COVID-19 in Chronic Liver Disease and Liver Transplantation

A Clinical Review

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has brought challenges to clinicians caring for patients with chronic liver disease. In the past 6 months, COVID-19 has led to over 150,000 deaths in the United States and over 660,000 deaths around the world. Mounting evidence suggests that chronic liver diseases can have an adverse effect on the clinical outcomes of patients with COVID-19. We present a comprehensive review of the latest literature on preexisting liver diseases and its interrelationship with COVID-19 infection in cirrhosis, hepatocellular carcinoma, nonalcoholic fatty liver disease, autoimmune hepatitis, and viral hepatitis B. As social distancing and telemedicine gain new footing, we synthesize recommendations from 3 major hepatology societies [American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL), and the Asian Pacific Association for the Study of Liver (APASL)] to present the best approaches for caring for patients with liver diseases as well as those requiring liver transplantation.

Key Words: cirrhosis, liver transplantation, hepatitis B, nonalcoholic liver disease, hepatocellular carcinoma, autoimmune hepatitis, review, COVID-19, SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus first identified in Wuhan, China.[1] The illness caused by the SARS-CoV-2 virus referred to as coronavirus disease 2019 (COVID-19), has reached pandemic proportions. At the time of compiling this paper, >13 million confirmed cases have been reported globally, of which 3.3 million are in the United States alone.[2] Older populations and comorbidities like diabetes, hypertension, and cardiovascular disease have been associated with an increased mortality rate.[3] It predominantly causes respiratory distress syndrome with gastrointestinal and hepatic manifestations. Mild cases present with fever, dyspnea, fatigue, cough, and diarrhea. Severe cases present with acute hypoxemia, respiratory distress syndrome, and multiple organ dysfunction.[4] SARS-CoV-2 causes concomitant liver injury similar to its counterparts, the Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome-associated coronavirus (SARS-CoV). However, the mechanism of injury is poorly understood.[5]

Chronic liver diseases are prevalent worldwide and impose a significant burden on health care services. Their relationship with COVID-19 is not well documented in the literature. The intricate interplay between immune dysfunction in preexisting liver diseases and the immune dysregulation triggered by the SARS-CoV-2 virus needs further evaluation. The prevalence of chronic liver diseases in COVID-19 was reported by Chinese centers to range from 2% to 11%.[6] In the United States, Singh and Khan[7] identified 2780 patients with COVID-19, of which 250 patients (9%) had preexisting liver disease. Mortality of COVID-19 patients with the known liver disease compared with those without was 12% versus 4% [95% confidence interval (CI): 1.5-6.0; relative risk: 3.0, $P=0.001$], and it remained high even after propensity score matching for body mass index, hypertension, and diabetes in addition to age, race, and nicotine use. Similarly, in the UK, OpenSAFELY, a secure health analytics platform for electronic health records in the National Health Service (NHS), analyzed data from 17 million patients. It showed that chronic liver disease was a risk factor for in-hospital death from COVID-19 with a hazard ratio of 2.39 (95% CI: 2.06-2.77).[8] Mortality from COVID-19 in patients with chronic liver diseases are often higher than those without liver disease (Table 1).[9–14]

New reports from several sources are now available that elucidate the epidemiological characteristics of preexisting liver disease in COVID-19 patients. In this article, we will review the effects of COVID-19 in patients with underlying liver disease and summarize guidance from 3 major hepatology societies, the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL), and the Asian Pacific Association for the Study of Liver (APASL) (Table 2).[15–17] In addition, we examine recent changes in liver transplantation (LT) as a result of the pandemic.

MECHANISM OF HEPATIC INJURY FROM SARS-CoV-2 VIRUS

There are 2 major binding sites on the SARS-CoV-2 virus. The spike glycoprotein (S) that is essential for viral entry and the nucleocapsid phosphoprotein (N) that interacts with the RNA. The virus binds to angiotensin-converting enzymes 2 receptors as a portal of entry into the target cell, where it replicates and infects other cells.[18] The expression of these receptors is seen in alveolar type 2 cells and bile duct epithelial cells. The expression in bile duct epithelial cells is much higher than that of liver parenchymal cells.[19] Elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), 1 to 2 times the upper limit of normal, were reported in 14% to 53% of cases. Gamma-glutamyl transpeptidase, a marker of biliary epithelial

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TABLE 1. Mortality in Patients With Coronavirus Disease 2019 and Underlying Chronic Liver Disease Versus Those Without Chronic Liver Disease

Liver Disease	References	Study Type	Sample Size (n)	Mortality Data
NAFLD	Hashemi et al[9]	Multicenter inpatient mortality rate	363	16.4% vs. 13.2% ($P=0.54$)
HBV	Chen et al[10]	Single-center inpatient mortality rate	123	13.3% vs. 2.8%
AIH	Gerussi et al[11]	Multicenter case fatality rate	10	10%*†
Cirrhosis	Iavarone et al[12]	Multicenter retrospective inpatient case fatality rate	50	34% (95% CI: 23%-49%)
	Bajaj et al[13]	Multicenter matched cohort inpatient case fatality	165	30% vs. 13% ($P=0.03$)
LT	Fraser et al[14]	Systematic review of case fatality	223	19.3%†

*The death event occurred in the frailest patient included in the cohort who already had decompensated cirrhosis, which is associated with significant morbidity and mortality.

†These are not comparative studies.

AIH indicates autoimmune hepatitis; CI, confidence interval; HBV, hepatitis B virus; LT, liver transplant; NAFLD, nonalcoholic fatty liver disease.

cell injury, is elevated in 24% of patients hospitalized with COVID-19.[20] Higher levels of hepatocellular enzyme elevation have been associated with more severe forms of COVID-19.[6,21] In addition, treatments used in the management of COVID-19 can increase liver enzyme levels. Elevated liver enzymes have been reported with remdesivir use. Remdesivir studied for compassionate use in severe COVID-19 patients showed improved outcomes and was even approved by the United States Food and Drug Administration (FDA) for emergency use authorization (EUA) based on the interim analysis. In a study of 61 patients with severe COVID who received compassionate use of remdesivir, 22% of patients showed increased hepatic enzymes. The increase in liver enzymes led to the discontinuation of remdesivir in 2 patients in the study.[22] Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, is also known to cause severe liver injury.[23] A retrospective, observational cohort study reported a decreased need for invasive mechanical ventilation and a lower risk of death in patients with severe pneumonia. In this study, when compared with the standard care group, the tocilizumab group had a significantly higher elevation of ALT.[24] Neither remdesivir nor tocilizumab is recommended for use when AST or ALT level is >5 times the upper limit of normal. Safety and side-effect profiles of treatments in patients with COVID-19 will require future assessment in placebo-controlled trials.

Whether hepatocellular inflammation is a direct consequence of virus-mediated cytokine release and a prognostic marker of disease severity or a direct cytopathogenic response is yet to be determined. In a study of 60 patients from Massachusetts General Hospital, median AST and ALT on admission were 46 and 30 U/L, respectively.[25] Ten patients (17%) developed aminotransferases >5 times the upper limit of normal.[25] Elevated levels of AST and ALT were seen in 93% of patients during hospitalization. Since AST is higher than ALT, a nonhepatic injury like myositis can be considered, but correlations with creatinine kinase were weak.[25] In short, aminotransferase elevations are common in COVID-19 and appear to mirror disease severity.

Pathologic analysis of tissue obtained from postmortem examination of the liver in patients whose deaths were a direct consequence of COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity. However, viral inclusions were not observed.[26]

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Obesity, diabetes, and hypertension have emerged as prominent risk factors for the development of severe disease in COVID-19.[27–30] These conditions are part of the metabolic syndrome that also predisposes to NAFLD.[31] The prevalence of NAFLD is estimated to be 20% to 30% in Western populations and 5% to 18% among Asian populations.[32] In a report of 324 patients with COVID-19 in Shanghai, 70 (21.6%) were diagnosed with fatty liver on computed tomography (CT) scan. This made up a significantly higher percentage of severe COVID-19 cases than the general prevalence of NAFLD in the population.[33]

A retrospective Chinese study by Ji and colleagues exclusively examined the patterns of liver injury and clinical outcomes in patients with NAFLD. A total of 202 consecutive patients with NAFLD and confirmed COVID-19 were included, and hepatocellular enzyme elevation was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization, respectively. Progression of COVID-19 was observed in 87.2% of patients with NAFLD. Progressive disease was associated with age above 60 years [odds ratio (OR): 4.8; 95% CI: 1.5-16.2], higher body mass index (OR: 1.3; 95% CI: 1.0-1.8), and NAFLD (OR: 6.4; 95% CI: 1.5-31.2). NAFLD patients also had a longer duration of viral shedding (17 d) compared with patients without NAFLD (12 d).[34]

Another Chinese study of 66 COVID-19 patients with the metabolic-associated fatty liver disease showed that obesity in this population was associated with 6-fold increased odds for severe COVID-19. The increased odds persisted after adjusting for age, sex, and metabolic features, such as diabetes, hypertension, and dyslipidemia (adjusted OR: 6.32; 95% CI: 1.16-34.54, $P=0.033$).[35] Targher and colleagues evaluated noninvasive liver fibrosis scores in 310 patients with COVID-19 and NAFLD. They reported that patients with increased fibrosis scores are at a higher likelihood of having severe COVID-19 illness.[36]

It is postulated that, in patients with NAFLD, inflammation-suppressing M2 macrophages are activated rather than inflammation-promoting M1 macrophages, leading to the progression of COVID-19, though further studies are needed.[37] There is currently no direct evidence that the SARS-CoV-2 virus has an increased affinity for fatty liver tissue.[38,39] However, mounting data suggest that patients with NAFLD, particularly those with diabetes and obesity, may have a higher risk for worse outcomes in COVID-19.

CHRONIC HEPATITIS B

A few studies have examined the impact of SARS-CoV-2 on patients with chronic hepatitis B virus (HBV) infection. Among 5700 patients hospitalized with COVID-19 in the New York City area, 0.1% of patients had a diagnosis of chronic hepatitis B.[40] In contrast, 2.1% of hospitalized patients in Wuhan, China had coexisting chronic HBV infection.[3] A single-center, retrospective study of 105 patients with SARS-CoV-2 and chronic HBV reported liver injury in 14 patients (13.3%) and acute-on-chronic liver failure in 4 patients (3.8%).

TABLE 2. Summary of Recommendations AASLD,[15] EASL,[16] and APASL[17]

Disease	AASLD	EASL	APASL
NAFLD	No specific recommendations	Continue treatment of hypertension with ACE inhibitors or ARBs Prioritize admission of all patients with NAFLD infected with SARS-CoV-2	No specific recommendations
HBV	Continue treatment for chronic HBV if already receiving treatment In patients with COVID-19, defer initiation of treatment for HBV until recovery In patients with COVID-19, initiate therapy if there is clinical suspicion of HBV flare or when initiating immunosuppressive therapy	Continue treatment for chronic HBV if already receiving treatment In patients with COVID-19, defer initiation of treatment for HBV until recovery In patients with chronic HBV and receiving immunosuppressive therapy of COVID-19, consider use of antiviral therapy	Continue treatment for chronic HBV if already receiving treatment In patients with COVID-19, defer initiation of treatment for HBV until recovery In patients with COVID-19, initiate therapy if there is clinical suspicion of HBV flare or when initiating immunosuppressive therapy
AIH	In AIH patients on immunosuppression without COVID-19 infection do not decrease immunosuppression In AIH patients on immunosuppression with COVID-19, consider lowering overall immunosuppression, particularly antimetabolites	In AIH patients on immunosuppression without COVID-19 infection do not decrease immunosuppression In COVID-19 patients consider budesonide to minimize systemic glucocorticoid exposure for management of acute flare of AIH In AIH patients on immunosuppression, maintain steroid dosing sufficient to prevent adrenal insufficiency	In AIH patients continue immunosuppressive therapy with mild COVID-19 infection Do not discontinue corticosteroids in AIH patients with severe COVID-19 infection and use stress doses as needed
HCC	Continue surveillance for HCC in patients at risk, although a delay of 2 mo is reasonable In patients positive for SARS-CoV-2 infection avoid HCC surveillance Consider virtual visits to discuss diagnosis and management of HCC	Resume HCC surveillance where possible. If resources are limited prioritize high risk patients in conjunction with the use of published HCC risk stratification score Multidisciplinary management of HCC should continue remotely	Consider postponing of elective transplant, resection surgery or radiotherapy for newly diagnosed HCC patients Consider initiation of ablative procedures, transcatheter arterial chemo embolization, kinase inhibitors or immunotherapy Withhold immunosuppressive therapy if HCC patients are infected with SARS-CoV-2
Cirrhosis	Maintain a low threshold to test patients with cirrhosis for SARS-CoV-2 Prioritize in-person evaluation of patients with decompensated cirrhosis	For patients infected with SARS-CoV-2, follow guideline directed therapy to prevent hepatic decompensation Prioritize in-person evaluation of patients with decompensated cirrhosis	No specific recommendations
LT	Prioritize LT for patients with acute liver failure, ACLF, high MELD score and HCC at upper limits of the Milan criteria Before organ procurement evaluate donor for COVID-19 infection with a nasopharyngeal swab and chest CT Avoid organ transplantation from donors positive for SARS-CoV-2 infection In SARS-CoV-2-positive transplant candidates consider transplantation at least 14-21 d after symptom resolution and 1 or 2 negative SARS-CoV-2 diagnostic tests	Prioritize LT for patients with acute liver failure, ACLF, high MELD score and HCC at upper limits of the Milan criteria Before organ procurement evaluate donor for COVID-19 infection with a nasopharyngeal swab and chest CT Avoid organ transplantation from donors positive for SARS-CoV-2 infection	Prioritize LT for patients with acute liver failure, ACLF, high MELD score and HCC at upper limits of the Milan criteria Before organ procurement evaluate donor for COVID-19 infection with a nasopharyngeal swab and chest CT Avoid organ transplantation from donors positive for SARS-CoV-2 infection Assess recipients for COVID-19 infection symptoms and exposure
Post-LT	In posttransplant patients without COVID-19, do not decrease immunosuppression In posttransplant patients with COVID-19, consider lowering overall immunosuppression, particularly antimetabolite therapy	In posttransplant patients without COVID-19, do not decrease immunosuppression Closely monitor drug levels of calcineurin inhibitors and mechanistic target of rapamycin inhibitors when they are administered together with drugs for COVID-19 Consider early admission for all LT recipients who develop COVID-19	In posttransplant patients without COVID-19, do not decrease immunosuppression In posttransplant patients with COVID-19, consider lowering overall immunosuppression. Immunosuppression should be reduced in patients with lymphopenia, fever, or worsening pneumonia

AASLD indicates American Association for the Study of Liver Disease; ACE, angiotensin-converting enzyme; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; APASL, Asian Pacific Association for the Study of Liver; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; CT, computed tomography; EASL, The European Association for the Study of Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LT, liver transplant; MELD, Model for End-stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The overall mortality was higher in patients with liver injury than those without (28.57% vs. 3.30%, $P=0.004$).[41] In a small retrospective study, Chen and colleagues showed that COVID-19 patients with preexisting HBV disease had a more severe disease course (46.7% vs. 24.1%) and a higher mortality rate (13.3% vs. 2.8%) when compared with patients without HBV coinfection. However, larger studies are needed to assess the impact of coinfection with HBV and SARS-CoV-2.

Since the first cases of COVID-19 were reported in December 2019, the treatment of COVID-19 has evolved dramatically. We now recognize the rapid clinical deterioration of patients from cytokine-mediated immune damage.[42] Immunosuppressants and steroids are now at the forefront of the management of COVID-19.[43] Reactivation of HBV in COVID-19 is a concern when using immunosuppressive therapy.[44] In a recent study of HBV patients with only positive HBV core antibody receiving corticosteroids, the risk of a hepatitis flare started to increase in those receiving corticosteroids at peak daily doses of 20 to 40 mg (adjusted hazard ratio: 2.19, $P=0.048$) or >40 mg (adjusted hazard ratio: 2.11, $P=0.015$) prednisolone equivalents for <7 days.[45] Consensus statements from major societies agree that antiviral treatment of HBV during immunosuppressive drug therapy is indicated in those with HBV surface antigen positivity or HBV core antibody positivity, depending on the level of immunosuppression.[46]

A prospective observational study reported an increased risk of HBV reactivation in patients with rheumatoid arthritis and chronic HBV infection receiving tocilizumab.[47] However, reactivation rates of chronic HBV infection in COVID-19 patients receiving tocilizumab are unknown. It remains unclear if antiviral prophylaxis should be initiated in these cases.[48]

The AASLD, EASL, and APASL do not recommend routinely initiating treatment of hepatitis B in patients with COVID-19 unless there is clinical suspicion of a hepatitis flare.[15–17]

AUTOIMMUNE HEPATITIS (AIH)

The impact of COVID-19 infection on AIH is unclear. It has been suggested that an immunosuppressive state can predispose to infection with the SARS-CoV-2 virus. However, a study of AIH patients under immunosuppression in Northern Italy reported a similar prevalence of COVID-19 infection in the study group as in the general population.[49] A similar study in Belgium did not find an increased susceptibility to contract COVID-19 patients in AIH patients on immunosuppression.[50] A retrospective analysis reported a similar disease course in AIH patients on immunosuppression when compared with patients not on immunosuppression.[11] Overall, AIH patients on immunosuppression did not have worse outcomes.

The EASL, AASLD, and APASL caution against withdrawing immunosuppression in AIH patients with COVID-19 as it may lead to hepatitis flares. In AIH patients with COVID-19 infection, the recommendation is to lower immunosuppression while maintaining a level of corticosteroids sufficient to prevent adrenal insufficiency.[15–17]

CIRRHOSIS

Cirrhosis predisposes to higher mortality in those affected by COVID-19. A retrospective Italian study of 50 patients with cirrhosis and concomitant COVID-19 infection reported a high 30-day mortality of 34%. Outcomes were worse in patients with higher Model for End-Stage Liver Disease (MELD) scores.[12] While respiratory failure was reported as the most common cause of death in these patients, it is important to note that decompensated cirrhosis can predispose to pulmonary complications. We need more studies to determine the correlation between pulmonary complications of decompensated cirrhosis and respiratory distress related to COVID-19.[51,52] Another cohort study of 250 patients with prior diagnoses of chronic liver diseases reported a higher mortality risk in patients with cirrhosis (relative risk: 4.6; 95% CI: 2.6-8.3).[7] Preliminary analysis of data from 2 international self-reporting registries, COVID-Hep.net and COVIDCirrhosis.org, reported high mortality in cirrhotic patients with COVID-19. Mortality is strongly correlated with the Child-Turcotte-Pugh (CTP) class with a mortality of 23.9% in CTP-A, 43.3% in CTP-B, and 63.0% in CTP-C. Hepatic decompensation in compensated cirrhosis patients strongly correlated with the risk of death when compared with patients without decompensation (63.2% vs. 26.2%).[38–40]

Furthermore, an international study comprised of cohorts from 13 Asian countries showed that acute-on-chronic liver failure or acute decompensation occurred in 20% of cirrhotic patients with COVID-19.[53] This is an important observation as it indicates that patients with cirrhosis are predisposed to severe hepatotoxic injury by the SARS-CoV-2 virus. SARS-CoV-2 selectively binds to angiotensin-converting enzymes 2 receptors on the bile duct epithelial cells that play important roles in liver regeneration and immune response.[54] The liver is a crucial component of the reticuloendothelial system and is responsible for innate immunity. Cirrhosis impairs this homeostatic response conferred by the reticuloendothelial system of the liver. As the disease progresses, it switches from a proinflammatory to an immune-deficient state.[55] The cytokine-mediated immune response in a patient with a diminished liver reserve may lead to hepatic decompensation.[56] Consequently, when patients with a diagnosis of cirrhosis present with acute elevation of liver enzymes, in addition to excluding infectious etiologies like hepatitis and drug-induced liver injury, testing for COVID-19 should be considered.

HEPATOCELLULAR CARCINOMA (HCC) SCREENING AND MANAGEMENT

HCC screening has taken a back seat because of social distancing practices and staffing shortages. Since the tumor doubling time is 4 to 8 months and current guidelines recommend screening every 6 months, in patients at lower risk for developing HCC, a 2-month delay in ultrasound surveillance has been suggested by the AASLD.[57] In patients with a high risk of developing HCC, 6-month interval screening should be continued.[58] The EASL and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggest deferring HCC surveillance in patients testing positive for COVID-19 until recovery or 2 negative reverse transcriptase-polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 are achieved.[59]

Nosocomial spread of infection is a cause of concern for patients presenting for the management of HCC. The objective is to minimize aerosolization procedures, conservative utilization of anesthesia resources, reduce the length of hospital stay, and provide adequate follow-up.

Screening questionnaires can be used for identifying patients with active symptoms and for identifying patients with close contact with patients diagnosed with COVID-19. Preprocedural workup including RT-PCR for SARS-CoV-2 can be performed in the outpatient setting.[60]

There is uncertainty regarding whether HCC treatment should be initiated in COVID-19 patients with newly diagnosed HCC. Delaying treatment can lead to the progression of HCC with detrimental outcomes, but surgical resection may increase the risk of transmission to health care workers. In addition, tyrosine kinase inhibitors or checkpoint inhibitors may worsen COVID-19 by worsening a cytokine storm. AASLD recommendation is for HCC treatment to proceed[57]; whereas, EASL recommends postponing locoregional therapies if possible and for checkpoint inhibitors to be temporarily withheld in patients with COVID-19.[59] The APASL recommends postponing elective transplant and resection for HCC and proceeding with locoregional therapy. APASL suggests tyrosine kinase inhibitor and immunotherapy can be started but given at a less frequent schedule of every 4 to 6 weeks.[17]

LT

In LT patients, the risk of infection with SARS-CoV-2 and the severity of outcomes remain unclear.[61] The University of Washington maintains a regularly updated registry of solid organ transplant (SOT) recipients with COVID-19. A preliminary analysis of data from this registry was reviewed at a webinar hosted by the AASLD. It reported that the risk of contracting SARS-CoV-2 in SOT recipients is comparable to the general population, with advanced age and comorbidities such as diabetes being risk factors that showed a disproportionate rate of infection. Although the 28-day all-cause mortality in LT recipients is reported $>20\%$, it is similar to the inpatient case fatality rate in the general population as reported by other registries.[62,63] COVID-Hep and SECURE-CIRRHOSIS are voluntary international registries that collect relevant data on COVID-19 patients and underlying chronic liver disease and LT. Of the 159 LT patients described in their latest report, 81% were hospitalized, 30% required intensive care unit (ICU) care, and 19% died.[64,65] Preliminary data from the European Liver and Intestine Transplant Association (ELITA) registry indicates that older LT recipients have higher mortality.[66] In a systematic review of SOT patients with COVID-19, 16 cases of LT were described. The fatality rate among LT recipients was 37.5%.[67]

The Centers for Medicare and Medicaid Services (CMS), in an effort to prioritize health care resources, have provided a tiered framework to classify nonemergent, elective medical services. They have designated transplant surgery as Tier 3b or do not postpone.[68] Yet, transplant centers are faced with the difficult task of devising region-specific models of care to combat the unique challenges presented to them.[69,70] Because of COVID-19-related limitations, there has been a decrease in organ procurement.[71] Before resuming transplant services, health care facilities are encouraged to consider the availability of resources, staffing issues, and nosocomial spread of infection. Telemedicine visits have become increasingly popular in evaluating LT recipients, who are likely to benefit from immediate transplant listing since patients are being discouraged from attending in-office visits and undergoing any invasive or noninvasive testing.[57] The Organ Procurement and Transplantation Network (OPTN) has temporarily relaxed the frequency of updating MELD scores for listed patients.[72]

As transplant activity resumes amidst the pandemic, all 3 liver societies recommend limiting LT to patients with high MELD scores, the risk for decompensation, or HCC progression.[17,57,59] Potential donors are assessed for exposure history with known or suspected COVID-19 patients and travel to an affected region. All donors are screened with an RT-PCR assay of the nasopharyngeal swab for the SARS-CoV-2 virus and a screening CT scan of the chest.[73] Ai et al[74] reported a sensitivity of 97% for chest CT imaging in detecting COVID-19, compared with a lower sensitivity of RT-PCR testing at 71%. Symptomatic donors who are positive by RT-PCR or CT chest are rejected.[73] AASLD recommends against LT in patients with COVID-19. However, LT can proceed 21 days after symptom resolution and negative diagnostic tests in recipients.[57]

POSTTRANSPLANT CARE AND IMMUNOSUPPRESSION

The postoperative period immediately following the transplant requires cardiovascular support and access to critical care units. To ensure optimum transplant success rate and to prevent nosocomial transmission, the Birmingham Liver Unit in the UK established a SARS-CoV-2-free pathway, which meant a dedicated ICU and ward for posttransplant care.[75] Perioperative transplant care should be encouraged where feasible through telehealth visits. At these encounters, patients should be routinely screened for symptoms related to SARS-CoV-2 like fevers, dyspnea, cough, diarrhea, and altered sense of taste or smell. Symptomatic patients should be encouraged to present to the hospital for further evaluation.[76]

In LT recipients without COVID-19, all 3 liver associations recommend against reducing immunosuppression.[17,57,59] There has been no data to suggest that posttransplant immunosuppression is a risk factor in COVID-19 severity. In contrast, reducing immunosuppression may increase the risk of graft rejection. AASLD advocates for telemedicine in posttransplant care as well as telework options for LT recipients.[57] In LT recipients with COVID-19, AASLD recommends lowering the overall level of immunosuppression, particularly antimetabolite dosages, while maintaining the dosage of calcineurin inhibitors (CNIs) the same.[57] This is based on the general principles for managing infections in transplant recipients.

Cytokine release from activation of the host's immune system is the primary driver of tissue damage in COVID-19.[77] Consequently, immunosuppression can potentially curb this response. The RECOVERY trial's preliminary, non–peer-reviewed report stated the effectiveness of short-term dexamethasone in reducing 28-day mortality in COVID-19 patients on the ventilator support by one third and those requiring noninvasive oxygen support without invasive ventilation by one fifth.[31] At the same time, it is important to note that inflammatory bowel disease patients on systemic corticosteroid therapy and COVID-19 had markedly worse outcomes in the form of increased admission to the ICU, mechanical ventilation, and death (adjusted OR: 6.87; 95% CI: 2.3-20.5).[65] In vitro studies show that coronavirus replication, which is dependent on immunophilin pathways, is inhibited by tacrolimus.[66] Similarly, limited data exist on the antiviral effects of cyclosporine. In kidney transplant patients infected with SARS-CoV-2 virus, the cyclosporine only group reported fewer deaths (13%) when compared with a group that minimized immunosuppression (50%).[67]

Immunosuppressive therapy also has the potential to complicate the treatment of SARS-CoV-2 in SOT recipients. The drug-drug interactions between dexamethasone and CNI and the liver toxicity associated with remdesivir and tocilizumab are well documented and may preclude their use in the treatment of COVID-19 in LT recipients.[24,68]

IMPACT OF THE MANAGEMENT OF COVID-19 ON UNDERLYING LIVER DISEASE

The therapeutic options for treatment of COVID-19 are continuously evolving. There are currently no medications approved for the treatment of COVID-19. Remdesivir received EUA from the FDA when an interim analysis showed improved recovery times.[78] Due to aminotransferase elevations, 2.5% of patients in the 5-day group and 3.6% of patients in the 10-day group discontinued treatment.[79] In the largest randomized controlled trial conducted, investigators did not report a significant difference between aminotransferase elevations in patients taking remdesivir compared with placebo.[78] Patients with aminotransferase elevations >5 times the upper limit of normal were excluded from the study. No data is available on the effect of remdesivir on underlying liver disease in COVID-19 patients. In fact, cirrhosis patients were excluded from the multicenter trial discussed above.

Monoclonal interleukin-6 receptor antagonists counter the cytokine-mediated injury in severe COVID-19. Tocilizumab has a significant hepatotoxic side-effect profile, and regular monitoring of liver biochemistries should be performed. A prospective study evaluated the risk of hepatitis B reactivation in rheumatoid arthritis patients on disease-modifying agents receiving tocilizumab. Among 63 rheumatoid arthritis patients with chronic hepatitis B, 3 patients developed reactivation. None of the patients in the study received any antiviral prophylaxis. All 3 patients were asymptomatic and improved with antiviral therapy.[47]

In addition, lopinavir-ritonavir has been studied in clinical trials for the management of COVID-19. Ritonavir inhibits CYP3A4, which regulates the metabolism of CNIs used in LT patients. Ritonavir increases tacrolimus concentration in blood and requires dosage reduction. When compared with standard of care in severe COVID-19 patients, lopinavir-ritonavir did not show any clinical benefit, while in some patients treatment had to be discontinued because of adverse events.[80]

Last, COVID-19 and cirrhosis both alter the coagulation pathway. It is unclear if the presence of both cirrhosis and COVID-19 increases the risk of thromboembolic events when compared with the risk of thromboembolism imposed by either condition alone. It remains to be determined if COVID-19 patients with cirrhosis benefit from therapeutic anticoagulation. A multicenter retrospective study did not observe any major hemorrhagic complications when thromboprophylaxis with heparin was given to patients with cirrhosis and confirmed SARS-CoV-2 infection.[12]

CONCLUSIONS

COVID-19 patients with the preexisting liver disease face a higher risk of decompensation and mortality. We presented the most up-to-date literature on preexisting liver disease and its interaction with COVID-19. Our article also focused on changes in current practices of LT. Epidemiological modeling predicts more waves of infection after the first wave unless a vaccine or effective treatment modality becomes available. We should draw on our current experiences and develop mitigation strategies to combat the next waves more effectively.

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