positive donors depends in some ways upon whether SARS-CoV-2 directly infects the liver, a question that remains controversial. Because hepatic cholangiocytes, endothelial cells, and hepatocytes express angiotensin-converting enzyme-2 (ACE-2), the proposed host cell receptor of SARS-CoV-2, and because abnormal liver function tests are common in patients with COVID-19, there is concern that SARS-CoV-2 could directly infect hepatic tissue [43]. Analysis of postmortem liver histology in a series of patients who had COVID-19 revealed weak-positive staining of cholangiocytes and of histiocytes within portal tracts in a minority of cases, but not of portal endothelial cells or hepatocytes [44]. In another postmortem series of liver histology in patients with COVID-19, viral RNA by PCR was detectable in half of patients [19]. One case series including two postmortem liver biopsies showed coronavirus particles in hepatocyte cytoplasm, with evidence of typical viral infectious lesions [45]. Other histologic findings were nonspecific, such as hepatic steatosis and acute hepatitis. In a series of three patients with prolonged cholestasis following critical COVID-19 illness, liver histology demonstrated severe cholangiocyte injury and intrahepatic microangiopathy, likely reflecting ischemic injury [23]. In all, these findings suggest that SARS-CoV-2 RNA is present in some patients with COVID-19. However, whether there is active viral replication in the liver—for example, in cholangiocytes—is unknown. Therefore, even if a transplant donor liver were to contain SARS-CoV-2 RNA, it is unknown whether this could lead to infection in the recipient. To date, the only described case of solid organ donor-to-recipient transmission of SARS-CoV-2 was in a lung transplant [46].

**Clinical outcomes of COVID-19 in liver transplant recipients**

Liver transplant recipients have theoretical increased risk for severe infection-related illness compared to the general population, especially due to use of immunosuppressive medications. A number of studies have evaluated clinical
outcomes of COVID-19 in liver and other solid organ transplant recipients (summarized in Table 1). Several multicenter studies in the U.S. and in Europe have described a mortality rate near or above 20% among liver transplant recipients with COVID-19 [4•, 47, 48, 49••, 50, 51]. In studies comparing liver transplant recipients to matched nonliver transplant comparator groups, however, mortality did not differ significantly, though liver transplant recipients did have higher rate of hospitalization [5, 49••]. Mortality in liver transplant recipients with COVID-19 has been associated with usual patient risk factors for severe disease, including increased age—especially age over 60 years—and medical comorbidities including renal dysfunction and nonliver cancer [•4, 48, 50, 52].

COVID-19 infection often leads to changes to immunosuppressive regimens in liver transplant recipients. In a multicenter study from Europe including 57 liver transplant recipients, for example, immunosuppression was reduced in 37% of patients and discontinued in 7% of patients [53]. In the U.S. multicenter COVID-19 in chronic liver disease (COLD) consortium, immunosuppression was modified in 49% of liver transplant recipients with COVID-19 [50]. In both studies, reduction of immunosuppression in this setting was not associated with acute liver injury or other clinical outcomes. Studies suggest that mycophenolate use may be associated with severe disease, potentially due to T-cell depletion synergistically with SARS-CoV-2 [4•, 54]. On the other hand, calcineurin inhibitors and everolimus have not been associated with more severe illness from COVID-19; in fact, in one study, tacrolimus use was associated with reduced mortality [51]. In all, in liver transplant recipients with COVID-19, management of immunosuppression must be individualized for each patient. In patients with severe disease or high risk for disease progression, reduction of immunosuppression can be considered, and in this case, providers should consider preferentially reducing the dose of mycophenolate over other medications. In patients receiving calcineurin inhibitors, serum medication levels should be closely monitored, as SARS-CoV-2 infection may increase serum tacrolimus concentration in solid organ transplant recipients [55].

Management of COVID-19 in liver transplant candidates and recipients

Multiple treatments have been evaluated for management of COVID-19, especially for patients with severe (SpO2 <94% on room air) or critical (ICU, mechanical ventilation, septic shock, or extra-corporeal membrane oxygenation [ECMO]) disease. Current recommendations from the Infectious Diseases Society of America (IDSA) updated in March 2021 suggest use of corticosteroids, tocilizumab (an interleukin [IL]-6 inhibitor), and/or remdesivir (an antiviral) in patients who are hospitalized with severe or critical disease [6]. There are no prospective clinical trials specifically evaluating these therapies in patients with chronic liver disease or in liver transplant recipients, and these patients are often managed similarly to other patients based on severity of acute illness. However, these therapies may entail significant hepatotoxicity that must be considered when selecting and monitoring response to therapy.
Drug-induced liver injury (DILI) characterized by elevations in serum aminotransferases may occur in 10–50% of patients receiving remdesivir, and has been noted as the most common drug-related adverse effect [56–60]. Hepatotoxicity increases with longer duration of drug use. Use of remdesivir is not currently recommended in patients with aminotransferase levels >5 times the upper limit of normal, and cessation of use is recommend in patients who develop alanine aminotransferase (ALT) level >10 times the upper limit of normal [61]. Tocilizumab has also been associated with elevated aminotransferases, including severe elevations [62–64]. While a large proportion of patients receiving tocilizumab may already have elevated aminotransferases prior to medication initiation, use of tocilizumab is associated with development of de novo liver function test abnormalities [65].

Additional combination therapies also suggested by the IDSA are bamlanivimab–etesevimab in ambulatory patients with mild-moderate disease or patients hospitalized for other reasons who have high risk of progression to severe disease, and baricitinib–remdesivir for hospitalized patients with severe disease who cannot receive corticosteroids [6]. Baricitinib, a janus kinase (JAK) inhibitor that may block the effects of IL-6, has shown efficacy when used in combination with remdesivir in patients with severe or critical COVID-19 [66]. In November 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for use of baricitinib-remdesivir in hospitalized adult and pediatric patients requiring supplemental oxygen, invasive mechanical ventilation, or ECMO in whom steroids cannot be used [67]. Baricitinib may be associated with hepatocellular DILI, and when this occurs then treatment interruption is recommended.

Multiple monoclonal antibodies targeting SARS-CoV-2 virus have been developed for treatment of COVID-19. The combination of bamlanivimab and etesevimab, two neutralizing monoclonal antibodies that bind epitopes in the spike protein of SARS-CoV-2, has shown efficacy in reducing viral load and preventing hospitalization in outpatients with mild-moderate disease [68]. In February 2021, the FDA issued an EUA for bamlanivimab-etesevimab combination therapy among ambulatory patients with mild-moderate COVID-19 with high risk of disease progression [69]. The specific eligible patients include those with an immunocompromising condition and those receiving immunosuppressive treatment [70]. This therapy is clearly indicated in liver transplant recipients, and we recommend its use for eligible patients. Where available and accessible, monoclonal antibody therapy may also be of benefit to patients with chronic liver disease.

It is important to exercise caution and to closely monitor liver function in patients with chronic liver disease and liver transplant recipients receiving targeted therapies for COVID-19. Considering the immense morbidity and mortality associated with COVID-19, however, use of these therapies is often appropriate even in light of the risk of hepatotoxicity. In studies in which liver transplant recipients have received targeted therapies for COVID-19, no significant adverse effects of medication have been noted. Among solid organ transplant recipients, the most data available is for remdesivir, with findings supporting its use in these patients [47, 49, 71, 72, 73].
COVID-19 vaccination in the context of liver transplantation

Vaccines against COVID-19 have recently become available, and are increasingly accessible nationwide. While no studies have been conducted specifically in patients with chronic liver disease or after liver transplantation, vaccination is recommended [7, 8]. For liver transplant candidates, society guidelines recommend vaccination in patients and their household contacts, to be completed at least two weeks prior to transplantation. Liver transplant recipients should also complete vaccination, which can be administered at least three months after transplantation in patients receiving B or T cell ablative therapies. Solid organ transplant recipients receiving immunosuppression may have less robust immune response to vaccination, as to natural COVID-19 infection, than other patients; as such, vaccine administration prior to transplant is preferred when possible [74, 75, 76, 77, 78].

Conclusions

COVID-19 has significantly impacted liver transplant candidates and recipients and the practice of liver transplantation. While morbidity and mortality from COVID-19 in patients with liver disease is substantial and may exceed that of the general population, advances in therapy and increased access to vaccination provide promising management strategies for these patients. SARS-CoV-2 testing of potential liver transplant donors and recipients has aimed to avoid transplantation involving patients with active COVID-19. There remains a dire need for improved understanding of the true risk of hepatic and systemic viral reactivation after transplantation involving SARS-CoV-2 positive donors or recipients. While controversial, there may be opportunity for safe and effective liver transplant even in patients with active COVID-19, including those with SARS-CoV-2-associated fulminant liver failure. Further studies of intrahepatic SARS-CoV-2 replication and of posttransplant outcomes using SARS-CoV-2-positive donors and recipients are needed.

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