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Contents

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COVID-19 in patients with pre-existing chronic liver disease – predictors of outcomes

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Abstract

Coronavirus disease 2019 (COVID-19) has affected patients with pre-existing chronic liver disease (CLD) in various ways. The maximum impact was seen on patients with underlying cirrhosis who have shown to have poor clinical outcomes in the form of increased risk of hepatic decompensation, acute-on-chronic liver failure, and even mortality. It is of paramount importance to identify various factors which are associated with unfavorable outcomes for prognostication and making informed management strategy. Many factors have been evaluated in different studies in patients with underlying CLD. Some of these factors include the severity of underlying chronic liver disease, comorbid conditions, age, and severity of COVID-19. Overall, the outcomes are not favorable in patients with cirrhosis as evidenced by data from various studies. The main purpose of this review is to identify the predictors of adverse clinical outcomes including mortality in patients with CLD for risk stratification, prognostication, and appropriate clinical management.

Core Tip: Coronavirus disease 2019 (COVID-19) has been shown to negatively affect the outcomes of patients with chronic liver disease. Some of the major factors predicting poor outcomes and mortality as shown by various studies include old age (> 60 years) and presence of comorbidities like diabetes, hypertension, and obesity. Apart from these, the most important outcome measure is the severity of underlying chronic liver disease and in some cases the etiology of chronic liver disease. Another major predictor of outcome is the severity of COVID-19, with respiratory failure being a common cause of mortality. Further data is required to draw a definitive relation between these risk factors and outcomes in these patients.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related coronavirus disease 2019 (COVID-19) has wreaked havoc since its outbreak in late 2019. As per the most recent estimates, it has affected more than 575 million people worldwide[1]. It has adversely affected the health care system even in developed nations. Although the most common manifestations of COVID-19 are either asymptomatic infection or mildly symptomatic infection with fever, cough, and generalized weakness, some patients developed severe respiratory failure requiring mechanical ventilation and even death[2].

Patients with chronic liver disease (CLD) have been affected due to the COVID-19 pandemic, such as lack of routine services like variceal and hepatocellular carcinoma (HCC) screening, lack of physical follow-up to monitor the response to treatment like ascites, re-allocation of health care facilities for COVID-19 management, *etc.* An acute insult in the form of COVID-19 in a background of CLD may lead to further decompensation and increased morbidity and mortality. Therefore, in this review, we will summarize and identify the predictors of adverse outcomes in patients with CLD, which will help in prognostication, risk stratifying, and providing optimal care to the patients.

EPIDEMIOLOGY

COVID-19 is a systemic disease affecting multiple organ systems and gastrointestinal system (GI) involvement may be seen in a subset of patients. Studies have shown that nearly 20% of the affected patients had some abnormalities in liver function as reflected by elevated liver enzymes (20%) and elevated bilirubin (16%)[3]. About 35% of patients showed abnormal alanine aminotransferase or bilirubin levels, out of which 77% showed elevation to levels less than 5 times the upper limit of normal [4]. The prevalence of underlying CLD in COVID-19 patients was 3%-6.3% in various studies[5-8]. A meta-analysis of 73 studies with 24299 patients, showed that the prevalence of CLD in COVID-19 positive patients was 3%, which was similar to that among COVID-19 negative patients[3]. The differences in prevalence might be due to admission bias, sampling bias, and retrospective nature of studies.

A recent study showed that mortality rates among alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) affected patients increased significantly during the pandemic while the rate of mortality among patients with viral hepatitis remained similar to the pre-pandemic times[9]. A recent meta-analysis of 40 studies has shown that patients with CLD had a significantly higher risk of severe COVID-19 (pooled odds ratio [OR]: 2.44) and death (pooled OR: 2.35) as compared to COVID-19 patients without[10]. Hence, COVID-19 does affect patients with CLD and in some cases with adverse outcomes.

PATHOPHYSIOLOGY OF LIVER INVOLVEMENT IN COVID-19

The liver involvement in COVID-19 is multifactorial, including direct viral hepatotoxicity, immune-mediated liver injury, sepsis, hypoxemia, or drug-induced liver injury[11]. Direct hepatotoxicity is due to entry of SARS-CoV-2 into the liver through the binding of viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor on cholangiocytes. The expression of ACE2 is highest in cholangiocytes followed by sinusoidal endothelial cells and hepatocytes as shown in healthy livers by single cell RNA sequencing methods[12]. After entering the cell, the S protein is primed by a specialized serine

protease, transmembrane serine protease 2 (TMPRSS2), in the host cell[13]. Once inside the cell, SARS-CoV-2 causes activation of the mTOR pathway which inhibits autophagy of the viral particles. Thus, the viral particles evade the immune system and increase in number, exerting direct hepatotoxicity *via* mitochondrial dysfunction, ER stress, and activation of the intrinsic pathway of apoptosis as depicted in Figure 1[14].

The second hit in the pathogenesis of liver injury is secondary damage caused by cytokine storm. Infection with SARS-CoV-2 has been postulated to cause a massive surge in proinflammatory cytokine levels. The predominant cytokines implicated include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and elevated levels of ferritin and CRP[15]. These proinflammatory cytokines result in cholestatic liver injury by causing downregulation of proteins and channels involved in uptake and secretion of bilirubin and bile salts similar to what is seen in sepsis-related cholestasis. Another postulated mechanism is decreased albumin synthesis due to IL-6 mediated suppression of C/EBP pathway[14]. TNF-α and IL-1 also activate and recruit macrophages to the liver and induce apoptosis of hepatocytes. These inflammatory cytokines also cause hypoxic liver injury by causing endothelial damage and inducing microvascular thrombosis[14]. Thus, various cytokines act in concert to cause liver injury reflected as biochemical alterations in liver function. Other mechanisms include hypoxemic injury secondary to type 1 hypoxemic respiratory failure and drug induced liver injury.

CHRONIC LIVER DISEASE AND COVID-19 OUTCOMES

Predictors of outcomes in chronic liver disease
Numerous studies across the globe have tried to identify the predisposing factors for poor outcomes of COVID-19 in patients with CLD as summarized in Figure 2 and Table 1. A summary of evidence available and the possible risk factors has been enumerated below.

Age: Increasing age is associated with a blunted immune response and multiple comorbidities, and thus may have an impact on the outcomes in patients with pre-existing CLD. Age more than 60 years had an adjusted hazard ratio (aHR) of 1.05 for mortality in cirrhotics with COVID-19[16]. Another study showed that the mortality increased from 6.1% in patients aged less than 50 years to 33.9% among those who were more than 65 years with an adjusted OR (aOR) of 7.2 in this group of patients[17]. Therefore, increasing age especially more than 60 years has been associated with increased mortality and risk of liver decompensation[16-18].

Ethnicity: African Americans with CLD were twice more likely to develop COVID-19 than Caucasians in a study[19]. Another study found that non-Hispanic blacks and Hispanics had higher chances of contracting COVID-19 in patients with CLD; however, they did not find any difference in outcomes of disease in different ethnicities[20]. Hispanics had more severe COVID-19 infection in patients with CLD [18]. Henceforth, Hispanics and blacks have been shown to have higher risk of contracting COVID-19 disease and having a severe course likely due to lower socioeconomic status, poverty, overcrowding, and inadequate access to health care services.

Etiology of CLD: Several studies have tried to relate the etiology of CLD with outcomes in COVID-19 patients. In the following sections, the determinants of outcomes are described according to etiology of CLD.

Alcohol
Alcohol is one of the most common etiologies of CLD. The pandemic led to a situation of social isolation and unemployment which lead to an increased consumption of alcohol in higher quantities[21]. A study found a higher rate of mortality among alcohol-related liver disease with an aHR of 1.79[22]. Kim *et al* [18] showed an aHR of 2.42 of mortality among alcohol-related liver disease. There was a three times increase in the monthly percent change of crude ALD-related mortality after February 2020 as compared to January 2017 to December 2017 in one study[23]. However, another study did not find alcohol as a poor outcome variable on multivariate analysis of retrospective data[24,25]. A recent study showed that the mortality among ALD patients was declining in the pre-pandemic era but increased fivefold during the pandemic[9]. Therefore, it seems that alcohol as an etiology increases the risk of adverse outcomes and mortality[26] in patients with COVID-19 and CLD as summarized in Table 2 and Supplementary Table 1.

NAFLD
NAFLD is rapidly becoming the most common cause of CLD across the world. It is considered to be the hepatic manifestation of metabolic syndrome and usually coexists with other components of metabolic syndrome. The COVID-19 pandemic showed a bidirectional relationship with NAFLD. Lockdown during the pandemic and lack of exercise lead to an increase in sedentary behavior and thus metabolic syndrome including NAFLD. Such patients had a more severe COVID-19 infection as evidenced by higher requirement of oxygen, mechanical ventilation, and prolonged intensive care unit (ICU) stay[27-

Table 1 Studies showing clinical outcomes of chronic liver disease in coronavirus disease 2019 and associated risk factors

Ref.	Type	Clinical outcomes	Predictors of outcomes
Iavarone *et al* [53]	Multicentric retrospective study of 50 cirrhotics	ACLF and *de novo* acute liver injury: 28%; 30-d mortality: 34%	Predictors of mortality: CLIF-OF (HR: 1.426); Moderate/severe respiratory failure (HR: 1.608)
Marjot *et al*[22]	Retrospective data from United Kingdom hospital network including 745 patients with CLD (386 with and 359 without cirrhosis)	Acute hepatic decompensation: 46%; ACLF: 50%; Mortality in cirrhosis, ACLF, and non-cirrhotics: 32%, 65%, and 8%	Predictors of mortality: ALD (OR: 1.79); Child-Pugh class: Child-Pugh A +2.0%, Child-Pugh B +20.0%, Child-Pugh C +38.1%. Predictors of decompensation: Child-Pugh class
Ge *et al*[16]	Data from the National COVID Cohort Collaborative (N3C) dataset of 6.4 million cases	3.31 times adjusted hazard of death in cirrhotics at 30 d than non-cirrhotics	Predictors of 30-d mortality: Age (aHR: 1.05 per year); Hispanic ethnicity (aHR: 1.20); Chronic hepatitis C (aHR: 1.27); ALD (aHR: 1.40); Modified CCI (aHR: 1.07 per point)
Elhence *et al*[24]	Retrospective analysis of 221 cirrhosis patients	Compensated cirrhosis: 8.1%; Acute decompensation: 62.9%; ACLF: 29.0%; MODS: 55.6%; Type 1 respiratory failure: 20.0%; Sudden cardiac arrest: 6.7%; GI bleeding: 3.3%	Predictors of mortality: Higher TLC [HR: 1.054]; Elevated creatinine [HR: 1.184]; MELD score [HR: 1.038]; Alkaline phosphatase [HR: 1.003]; COVID-19 severity [HR: 2.573]; ACLF on presentation (HR: 2.573)
Xiao *et al*[52]	Medical records collected from 23 Chinese hospitals	Decompensated cirrhosis: 57.5%; Mortality: 28.9%	Factors associated with mortality: Child-Pugh class (OR: 5.71); CURB65 (OR: 5.88)
Grgurevic *et al* [48]	4014 patients	Four times higher risk of 30-d mortality in cirrhosis	Predictor of 30-d mortality: Cirrhosis (HR: 2.95)
Mendizabal *et al* [17]	Prospective cohort of 96 cirrhosis patients	Mortality in cirrhotic: 47% *vs* 16% in non-cirrhotics; Acute decompensation: 61.4%; ACLF: 55.2%	Factors associated with mortality: Age > 65 yr (OR: 7.2); Male gender (OR: 1.8); BMI > 30 (OR: 1.7); Cirrhosis (OR: 3.1)
Kim *et al*[18]	Multicentre observational cohort study in 21 institutes in United States with 867 CLD cases (227 with cirrhosis)	Mortality: 25%; Hepatic decompensation: 7.7%; Hepatic encephalopathy: 34.3%; Ascites: 16.4%; Variceal bleed: 10.4%	Predictors of all-cause mortality: ALD (HR: 2.42); Hepatic decompensation at baseline (HR: 2.91); HCC (HR: 3.31); Increasing age (HR:1.44 per 10 yr); Diabetes (HR: 1.59); Hypertension (HR:1.77); COPD (HR:1.77); Current smoking (HR: 2.48)
Sarin *et al*[37]	Retrospective data from 13 Asian countries with228 patients [185 CLD without cirrhosis and 43 with cirrhosis]	ACLF: 11.6%; Acute decompensation: 9%; Mortality rate: 43% among decompensated cirrhotics	Predictors of sever liver injury: In CLD without cirrhosis, diabetes [57.7% *vs* 39.7%, OR: 2.1 (1.1-3.7)]; In cirrhotics, obesity [64.3% *vs* 17.2%, OR: 8.1 (1.9-38.8). Predictor of mortality: CTP score of 9 or more at presentation [AUROC 0.94, HR:19.2]
Xiang *et al*[54]	Retrospective cohort study of 267 patients	Severe COVID-19: 15%; High-flow oxygen support: 14%; Mechanical ventilator support: 4%; Death: 1	Predictor of severity: FIB-4 > 3.25

ACLF: Acute-on-chronic liver failure; ALD: Alcohol related liver disease; AUROC: Area under the receiver operator curve; BMI: Body mass index; COVID: Coronavirus disease; CLD: Chronic liver disease; CCI: Charlson's comorbidity index; CLIF OF: Chronic liver failure consortium organ failure; CLIF-C: Chronic liver failure consortium; COPD: Chronic obstructive pulmonary disease; CTP: Child-Turcotte-Pugh score; FIB-4: Fibrosis 4; HCC: Hepatocellular carcinoma; MELD Na: Model for end stage liver disease sodium score; MODS: Multiorgan dysfunction syndrome; NACSELD: North American Consortium for the Study of End-Stage Liver Disease.

Table 2 Clinical outcomes in patients with underlying alcoholic liver disease during coronavirus disease 2019

Ref.	Study	Outcomes
Deutsch-Link *et al*[23]	Retrospective analysis - pre (January 2017 to December 2017) and post-COVID era (February 2020)	Increase in the monthly percent change of crude ALD-related mortality: Males: 3.18 *vs* 0.96; Females: 3.8 *vs* 1.18
Yeo *et al*[26]	16813 patients with ALD before and 11625 during the pandemic	OR of death in ALD - 18.7 during the pandemic *vs* 0.995 in the pre-pandemic era

ALD: Alcohol related liver disease; COVID: Coronavirus disease; LT: Liver transplant; NASH: Non-alcoholic fatty liver disease; OR: Odds ratio; UNOS: United network for organ sharing.

30] (Table 3). Studies have demonstrated that patients with features of metabolic syndrome including higher body mass index (BMI) and waist circumference and presence of diabetes and hypertension had adverse effects on outcomes[29-31].

Patients with COVID-19 and underlying NAFLD have multiple associated comorbidities including diabetes, hypertension, dyslipidemia, and obesity. These factors have been independently associated with poor outcomes in patients with COVID-19[32,33]. Different studies have estimated different

Table 3 Studies evaluating outcomes and predictors of severity in non-alcoholic fatty liver disease with coronavirus disease 2019

Ref.	Type of study	Patients included	Outcomes	Predictors
Chang *et al* [27]	Retrospective study	3122 COVID-19 cases [FLI (fatty liver index) was calculated]	Severe disease: 223 (7.14%); Mechanical ventilation: 82 (2.63%); ICU admission: 126 (4.04%) High-flow oxygen therapy: 75 (2.40%); Death: 94 (3.01%)	FLI associated with severe complications from COVID-19 (aOR: 1.77)
Vrsaljko *et al*[28]	Prospective observational study	120 NAFLD patients (of 216 COVID-19 patients)	Patients with NAFLD had more high-flow nasal cannula or non-invasive ventilation (21.66%, *vs* 10.42%), longer duration of hospitalization (10 d *vs* 9 d), and more pulmonary thromboembolism risk (26.66% *vs* 13.54%)	Delayed time to recovery (HR: 0.64); Increased pulmonary thrombosis (OR: 2.15) among NAFLD patients
Velazquez *et al*[29]	Retrospective cohort study	359 NAFLD patients as per Dallas steatosis index (DSI) out of total 470 cases	Lower oxygen saturation levels; Higher D-dimer; Elevated LDH; Higher lymphocyte count among NAFLD	On multivariable analysis, NAFLD is a predictor of mortality (OR: 2.13)
Madan *et al* [36]	Retrospective observational case control study	289 NAFLD patients among 446 cases	Similar in-hospital mortality, ICU requirement, ventilatory support, and duration of ICU and hospital stay	Predictors of in-hospital mortality: High total leukocyte count (OR: 1.082); High FIB-4 (OR: 1.606)
Chen *et al* [34]	Retrospective single centre cohort study	172 patients with hepatic steatosis (HS) among 342 cases	19% of patients expired; > 50% required ICU admission	Increased intubation (aOR: 2.75); Vasopressor requirements (aOR: 1.22); ALT > 5 x ULN (aOR: 7.09)
Sarin *et al* [37]	Retrospective multinational cohort	113 NAFLD cases out of 228 cases (185 without cirrhosis and 43 with cirrhosis)	Higher risk of acute liver injury in obese cirrhotics *vs* normal weight patients (OR: 8.9)	Higher risk of liver injury: In non-cirrhotics, diabetes [57.7% *vs* 39.7%, OR: 2.1]; In cirrhotics, obesity, [64.3% *vs* 17.2%, OR: 8.1]
Li *et al*[31]	Observational study	Genome-wide meta-analysis (GWMA) of 3711 NAFLD cases and 426252 controls from United Kingdom Biobank data	No significant association of NAFLD and severe COVID-19 after adjusting for confounders	Predictors of severity: Body mass index (OR: 1.73); Waist circumference (OR: 1.76); Hip circumference (OR: 1.33)
Yao *et al* [30]	Retrospective study in China	86 COVID-19 patients with NAFLD	NAFLD patients with advanced fibrosis (NFS > -1.5) had more fever (81.6% *vs* 50%), shortness of breath (18.4% *vs* 0%), and severe disease (28.9% *vs* 2.1)	Predictors of severe disease: Diabetes (OR: 8.264); Advanced liver fibrosis [NFS > -1.5] (OR: 11.057)
Targher *et al*[35]	Retrospective study	94 NAFLD cases among 310 patients		Factors associated with severity: Increasing FIB-4 (aOR: 1.90); Increasing NFS (aOR: 2.57)

aOR: Adjusted odds ratio; ALT: Alanine transaminase; AST: Aspartate aminotransferase; COVID: Coronavirus disease; CLD: Chronic liver disease; FIB-4: Fibrosis 4; NFS: NAFLD fibrosis score; FLI: Fatty liver index; GWAS: Genome wide association studies; ICU: Intensive care unit; LDH: Lactate dehydrogenase; NAFLD: Non-alcoholic fatty liver disease; TLC: Total leukocyte count; ULN: Upper limit of normal.

prevalence of comorbidities in NAFLD. The prevalence of obesity, diabetes mellitus, and hypertension was 47%, 27%, and 31%, respectively, in NAFLD patients in a study, in which 27% of patients required non-invasive mechanical ventilation, 44% required ICU admission, and 27% were expired[29]. Another study showed that 69% of patients had hypertension, 43% had diabetes, 47% had dyslipidemia, 85% were overweight, and 52% were obese, and out of total 342 patients, > 50% required ICU admission and 19% were expired[34]. Thus, the presence of comorbidities is associated with poor outcomes in patients with NAFLD and COVID-19.

Advanced fibrosis in patients with NAFLD was associated with more severe COVID-19 and adverse outcomes with an almost two-fold increased risk of severity in patients with an FIB-4 score of more than 2.67[35,36]. Another study showed that presence of cirrhosis with diabetes was associated with poor outcomes in COVID-19 patients with higher risk of liver injury (OR: 2) and NAFLD was the most common cause of CLD in this study[37]. The rate of severe illness was significantly higher in patients with advanced fibrosis [NAFLD fibrosis score (NFS) > -1.5] compared to those with non-advanced fibrosis with an NFS < -1.5 (28.9% *vs* 2.1%, $P < 0.001$)[30]. Therefore, the underlying degree of fibrosis in NAFLD patients and various components of metabolic syndrome has been associated with poor outcomes as compared to those without significant fibrosis.

Hepatitis B
Patients with chronic hepatitis B (CHB) had a higher rate of ICU admission (HR: 1.86) and increase risk of mortality (HR: 3.19) among hepatitis B virus "e" antigen positive (HBeAg+) CHB cases as shown in Table 4[8,38,39]. Another study showed that although the mortality rate was higher among patients with hepatitis B, it was not statistically significant after adjusting for other factors[40]. The study had shown that patients with COVID-19 had a lower positive rate for CHB[41,42]. One of the postulated

Table 4 Studies showing outcomes and predictors of severity in hepatitis B virus-infected patients with coronavirus disease 2019

Ref.	Study	Patients	Results	Predictors
Yang *et al* [38]	Single centre retrospective study	Patients with HBV infection out of 2899 COVID patients. Resolved hepatitis B (*n* = 503); HBeAg (-) CHB/infection (*n* = 44); HBeAg (+) CHB/infection (*n* = 55); HBV reactivation (*n* = 6)	HBeAg (+) CHB/infection and HBV reactivation were associated with more abnormal liver function, severe disease, longer ICU stay, and death	Increased ICU admission (HR: 1.86) and mortality (HR: 3.19) in HBeAg (+) CHB/infection
Choe *et al* [40]	Nationwide population-based cohort study	676 chronic HBV infection cases (19160 COVID-19 cases)	Mortality in HBV infected *vs* non-infected patients with COVID-19: 8.2% *vs* 13.5%	No difference in mortality, ICU admission, or organ failure
Wang *et al*[8]	Multicentre retrospective cohort study	109 CHB and 327 non-CHB patients with COVID-19	CHB *vs* non-CHB patients: Severe disease (27.5% *vs* 12.84%) and more dyspnoea (55.05% *vs* 43.12%) and mechanical ventilation requirement (22.49% *vs* 7.95%) in CHB	Increased mortality in CHB patients (OR: 3.748). Predictors of mortality: AST; ALT; ALP; Bilirubin; LDH; Elevated D-dimer. Protective effect: ALB (HR: 0.13); ALB/GLO (HR: 0.123)
Yip *et al*[44]	Retrospective cohort study	Current (353) and past HBV infection (359) out of total 5639 COVID cases	Mortality in current HBV *vs* past HBV *vs* non-HBV infection: 2.3% *vs* 5.8% *vs* 2.2%	Acute liver injury associated with mortality (aHR: 2.45), more than current (aHR: 1.29) or past (aHR: 0.90) HBV infection
Kang *et al* [42]	Nationwide cohort study	7723 COVID-19 cases and 46231 controls	Lower SARS-CoV-2 positivity rate in CHB, after adjusting for comorbidities (aOR: 0.65)	Reduced SARS-CoV-2 positivity (aOR: 0.49) on antivirals
Liu *et al*[39]	Retrospective cohort study	347 COVID-19 patients (21 *vs* 326 with or without chronic HBV infection)	Severe COVID-19 in 30% *vs* 31.4% in the HBV *vs* non-HBV group	Similar SARS-CoV-2 clearance and severe COVID-19

ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID: Coronavirus disease; CHB: Chronic hepatitis B; GLO: Globulin; HBV: Hepatitis B virus; LDH: Lactate dehydrogenase.

reasons for this finding is that patients with CHB mount a reduced T cell mediated immune response termed as 'immune exhaustion' which may reduce the extent of cytokine storm seen in patients with COVID-19[41]. The major predictor of poor outcomes was positivity for HBeAg suggestive of active viral replication and ongoing liver injury in addition to liver injury inflicted by SARS-CoV-2[38]. Reactivation of hepatitis B virus (HBV) with anti-IL6 therapy (tocilizumab) was found to be 3.3% in a systematic review[43]. In short, patients with HBeAg positive CHB are more likely to have a poor outcome in terms of hospitalization requirement and mortality[44] and some specific treatment for COVID-19 will lead to reactivation of HBV like anti-IL6 antibody (tocilizumab).

Hepatitis C

Hepatitis C predominantly causes a chronic indolent infection. Various management aspects of hepatitis C have been impacted during the COVID-19 pandemic. The impact of COVID-19 on chronic hepatitis C depends on the extent and severity of underlying CLD as discussed previously. A study by Ronderos *et al*[45] showed an increased mortality among hepatitis C virus (HCV)-infected patients, and increasing age, elevated D-dimer, ferritin, and FIB-4 score were identified as predictors on multivariate analysis. However, more data are required to draw a conclusion regarding the effect of HCV infection on COVID-19, excluding the severity of liver disease.
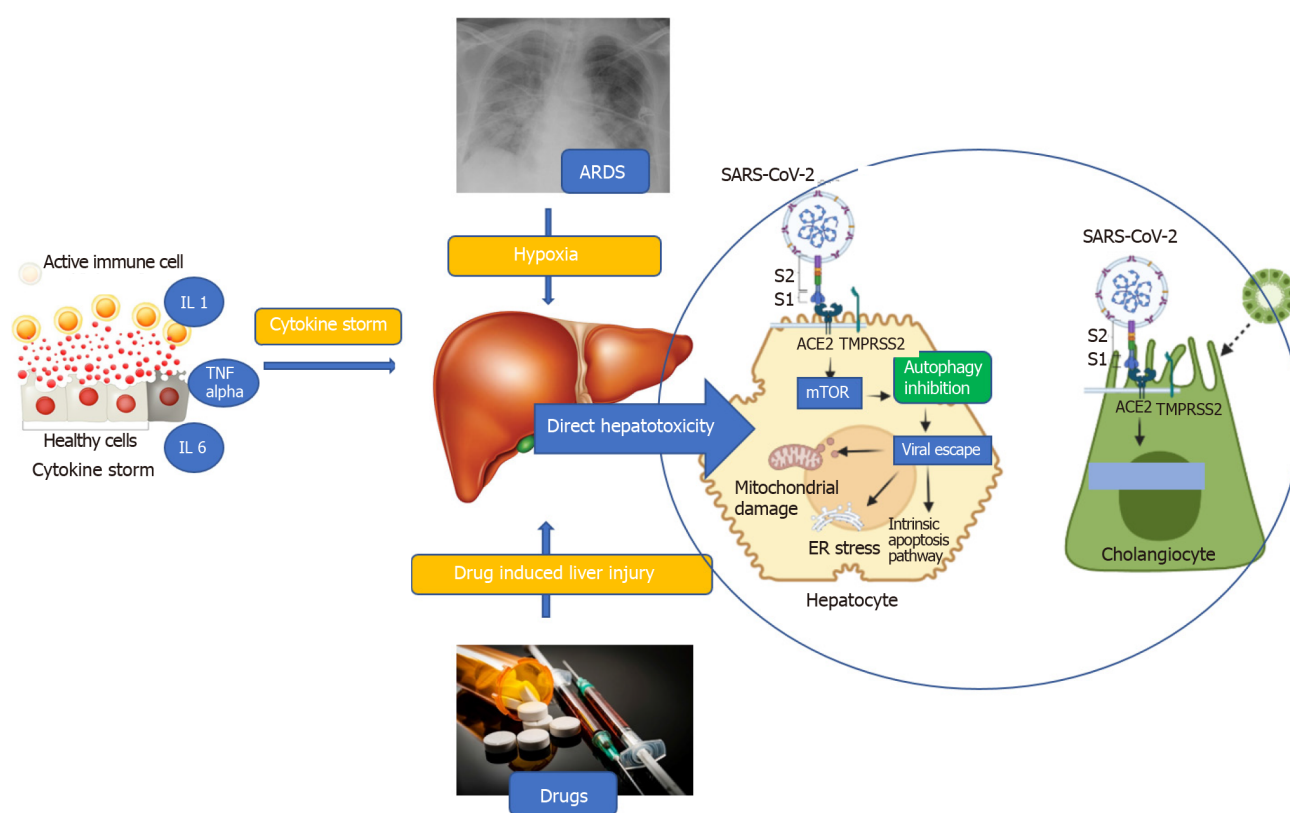
Autoimmune hepatitis

Autoimmune hepatitis (AIH) patients are a vulnerable group due to underlying liver disease, use of immunomodulators, and associated systemic diseases. Different studies have tried to identify the risk factors of severity and outcomes in these patients including those on immunosuppressants. Di Giorgio *et al*[46] demonstrated that the predictors of outcomes were same in AIH as in the general population, including increasing age and presence of comorbidities. Cirrhosis was the most important predictor of mortality among patients with underlying autoimmune liver diseases (OR: 17.46) in a study[47,48]. Among cirrhotics, outcomes worsened with progressive underlying liver dysfunction measured by increasing Child-Pugh-Turcotte (CTP) scores with an OR of mortality increasing from 42 to 69 in Child-Pugh classes B and C, respectively[49] (Table 5).

The effect of immunosuppressive treatment on outcomes in COVID-19 patients has shown some diverging results. A study by Efe *et al*[50] in 254 AIH patients showed that systemic glucocorticoids (aOR: 4.73), thiopurines (aOR: 4.78), mycophenolate mofetil (MMF) (aOR: 3.56), and tacrolimus (aOR: 4.09) were associated with a more severe COVID-19 course. The study showed that outcomes were worse in patients on steroids at a prednisolone equivalent dose of > 5 mg/d. Similarly, another study showed that baseline treatment with steroids, thiopurines, MMF, and tacrolimus were associated with a severe disease course[51]. Therefore, patients with AIH having cirrhosis and stage of cirrhosis reflected

Table 5 Studies evaluating outcomes and predictors in autoimmune hepatitis with coronavirus disease 2019

Ref.	Study	Patients	Results	Predictors of outcomes
Efe *et al* [47]	Multicentre retrospective study from 34 centres in Europe and the Americas	110 AIH patients	Acute liver injury: 37.1%	Predictor of severe COVID-19: cirrhosis (OR: 17.46); Immunosuppression not associated with severe COVID-19 (OR: 0.26)
Di Giorgio *et al*[46]	Phone based survey in tertiary centre	adult AIH patients: AIH (n = 97, 96%); PSC/AIH overlap (n = 2, 2%); PBC/AIH (n = 2, 2%); 4 patients had confirmed COVID	Severe COVID: 1; Death: 1	No difference in risk factors of mortality
Marjot *et al*[49]	Retrospective data from three international registries	70 AIH cases among 932 patients with CLD with COVID-19	No differences between AIH and non-AIH related CLD in Hospitalization (76% *vs* 85%); ICU admission (29% *vs* 23%); Death (23% *vs* 20%)	Factors predicting mortality in AIH: Age (OR: 2.16/10 yr); Child-Pugh class [B (OR: 42.48) and C (OR: 69.30)] cirrhosis
Efe *et al* [50]	Retrospective data from 15 countries	254 AIH patients	Hospitalization: 94 (37%); Death: 18 (7.1%)	Factors associated with COVID-19 severity: Systemic glucocorticoids (aOR: 4.73); Thiopurines (aOR: 4.78); Mycophenolate mofetil (aOR: 3.56); Tacrolimus (aOR: 4.09)

AIH: Autoimmune hepatitis; COVID: Coronavirus disease; CLD: Chronic liver disease; ICU: Intensive care unit; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

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Figure 1 Pathophysiology of liver involvement in coronavirus disease 2019.

by CTP score are predictors of adverse outcomes. The use of immunosuppressive drugs is also associated with worse outcomes among COVID-19 patients with AIH.

Severity of CLD: One of the most important determinants of clinical outcomes is the presence and severity of underlying cirrhosis as shown in various studies. There was an increasing risk of mortality with increasing CTP score ranging from additional +2% in Child-Pugh A to +20% in Child-Pugh B and +38% in Child-Pugh C. Similarly, another study showed that Child-Pugh score was associated with mortality[52]. CTP score of more than 9 was associated with a high mortality (HR: 19) in another study
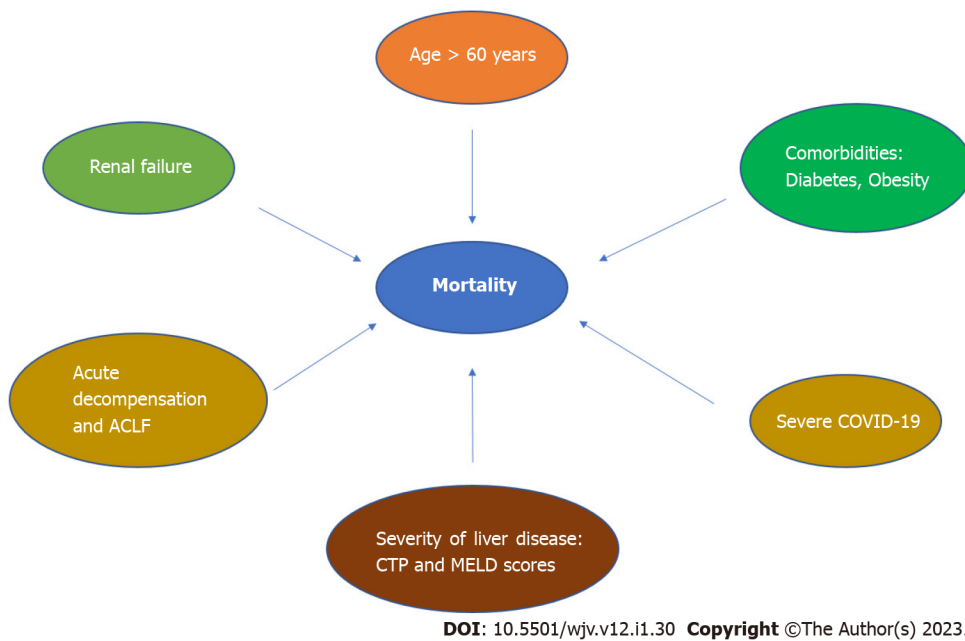
Figure 2 Predictors of mortality in pre-existing chronic liver disease with coronavirus disease 2019. ACLF: Acute-on-chronic liver failure; CTP: Child-Turcotte-Pugh score; COVID-19: Coronavirus disease 2019; MELD: Model for end stage liver disease.

[37]. Mortality in cirrhotics increased with worsening chronic liver failure consortium score (HR: 1.42), which is an indicator of hepatic and extrahepatic organ failures[53]. Model for end stage liver disease (MELD) score more than 25 is associated with a two-fold increase in mortality as demonstrated by univariate analysis in a study from India[24]. Similarly, a study from Italy showed that MELD score more than 15 was associated with a higher mortality (HR: 5.18) at 30 d[53]. Various factors associated with adverse outcomes in cirrhosis are summarized in Table 1. Therefore, the currently available evidence suggests that increasing severity of underlying CLD is associated with poor outcomes including mortality.

Degree of liver fibrosis: A study from China showed that higher FIB-4 score, which is a marker of liver fibrosis, was associated with a more severe COVID-19 disease[36] with greater requirement of high flow oxygen, prolonged hospitalization, and even death[54]. They postulated that FIB-4 score could be a prognostic marker of disease outcomes but more data is required to increase external validity. Similar findings were seen in a meta-analysis which showed that elevated FIB-4 score was associated with severe COVID-19 and mortality[54]. Hence, the degree of liver fibrosis is an important determinant of disease outcome with higher degree of fibrosis being negatively associated with outcomes[55].

Comorbidities: Another predictor of mortality was the presence of comorbidities, with the most common being diabetes, obesity, dyslipidemia, and hypertension[16-18,37]. This may be due to a more severe COVID-19 infection seen in this subgroup of patients irrespective of the presence of cirrhosis. A prospective study showed that a BMI of more than 30 was associated with mortality[17]. Another study showed that diabetes and hypertension were predictors of mortality[18]. A study from Asia showed that diabetes was associated with severe liver injury without cirrhosis (OR: 2.1), as was obesity in cirrhotics (OR: 8.1)[37]. Therefore, the presence of comorbidities increases the severity of liver disease and has unfavorable outcomes.

Severity of COVID-19: Some studies showed that respiratory failure was the main cause of mortality among cirrhotic COVID-19 patients. Outcomes were poor for patients with higher CURB-65 (confusion, uremia, respiratory rate, blood pressure, age > 65) scores, substantiating the fact that respiratory failure was associated with mortality[44]. In this study, they observed that CURB-65 score was associated with a 5-fold increased risk of mortality[52]. Severe COVID-19 with respiratory failure was a significant predictor of mortality (HR: 2.5) in patients with chronic liver disease in another study[24]. Henceforth, more severe COVID-19 is associated with an increased risk of liver injury and mortality.

Biomarkers: A recent study evaluated the role of inflammatory biomarkers in risk-stratifying the patients with regard to liver injury and mortality in 221 COVID-19 patients[56]. They included CRP, IL6, D-dimer, and blood lymphocyte counts as inflammatory biomarkers, which were all significantly elevated in the patients who subsequently expired as compared to survivors. They found that patients who showed rising aspartate transaminase and alkaline phosphatase over time, as markers of liver

injury, had a higher mortality. These correlations attenuated with age. Thus, inflammatory biomarkers may serve as predictors of poor outcomes, but more studies are required for identification of biomarkers and their validation.

Miscellaneous factors: Some other factors affecting the severity and outcomes of COVID-19 have also been seen in some studies. As discussed previously, obesity and physical inactivity have been associated with worse outcomes. Recently, it has been shown that obesity, physical inactivity, and diet rich in simple sugars predisposes to chronic low-grade inflammation in the mucosal barrier along with microbial dysbiosis. This state of chronic inflammation has been shown to be associated with worse clinical outcomes in COVID-19 patients[57]. Similarly, obese individuals with excessive visceral fat have excessive proinflammatory adipokines that have been postulated to be associated with poor outcomes [57]. Extrapolating the role of inflammation, patients with CLD have low level endotoxemia with increased gut permeability which may be associated with unfavorable outcomes; however, concrete evidence for the same is lacking[58]. A summary of risk factors associated with poor outcomes is shown in Table 6.

PREDICTORS RELATED TO OUTCOMES OF UNDERLYING CHRONIC LIVER DISEASE

Acute decompensation and acute-on-chronic liver failure
In patients with CLD, acute decompensation and acute-on-chronic liver failure (ACLF) usually develop due to a precipitating factor, with infections being the most common such factor. COVID-19 may act as a trigger for such decompensation. Marjot *et al*[22] observed in their study that the major predictor of decompensation was Child-Pugh class, with a rate of decompensation of 30%, 56%, and 64% observed in Child-Pugh A, B, and C patients, respectively. Hepatic decompensation at baseline was associated with an increased mortality (HR: 2.91) in another study[18]. Acute decompensation developed in 9% and ACLF in 11.6% among 43 cirrhotic patients, and CTP score was the major predictor of mortality, with a CTP score of 9 or more at presentation associated with high mortality (HR, 19.2)[37]. Another study showed that acute decompensation developed in 62.9% and ACLF in 29% with a mortality as high as 72% among ACLF patients, with major predictors of mortality being MELD score, leukocytosis, elevated creatinine, and COVID-19 severity on multivariate analysis[24]. The mortality in grades 1, 2, and 3 ACLF patients was 56.3%, 50%, and 93.3%, respectively (P = 0.001) in the same study. In a prospective study of 96 cirrhotic patients, 61.4% developed acute decompensation and ACLF in 55% according to CLIF-C criteria. The major predictors of mortality were CLIF-C organ failure score (AUROC: 0.85) and MELD Na score (AUROC: 0.70)[17].

These observations suggest that SARS-CoV-2 infection may be a triggering factor for decompensation and subsequent ACLF in cirrhotic patients by triggering a pro-inflammatory cascade as discussed earlier. Possible factors that can be postulated could be a proinflammatory milieu, multi-organ dysfunction due to severe COVID-19, direct hepatotoxicity to a compromised liver, or sepsis. In summary, COVID-19 patients with underlying CLD are more prone to develop acute decompensation and may progress to ACLF. The major predictors of these outcomes are the baseline severity of liver disease reflected by CTP and MELD score, and the severity of hepatic and extra-hepatic organ failure as indicated by CLIF-C scores.

Upper gastrointestinal bleeding
The data on the rate and risk factors of variceal bleed in patients with COVID-19 positive patients with underlying CLD is scarce. Upper gastrointestinal (UGI) bleeding developed in 24/1342 (1.8%) of all patients admitted with COVID-19[24]. Most of bleeding episodes (88%) were variceal bleeding in patients with cirrhosis with no rebleeding or death at 5 d with medical management alone[24]. The same group also observed that the initial control of UGI bleeding was achieved in all patients with no one requiring an emergency endoscopy. Thus, emphasizing the utility of conservative management of variceal bleeding with endoscopic therapy is only needed on a case-to-case basis[25].

Another study from Hong Kong showed that although peptic ulcer bleeding was the most common cause of UGI bleeding both before (66.0%) and during (66.1%) the COVID-19 pandemic, there was a significant increase in the proportion of patients with UGI bleeding with variceal bleeding after COVID-19 (5.3% *vs* 10.5%, P < 0.01)[51]. Patients had significantly lower hemoglobin (7.5 *vs* baseline 8.3 g/dL) and higher requirement for blood transfusion (64.5% *vs* baseline 50.4%) but had similar rates of all-cause mortality (6.9% *vs* 7.1%) and rebleeding (6.7% *vs* 5.1%)[59]. There was no significant difference in the timing of endoscopy after admission or the percentage of patients requiring endoscopic hemostasis (77.3% *vs* 76.3%) before and during the COVID-19 pandemic[59]. Thus, patients with variceal bleeding in the COVID-19 pandemic have similar management principles as the pre-COVID-19 era.

HCC
The major impact of the COVID-19 pandemic on patients with HCC was multifactorial. A decline of

Table 6 Risk factors associated with adverse outcomes in coronavirus disease 2019 affected patients with chronic liver disease

Demographics	Etiology	Clinical parameters	Underlying disease severity	Biochemical parameters
Age > 60 yr; Hispanic and black ethnicity; Diabetes mellitus; Hypertension; Obesity	Alcohol; HBeAg positivity among CHB; AIH on immunosuppressants	Respiratory failure: CURB-65 score; Decompensation at baseline; ACLF at presentation	CTP score; MELD score; FIB-4 index	Elevated creatinine; Leucocytosis; AST levels; ALT levels; CRP

ACLF: Acute-on-chronic liver failure; AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; CTP: Child-Turcotte-Pugh score; CURB-65: Confusion, Uremia, Respiratory rate, BP, age > 65 years, FIB-4: Fibrosis 4 score; MELD: Model for end stage liver disease.

26.7% in new HCC cases was reported during the pandemic compared to the pre-pandemic era[60]. Advanced BCLC stage and higher tumor burden at diagnosis were due to resource limitation and lack of physical appointments, and were associated with a higher incidence of spontaneous tumoral hemorrhage[61]. Delayed treatment initiation longer than 1 month (21.5% *vs* 9.5%; *P* < 0.001) due to re-allocation of services for the pandemic was reported[62]. Muñoz-Martínez *et al*[63] reported an increase in mortality rate proportional to advanced BCLC stage. Thus, the impact of COVID-19 on patients with HCC is predominantly due to delayed diagnosis, delayed presentation, delay in initiating treatment, and availability of imaging and locoregional or transplant facilities.

COVID-19 waves and impact on liver disease

Some studies identified the impact of different waves of the pandemic on liver disease. The waves of COVID-19 occurred due to mutations and spread of newer variants of the virus that evaded the immune response. The second wave was predominantly caused by delta variant[64]. Nawghare *et al*[65] showed that the second wave had more number of acute decompensations and the factors predicting outcomes were renal dysfunction and elevated D-dimer. Elhence *et al*[24] compared outcomes in the first wave to those in the second wave and reported that although the disease severity was more during the second wave but the mortality rate and duration of hospital stay were similar with no significant differences.

CONCLUSION

COVID-19 has a major impact on patients with pre-existing CLD in the form of severe COVID infections and worsening of underlying hepatic disease. The predictors of poor outcomes of COVID-19 patients with underlying CLD are multiple and have been different in numerous studies across the globe, with the most important predictor being presence of cirrhosis with outcomes progressively deteriorating with increasing severity of underlying liver dysfunction estimated by CTP and MELD scores. These are the subgroups of patients who are more prone to risk of decompensation, further decompensation, and ACLF.

The predictors may be related to demographic factors, with increasing age and black and Hispanic ethnicity being associated with poor outcomes. Another major predictor of the severity of COVID-19 is cytokine storm, which may even lead to multiorgan failure, with the liver being one of the organs involved. Other predictors include the presence of comorbidities, whose prevalence is estimated to be around 30%-50% in various studies, and these have been associated with poor outcomes even in the absence of underlying liver disease. Major comorbidities found in studies that are negatively associated with outcomes include diabetes mellitus, hypertension, and obesity. The COVID-19 pandemic also adversely affected routine services for patients with hepatitis B, hepatitis C, and HCC, which will have long-term impacts in the form of increased disease burden, delayed implementation of eradication programs, and poor outcomes in the times yet to come.

FOOTNOTES

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