Recent challenges facing patients with preexisting chronic liver disease in the era of the COVID-19 pandemic

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Abstract
COVID-19 pandemic has resulted in a growing number of beds in common hospital wards and intensive care units being occupied by COVID-19 patients and the majority of medical and nursing staff being dedicated to their care. The present review summarizes the impact of COVID-19 on patients with underlying chronic liver diseases (CLD). Deferrals of all non-urgent activities in healthcare facilities, including a decrease in liver-clinic visits for patients with CLD, inadequate hepatocellular carcinoma (HCC) surveillance, and postponement of liver transplant activities are the most important consequences. Delays in viral hepatitis elimination programs were also reported, leading to future development of advanced CLD and HCC. Patients with chronic hepatitis B (CHB) and C without cirrhosis are not at risk for a more severe COVID-19 infection course. However, CHB status must be known in patients who are going to receive immunosuppression for preventing disease flare. In addition, checking for drug-drug interactions and potential hepatotoxicity reactions from agents administered to treat both SARS-CoV-2 and CLD are required. Patients with nonalcoholic fatty liver disease appeared to be at a high risk for severe COVID-19, even after adjustment for comorbidities. Patients with cirrhosis may develop decompensation, acute-on-chronic liver failure, or severe COVID-19. The mortality rate is worse in patients with high model for end-stage liver disease score, regardless of the etiology of cirrhosis.

Keywords COVID-19, viral hepatitis, nonalcoholic fatty liver disease, cirrhosis, liver transplantation

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Introduction

The novel coronavirus, named SARS-CoV-2, is responsible for COVID-19 pandemic. SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE2) receptor for its entry into host cells. Then, the cellular transmembrane protease serine 2 (TMPRSS2) cleaves the SARS-CoV-2 spike protein, allowing fusion of cellular and viral membranes [1]. The ACE2 receptor is present in more than 80% of the alveolar cells of the lungs [2,3], the gastrointestinal tract, 60% of cholangiocytes, the endothelium of small blood vessels in the liver and to a smaller extent in hepatocytes, indicating that the liver could be a potential target for SARS-CoV-2 [2] (Fig. 1).

Liver histological features in COVID-19 include microvesicular steatosis, mild lobular and portal inflammatory infiltrate, or mild sinusoidal dilatation and focal macrovesicular steatosis [4]. Potential mechanisms inducing liver damage include a direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis, drug-induced liver injury, ischemic liver injury, and deterioration of underlying chronic liver disease (CLD) [2,5] (Fig. 1).

Alanine aminotransferase (ALT), total bilirubin and γ-glutamyl transferase elevation were evident in a total of 28%, 18% and 72% of COVID-19 patients, respectively [6,7]. Liver dysfunction has been considered a bad prognostic factor in patients with COVID-19, even after adjustment for multiple cofactors [8]. Elevated aspartate aminotransferase (AST) or ALT levels were observed in 18% or 20% and 28% or 39% of patients with non-severe and severe liver disease, respectively [9]. In another study, AST elevation was found in 25% or 62% of patients not requiring or requiring intensive care unit (ICU) admission, respectively [10]. Although some studies have suggested that abnormal liver function tests were not associated with mortality [11,12], close monitoring of liver biochemical tests is advised [12]. The aim of this review
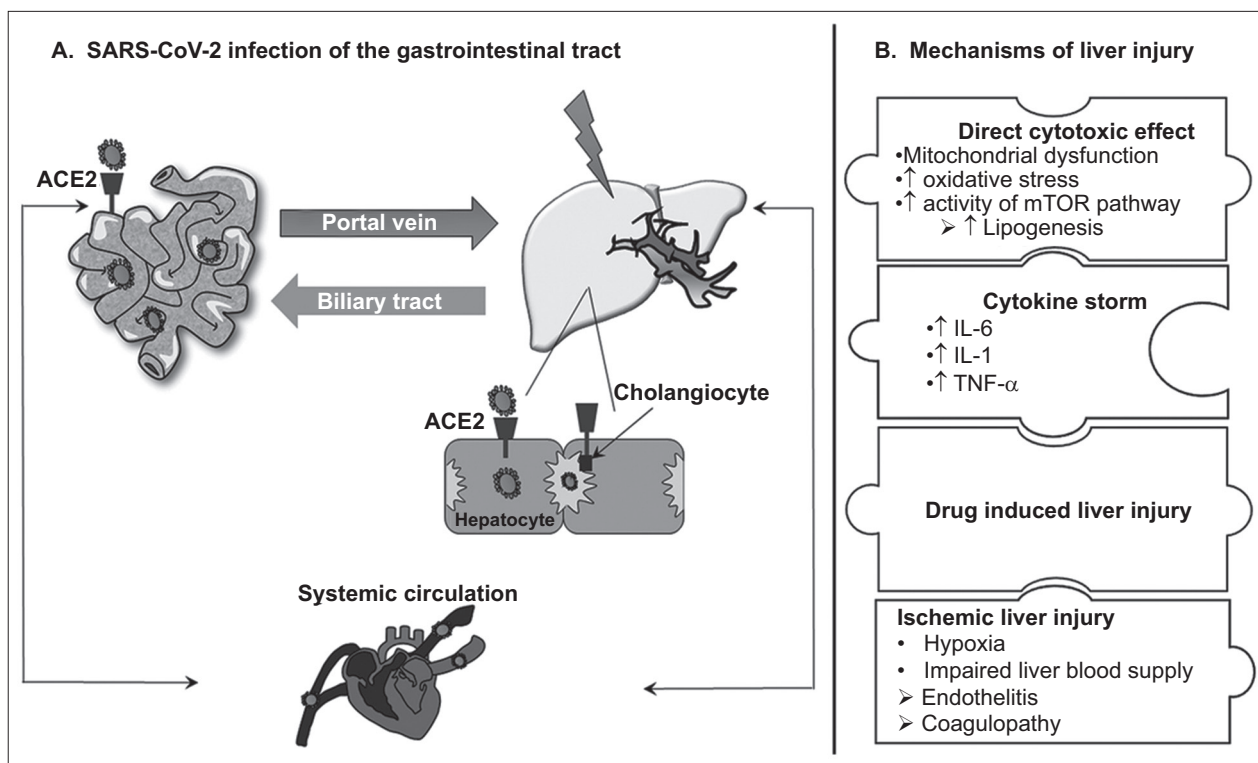
Figure 1 Possible mechanisms for SARS-CoV-2-induced liver injury
ACE2, angiotensin-converting enzyme 2; mTOR, mammalian target of rapamycin; IL, interleukin; TNF-α, tumor necrosis factor-α

was to investigate the impact of COVID-19 infection on the management, course, and outcome of CLD.

Search strategy

We searched PubMed for the search terms "coronavirus" or "COVID-19" or "SARS-CoV-2" and "liver disease" or "viral hepatitis" or "non-alcoholic steatohepatitis" or "cirrhosis" or "alcoholic hepatitis" or "liver transplantation" or "autoimmune hepatitis", with no time limits. Only studies in the English language were included. We reviewed the relevant studies and scrutinized the reference lists of the included studies to identify additional references.

Impact of COVID-19 on the management of patients with preexisting liver disease

Impact of COVID-19 on hepatitis elimination programs

Hepatitis B and C affect more than 320 million people globally and can result in CLD and mortality from cirrhosis and hepatocellular carcinoma (HCC). More than 248 million individuals are chronically infected with hepatitis B virus (HBV), and over 700,000 deaths annually are attributed to HBV. On the other hand, 80 million people are chronically

infected with hepatitis C virus (HCV), resulting in nearly 500,000 deaths per year [13].

The World Health Organization (WHO) adopted a target in 2016 to eliminate hepatitis by 2030, by achieving a 90% reduction in new infections and a 65% reduction in liver-related deaths [13]. The World Hepatitis Alliance assessed the effects of the COVID-19 pandemic on viral hepatitis services and on people with chronic hepatitis [14]. Civil society organizations that are main contributors to national hepatitis elimination programs reported that their services were affected by the crisis, including halting screening programs and community-based education [14].

Fewer people have access to testing facilities and many testing facilities have been closed. Moreover, people avoid visiting healthcare facilities for fear of COVID-19. In addition, people on hepatitis treatment have limited access to their medication. Travel restrictions make patients living in remote rural communities unable to access hepatitis medication. As a result, they reported delays in taking their antiviral drugs for chronic HBV or starting HCV treatment. Inadequate information about COVID-19 is provided for persons living with viral hepatitis, leaving them reluctant to seek advice from hepatitis healthcare facilities [14].

Disruptions to HCV elimination programs were reported in Italy and Egypt, where delays in birth cohort screening for hepatitis were recorded in the former and reduction or halting of screening programs (including children, pregnant women, foreigners and prisoners) were reported in the latter [15] (Table 1). It was estimated that according to the "one-year

Table 1 Direct and indirect effects COVID-19 on patients with preexisting liver diseases

Direct effects on preexisting liver diseases	Collateral effects due to overwhelmed health systems, social distancing and isolation	No or limited evidence for significant effects
Cirrhosis • Increased risk for severe COVID-19 and death [66-69] • Increased risk for decompensation/acute-on-chronic liver failure [66,68]	• Delays in viral hepatitis elimination programs [14,15,16] • Deferrals of liver clinic visits [17,18] • Inadequate surveillance of cirrhosis complications and HCC [17,18] • Inadequate management of hepatocellular carcinoma [24,25]	• Liver transplant recipients* [23] • Autoimmune hepatitis* [34-36] • Chronic viral hepatitis without cirrhosis*# [25,53-56]
NAFLD/NASH • Increased risk for severe COVID-19 [37,38,39,40]	• Postponement of liver transplantation activities [19-22] • Limited resources for chronic liver diseases • Possible increased risk or relapse of alcoholic liver disease [46]	

*Monitoring for drug-drug interactions and/or renal impairment; #Attention for possible chronic hepatitis B reactivation

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma

delay" scenario no patients would be newly diagnosed in 2020 and no regions were expected to meet the WHO target for new HCV diagnoses and treatments by 2030. It was calculated that this delay would apply to only 89% of the 2015 HCV population being diagnosed by 2030, and these 11% missed diagnoses would result in approximately 45,000 excess HCC cases and 72,000 excess liver-related deaths predicted in the next 10 years, globally. A country previously considered to have completed its elimination targets in due time but lost progress is Italy, where there was a 35% reduction in patients initiating HCV treatment in 2019 vs. 2018 [15].

Kondili *et al*, using a Markov model for liver-disease progression, quantified the effect the deferrals of HCV cure would have on disease outcome [16]. They found that the numbers of additional cases of advanced liver disease and HCV-related deaths increased with the length of delay. In Italy, for delays of 3, 6, 9 and 12 months, advanced liver disease cases increased by 2, 5, 7 and 10, respectively, and the same increases were demonstrated for HCV-related deaths per 1000 standardized patients. In the United Kingdom, increases of 3, 8, 12 and 17 advanced liver disease cases and 1, 4, 5 and 7 HCV-related deaths per 1000 standardized patients was computed. The investigators stressed that healthcare systems were overwhelmed by patients with COVID-19 and limited care resources were directed particularly to their care (Table 1). However, they advised that the ambitious target set by the WHO in 2016 for viral hepatitis should not stop, and patients with chronic hepatitis C should be diagnosed and treated in time. If they remain undiagnosed and untreated, patients with less severe stages will proceed further and those with severe fibrosis will die from a liver-related condition.

Toyoda *et al* obtained data on the number of outpatient clinic visits, abdominal ultrasound, computed tomography and magnetic resonance imaging at 3 medical centers—in the United States (US), Japan, and Singapore—during certain periods of 2018, 2019 and 2020 [17]. They found significant decreasing trends in the clinic visits for patients with chronic hepatitis B and C. HCC/cirrhosis visits dropped by about 40% overall and by 47% at the US site (Table 1), and the number of imaging tests decreased significantly. The authors warned of inadequate HCC surveillance in patients with chronic hepatitis, prone to developing HCC, and urged care providers

to recall patients for monitoring, especially concerning HCC surveillance.

Impact of COVID-19 on the management of patients with advanced CLD

The experience of Italian doctors regarding the impact of COVID-19 in the management of cirrhosis and its complications is described in a web-based survey by the active members of the Italian Association for the Study of the Liver, encompassing all Italian Liver Units [18]. The reduction in daily outpatient activity was linked to the severity of the underlying liver disease. Screening of esophageal varices was reduced or postponed in 46% and 20% of cases, respectively, while for endoscopic band ligation as primary or secondary prophylaxis for variceal hemorrhage the figures were 33% and 12%, respectively. A preference for remote contact was recorded in 40%, 44%, 25% and 17% of patients with chronic hepatitis, compensated cirrhosis, HCC and decompensated cirrhosis, respectively. A 30% reduction in pre-transplant assessment and 44% deferral in post-transplant reviews were reported by Liver Transplant Centers (Table 1) [18].

More specifically, COVID-19 pandemic had immediate effects on liver transplantation worldwide, due to the vast number of people seeking medical care and the excruciating burden on intensive care facilities [19]. Although some large centers worldwide opted to maintain routine liver transplantation activities at the same level as usual [20], others failed to do so [21]. Most transplant centers were constrained to limit transplant activity because of low rates of deceased donation, limited resources, decreased availability of ICU beds, a shortage of ICU specialists for liver transplant programs, reduction of use of marginal grafts, or exclusion of donors on clinical suspicion of respiratory infection or positive contact history [22]. High waiting-list mortality is expected as one of the consequences of all the above. Hence, protocol changes in response to the pandemic have been suggested by most liver transplantation specialists worldwide [22].

Regarding liver transplant recipients, an International registry study including patients with confirmed SARS-CoV-2 infection from 2 international registries found satisfactory outcomes in 151 liver transplant recipients with COVID-19

compared to 627 with COVID-19 who had not received a liver transplant (control group). Despite the fact that ICU admission and invasive ventilation were more common in liver transplant recipients compared to the control group, the former had a lower mortality rate (19% vs. 27%). In the propensity score matched analysis (adjusting for multiple covariates), liver transplantation did not increase the risk of death [23].

The disruption of health systems as a consequence of the pandemic was highlighted by a French study dealing with changes in the diagnosis and management of HCC during the first 6 weeks of the pandemic, in comparison with the same time period in 2019 [24]. Initially, in 2020, significantly fewer patients were referred to oncologists. Moreover, patients first diagnosed with HCC in 2020 had larger tumor burden, as indicated by differences in tumor size—49 (25-80) mm vs. 32 (22-60) mm—but did not differ as regards Barcelona cancer stage. In the total cohort, therapeutic intervention was delayed by ≥1 month in 21.5% in 2020 vs. 9.5% in 2019. The difference was even wider for patients with known HCC, estimated at 23.3% vs. 4.7%, respectively (Table 1).

The above observations led to amendment of the existing guidelines for surveillance and treatment of HCC in the era of COVID-19. Emphasis is placed on individualized decision-making, taking into consideration the local spread of COVID-19, the accessibility and availability of healthcare resources, and the patient's risk factors for severe COVID-19 disease, stage of HCC and severity of liver impairment [25,26]. According to the European Association for the Study of Liver Disease (EASL), care for HCC should be maintained according to guidelines, continuing systemic treatment and evaluation for HCC [27].

The impact of COVID-19 on the course and prognosis of patients with preexisting liver disease

Autoimmune liver diseases

Concerns have been raised about the management of autoimmune liver diseases during the pandemic. There are limited data to draw safe conclusions regarding primary biliary cholangitis and primary sclerosing cholangitis. For the diagnosis of autoimmune hepatitis (AIH), the EASL and the American Association for the Study of Liver Diseases (AASLD) recommend following the existing guidelines in areas with a low prevalence of COVID-19 [27,28]. A different approach could be to postpone liver biopsy and initiate immunosuppressive therapy, based on the presence of biochemical and immunological tests compatible with AIH, in order to avoid exposing patients to the hospital environment [29].

Regarding the impact of immunosuppressive therapy, the hypothesis that immunosuppressed patients are more vulnerable to SARS-CoV-2 infection compared to the general population cannot be justified [30]. In particular, systemic corticosteroids were found to be an independent risk factor

for severe COVID-19 in patients with inflammatory bowel disease [31] and rheumatologic diseases [32,33].

The outcome of patients with preexisting AIH and COVID-19 has been investigated in a few studies. A center in northern Italy studied 148 patients with autoimmune liver disease, the majority of whom (90%) had a diagnosis of AIH and were under immunosuppressive therapy. The incidence of COVID-19 did not differ compared to the general population. Overall, 26% of patients reported symptoms suggestive of COVID-19 but did not require hospitalization. There were only 4 confirmed cases, 3 of which were hospitalized. Only 1 patient, 78 years old with comorbidities, died [34]. Similar results were described in a second Italian study of 10 patients with COVID-19 and AIH under immunosuppressive regimens, mainly corticosteroids. Only 1 patient died, but had a history of decompensated liver disease, and another one experienced relapse of AIH after corticosteroid discontinuation [35]. In a recent International Registry study, 70 patients with AIH (taking one or more immunosuppressive drugs) and SARS-CoV-2 infection were compared with patients with CLD without AIH (non-AIH CLD). There was no difference between AIH and non-AIH CLD regarding hospitalization, ICU admission and death. In the propensity score matched analysis, no increase in the risk for adverse outcomes including death was demonstrated in AIH vs. non AIH CLD patients [36] (Table 1).

Although the results are insufficient and not well documented, the EASL and AASLD recommendations suggest continuation of immunosuppressive regimens without any dose modification in patients without COVID-19. To avoid exposure to high doses of corticosteroids, it is recommended to use budesonide as first-line agent to achieve remission in non-cirrhotic patients with exacerbation of AIH [27]. The statements differ for patients with AIH who become infected with COVID-19. According to the EASL recommendations, switching to dexamethasone or adding it to the basic corticosteroid should be an option only for patients with severe disease, but there were no instructions for the other immunosuppressive agents. According to the AASLD, corticosteroids as well as azathioprine or mycophenolate mofetil should be reduced to the lowest possible doses, particularly if the course of COVID-19 is severe [28].

Nonalcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD)

Multiple studies demonstrated that the individual components of metabolic syndrome (MetS) were independent risk factors for severe COVID-19. In a US study of 8885 COVID-19 patients (215 with MetS), the incidence of COVID-19 was higher in the MetS group. Among all comorbid metabolic conditions, including hypertension, hyperlipidemia, obesity and diabetes mellitus, nonalcoholic steatohepatitis (NASH) had the strongest association with COVID-19 [37]. In a Chinese retrospective study of 202 patients with COVID-19, NAFLD, other comorbidities, age over 60 years, male sex, and

high body mass index (BMI) were associated with a more severe course of COVID-19 [38]. Other Chinese investigators have shown that the risk of severe COVID-19 illness in NAFLD patients was higher in patients younger than 60 years, even after adjusting for comorbidities [39,40] (Table 1). Apart from age, moderate/high noninvasive fibrosis markers of NAFLD, such as FIB-4 and NAFLD fibrosis score [41], and the inflammation marker neutrophil-to-lymphocyte ratio were also associated with poor outcomes [42].

An upregulation of *ACE2* and *TMPRSS2* genes was observed in the liver of obese patients with NASH [43]. Moreover, *ACE2* and *TMPRSS2* expression was positively correlated with NAFLD activity score [44]. Another interpretation is that both NAFLD and COVID-19 derange the immune response in a similar way. Specifically, NAFLD, as well as obesity, is characterized by immune dysfunction, expressed as activation of macrophages and adipocytes leading to release of proinflammatory cytokines and chemokines. In subjects with MetS, the chronic low-grade inflammatory state could further deteriorate the inflammatory response to SARS-CoV-2 infection, inducing a hypersensitivity state and cytokine storm [45] (Fig. 2).

Patients with ALD may be among the populations affected the most severely. This population is at high risk for severe COVID-19 infection, given their impaired immune system, neglected general health with multiple comorbidities, social isolation resulting in psychological disturbances, increased drinking or relapse during lockdown, and difficulty asking for assistance and supportive care. Specialists fear that the COVID-19 pandemic will be followed by a dramatic rise in alcohol relapse and in admissions for decompensated ALD or acute alcoholic hepatitis, and an increase in patients with newly diagnosed ALD. Thus, they advise the implementation of preemptive strategies to contain this anticipated problem [46].

Management and course of patients with chronic viral hepatitis (except cirrhosis) and infection with SARS-CoV-2

Chronic HBV infection is characterized by functional exhaustion of HBV-specific CD8+ T-cells due to HBs antigenemia and failure to neutralize circulating virions as a result of an insufficient B-cell response [47]. On the other hand, lymphocytopenia, especially reduced CD4+ and CD8+ T cell counts on hospital admission, is predictive of COVID-19 progression [48]. Hence, dysfunctional T-lymphocytes present in chronic HBV infection might be expected to be associated with a more severe COVID-19 course [49-51]. Zou *et al* demonstrated a poor prognosis in 105 patients with chronic HBV infection who had been co-infected with SARS-CoV-2 [52]. However, no control group was included in the study (SARS-CoV-2 without HBV) and baseline data such as clinical stage (cirrhosis or not) and active HBV replication status, as well as the administration of antiviral HBV drugs during hospitalization, were not reported [53]. Chen *et al* found no significant differences in liver function parameters, hospitalization time, discharge rate, severity or mortality in patients with pre-existing chronic HBV infection compared
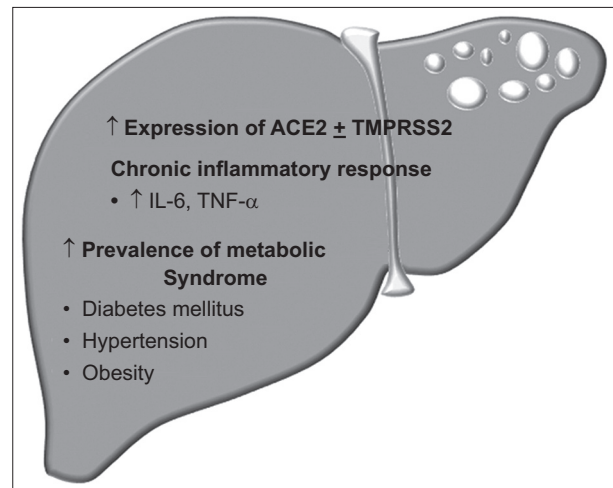
Figure 2 Mechanisms likely to predispose patients with nonalcoholic fatty liver disease to a more severe course of COVID-19
ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2; IL, interleukin; TNF-α, tumor necrosis factor-a

to those without [54]. Zhang *et al* presented 23 patients hospitalized for SARS-CoV-2 who had chronic HBV infection. A severe course of COVID-19 was reported in 34%, but all of them were discharged [55].

Abnormalities in liver function tests have been described in patients with chronic HBV infection hospitalized for COVID-19 [56]. The administration of corticosteroids and/or tocilizumab in patients with chronic HBV infection without antiviral prophylaxis and the potential hepatotoxicity of lopinavir/ritonavir may be involved [8] (Table 1). The status of viral hepatitis has to be known in patients who are going to receive immunosuppression with dexamethasone and/or tocilizumab [25]. Current guidelines recommend not deferring treatment in patients with chronic active hepatitis B without COVID-19. Given the unknown impact of interferon-α on systemic inflammation associated with COVID-19, treatment with nucleos(t)ide analogs is preferred [27]. In addition, it is not advisable to stop antiviral drugs in patients with chronic HBV infection suffering from COVID-19, in view of the high risk of reactivation when stopping nucleos(t)ide analogs.

Regarding drug–drug interactions, it is necessary to check for potential hepatotoxicity reactions between agents administered to treat both SARS-CoV-2 and HBV, using proper online platforms. For example, coadministration of lopinavir/ritonavir with tenofovir disoproxil or alafenamide may increase tenofovir concentrations by 32-51% or 275-316%, respectively. Moreover, close monitoring of renal function is mandatory, and in the case of renal impairment a switch to entecavir is required [25].

Direct acting antivirals (DAAs) used for the treatment of HCV were also investigated for the treatment of SARS-CoV-2. As both viruses use RNA-dependent RNA polymerase (RdRp) for their replication, and nucleotide analogs can be incorporated into RNA by SARS-CoV-2 RdRp, the incorporation of some of them may lead to chain termination. Many researchers have evaluated the incorporation efficiency of nucleotide

analogs compared to natural nucleotide [57-63]. However, the incorporation of sofosbuvir is very low, suggesting that sofosbuvir may not be very effective in treating SARS-CoV-2 infection [64]. In contrast, another report stated that sofosbuvir terminated RNA and resisted removal by the exonuclease to a substantially higher extent than RNA terminated by remdesivir [65]. Clinical trials concerning the efficacy of DAAs (sofosbuvir with daclatasvir and/or ledipasvir) in the treatment of COVID-19 remain to be completed (NCT04497649, NCT04535869, NCT04561063, NCT04468087, etc.).

In patients who have recently been diagnosed with chronic hepatitis C, deferral of HCV therapy until COVID-19 clearance is recommended [27]. In case HCV treatment has already been initiated, it can be continued while monitoring for drug–drug interactions [27]. More specifically, lopinavir/ritonavir is expected to increase the concentrations of protease inhibitors in protease-inhibitor-containing regimens (glecaprevir/pibrentasvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir) and consequently a hepatotoxicity reaction may develop. Hence, lopinavir/ritonavir should not be added when the patient is taking the above DAAs [25].

Impact of COVID-19 on the mortality of patients with liver cirrhosis

COVID-19 is associated with a high risk of liver function deterioration and death in patients with liver cirrhosis (Tables 1, 2). In a study from Italy that included 50 patients with cirrhosis (38% viral hepatitis-related, 48% decompensated cirrhosis), the 30-day mortality rate was 34%. Liver disease severity deteriorated after infection with coronavirus and the proportion of patients with model for end-stage liver disease (MELD) score ≥15 increased from 13% to 26%, while 46% of compensated cirrhotics decompensated and acute-on-chronic liver failure (ACLF) developed in 28%. The death rate was higher in patients with a high MELD score (≥15) or Chronic Liver Failure Consortium organ failure score ≥9. The death rate in cirrhotics with COVID-19 was higher compared to either cirrhotics with common infections (34% vs. 17%) or to another group with COVID-19 without cirrhosis (34% vs. 20%) [66]. In another investigation from 21 countries, including 103 patients with cirrhosis, the mortality rate from COVID-19 was 39.8% in cirrhotics compared with 12.2% in

Table 2 Characteristics and findings in studies concerning COVID-19 in patients with cirrhosis

Author [Ref.]	Date of study	Study design	Patients (N)	Deterioration of chronic liver disease	Severe COVID-19	Death rate	Predictors of mortality
Iavarone *et al* [66]	2020	Multicenter retrospective	• 50 cirrhotics with COVID-19	• Patients with MELD ≥15 increased from 13% to 26% • ACLF in 28% • Liver-related mortality in 12%	• Respiratory support in 71% • COVID-19-related mortality in 25%	• 34% overall	CLIF-C OF and moderate/severe lung failure or MELD, CLIF-C ACLF and moderate/severe lung failure

Moon *et al* [67]	2020	Multicenter retrospective	All infected with COVID-19
			• 103 cirrhotics
			• 49 with CLD without cirrhosis
				• Decompensation in 36.9%
				• Liver-related mortality in 12.2%
					• COVID-19 lung disease in 78.7%
					• ICU admission in 23%
					• Invasive ventilation in 17.5%
					• Non-invasive ventilation in 18.6%
						• 12.2% in CLD without cirrhosis
						• 39.8% in cirrhotics
						  • 23.9% in CTP class A
						  • 43.3% in CTP class B
						  • 63% in CTP class C
							Age, obesity and hepatic decompensation

Bajaj *et al* [70]	2020	Multicenter retrospective	• 37 with cirrhosis plus COVID-19 • 108 with COVID-19 alone • 127 with cirrhosis alone	• Similar ACLF related mortality rates between cirrhosis groups	Similar rates in ICU transfer, mechanical ventilation and central line placement between COVID-19 groups	• 30% in cirrhosis plus COVID-19 • 12% COVID-19 alone • 20% in cirrhosis alone	

(Contd...)

Table 2 *(Continued)*

Author [Ref.]	Date of study	Study design	Patients (N)	Deterioration of chronic liver disease	Severe COVID-19	Death rate	Predictors of mortality
Singh *et al* [69]	2020	Multicenter retrospective	All infected with COVID-19 • 2530 without CLD • 250 with CLD including • 50 with cirrhosis			Patients with cirrhosis had a higher RR for death vs. those without CLD (RR 4.6, 95%CI 2.6-8.3; P<0.001)	
Qi *et al* [71]	2020	Multicenter retrospective	All infected with COVID-19 • 16 CTP class A • 3 CTP class B • 2 CTP class C		Respiratory failure was the cause of death	23.8%	Non-survivors had lower platelets and higher total bilirubin vs. survivors
Sarin *et al* [68]	2020	Multicenter retrospective	All infected with COVID-19 • 43 cirrhotics • 185 with CLD without cirrhosis	• ACLF in 11.6% • Acute decompensation in 9%	Severe COVID-19 • 20% in compensated cirrhosis • 33% in decompensated cirrhosis • 11.5% in CLD without cirrhosis	• 2.1% in CLD without cirrhosis • 16.7% in cirrhosis in overall • 43% in decompensated cirrhosis	Poor outcome for CTP score ≥9

Case reports are not included

ACLF, acute-on-chronic liver failure; CLD, chronic liver disease; CTP, Child-Turcotte-Pugh score; ICU, intensive care unit; CLIF-C OF, Chronic Liver Failure Consortium organ failure; MELD, model for end-stage liver disease; RR, risk ratio; CI, confidence interval

patients who had CLD without cirrhosis. Mortality was strongly related to baseline Child-Pugh score (23.9%, 43% and 63% in A, B, and C, respectively) or MELD score. In addition, hepatic decompensation was associated with a higher risk of death compared to compensated cirrhosis (63.2% vs. 26.2%) [67]. Similarly, in an Asian study that evaluated 43 cirrhotics and 185 patients who had CLD without cirrhosis, ACLF developed in 11.6% and acute decompensation in 9%. The death rate was 16.7% for cirrhosis overall and 43% in patients with decompensated cirrhosis. A Child-Pugh score ≥9 predicted a poor outcome in patients with cirrhosis [68]. In a large US registry with a total of 2780 patients with COVID-19, 9% had preexisting CLD and 1.8% were diagnosed with cirrhosis [69]. Patients with liver disease had a higher hospitalization and mortality risk (risk ratio [RR] 3.0, 95% confidence interval [CI] 1.5-6.0; P=0.001) compared to patients without liver disease, after propensity score matched analysis for age, race, nicotine use, BMI, hypertension and diabetes. The risk increased further in patients with cirrhosis compared to those without liver disease (RR 4.6, 95%CI 2.6-8.3; P<0.001). In a multicenter North American trial where 3 groups were compared, patients with cirrhosis and COVID-19 had higher mortality compared to those who had COVID-19 without cirrhosis, but did not differ significantly from those hospitalized with complications of cirrhosis (30% vs. 13% vs. 20%, respectively). Chronic hepatitis C, alcohol-related liver disease or both were the most prevalent etiologies. ACLF development and length of stay did

not differ between cirrhosis groups. ICU transfer was higher in patients with cirrhosis and COVID-19 [70]. In a Chinese study involving 21 cirrhotics, no significant differences were found between survivors and non-survivors regarding disease severity scores (MELD, Child-Pugh). However, the sample was small and most patients had Child-Pugh score A (Child-Pugh A=16, B=3 and C=2), so no safe conclusions could be drawn [71].

Concluding remarks

The severe crisis generated by the overwhelmed healthcare systems has diverted the attention of healthcare professionals from viral hepatitis elimination and liver transplantation programs, HCC surveillance and management of advanced liver disease, to COVID-19 care. Moreover, patients with CLD avoid attending healthcare facilities, either because of travel restrictions or for fear of becoming infected. COVID-19 does not appear to run a more severe course in patients with chronic viral hepatitis without cirrhosis. On the other hand, patients with NAFLD/NASH, with or without comorbidities, are at risk for a more severe COVID-19 outcome, particularly those with moderate/advanced fibrosis. Similarly, patients with cirrhosis (regardless of etiology) were demonstrated to have a high mortality rate when infected with SARS-CoV-2. The mortality rate from COVID-19 was related to the severity of

liver cirrhosis. Finally, patients with alcohol-use disorder or alcohol-related liver disease may deteriorate and professionals should expect an increase in alcohol-risk behavior, resulting in newly diagnosed cases or a relapse of old ones.

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