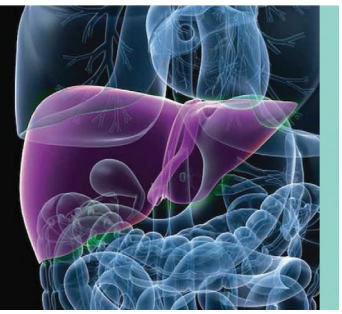

Chronic Liver Disease and COVID-19: Alcohol Use Disorder/ Alcohol-Associated Liver Disease, Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis, Autoimmune Liver Disease, and Compensated Cirrhosis

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Because between 1% and 11% of patients with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may have chronic liver disease,[1,2] understanding interactions between the infection and underlying hepatic disease is essential for clinical management. Both emerging data and clinical experience have revealed the influence of underlying liver disease on coronavirus disease 2019 (COVID-19) outcomes, as well as the impact of COVID-19 on the course of liver disease. The SECURE-Cirrhosis Registry (Americas, China, Japan, and Korea) and the COVID-HEP registry (Europe) have been created to collect data on patients with preexisting liver disease and SARS-CoV-2 infection.

COVID-19 IN PATIENTS WITH ALCOHOL USE DISORDER

The psychosocial stressors and social distancing needed for initial control of the pandemic have resulted in significantly

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACE2, angiotensin-converting enzyme 2; AIH, autoimmune hepatitis; AUD, alcohol use disorder; COVID-19, coronavirus disease 2019; CT, computed tomography; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HCC, hepatocellular carcinoma; HSI, hepatic steatosis index; MAFLD, metabolic-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug; SOT, solid organ transplant.

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increased alcohol use and alcohol use disorders (AUDs) throughout the world, as well as limiting in-person participation in substance use disorder support groups.[3,4] AUD is often associated with comorbidities such as diabetes mellitus and chronic kidney disease, which also increase the risk for complications in COVID-19.[5] Furthermore, the immunosuppressive effects of corticosteroid therapy for alcoholic hepatitis, as well as AUD itself, are risk factors for severe disease.[5] Although there is no specific guidance on management of alcoholic hepatitis during the COVID-19 pandemic, caution is advised regarding glucocorticoids therapy in SARS-CoV-2 infection.[5,6] The pandemic has also raised significant barriers for patients with AUD being considered for liver transplantation, resulting in both increased risk for relapse and difficulties in maintaining linkage to care.[5]

Unfortunately, many have consumed alcohol in a misguided attempt to protect against coronavirus infection, resulting not only in the risk for alcoholic hepatitis but also in hundreds of deaths from acute methanol poisoning.[7]

Observations that use of nonsteroidal anti-inflammatory drugs (NSAIDS) were linked to more severe disease in COVID-19 led health authorities to recommend avoiding use of NSAIDS.[8] This subsequently resulted in increased usage of acetaminophen (paracetamol), and although this guidance has since been rescinded,[9] the potential remains for increased utilization of acetaminophen and associated hepatotoxicity, especially when combined with alcohol use.

COVID-19 IN PATIENTS WITH AUTOIMMUNE LIVER DISEASE

Preliminary guidance on the management of autoimmune hepatitis (AIH) has been published by both the American Association for the Study of Liver Diseases (AASLD)[6] and the European Association for the Study of the Liver (EASL).[10] In addition, a detailed management protocol was developed for patients in three referral centers in Europe (Table 1).[11] This recommends stratification of existing patients by risk of complications, with all health care encounters performed via a "COVID-free" pathway.

The effect of immune-modulating therapy on COVID-19, as well as the effect of COVID-19 on immunosuppressed patients with chronic liver disease, is incompletely understood; however, insight may be gained from transplant and other immunosuppressed patients. A preliminary evaluation of solid organ transplant (SOT) recipients hospitalized with COVID-19 showed significantly higher rates of critical illness, mechanical ventilation, and death, although this likely undercounted mild illness.[12] Conversely, preliminary analysis of COVID-19 in SOT recipients from Italy showed no increases in severe illness or hospitalization.[13] Finally, use of immune-modulating agents for other conditions such as rheumatological disease[14] has not resulted in an increased risk for severe SARS-CoV-2 infection.

In an attempt to clarify these data, AASLD and EASL have provided guidance on the use of immune-modulating therapy during the COVID-19 pandemic, which is summarized in Table 2. These guidelines emphasize that reduction in immune modulation is not recommended in the absence of SARS-CoV-2 infection and may be considered in certain subsets of patients with COVID-19 (i.e., severe disease, lymphopenia, bacterial or fungal superinfection).[6,10]

COVID-19 IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE/ NONALCOHOLIC STEATOHEPATITIS

Given the association of COVID-19 severity with metabolic disease, the association with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) has

TABLE 1. EXPERT GUIDANCE FOR MANAGEMENT OF AUTOIMMUNE LIVER DISEASE DURING COVID-19 PANDEMIC

Risk for Complications from AIH	Suggested Management Pathway
Low (i.e., AIH stable on immunosuppressive therapy)	• Frequent communication to evaluate for potential problems • Telephone and Web evaluation when possible • Proactively arrange for drug refills[11]
Moderate (i.e., acute symptoms in patients without cirrhosis, chronic management of decompensated cirrhosis)	• Avoid liver biopsy if able • Initiate empiric therapy via Web-based consultation with interval follow-up to evaluate effect[11]
High (i.e., flare of AIH, obstructive jaundice, variceal hemorrhage)	• Limit invasive procedures as able • In case of infection, reduce antimetabolites if lymphopenic and taper steroids as quickly as possible[11]
All	• Minimize in-person contact with medical system • Interaction with the health care system should be via a "COVID-free" pathway[6,10] • Test for SARS-CoV-2 in the setting of acute decompensation or acute-on-chronic liver failure[10]

TABLE 2. EXPERT GUIDANCE ON IMMUNOSUPPRESSION FOR LIVER DISEASE IN THE SETTING OF COVID-19

Condition	Society Guidance	
	AASLD[6]	EASL/ESCMID[10]
Patients with immunosuppressed liver disease without COVID-19	Avoid anticipatory adjustment of immunosuppressive therapy	Avoid reducing immunosuppressive therapy
Patients with immunosuppressed liver disease with COVID-19	• Minimize glucocorticoids while avoiding adrenal insufficiency • Consider reductions in azathioprine, cyclosporine, or mycophenolate dosing, particularly with lymphopenia or severe disease	Reduce only in special circumstances (drug-induced lymphopenia, severe bacterial or fungal superinfection) after consultation with specialist
Patients with liver disease with strong indication for initiation of immunosuppressive therapy	Initiate treatment regardless of presence of SARS-CoV-2 infection	Not specifically addressed
All patients with liver disease and COVID-19	Carefully assess risk/benefit ratio when initiating glucocorticoids or other immunosuppressive therapy	Not specifically addressed

TABLE 3. STUDIES OF MAFLD/NAFLD/NASH AND COVID-19

Study	Site	Number of patients	Diagnostic Criteria	Outcomes Described	Conclusions
Qian et al. (2020)[16]	Shanghai, China	70	CT scan	Patients with NAFLD accounted for 34.6% of severe patients	High prevalence of NAFLD among patients with severe COVID-19
Ji et al. (2020)[17]	China	76	HSI +/– ultrasound	34/39 (87.2%) progressive disease versus 42/163 (25.8%) stable disease	Higher risk for progression to severe COVID-19; longer viral shedding time
Zheng et al. (2020)[18]	Wenzhou, China	66	CT scan + MAFLD consensus diagnostic criteria	6-Fold increased risk for severe COVID-19 in patients with MAFLD	Risk of obesity to COVID-19 severity is higher in those with MAFLD

also been investigated (Table 3). In a report of more than 5000 patients in New York with COVID-19, hypertension, obesity, and diabetes were the most common comorbidities in patients with COVID-19, and diabetes appeared to be associated with higher risk for requiring mechanical ventilation.[2] Although the presence of NAFLD was not directly evaluated, only 23% of patients were Hispanic, the group most prone to NASH, and prior reports actually suggest higher death rates among African Americans (who are less likely to have NASH) with COVID-19.[15] In an early report of 324 patients with COVID-19 in China, 70 (21.6%) were diagnosed with fatty liver on computed tomography (CT) scan and also made up a significantly higher percentage of the severe COVID-19 cases than the general prevalence of NAFLD in the population.[16]

In a study from China, conducted at two designated COVID-19 hospitals, NAFLD was defined using the hepatic steatosis index (HSI) or by abdominal ultrasound examination.[17] Patients with COVID-19 were divided into stable and progressive, and NAFLD was found to be associated with COVID-19 progression (defined by worsening respiratory distress or lung CT findings during hospitalization) with an odds ratio of 6.4 (95% confidence interval: 1.5-31.2). However, although higher body mass index was also associated with progression, diabetes and other metabolic factors were not considered as unique risk factors, so their individual contribution to increased disease severity could not be determined. Patients with NAFLD were also found to have higher risk for disease progression, higher rates of abnormal liver chemistries during admission and disease course, and longer duration of viral shedding (17 versus 12 days) when compared with patients without NAFLD.

Finally, in another study of 214 patients in China, the presence of obesity in metabolic-associated fatty liver disease (MAFLD) was associated with a 6-fold increased risk for severe COVID-19. This risk persisted after adjusting for age, sex, and metabolic features, such as diabetes, hypertension, and dyslipidemia.[18] Because SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for cellular entry, increased ACE2 expression on hepatocytes of patients with NAFLD,[19] as well as impaired hepatic innate immune system in patients with NAFLD, are potential mechanisms for increased risk for disease, although further study is required. Given these data, patients with NAFLD, particularly those with diabetes and obesity, should be considered high risk for COVID-19.

COVID-19 IN PATIENTS WITH COMPENSATED CIRRHOSIS

There are several key issues surrounding COVID-19 infection in patients with cirrhosis, including potentially increased risk for SARS-CoV-2 infection, higher risk for severe disease, and increased risk for hepatic decompensation (Fig. 1). Furthermore, the pandemic has significantly affected the management of patients with cirrhosis, both with and without COVID-19.

There is currently a global effort to determine severity of disease, mortality, and incidence of complications in patients with COVID-19 with cirrhosis. In the combined COVID-HEP and SECURE-Cirrhosis registries, there have been 151 patients reported to date. Alcohol is the most common causative factor, followed by NASH and hepatitis B.[2] Of patients reported thus far, 24% required intensive care admission, 16% required mechanical ventilation, and 40% had reported deaths. Although this is a small sample size, this is significantly higher than the 6% overall mortality rate reported by the Centers for Disease Control and Prevention,[4] underscoring the increased severity of disease in patients with cirrhosis.

Of patients in the combined registries, 38% decompensated during their disease course (worsening ascites, encephalopathy, or acute kidney injury). It is well established that infection places patients at risk for decompensation, and in this particular setting of COVID-19 characterized by significant cytokine activation, cytokine-induced hepatocyte apoptosis and necrosis in the setting of diminished liver reserve may lead to hepatic decompensation.[20] Thus, patients with cirrhosis who present with decompensation should be tested for COVID-19 as a potential cause.

Aside from complications of SARS-CoV-2 infection, cirrhosis care in general has significantly been impacted by the COVID-19 pandemic, with significant disruptions in care flow.[21] Screening for esophageal varices and hepatocellular carcinoma (HCC) is now considered nonurgent and is delayed for all but the highest-risk patients (i.e., endoscopy for variceal bleeding or follow-up band ligation in those with recent variceal bleed). AASLD guidance suggests that it is appropriate to defer HCC surveillance for 2 months, after a discussion of the risks and benefits of doing so with the patient.[6] These changes in care pathways have the potential to increase the risk for variceal bleed and later-stage HCC occurrence. In addition, elective procedures, such as living donor liver transplantation and locoregional therapy for HCC, have been deferred in many centers, potentially increasing both progression of disease and overall mortality.[21] Alternative management strategies,

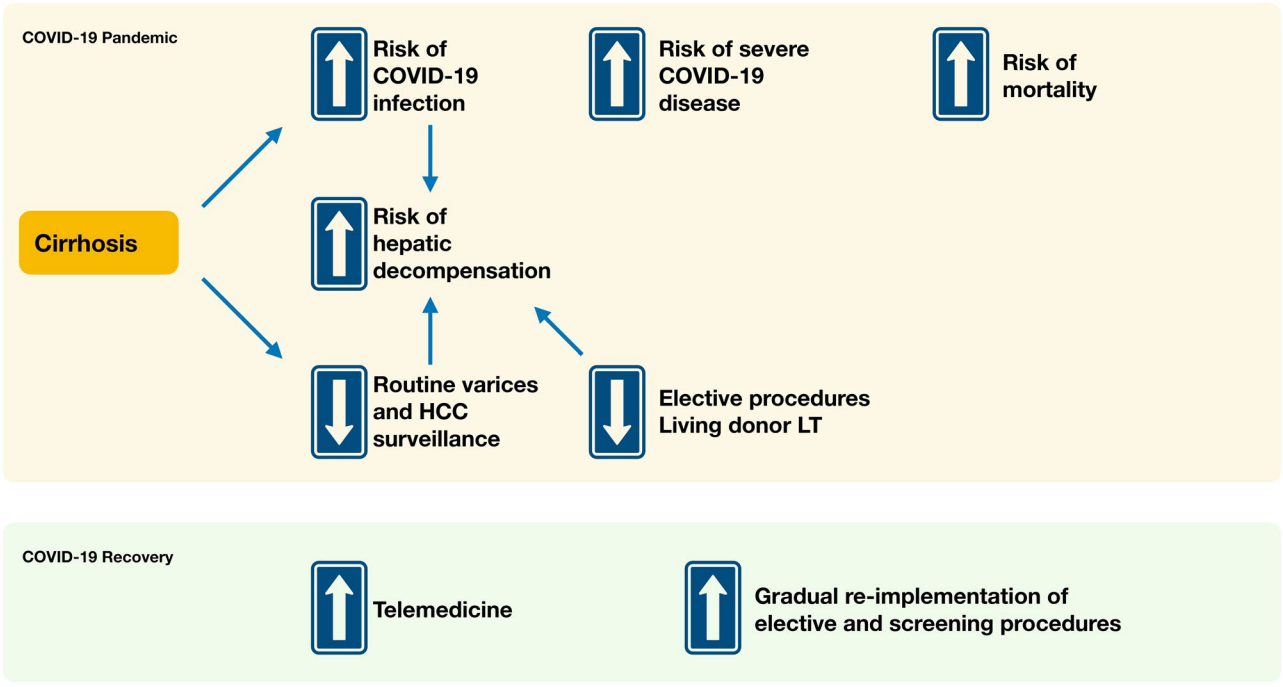

FIG 1 Implications of COVID-19 on cirrhosis.

such as increased use of nonselective beta-blockade, greater use of serum-based markers, increased outpatient interventions (including albumin infusions), and emphasis on integrated telehealth, have been proposed.[21]

CONCLUSIONS

Our knowledge of the impact of chronic liver disease on risk and severity of COVID-19 infection, as well as understanding of the COVID-19 pandemic and effect on hepatic disease, will continue to evolve. A paradoxical effect of immune suppression on disease severity should not be discounted and may play a significant role in future therapeutic strategies. Optimizing care pathways for those with these liver diseases, particularly if infected with SARS-CoV-2, will be critical to improve outcomes of both liver disease and COVID-19.

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