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REVIEW

COVID-19 and liver diseases, what we know so far

Mohamed Elnaggar, Ahmed Abomhya, Ismail Elkhattib, Nabila Dawoud, Rajkumar Doshi

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Abstract

Coronavirus disease 2019 (COVID-19) pneumonia outbreak started in December 2019. On March 12, 2020, the World Health Organization (WHO) declared that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) constitutes a pandemic, and as of May 2021, SARS-CoV-2 has infected over 167.3 million patients, including 3.4 million deaths, reported to WHO. In this review, we will focus on the relationship between SARS-CoV-2 infection and the liver. We will discuss how chronic liver diseases affect the COVID-19 disease course and outcomes. We will also discuss the SARS-CoV-2 effects on the liver, mechanisms of acute liver injury, and potential management plans.

Key Words: COIVD-19; SARS-CoV-2; Liver diseases; Transaminases; Non alcoholic fatty liver; Hepatocellular carcinoma

Core Tip: On March 12, 2020, the World Health Organization declared that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a pandemic. SARS-CoV-2 is notorious for causing gastrointestinal and liver injuries. Liver injury mechanisms include SARS-CoV-2-induced hepatic steatosis, reactivation of pre-existing liver disease, mitochondrial dysfunction, cardiomyopathy with hepatic congestion, immune-mediated damage, hypoxic hepatitis, direct cytotoxicity, drug-induced liver injury, ischemic hepatitis, microthrombotic disease, and extrahepatic release of transaminases. The coronavirus disease 2019 (COVID-19) pandemic has various effects on pre-existing liver conditions that range from care disruptions, exacerbation of liver condition, and higher mortality rates. It is necessary to know the mechanisms of liver injury in COVID-19 disease, epidemiology, clinical presentations, diagnosis, and effects on pre-existing liver conditions.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) pneumonia outbreak started in December 2019. On March 12, 2020, the World Health Organization (WHO) declared that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) constitutes a pandemic, and as of May 2021, SARS-CoV-2 has infected over 167.3 million patients, including 3.4 million deaths, reported to WHO. The healthcare industry around the globe was mobilized in an unprecedented way to face the pandemic, and vaccines developed at an unprecedented pace. As of May 25, 2021, a total of 1489727128 vaccine doses were administered[1].

Middle East respiratory syndrome coronovirus (MERS-CoV), SARS-CoV and SARS-CoV-2 belong to Beta Coronavirus Genus. The three viruses have a significant genetic similarity. Genomes of SARS-CoV and SARS-CoV-2 have 82% nucleotide identity[2].

The highly pathogenic human coronaviruses have demonstrated the ability to cause gastrointestinal and liver injuries. SARS-CoV and MERS-CoV can cause GI symptoms and transaminitis[3,4]. COVID-19 cases presenting solely with GI symptoms have been reported in both adults and children[5]. Over 50% of SARS-CoV patients have a mild self-resolving elevation of liver function tests, and high alanine aminotransferase (ALT) was considered a prognostic indicator of intensive care unit (ICU) admission and mortality[6,7].

MERS-CoV non-survivors had a higher incidence of acute liver injury compared to survivors. Hypoalbuminemia is an independent predictor of severe MERS-CoV course, and liver biopsy showed mild hydropic hepatocytes degeneration and lymphocytic infiltration[8-10].

SARS-CoV-2 was detected in the stools of over 50% of COVID-19 hospitalized patients[11,12]. SARS-CoV-2 has been shown to infect enterocytes[13,14]. In situ hybridization detected viral RNA in intestinal epithelial cells, endothelial cells, and hepatocytes. Viral protein and RNA persist in intestinal biopsies after the clinical infection has resolved. Positive Stool SARS-CoV-2 polymerase chain reaction was also seen long after COVID-19 pneumonia had resolved[11,14].

Due to socioeconomic status, healthcare disparities, and the nature of some chronic medical conditions, the underserved populations were affected the most by care disruptions and had to live with the risk of potential long-term consequences. In a Global Multi-Center Propensity Matched Analysis, Perisetti *et al*[15] reported Increased Diagnosis of Hepatocellular Carcinoma in Hospitalized Patients with Alcohol-Related Hepatitis after the COVID-19 Outbreak[15].

Chronic liver disease (CLD) is more common among low Socioeconomic status populations. COVID-19 pandemic has brought attention to racial and socioeconomic disparities, and the health care systems should adapt to account for the various challenges that face underserved populations[16].

Old age, diabetes, hypertension, obesity, smoking, COPD, Malignancy, coronary heart disease, CLD, CKD are risk factors for severe COVID-19 course and worse outcomes[17]. Chornenkyy *et al*[18] found that most patients who died of COVID-19 had histological evidence of mild focal hepatitis[18].

In this review, we will focus on the relationship between SARS-CoV-2 infection and the liver. We will discuss how CLDs affect the COVID-19 disease course and outcomes. We will also discuss the SARS-CoV-2 effects on the liver, mechanisms of acute liver injury, and potential management plans.

EPIDEMIOLOGY

Worldwide over 122 million patients suffer from Liver cirrhosis, of whom over 10 million have

decompensated liver cirrhosis, but the most common CLD worldwide is nonalcoholic fatty liver disease (NAFLD)[19-21].

Over 24% of the United States population has NAFLD, and its prevalence goes up to 30% in the Middle East and South America. Nonalcoholic steatohepatitis (NASH) is a more severe condition where fat accumulation triggers inflammation which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma[21,22]. Metabolic-associated fatty liver disease (MAFLD) is a novel definition that can better identify patients with fatty liver disease with a high risk of disease progression[23].

The literature shows that 15%-65% of COVID-19 patients have some abnormalities in liver biochemistry[24]. In a systematic review and meta-analysis of 128 studies, the most frequent derangement in liver functions of COVID-19 patients was hypoalbuminemia followed by elevations in gamma-glutamyl transferase and aminotransferases. These abnormalities were observed more frequently in severe COVID-19 disease[25]. The transaminitis observed with COVID-19 disease is believed to be due to hepatic injury as high serum aspartate aminotransferase (AST) levels positively correlate with ALT levels but not with creatinine kinase or markers of systemic inflammation like C-reactive protein (CRP) or ferritin[26].

MECHANISMS OF LIVER INJURY IN COVID-19 DISEASE

Transaminitis has been reported in some systemic viral infections, such as parvovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and adenovirus. The highly pathogenic human coronaviruses have demonstrated the ability to cause gastrointestinal and liver injuries. SARS-CoV and MERS-CoV can cause GI symptoms and transaminitis[3,27]. Autopsy tissue from the liver of deceased SARS patients showed mitotic liver cells, mid inflammation, steatosis, central lobular necrosis, apoptosis, and liver cells expressing SARS-CoV protein[4].

The variability in liver injury severity and prevalence suggests that liver injury in COVID-19 disease is multifactorial. Multiple mechanisms of liver injury have been reported. Immune-mediated damage because of the severe dysregulated inflammatory response, direct cytotoxicity, systemic hypoxia with hypoxic hepatitis, drug-induced liver injury, reactivation of pre-existing liver disease, mitochondrial dysfunction, SARS-CoV-2-induced hepatic steatosis, microthrombotic disease, ischemic hepatitis, cardiomyopathy with hepatic congestion, and extrahepatic release of transaminases have been reported as potential mechanisms of liver injury.

SARS-CoV-2 hepatotropism and its direct impairment of liver function have been proposed by multiple studies, and it's believed to play a role in COVID-19 induced liver injury, yet further research is needed to define factors that determine SARS-CoV-2 hepatotropism.

Angiotensin converting enzyme-2 (ACE2) serves as receptors for the SARS-CoV-2 spike protein, while transmembrane serine protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN) are essential for cell entry. Single-cell RNA sequencing analysis of healthy liver samples showed ACE2 expression in Hepatocytes, Sinusoidal endothelial cells, and Cholangiocytes with the highest expression level in cholangiocytes. TMPRSS2 and FURN are widely expressed among different liver cell types. Combined analysis showed few hepatocytes coexpressed ACE2 and TMPRSS2[28].

ACE2-expressing and TMPRSS2-expressing human liver ductal organoids were able to recapitulate SARS-CoV-2 infection[29]. Human pluripotent stem cell-derived liver organoids express ACE2 and permitted SARS-CoV-2 pseudoparticle entry[30]. Another study showed that hepatocellular carcinoma-derived cell lines like Huh-7 can support the complete viral life cycle[31].

Literature suggests that liver injury could potentiate SARS-CoV-2 hepatotropism. Hepatitis C virus (HCV)-related cirrhosis has a 30-fold increase in ACE2 expression compared to healthy liver samples [32]. *ACE2* gene is interferon-inducible in human respiratory epithelia[33,34]. This can explain the severe COVID-19 disease course observed in those with CLD, but the upregulated ACE2 could be a truncated dACE2 and is not associated with increased hepatotropism[35].

Liver biopsy samples from 48 patients deceased to severe COVID-19 disease showed microvascular and macrovascular steatosis, mild portal inflammation, portal fibrosis, and portal venous and sinusoidal microthromboses. SARS-CoV-2 was detected *via* in situ hybridization in 68% of samples, and electron microscopy (EM) showed mitochondrial swelling and apoptosis[28].

SARS-CoV-specific protein 7a can induce hepatocytes apoptosis through the caspase-dependent pathway[36].

Mitochondrial functions are central to cell physiology. Oxidative phosphorylation drive hepatocyte polarization[37]. Proteomic analysis of autopsy tissue from 19 patients deceased to severe COVID-19 disease showed mitochondrial dysfunction with dysregulated fatty acid oxidation and oxidative phosphorylation[38,39].

One of the main features of COVID-19 disease is the dysregulated systemic immune response. Cytokines storms can cause shock and multiorgan failure[40]. Liver injury with SARS-CoV-2 infections is associated with CRP levels and lymphocytopenia[41-43].

Interleukin (IL)-6 plays a role in the systemic inflammatory response during COVID-19 disease, and its levels decline as patients recover. High levels of ALT were associated with high levels of IL-6, D-

dimer, ferritin, and CRP[44,45].

Hypercoagulability with venous and arterial thromboses is a well-recognized feature of COVID-19 disease[46,47]. A systematic review and meta-analysis of histopathological reports from deceased COVID-19 patients found a high prevalence of hepatic vascular thrombosis among deceased COVID-19 patients[48]. Kolli *et al*[49] reported a case of COVID-19 disease with portal venous thrombosis[49].

SARS-CoV-2 causes acute hypoxic respiratory failure, and hypoxic liver injury can contribute to the severity of liver injury in COVID-19 patients. High levels of AST were reported with influenza A/H1N1 pneumonia, and levels increased with worsening of hypoxemia[50].

Nearly all classes of medications can cause liver injury. Most of the time is self-resolving and improves with drug withdrawal. When the COVID-19 pandemic erupted, so many medications were proposed and tried as a potential treatment. A meta-analysis of COVID-19 patients showed a pooled incidence of DILI of 25%[51].

Drug-induced liver injury was associated with lopinavir-ritonavir, tocilizumab, tofacitinib, dexamethasone, Ivermectin, antibiotics (macrolides, quinolones), and Remdesivir[52,53].

Randomized controlled clinical trials of Remdesvir and tocilizumab in COVID-19 patients did not show any significant difference in the prevalence of liver injury in the treatment compared to the placebo groups[54,55].

When it comes to the association between transaminitis and COVID-19 prognosis, the literature shows a mixed picture with some reports showing no association between transaminitis and mortality, while others reported that transaminitis was associated with worse outcomes including shock, ICU admission, respiratory failure, and mechanical ventilation[56].

Mild AST elevation was an early sign of severe COVID-19 disease[57]. A Meta-analysis showed that patients with severe COVID-19 disease had higher values of total bilirubin and ALT while having lower albumin levels[58].

High ALT levels were an independent predictor of prolonged SARS-CoV-2 RNA shedding[59]. A retrospective cohort study showed that hypoalbuminemia on admission was associated with increased mortality, shock, intubation, and need for hemodialysis while elevations of ALT, AST, or alkaline phosphatase at any time during hospital admission increased the odds of ICU admission[60]. AST and ALT levels greater than three times the upper limit of normal were associated with increased mortality [61].

The mixed picture can be explained by the various potential mechanisms of liver injury and further research is needed to find the synergistic effects of different risk factors and mechanisms of injury on prognosis.

CLINICAL PRESENTATION

The incidence of liver injury in COVID-19 patients is highly variable, ranging from 15%-65%[24]. Current studies have consistently shown an increased risk of severe COVID-19 course in patients with preexisting liver disease.

In China, a meta-analysis of 46248 patients done in Wuhan showed that the mortality rate in patients with underlying CLD was 0%-2% which was lower than most of the other common comorbidities in that study like hypertension (14%-22%), DM (6%-11%), cardiovascular diseases (4%–7%) and respiratory disease (1%–3%)[62].

The severity of liver disease seems to be proportionate to COVID-19 infection severity. Two studies from Wuhan showed that AST, ALT, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase were significantly higher in value and presented more in several patients in the non-survivor group *vs* the survivor group.

In the United States, several studies showed no association between liver biochemistry levels, and mortality Whereas others found that elevated levels, particularly five times the upper limit of normal, were associated with mortality[63].

Implementation of liver biochemistry to predict mortality needs more investigations before it can be considered an independent risk factor for outcome.

DIAGNOSIS

Patients hospitalized with abnormal liver biochemistries should receive a diagnostic evaluation to determine the etiology, whether medication-related, infectious, or noninfectious. Here, we highlight COVID-19 disease as a notorious cause of liver injury that should be considered in the differential diagnosis giving the high incidence rate of COVID-19 disease. There are no studies that looked into a specific workup for COVID-19 and related elevated liver biochemistries, so general workup should be considered, especially in patients with elevated biochemistry but rather a mild COVID-19 infection or failure to normalize the biochemistries after hospital discharge.

COVID-19 INDUCED LIVER INJURY IN SPECIFIC PATIENT POPULATIONS

Advancing age, obesity, and diabetes are the major risk factors for severe COVID-19 disease and are very common in patients with CLD. Due to the overlapping risk factors, it is critical to investigate the association between chronic liver conditions and COVID-19 disease. We will summarize the literature on COVID-19 infection in patients with liver cirrhosis, NAFLD, metabolic dysfunction-associated liver disease, fatty liver disease, HBV infection, and HCC. Figure 1 summarizes mechanisms of liver injury in COVID-19 disease.

After adjusting for baseline characteristics, COVID-19-related mortality was significantly associated with the severity of liver cirrhosis, and the odds ratio for death increased across the stages of liver cirrhosis as measured by Child-Pugh (CP) class. The higher mortality was observed in the acute infective period while rates of 90-d readmission were similar to those without COVID-19 diagnosis[64,65].

The liver plays a homeostatic role in the systemic immune response. With cirrhosis, damage to the reticuloendothelial system compromises the liver immune surveillance function. The cirrhosis-associated immune dysfunction (CAID) phenotypes represent the extremes of a spectrum of dynamic events that switch from predominantly proinflammatory to predominantly immunodeficient.

CAID is characterized by decreased bacterial opsonization, phagocytosis, protein C activity, antigen T lymphocyte dependent responses, hypoalbuminemia, hypocomplementemia, decreased vaccine response, and intestinal dysbiosis[66,67].

CAID is associated with increased serum levels of tumor necrosis factor α, IL-1β, IL-6, IL-17, IL-18, and IFNγ[68]. CAID phenotypes are associated with increased susceptibility to bacterial, fungal, and viral infections.

There has been no evidence that patients with CLD have a higher incidence of COVID-19 disease and the data demonstrates a lower risk of testing positive for SARS-CoV-2 in patients with liver cirrhosis. This can be attributed to frequent testing and compliance with preventive measures[69]. Patients with liver cirrhosis have worse clinical outcomes with any type of infection compared to those without any underlying liver disease.

Microbial infections have a significant association with higher mortality in patients with liver cirrhosis. A cohort study found a 4-fold increase in mortality in infected patients with liver cirrhosis compared to the noninfected group[70].

TROP2+ liver progenitor cells co-expressed ACE2 and transmembrane serine protease 2. SARS-CoV-2 infection of the TROP2+ liver progenitor population might impair regeneration capacity in patients with liver cirrhosis[71].

Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of liver cirrhosis, organ failure(s), and high short-term mortality. ACLF patients have profound inflammatory markers and proinflammatory cytokines, features that are common in severe SARS-CoV-2 infection[72].

SARS-CoV-2 infection in patients with liver cirrhosis was associated with worsening MELD score, ACLF, and death[73]. SECURE-Cirrhosis and COVID-Hep registries showed a higher incidence of ACLF with increasing severity of CLD, and mortality increased with worsening ACLF as measured by the CLIF-C score[74].

Fibrosis-4 score can be a prognostic indicator for estimating adverse outcomes of COVID-19 disease in patients with liver cirrhosis[75]. The consequences of COVID-19 infection in liver transplant recipients were highlighted in multiple studies with mixed conclusions.

Liver transplantation can involve the donor-to-recipient transmission of SARS-CoV-2[76]. Waisberg *et al*[77] found that COVID-19 infection is associated with worse postoperative transplant outcomes, especially in older and obese patients with multiple comorbidities[77]. Colmenero *et al*[78] reported that liver transplant recipients had an increased risk of SARS-CoV-2 infection but lower mortality compared to a matched general population[78]. Case reports for post-transplant patients who had a mild or severe COVID-19 disease with complete recovery were published[79,80]. Acute liver injury was found to be associated with higher mortality and ICU admission in LT recipients with SARS-CoV-2 infection. The rate of ALI in liver transplant recipients with COVID-19 disease was lower than in the nontransplant cohort[81]. Liver transplant recipients usually have several coexisting comorbidities and collectively the literature shows that COVID-19 disease prognosis depends on the coexisting comorbidities and the development of ALI.

The current recommendations favor the continuation of systemic immunosuppression at stable doses for most liver transplant recipients with COVID-19 disease[82]. Reduction of systemic immunosuppression was not associated with increased risk for mortality or graft failure[81]. During the SARS-CoV outbreak, there was no evidence of worse outcomes in transplant patients[83]. Systemic immunosuppression was not found to be a risk factor for MERS-CoV during its outbreak in 2018[84]. Colmenero *et al*[78] evaluated the relationship between immunosuppressive treatments and COVID-19 disease and found that only mycophenolate treatment was an independent risk factor for severe COVID-19 disease [78].

The liver's homeostatic role in controlling bleeding and thrombosis gets lost with liver cirrhosis, with the predilection toward bleeding or thrombosis depending on the individual and precipitant factors. One of the features of COVID-19 disease is hypercoagulability with venous and arterial thrombosis[85].

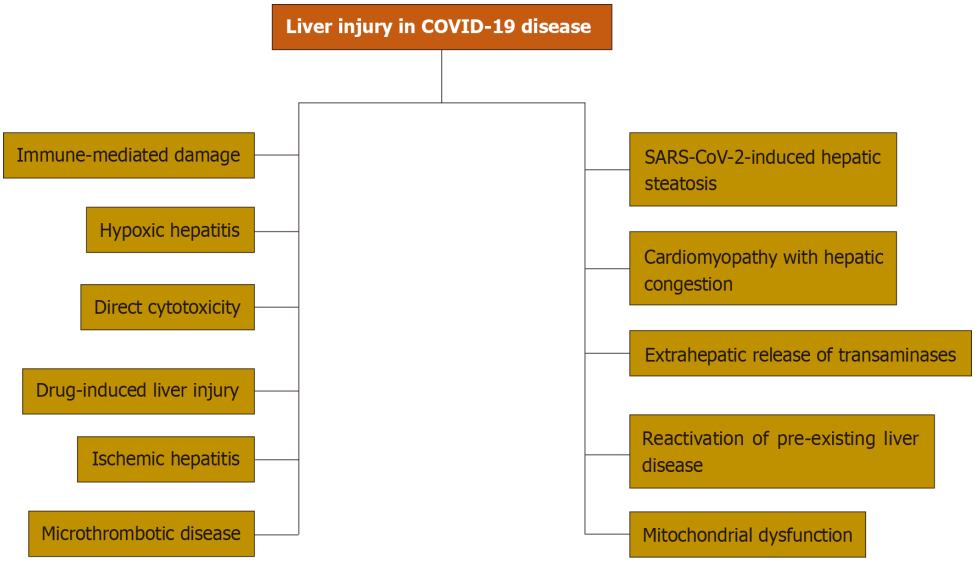

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Figure 1 Mechanisms of liver injury in coronavirus disease 2019. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Patients with Cirrhosis and COVID-19 disease are at significant risk for thrombotic disease[48].

Alcohol-related liver diseases (ALD) are the most frequent hepatic diseases and the main cause of liver transplantation and liver disease-related death. Management of ALD was disrupted by the COVID-19 pandemic and telemedicine visits should be an integral part of future ALD management[86].

Retrospective studies for patients with COVID-19 disease have shown that NAFLD is a risk factor for progressive COVID-19 disease course, acute liver injury, ICU admission, mechanical ventilation, and prolonged viral shedding. There was no association between NAFLD and increased mortality in patients with COVID-19 disease, while ALD showed statistically significant odds for death[87]. As patients with NAFLD or its severe form NASH usually have diabetes, hypertension, and obesity, it's very challenging to separate the effect of NAFLD on COVID-19 disease, yet NAFLD is considered an independent risk factor for severe COVID-19 disease[88].

NAFLD is associated with a fourfold increased risk of severe COVID-19 disease, after adjusting for confounders[89]. Targher *et al*[90] reported that patients with NAFLD and moderate-to-high liver fibrosis scores using the fibrosis-4 index are at higher risk of severe COVID-19 disease, irrespective of their metabolic comorbidities[90].

High-density lipoprotein scavenger receptor B type 1 (SR-B1) facilitates ACE2-dependent coronavirus attachment[91]. NAFLD is associated with decreased vitamin D levels. Vitamin D receptors are expressed on immune cells, and vitamin D deficiency can impair innate immunity[92,93]. Adiponectin is an anti-inflammatory cytokine known to be reduced in NAFLD[94].

Chronic hepatitis B patients with SARS-CoV infection have longer infection duration and prolonged virus shedding, similar findings were reported with SARS-CoV-2[95,96]. In hepatitis B virus (HBV) and HCV coinfected patients, Lopinavir may cause an exacerbation of the underlying CHB or chronic hepatitis C[97]. SARS-CoV-2 associated lymphopenia might increase the risk of HBV reactivation. Tocilizumab is also known to increase the risk of HBV reactivation[98,99]. Yip *et al*[100] found that current and past infections of HBV do not increase mortality in patients with COVID-19 infection while acute liver injury was found to be associated with higher mortality. corticosteroid, antifungal, ribavirin, and lopinavir-ritonavir use were associated with acute liver injury[100].

HCC patients with COVID-19 disease have a high risk for worse outcomes. AASLD and EASL recommend delaying HCC surveillance. EASL recommended that locoregional therapies should be postponed whenever possible and temporarily withdrawing immune-checkpoint inhibitor therapy[101].

The COVID-19 pandemic has various effects on preexisting liver conditions that range from care disruptions, the long-term negative consequences for cirrhosis care, exacerbation of liver condition, and higher mortality rates[102]. Singh *et al*[103] performed propensity score matching to account for covariates like diabetes and hypertension and found a higher risk for mortality and hospitalization in patients with preexisting liver disease[103].

CONCLUSION

SARS-CoV-2 is notorious for causing acute liver injury through various mechanisms. While most of the

time it causes a self-resolving acute liver injury, it can exacerbate chronic liver conditions with an associated increase in morbidity and mortality. The high variability in the severity of SARS-CoV-2-induced liver injury is related to the variability in COVID-19 disease severity, patient's comorbidities, and social determinants of health. COVID-19 disease impacts the management of different chronic liver conditions and liver transplant recipients. Among immunosuppressive treatments, only mycophenolate is an independent risk factor for severe COVID-19 disease. While reduction of systemic immunosuppression was not associated with increased risk for mortality or graft rejection, the current recommendations favor the continuation of immunosuppressive treatment at stable doses for most patients. While healthcare systems face an existential crisis, vaccines are a promising solution for the current challenges, and it's our responsibility to reach out to patients and deliver appropriate counseling about the importance of vaccines. Care disruption continues to be a consequence of the COVID-19 pandemic, and evolvement of the healthcare system is essential, so we continue to provide appropriate care to those with CLD.

FOOTNOTES

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