Effect of COVID-19 on Pre-existing Liver disease: What Hepatologist Should Know?

Praveen Sharma , Ashish Kumar , ShriHari Anikhindi , Naresh Bansal , Vikas Singla , Khare Shivam , Anil Arora

Department of Gastroenterology Sir Ganga Ram Hospital New Delhi, India

COVID-19 is characterized by predominant respiratory and gastrointestinal symptoms. Liver enzymes derangement is seen in 15–55% of the patients. Advanced age, hypertension, diabetes, obesity, malignancy, and cardiovascular disease predispose them to severe disease and the need for hospitalization. Data on pre-existing liver disease in patients with COVID-19 is limited, and most studies had only 3–8% of these patients. Patients with metabolic dysfunction-associated fatty liver (MAFLD) had shown a 4–6 fold increase in severity of COVID-19, and its severity and mortality increased in patients with higher fibrosis scores. Patients with chronic liver disease had shown that cirrhosis is an independent predictor of severity of COVID-19 with increased hospitalization and mortality. Increase in Child Turcotte Pugh (CTP) score and model for end-stage liver disease (MELD) score increases the mortality in these patients. Few case reports had shown SARS-CoV-2 as an acute event in the decompensation of underlying chronic liver disease. Immunosuppression should be reduced prophylactically in patients with autoimmune liver disease and post-transplantation with no COVID-19. Hydroxychloroquine and remdesivir is found to be safe in limited studies in a patient with cirrhosis and COVID-19. For hepatologists, cirrhosis with COVID-19 is a pertinent issue as the present pandemic will have severe disease in patients with chronic liver disease leading to more hospitalization and decompensation. (J Clin Exp Hepatol 2021;11:484–493)

Coronaviruses are a family of viruses that can affect humans. The upper respiratory tract is the predominant site of infection although it can affect the liver and intestine also. While most patients with COVID-19 have mild disease, 10–15% of these patients need admission, and of these, few develop respiratory failure, septic shock, and/or multiple organ dysfunctions with a mortality rate that varies from 3 to 8%.[1,2] Liver involvement as suggested by impaired liver enzymes was seen in more than one-third to half of the patients with COVID-19.[3–7] Only 3–8% of the patients with pre-existing liver disease were seen, and increased severity of COVID-19 in these patients had not yet been fully evaluated.[4–8] Published studies had not stated the severity of the pre-existing liver disease, so how COVID-19 affected these patients were not well known till the publication of a few studies in patients with chronic liver disease.[9-12] This short review assessed the effect of COVID-19 in patients with pre-existing liver disease (compensated and decompensated) and special precautions that a hepatologist should follow.

Mechanism of liver injury in COVID-19

The attachment of SARS-CoV-2 to the target cell is initiated by interactions between the spike glycoprotein (S) and its cognate receptor, angiotensin-converting enzyme 2 (ACE2). Following receptor engagement, SARS-CoV-2 S is processed by a plasma membrane-associated type II transmembrane serine protease, TMPRSS2, before membrane fusion that is essential to release the viral contents into the host cell cytosol. This hypothesis is supported by the dramatic increase of SARS-CoV-2 genomic RNAs viral load in human liver ductal organoids at 24 h postinfection. These data demonstrate that human liver ductal organoids are susceptible to SARS-CoV-2 and support robust viral replication.[13,14] However, hepatocellular injury is more common than cholestasis pattern secondary to cholangiocytes injury. In our opinion hepatocellular type of injury seen in COVID-19 is probably due to temporary damage of hepatocytes by nonviral causes and an impaired ability of liver regeneration

Keywords: COVID-19, Severity, Liver disease, Cirrhosis
Received: 2.6.2020; *Accepted:* 24.12.2020; *Available online 31 December 2020*
Address for correspondence. Praveen Sharma (MD, DM), Department of Gastroenterology and Hepatology Sir Ganga Ram Hospital, New Delhi, India
E-mail: Drpraveen_sharma@yahoo.com
Abbreviations: ALP: Alkaline Phosphatase; AASLD: American Association for the Study of Liver Diseases; ACE2: Angiotensin-Converting Enzyme 2; AST/ALT: Aspartate and Alanine Aminotransferase; AIH: Autoimmune Hepatitis; CRP: C Reactive Protein; CTP: Child Turcotte Pugh; CKD: Chronic Kidney Disease; CLD: Chronic Liver Disease; CLIF-OC: Chronic Liver Failure Organ Cirrhosis; CLIF-OF: Chronic Liver Failure Organ Failure; CHF: Congestive Heart Failure; DILI: Drug-Induced Liver Injury; EASL: European Association for the Study of Liver; HCC: Hepatocellular Carcinoma; HBV: Hepatitis B; HBC: Hepatitis C; HCQ: Hydoxycholoroquine; LT: Liver Transplantation; MAFLD: Metabolic Associated Fatty Liver Disease; MELD: Model for End-stage Liver Disease; NAFLD: Nonalcoholic Fatty Liver Disease; PPE: Personal Protection Kit; RR: Relative Risk; RTPCR: Reverse Transcription-Polymerase Chain Reaction
https://doi.org/10.1016/j.jceh.2020.12.006

by cholangiocyte precursor cells, which might impair liver regeneration and leading to further deterioration of liver function. However, various mechanism of altered liver function is postulated in COVID-19 infection. The direct cytotoxicity is due to active viral replication in hepatic cells and cholangiocytes by SARS-CoV-2. The virus binds to target cells through ACE2 receptors; however, normal serum alkaline phosphatase (ALP) in the majority of patients is against this hypothesis. Cytokine storm hypothesis includes immune-mediated damage due to the severe inflammatory response following COVID-19 infection. This hypothesis is supported by significantly elevated markers of inflammation like C reactive protein (CRP), serum ferritin, LDH, IL-6, and IL-2. Postmortem liver biopsy in patients who died from COVID-19 showed only microvesicular steatosis, accompanied by hyperactivation of T cells suggesting that liver injury is likely immune-mediated rather than direct cytopathic damage. Ischemic damage of liver hypothesis postulated that as a majority of sick patients were on the ventilator and inotropic support, so deranged liver enzymes could be due to ischemic hepatitis. However, aspartate and alanine aminotransferase (AST/ALT) rise is one to two times the upper limit of normal, which is against ischemic or hypoxic liver injury. Another probable reason is drug-induced liver injury (DILI), as a majority of the patients are on several drugs like lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab, and Chinese traditional medicine, which have some hepatotoxic effects.[15,16]

Cirrhosis as a risk factor for severity of COVID-19

There is a paucity of patients with pre-existing liver disease in studies on COVID-19, and characteristics of these patients according to Child's status or MELD score had not been evaluated separately in these studies.[3–8,17] Mantovani A et al.[17] included 11 observational studies for a total of 2034 adult individuals (median age 49 years [IQR 45–54], 57.2% men). The overall prevalence of chronic liver disease (CLD) at baseline was 3%. Individuals with severe COVID-19 disease had relevant alterations of liver enzymes and coagulation profile, probably due to the innate immune response against the virus, and CLD was not shown to influence the severity of COVID-19. In a pooled analysis by Lippi et al.[18] CLD was not found to be associated with increased odds of the severe form of COVID-19 (odds ratio of 0.96) or increased odds of mortality (OR 2.33). Based on the pooled results of early COVID-19 data, CLD played a minor role in influencing patient progression toward the severe form of the disease. However, newer studies had come after this pooled analysis, which had convincingly proved that underlying CLD had worse outcomes and more severe COVID-19 disease.

Singh et al.[10] studied 250 patients with CLD [42% metabolic fatty liver disease (MAFLD) and n = 50 with cirrhosis]. These patients had associated comorbidities like hypertension (68%), diabetes mellitus (48%), chronic kidney disease (CKD, 32%), chronic respiratory disease (40%), and congestive heart failure (CHF, 24%). Propensity matched controls except for CKD and CHF were taken, and it was found that increased mortality (12% vs 4%) in CLD compared to non-liver disease patients. Relative risk (RR) of mortality in cirrhosis was (RR, 4.6) and in CLD (RR 3.0) compared to non-CLD patients. Patients had an increased risk of hospitalization in CLD patients compared to non-CLD patients. In a small study by Qi et al.[11] twenty-one, COVID-19 patients with pre-existing cirrhosis (Child-Pugh class A, B, and C in 16, 3, and 2 patients, respectively) were included in the analysis. Most patients had compensated cirrhosis (81.0%), and chronic HBV infection was the most common etiology (57.1%). Comorbidities other than cirrhosis were present in most patients (66.7%). There were no significant differences between survivors (n = 16) and nonsurvivors (n = 5) concerning the stage of cirrhosis. The frequency of respiratory failure and gastrointestinal bleeding were higher in nonsurvivors than survivors, and one patient developed acute on chronic liver failure. However, the limitation was a small number of patients.

However, in a large study by Moon et al.[12] 103 patients with cirrhosis and 49 with noncirrhotic CLD were enrolled, and deaths occurred in 12.2% of CLD without cirrhosis, 24% CTP-A cirrhosis, 43% CTP-B cirrhosis, and 63.0% CTP-C cirrhosis. The cause of death in patients with cirrhosis was reported as COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%.

A multicenter study was done by Bajaj et al.[19] and enrolled inpatients with cirrhosis + COVID-19 (n = 37) compared with age/gender-matched patients with COVID-19 alone (n = 108) and cirrhosis alone (n = 127). It was concluded that cirrhosis + COVID-19 had similar mortality compared with patients with cirrhosis alone but higher than patients with COVID-19 alone. Mortality was predicted by the Charlson Comorbidity Index only.

In a study by Sarin et al.[20] 228 patients (185 CLD without cirrhosis and 43 with cirrhosis) were enrolled, with comorbidities in nearly 80%. Metabolism-associated fatty liver disease (113, 61%) and viral etiology (26, 60%) were common. Forty-three percent of CLD without cirrhosis presented with acute liver injury and 20% of cirrhotics presented with either acute-on-chronic liver failure. In decompensated cirrhotics, the liver injury was progressive in 57% of patients, with 43% mortality. Patients with CLD and associated diabetes and obesity had a worse outcome. Similar were the results of Iavarone et al.,[21] who enrolled 50 patients with cirrhosis with COVID-19 and concluded high 30-day mortality in these patients and found MELD score with (European Foundation for the study of chronic liver failure organ failure and cirrhosis) CLIF-C and CLIF-OF as predictors of increased mortality.

Table 1 Studies Showing Impact of COVID-19 in Patients With Chronic Liver Disease.

Author	Number of patients/etiology	Type of chronic liver disease	Conclusion
Singh et al.[10] (2020)	N = 250 with chronic liver disease, Etiology: MAFLD,n = 105	Cirrhosis,n = 50	Chronic liver disease patients had higher mortality (12% vs 4%) and increase hospitalization days compared to nonchronic liver disease.
Qi et al.[11] (2020)	N = 21 HBV/HCV/ Alcohol/others: (9/2/2/8)	Child's-A, n = 16 Child's-B, n = 3 Child's-C, n = 2	Mortality 25% in cirrhosis with no impact of Child's status on mortality
Moon et al.[12] (2020)	N = 252 (cirrhosis + CLD without cirrhosis) MAFLD:58,Alcohol:50,Viral:58 Others:86	Cirrhosis, n = 103 Chronic liver disease, n = 49	Mortality in CLD with cirrhosis = 12% Mortality: CTP-A = 24%,CTP-B = 43% and CTP-C = 63%
Bajaj et al.[19] (2020)	N = 272 N = 37 cirrhosis with COVID-19 HCV/alc/HCV + alc/NASH/other: (9/9/4/9/6)	N = 37 with cirrhosis and COVID, 127 with cirrhosis and no COVID, and 108 with COVID and no cirrhosis	No increased mortality in patients with cirrhosis with COVID-19. Increase in the Charlson comorbidity index was only predictive of increased mortality
Sarin et al.[20] (2020)	N = 228 EtiologyCirrhosis N=43CLD N=185 MAFLD 14 113 Viral 26 44 Alcohol 2 13 Others 1 15	N = 43 cirrhosis N = 185 with chronic liver disease	20% presentation with ACLF in patients with cirrhosis and 43% mortality in decompensated cirrhosis. Cirrhosis with obesity are predictor of increased mortality
Iavarone et al.[21] (2020)	N = 50 HCV/HBV/Alcohol/others: (14/5/12/19)	Cirrhosis Child's A:B:C::26:18:6	30 mortality is 34% and MELD,CLIF-C and CLIF-OF independent predictors of mortality.

HCV:Hepatitis C, HBV:Hepatitis B, MAFLD: metabolic associated fatty liver disease, Alc:alcohol, CLD: chronic liver disease, CTP:Child Turcotte pugh score, ACLF:acute on chronic liver failure, CLIF-C: European Foundation for the study of chronic liver failure organ failure and cirrhosis.

These studies (Table 1) had shown that underlying pre-existing liver disease is a risk factor for increased severity of COVID-19, and these patients should be looked upon by trained hepatologists and Internists.

Chronic viral hepatitis and COVID-19

There is limited data on chronic hepatitis B and the severity of COVID-19. In a study of 1099 patients with laboratory-confirmed COVID-19, 23 (2.1%) patients had hepatitis B infection, 22 patients had nonsevere, and one patient had a severe infection.[3] There is no published data on hepatitis C and COVID-19 coinfection till June 2020. In a large pooled study by Lei et al.[22] eighty-one (1.4%) patients of 5,771 patients had a history of chronic liver disease (4 with nonalcoholic fatty liver disease and 77 with viral hepatitis). Of these eighty one patient, 56 (1.2%) of 4,585 had the nonsevere disease while 25 (2.1%) of 1,186 had severe disease ($p = 0.03$). However, in both categories serum, AST/ALT, and total bilirubin were less than two times the upper limit of normal. In this pooled study, they could not assess whether the coexistence of chronic liver comorbidities increases susceptibility to liver injury in SARS-CoV-2 infection.

Alcohol associated liver disease and COVID

Consumption of alcohol has increased in the present pandemic due to various reasons like home quarantine, stress related to COVID like the loss in business, job insecurity, and the myth that alcohol consumption will reduce chances of getting COVID in the present pandemic. There is very limited data on the effect of COVID-19 in patients with alcoholic liver disease or in patients with alcoholic hepatitis.[12,19–21] However, limited studies in patients with cirrhosis who had enrolled patients with alcohol-related cirrhosis had shown increased mortality in these patients as in other patients with cirrhosis.[12,20,21] Patients with alcohol-related disease often had associated comorbidities such as obesity, diabetes mellitus, and chronic kidney disease, which also increase the risk for complications in COVID-19.[23] Although there is no specific guidelines on the management of alcoholic hepatitis during this COVID-19 pandemic. In our view, patients with severe alcoholic hepatitis or ACLF due to severe AH and no contraindication for steroids should be treated with a steroid if the COVID-19 test is negative in view of high short-term mortality in these patients. Liver biopsy should be avoided if there is no alternative diagnosis except for alcoholic hepatitis. No data exist for patients with severe AH and COVID-19 positive and glucocorticoid therapy for AH should be individualized on case to case basis. Patients with severe AH with COVID-19 negative and not responding for standard medical management should be listed for liver transplantation as in other patients; however, there is no data for liver transplantation in patients with severe AH and COVID-19 positive.

MAFLD and severity of COVID-19

The term "nonalcoholic fatty liver disease (NAFLD)" was coined way back in 1980 to describe a disease similar to alcoholic fatty liver disease but without a history of excessive alcohol intake. Hence considered a disease of exclusion after ruling out viral, autoimmune, and alcohol as the cause of fatty liver, and this definition of NAFLD underplay the role of metabolic dysfunction. To denote a positive diagnosis of the fatty liver associated with metabolic dysfunction, the term MAFLD (metabolically associated fatty liver disease) is considered a better terminology. MAFLD is the hepatic manifestations of metabolic syndrome and one of the commonest liver disorders. Obesity and MAFLD have been associated with increased production of proinflammatory cytokines like TNF-α by adipose cells and Kupffer cells. It is postulated that dysregulated hepatic innate immunity in patients with MAFLD contributes to the pathogenesis. Probably the polarization status of hepatic macrophages is skewed from inflammation-promoting M1 macrophages to inflammation suppressing M2 macrophages, leading to the progression of COVID-19. MAFLD with significant/advanced fibrosis might exacerbate the virus-induced cytokine 'storm' possibly through the hepatic release of multiple proinflammatory cytokines, thereby contributing mechanistically to severe COVID-19.[24]

There are limited studies in patients with MAFLD and COVID-19, and the results of all reflect MAFLD increases the severity of COVID-19 in these patients.

In a retrospective study by Ji D et al.,[25] 202 consecutive patients with COVID-19 and MAFLD were studied. The majority of patients had mild disease, and 14% had severe disease. Liver injury was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization, respectively. Sixty-seven (33.2%) patients had persistent abnormal liver function from admission to the last follow-up. Patients with progressive disease were older, had higher BMI, and a higher percentage of comorbidity and MAFLD. The patients with MAFLD had a higher risk of disease progression, a higher likelihood of abnormal liver function from admission to discharge, and longer viral shedding time compared to patients without NAFLD.

In another study By Zheng et al.[26] 66 patients [obese, n = 45 and nonobese, n = 21] with COVID-19 and MAFLD were included. Of them, 47 (71.2%) patients had nonsevere COVID-19, and 19 (28.8%) had severe COVID-19. The patients who were obese and had MAFLD had significantly higher AST and ALT compared to nonobese MAFLD patients. Patients with severe disease were more obese (89.5% vs. 59.6%, $p = 0.021$), and the presence of obesity in MAFLD patients was associated with a 6-fold increased risk of severe COVID-19 illness independent of hypertension, diabetes, and dyslipidemia.

Targher et al.[27] enrolled 94 (30%) patients of MAFLD out of 310 COVID-19 patients. Forty-four patients had

Table 2 Studies on MAFLD and COVID-19.

Author	Imaging	No of patients	outcome	conclusion
Ji et al.[25] (2020)	hepatic steatosis index and USG	202	67 (33%) persistent liver dysfunction Older and obese had progressive disease	MAFLD had a high risk of severe COVID, persistent liver dysfunction, and prolonged viral shedding
Zheng et al.[26] (2020)	CT scan	66	Obese patient had significantly severe COVID-19	6-Fold increased risk for severe COVID-19 in patients with MAFLD and obesity
Targher et al.[27] (2020)	CT scan	94	FIB-4<1.3,N = 44 FIB-4,1.3-2.6,N = 36 FIB-4>2.6,N = 14	Higher FIB-4 with MAFLD had more severe COVID-19
Gao et al.[28] (2020)	CT scan	65	Patients with no diabetes and MAFLD had high severity	MAFLD associated with 4-fold high severity, and severity increases with more metabolic factors
Zhou et al.[29] (2020)	CT scan	74 elderly (>60yr) 93 (<60 yr)	24%:severe 56%:severe	<60 yr MAFLD had two-fold increase severity than>60 yr

CT scan:computed scan, MAFLD:metabolic associated fatty liver disease, FIB-4:fibrosis −4 score.

FIB-4 ≤1.3, thirty-six patients had FIB-4 (>1.3–2.6), and 14 patients had FIB-4 >2.6. Notably, the severity of COVID-19 illness markedly increased among patients with MAFLD with intermediate or high FIB-4 scores. This data demonstrates that patients with MAFLD with increased FIB-4 or NFS are at a higher likelihood of having severe COVID-19 illness, irrespective of metabolic comorbidities.

In 65 patients with MAFLD and no diabetes, Gao F et al.[28] concluded that in nondiabetic patients with COVID-19, the presence of MAFLD was associated with a 4-fold increased risk of severe COVID-19; the risk increased with increasing numbers of metabolic risk factors. The association with COVID-19 severity persisted after adjusting for age, gender, and coexisting morbid conditions. A similar study by Zhou et al.[29] concluded that patients with MAFLD and younger than 60 years of age had severe disease compared to patients with more than 60 years of age, and this is independent of other risk factors of severity of COVID-19.

These studies suggest patients with MAFLD had higher chances of getting severe COVID-19. MAFLD patients are more likely to have abnormal AST and ALT, had higher viral shedding time, more liver injury during the hospital stay. MAFLD with significant fibrosis is another risk factor for the severity of COVID-19 compared to intermediate or no fibrosis patients (Table 2).

Autoimmune liver disease and COVID-19

Due to a lack of data in patients with autoimmune liver diseases (autoimmune hepatitis AIH, primary biliary cholangitis and primary sclerosing cholangitis) and COVID-19 definitive recommendations cannot be made in these patients. In small case series by Gerussi et al.[30] ten patients were recruited, and eight were in remission. Six subjects received a combination of antiretroviral and antimalarial drugs. In seven patients, the dosage of immunosuppressive medication was changed. Patients under immunosuppressive therapy for AIH developing COVID-19 show a disease course presumptively similar to that reported in the non-immunosuppressed population. There are no data to suggest these patients, even if immunosuppressed, are at increased risk of severe infection. There is a significant risk of under-treatment if the diagnosis is delayed in patients with the new-onset disease or if doses of immunosuppressive medications are reduced based on theoretical concerns that immunosuppressed patients are at particular risk.

Preliminary guidance on the management of autoimmune hepatitis (AIH) has been published by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of Liver (EASL) and the Asian pacific association for the study of Liver (APASL).[31–33] 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.

Decompensated liver disease and COVID-19

There is a scarcity of data on decompensated cirrhosis and COVID-19. However, Xiao et al.[34] studied 111 decompensated patients who were given standard precautions for prevention of COVID-D on WeChat every 3 days for a total of 12 times and compared with a cohort in a different province where such instructions were not given. The author found that none of their patients developed symptoms suggestive of COVID-19 compared to 17% of 101 patients. They concluded that standard preventive measures were effective in the prevention of COVID-19 in decompensated patients. In the first 152 (n = 103 with cirrhosis and n = 40 chronic liver disease) consecutive submissions of clinician-reported cases of laboratory-confirmed COVID-19 in patients with CLD to two international reporting registries (COVID-Hep.net and COVIDCirrhosis.org). Hepatic decompensation during COVID-19 was strongly associated with a subsequent risk of death: 63.2% of those with new decompensation died compared to 26.2% of those without new decompensation. Notably, 24.3% of those with new hepatic decompensation had no respiratory symptoms of COVID-19 at the time of diagnosis. Hence decompensated liver disease is a significant risk factor of mortality in patients with COVID-19, and all these patients should be hospitalized, and recent decompensation in a patient with cirrhosis should be evaluated for COVID-19 in this present pandemic.[12]

Acute on chronic liver failure

SARS-CoV2 as an acute event for decompensation in underlying liver disease has been reported in a single case by Qui et al.[35] Similarly, one case was mentioned in a study by Qi et al.[11] Sarin .[20] had 20% cirrhotics presented with acute-on-chronic liver failure. In decompensated cirrhotics, the liver injury was progressive in 57% of patients, with 43% mortality in these patients. Hepatologists dealing with acute decompensation of underlying chronic liver disease should keep this in mind while dealing with their patient when other common causes have been ruled out.

Hepatocellular carcinoma and COVID-19

Patients with hepatocellular carcinoma (HCC) need special attention during this present pandemic. There is hardly any data on patients with COVID-19 and HCC and patients developing HCC during this current pandemic and its treatment. Patients with cancer are at risk of increased morbidity and mortality.[36] Patients with HCC are at further risk of increased morbidity and mortality due to two combined risk factors that are cirrhosis and HCC itself

in this pandemic. COVID-19 affects the management of HCC in many ways that include reduce screening of HCC due to limited access to imaging like an ultrasound for screening and computed scan for confirmation. Hepatology center referrals have reduced, and the availability of limited beds, both ICU and non-ICU for non-COVID patients, hamper further management of diagnosed HCC patients.

Most patients with COVID-19 normally recover within 3–4 weeks, and it would be reasonable to defer treatment of HCC for a few weeks after the recovery of COVID-19. Oncologists and hepatologist societies suggest that patients undergoing systemic treatment for HCC should temporarily discontinue their medications if found to be COVID-19 positive as no data available in these patients. Treatment should only resume once the patient has been afebrile and free from respiratory symptoms for at least 3 days.[31–33,37] Patients with HCC who are scheduled to receive locoregional (radiofrequency ablation, transarterial chemotherapy, or transarterial radioembolization) or surgical treatment (resection/Liver transplantation) but are suspected/positive of having COVID-19 should have the treatment postponed until at least two weeks after the onset of symptoms and when fever or respiratory symptoms have been absent for at least three days.[33,37] However, the risks and benefits of HCC treatment should be individualized depending upon local resources and factors like tumor stage, liver function, age, comorbidities, and the risk of SARS-CoV-2 infection. Therapeutic decisions should be discussed in online multidisciplinary meetings and properly documented for legal purposes in the present pandemic, especially for patients who have a high risk for liver decompensation or recently recovered severe COVID-19.

Patients with the highest chance for the cure, as well as those on top of the liver transplant waiting list, should be prioritized for treatment of HCC. Management protocol does not differ in patients with COVID-19 negative by RT PCR, and these patients should be managed as per standard protocol. Patients should be hospitalized in "COVID-19-free" areas and should be tested for SARS-CoV-2 72 h before any procedure with reverse transcription-polymerase chain reaction (RT-PCR) and computed scan of the chest. Systemic therapy should be initiated as per the standard HCC management guidelines in a patient with COVID-19 negative.[32,33,37] Online consultations should be conducted within 2–4 weeks after the patient started systemic treatment to aid in the early assessment and identification of adverse events.

Liver transplantation and COVID-19

The COVID-19 pandemic has had enormous impacts on all elective surgeries all over the world, and this has also affected liver transplantation (LT). Diversion of hospital resources that includes nurses, paramedical staff, and hospital beds, including ICU to COVID-19 patients, has affected the LT program. The risk of LT recipients or live donors acquiring SARS-COV-2 infection during hospitalization and its impact in the post-LT period is also a major concern. How immunosuppression therapy will affect the course of liver transplant recipients in the initial days and later in the case of SARS-COV-2 infection is unclear from the present data available.

Becchetti et al.,[38] in a European multicenter prospective study of liver transplant recipients (n = 57), concluded that COVID-19 was associated with an overall and in-hospital fatality rate of 12% (95% CI 5%–24%) and 17% (95% CI 7%–32%), respectively. Immunosuppression had reduced in 22 recipients (37%) and discontinued in 4 (7%). Five of seven patients who died had underlying malignancy, and it was concluded that underlying malignancy in a patient with LT increases mortality. A systemic review by Gavriilidis.[39] based on case reports and series demonstrated lower mortality in liver transplant recipients compared to the general population. A large-scale European snapshot study clearly shows that both LT candidates and recipients are at high risk for COVID-19.[40] However, experience from Spain in 19 patients with LT had a favorable outcome with two patients (10.5%) died, 10 (52.6%) were discharged home, and 2 (10.5%) were still hospitalized after a median follow-up of 41 days from the onset of symptoms. Baseline immunosuppression regimen remained unchanged in all surviving recipients, with good liver function.[41] Current evidence suggests that the profile of COVID-19 infection may be no worse in LT patients than in nontransplant patients. However, high mortality rates in long-term transplant recipients in patients on low immunosuppression and with the metabolic comorbidities that predict severe disease and mortality as in nontransplant patients.[42] Immunosuppression doses should not be reduced in long-term LT patients in the absence of COVID-19 infection. Reduction of immunosuppression may be considered in patients diagnosed with moderate COVID-19 infection and in patients with lymphopenia, fever, or worsening pneumonia.

Endoscopy in patients with cirrhosis and COVID-19

Upper gastrointestinal endoscopy and colonoscopy are considered high-risk aerosol-generating procedures because of the high concentration of Sars-Cov-2 virus in pulmonary and gastrointestinal secretion. Routine screening endoscopy should be avoided in the present pandemic. Emergency procedures for variceal bleed and cholangitis should be done with a proper personal protection kit (PPE) and standard measures to avoid unnecessary exposure to the doctor, as well as endoscopy staff.

Table 3 Drugs Used in the Treatment of COVID-19 in Patients With Cirrhosis.

Author	Patients with cirrhosis	Drugs used,N
Qi et al.[11] (2020)	N = 21	17 (Lopinavir and Ritonavir) 8 (steroid): more deaths in steroid group 5 (Intravenous Immunoglobin)
Moon et al.[12] (2020)	N = 103	15 (HCQ) 4 (Lopinavir and Ritonavir), 4 (Tocilizumab), 4 (interferon alfa)
Bajaj et al.[19] (2020)	N = 37 cirrhosis with COVID-19	11(HCQ), 9 (Tocilizumab), 1 (ramdesivir), 1 (sarilumab)
Sarin et al.[20] (2020)	N = 43 cirrhosis N = 185 with chronic liver disease	14 (HCQ + Azathioprin),12 (Lopinavir and Ritonavir), 6 (steroids), 3 (intravenous immunoglobin), 5 (plasma therapy) 48 (HCQ + Azathioprin), 59 (Lopinavir and Ritonavir), 11 (steroids), 5 (intravenous immunoglobin), 4 (plasma therapy)
Iavarone et al.[21] (2020)	N = 50 HCV/HBV/Alcohol/others: (14/5/12/19)	9 (HCQ), 3 (Lopinavir and Ritonavir), 14 ((Lopinavir and Ritonavir and HCQ)

HCQ; Hydoxycholoroquine,HCV:Hepatitis C,HBV:Hepatitis B.

Secondary prophylaxis of variceal bleed should be done with proper hospital protocol in the present pandemic. Care must be taken in donning and doffing the PPE. In cirrhosis patients with liver encephalopathy or upper gastrointestinal bleeding, intestinal lavage from rectal approach should be discouraged, and replaced by oral lactulose or other laxatives.[32,33] COVID-19 testing for every patient is done before doing any endoscopy or colonoscopy in many centers, and the procedure is done in a dedicated endoscopy suite room for a patient who is positive for COVID-19. If there is no facility of separate suite room for endoscopy procedures, then suitable timing difference between COVID positive and negative patients should be followed, and proper cleaning of all surfaces in the procedure room with chlorine-containing detergents are recommended.

Postulated treatment in patients with chronic liver disease and COVID-19

In the majority of patients with COVID-19 and no coexisting comorbidities, supportive therapy is enough for complete recovery, and no specific drug is required. Patients with MAFLD and cirrhosis are independent predictors of severity of COVID-19, and these patients should be closely monitored and admitted if needed. Several drugs, namely chloroquine, hydroxychloroquine, remdesivir, favipiravir, and lopinavir/ritonavir, are being used in the treatment of COVID-19 with a variable degree of hepatotoxicity and success. Drugs have been tried in patients with COVID-19 with cirrhosis and MAFLD, but data is limited (Table 3).

Remdesivir is a viral RNA polymerase inhibitor with limited experience in patients with cirrhosis and COVID-19. However, limited experience in studies with cirrhosis had not shown any side effects and might be safer than other drug classes based on experience with nucleoside analogs. Chloroquine/Hydroxychloroquine are often used along with azithromycin, and few case reports of the prolonged QT interval have been documented in the literature.[21] Hydroxychloroquine therapy has not been associated with ALT abnormalities and is the commonest drug used in the majority of studies in a patient with cirrhosis. Tocilizumab is a humanized monoclonal antibody targeting interleukin-6 receptor; ALT elevations are frequent, but clinically apparent liver injury with jaundice seems to be rare.[43] Patients with decompensated cirrhosis should not be treated with Tocilizumab. Patients with cirrhosis and hepatitis B not on treatment should be watched for reactivation of hepatitis B. Methylprednisolone (steroids) may predispose to infections (e.g., SBP) in decompensated cirrhosis and should be used with caution. The role of other drugs in patients with cirrhosis is very limited. World Health Organization's Phase II/III SOLIDARITY trial that is designed to investigate the effectiveness of four different drugs or combinations—remdesivir, a combination of lopinavir and ritonavir, interferon beta, and chloroquine or hydroxychloroquine—compared to standard of care in subjects hospitalized with COVID-19. These drugs given by themselves or in combination had little to no effect on the 28-day mortality or the in-hospital course. However, details of the study are yet to be published after peer-review, and results should be read with caution.[44]

All patients with cirrhosis and MAFLD should be monitored closely with liver function tests, and early decompensation should be noted as it predicts increased mortality. In our opinion, most of the drugs should be stopped when ALT/AST > 5 × upper limit of normal and/or bilirubin > 2 × upper limit of normal.

Telemedicine in hepatology

Telemedicine is a rapidly expanding area in the medical health system in the present pandemic to prevent COVID-19. The rapid advancement and easy availability

of mobile communication technologies have helped many patients and doctors to interact. This has also overcome barriers to access as many patients are unable to travel due to physical constraints, distance, and a financial reason to see a specialist. The role of telemedicine has already been proved in the management of hepatitis C, and the same principles can be followed for the management of chronic hepatitis B and in a patient with cirrhosis. Telemedicine can be utilized in the management of HCC, liver transplant, and management of cirrhosis complications in the hospital where there are no such facilities.[45–47]

Telemedicine deviates from the traditional patient-physician office visit that has its own limitation in developing countries as many patients are not friendly with newer technologies or have no access to them. It requires costs to the institution to implement, support for legal liabilities as they may miss some important findings, which can be picked up on physical examination, the security of data, policies in reimbursements, and training to staff members. In developing countries, it requires significant cultural change and modifications to teaching techniques.

Liver enzyme abnormalities were seen in 15–55% of patients with COVID-19. Patients with MAFLD had shown a 4–6 fold increase in severity of COVID-19, which increases with the severity of fibrosis, younger age, obesity, and increased number of components of metabolic syndrome. Patients with cirrhosis are now an independent predictor of severity of COVID-19 and increased hospitalization. Patients with cirrhosis havea higher mortality rate, and this rate increased with increasing severity of liver disease as assessed by CTP score or MELD score. Patients with cirrhosis had a 20–30% risk of decompensation presenting as acute on chronic liver failure and high 30 days mortality. There is limited data in patients with alcoholic liver disease, chronic viral hepatitis, and autoimmune hepatitis, and associated COVID-19. Patients on immunosuppression, either post-transplant or autoimmune hepatitis, should continue with their immunosuppressive drugs, and a reduction in immunosuppressive drugs for fear of COVID-19 should be avoided. Limited data in post-transplantation patients had not shown excessive mortality due to COVID-19 in the early transplant period. Routine endoscopy procedure and liver biopsy should be avoided; however, the urgent procedure for variceal bleed and cholangitis should be done with proper guidelines meant for COVID-19 patients. Drug therapy for the treatment of COVID-19 in patients with cirrhosis is still evolving, and various combinations of drugs are being used with limited efficacy.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Praveen Sharma: Writing – original draft, Conceptualization, Data curation. **Ashish Kumar:** Writing – review & editing. **ShriHari Anikhindi:** Writing – review & editing. **Naresh Bansal:** Writing – review & editing. **Vikas Singla:** Writing – review & editing. **Khare Shivam:** Writing – review & editing. **Anil Arora:** Validation, Writing – review & editing.

CONFLICTS OF INTEREST

All authors have none to declare.

FUNDING

None.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727–733.
2. Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565–574.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720, 30.
4. Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*. 2020 Feb 27;368:m792.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
6. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *J Am Med Assoc*. 2020;323:1061–1069, 7.
7. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int*. 2020;40:2095–2103.
8. Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. *J Gerontol A Biol Sci Med Sci*. 2020;75:1788–1795.
9. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. *Clin Gastroenterol Hepatol*. 2020;18:1561–1566.
10. Singh S, Khan A. Clinical Characteristics and Outcomes of COVID-19 Among Patients with Pre-existing Liver Disease in United States: A Multi-Center Research Network Study. *Gastroenterology*. 2020 May 3.
11. Qi Xiaolong, Liu Yanna, Wang Jitao, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut*. 2020;70:433–436.
12. Moon AM, Webb GJ, Aloman C, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. *J Hepatol*. 2020;73:705–708.
13. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020 Apr 16;181(2):271–280.
14. Zhao B, Ni C, Gao R, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell*. 2020 Apr 17:1–5.
15. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420–422.

16. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol*. 2020;73:566–574.
17. Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: a meta-analysis. *Liver Int*. 2020;40:1316–1320.
18. Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol*. 2020;33:114–115.
19. Bajaj J, Garcia-Tsao G, Biggins S, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut*. 2020;0:1–6.
20. Sarin S, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; the APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int*. 2020 Jul 4:1–11.
21. Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020;73:1063–1071.
22. Lei F, Liu YM, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology*. 2020;72:389–398.
23. Kushner T, Cafardi J. 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. *Clin Liver Dis*. 2020;15:195–199.
24. Lefere S, Tacke F. Macrophages in obesity and non-alcoholic fatty liver disease: crosstalk with metabolism. *JHEP Rep*. 2019;1:30–43.
25. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. *J Hepatol*. 2020;73:451–453.
26. Zheng KI, Gao F, Wang XB, et al. Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism*. 2020;19:154244.
27. Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut*. 2020;69:1545–1547.
28. Gao F, Zheng KI, Wang XB, Yan HD, Sun QF. Pan KHet al Metabolic associated fatty liver disease increases COVID-19 disease severity in non-diabetic patients. *J Gastroenterol Hepatol*. 2020;36:204–207.
29. Zhou YZ, Zheng IK, Wang XB, Yan HD, Sun QF, Pan KH, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. *J Hepatol*. 2020;73:719–721.
30. Gerussi A, Rigamonti C, Elia C, et al. Coronavirus Disease 2019 (COVID-19) in autoimmune hepatitis: a lesson from immunosuppressed patients. *Hepatol Commun*. 2020;4:1257–1262.
31. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. *Hepatology*. 2020 Jul;72:287–304.
32. Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep*. 2020;2.
33. APASL Covid-19 Task Force, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int*. 2020 May 23:1–14.
34. Xiao Y, Pan H, She Q, Wang F, Chen. Prevention of SARS-CoV-2 infection in patients with decompensated cirrhosis. *Lancet Gastroenterol Hepatol*. 2020;5:528–529.
35. Qiu H, Wander P, Bernstein D, Satapathy SK. Acute on chronic liver failure from novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Liver Int*. 2020;40:1590–1593.
36. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395:1907–1918.
37. Chagas AL, Fonseca LG, Coelho FF, et al. Management of hepatocellular carcinoma during the COVID-19 pandemic – são paulo Clō'nicas liver cancer group multidisciplinary consensus statement. *Clinics*. 2020;26e2192.
38. Becchetti C, Zambelli MF, Pasulo L, et al. COVID-19 in an international European liver transplant recipient cohort. *Gut*. 2020;69:1832–1840.
39. Gavriilidis P, Pai M. The impact of COVID-19 global pandemic on morbidity and mortality of liver transplant recipients children and adults: a systematic review of case series. *J Clin Med Res*. 2020 Jul;12:404–408.
40. Polak WG, Fondevila C, Karam V, Adam R, Baumann U, Germani G, et al. Share impact of COVID-19 on liver transplantation in europe: alert from an early survey of European liver and intestine transplantation association (ELITA) and European liver transplant registry (ELTR). *Transpl Int*. 2020;33:1244–1252.
41. Loinaz C, Marcacuzco A, Fernández-Ruiz M, Caso O, Rafael FC, Juan S, et al. Varied clinical presentation and outcome of SARS-CoV-2 infection in liver transplant recipients: initial experience at a single center in Madrid, Spain. *Transpl Infect Dis*. 2020;22:13372.
42. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 2020;5:532–533.
43. Muhović D, Bojović J, Bulatović A, et al. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int*. 2020;40:1901–1905.
44. Pan H, Peto R, Karim QA, et al, WHO Solidarity trial consortium. *Repurposed antiviral drugs for COVID-19–interim WHO solidarity trial results*. medRxiv; 2020.
45. Nazareth S, Kontorinis N, Muwanwella N, Hamilton A, Leembruggen N, Cheng WS. Successful treatment of patients with hepatitis C in rural and remote Western Australia via telehealth. *J Telemed Telecare*. 2013;19:101-106.
46. Ertel AE, Kaiser T, Shah SA. Using telehealth to enable patient-centered care for liver transplantation. *JAMA Surg*. 2015;150:674-675.
47. Thomson M, Volk M, Kim HM, Piette JD. An automated telephone monitoring system to identify patients with cirrhosis at risk of rehospitalization. *Dig Dis Sci*. 2015;60:3563–3569.