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COVID-19 in 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 infection. 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.

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 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, 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 an abnormal alanine aminotransferase or bilirubin levels, out of which 77% of cases showed elevation to levels less than 5 times the upper limit of normal [4]. The prevalence of underlying CLD in COVID-19 infected 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 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 ALD and NAFLD affected patients increased significantly during the pandemic while the rate of mortality among 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 infection (pooled OR: 2.44) and death (pooled OR: 2.35) as compared to COVID-19 patients without CLD [10]. Hence, COVID-19 do affect patients with CLD and in some cases with adverse outcomes.

PATHOPHYSIOLOGY OF LIVER INVOLVEMENT IN COVID-19

The involvement of liver 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 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 CoV2 causes activation of mTOR pathway which inhibits autophagy of the viral particles. Thus, the viral particles evade immune system and increase in number exerting direct hepatotoxicity *via* mitochondrial dysfunction, ER stress and activation of 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 IL-1, IL-6, TNF alfa and elevated levels of ferritin and CRP [15]. These proinflammatory cytokines result in cholestatic type of 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 alpha and IL-1 also activate and recruit macrophages to 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 reflecting in biochemical alteration 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 infections in patients with CLD as summarized in Figure 2 and Table 5. A summary of evidence available and the possible risk factors has been enumerated as 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 adjusted odds ratio (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 [8]. 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 [19]. 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 infected patients. In 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 [20]. A study found higher rate of mortality among alcohol-related liver disease with aHR of 1.79[21]. Kim *et al* [18] showed aHR of 2.42 of mortality among alcohol-related liver disease. There was 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. [22] However, another study did not find alcohol as a poor outcome variable on multivariate analysis of retrospective data [23,24]. A recent study showed that the mortality among ALD 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 in patients with COVID-19 infection and CLD as summarized in 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. COVID-19 pandemic showed a bidirectional relationship with NAFLD. Lock down during 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 [25-28] (Table 2). Studies have demonstrated that patients with features of metabolic syndrome including higher body mass index (BMI), waist circumference and presence of diabetes and hypertension had adverse effects on outcomes [27,28].

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[29,30]. Different studies have estimated different prevalence of comorbidities in NAFLD. The prevalence of obesity, diabetes mellitus, and hypertension were 47%, 27%, and 31%, respectively in NAFLD patients in a study, in which 27% patients required non-invasive mechanical ventilation, 44% required ICU admission and 27% patients were expired [27]. Another study showed 69% of patients had hypertension, 43% had diabetes, 47% had dyslipidemia, 85% patients were overweight, 52% were obese; and out of total 342 patients, > 50% required ICU admission and 19% patients were expired [31]. Thus, the presence of comorbidities is associated with poor outcomes in patients with NAFLD and COVID-19 infection.

Advanced fibrosis in patients with NAFLD was associated with more severe COVID-19 infection and adverse outcomes with almost two-fold increased risk of severity in patients with FIB-4 score of more than 2.67[32]. 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 [33]. Severe illness was significantly higher in those with advanced fibrosis [NAFLD fibrosis score (NFS) >-1.5] compared to patients with non-advanced fibrosis with NFS <-1.5 (28.9% vs. 2.1%, $P < 0.001$) [28]. 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 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+) chronic hepatitis B (CHB) cases as shown in Table 3[34]. Another study showed that although the mortality rate was higher among patients with hepatitis B infection, it was not statistically significant after adjusting for other factors [35]. The study had shown that patients with COVID-19 had a lower positivity rate of chronic hepatitis B [36]. One of the postulated reasons for this finding is that patients with chronic hepatitis B infection 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[36]. The major predictor of poor outcomes was positivity of HBeAg suggestive of active viral replication and ongoing liver injury in addition to liver injury inflicted by SARS-CoV-2[34]. Re activation of HBV with anti-IL6 therapy (tocilizumab) was found to be 3.3% in a systematic review [37]. In short, patients with HBeAg positive chronic hepatitis B are more likely to have a poor outcome in terms of hospitalization requirement and mortality and some specific treatment of COVID-19 will lead to reactivation of CHB like anti IL 6 (tocilizumab).

Hepatitis C

Hepatitis C predominantly causes a chronic indolent infection. Various management aspects of hepatitis C have been impacted during 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* [38] 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, we require more data to draw a conclusion regrading effect of HCV infection on COVID-19 infection, excluding the severity of liver disease.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) subgroup of patients is 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 immunosuppressives. Giorgio *et al* [39] demonstrated that the predictors of outcomes were same in AIH as in 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 [40]. Among cirrhotics, outcomes worsened with progressive underlying liver dysfunction measured by increasing Child-Pugh-Turcotte (CTP) scores with OR of mortality increasing from 42 to 69 in Child class B and C, respectively [41] (Table 4).

The effect of immunosuppressive treatment on outcomes in COVID-19 infected patients have shown some diverging results. A study by Efe *et al* [42] 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 more severe COVID-19 course. The study showed that outcomes were worse in patients on steroids dose of prednisolone equivalent of > 5 mg/d. Similarly, another study showed that baseline treatment with steroids, thiopurines, MMF and tacrolimus were associated with a severe disease course [43]. So, patients with AIH having cirrhosis and stage of cirrhosis reflected by CTP score are predictors of adverse outcomes. The use of immunosuppressive drugs is also associated with worse outcomes among COVID-19 infected 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 predicting mortality [44]. CTP score of more than 9 was associated with high mortality (HR: 19) in another study [33]. Mortality in

cirrhotic increased with worsening CLIF C (Chronic liver failure consortium) scores (HR: 1.42) which is the indicator of hepatic and extrahepatic organ failures [45]. MELD more than 25 is associated with two-fold increase in mortality as demonstrated by univariate analysis from a study from India [23]. Similarly, a study from Italy showed that MELD more than 15 had higher mortality (HR: of 5.18) at 30 days [45]. Various factors associated with adverse outcomes in cirrhosis are summarized in Table 5. 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 with greater requirement of high flow oxygen, prolonged hospitalization and even death [46]. They postulated that FIB 4 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 elevated FIB 4 was associated with severe COVID-19 and mortality [47]. Hence, the degree of liver fibrosis is an important determinant of disease outcome with higher degree of fibrosis being negatively associated with outcomes.

Comorbidities

Another predictor of mortality was the presence of comorbidities, the most common being diabetes, obesity, dyslipidemia and hypertension [16-18,33]. This may be due to a more severe COVID-19 infection seen in this subgroup of patients irrespective of presence of cirrhosis. A prospective study showed that a BMI 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) and as obesity in cirrhotic (OR: 8.1) [33]. Therefore, presence of comorbidities increases the severity of liver disease and has unfavorable outcomes.

Severity of COVID-19 infection

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 was associated with five times increased risk of mortality [44]. Severe COVID-19 with respiratory failure was a significant predictor of mortality (HR: 2.5) in patients with chronic liver disease in another study [23]. Henceforth, more severe COVID-19 infection is associated with increased risk of liver injury and mortality.

Biomarkers

A recent study evaluated the role of inflammatory biomarkers in risk stratifying the patients with regards to liver injury and mortality in 221 COVID-19 patients [48]. 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 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 at 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 [49].

Similarly in obese individuals with excessive visceral fat have excessive proinflammatory adipokines that have been postulated to be associated with poor outcomes [49]. 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 [50]. 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* [21] observed in their study that the major predictor of decompensation was Child Pugh class with the rate of decompensation of 30%, 56% and 64% in Child Pugh A, B and C, respectively. Hepatic decompensation at baseline was associated with 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 CTP score of 9 or more at presentation associated with high mortality (HR, 19.2) [33]. 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 [23]. The mortality in grades 1, 2, and 3 ACLF were 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 infection with SARS CoV2 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, patients with underlying CLD with COVID-19 infection 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 bleed

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) bleed developed in 24/1342 (1.8%) of all patients admitted with COVID-19[23]. Most of bleeding episodes (88%) were variceal bleeds in patients with cirrhosis with no rebleed or death at 5 d with medical management alone[23]. 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 bleed with endoscopic therapy only needed in case-to-case basis[24].

Another study from Hong Kong showed that although peptic ulcer bleeding was the most common cause of UGIB both before (66.0%) and after (66.1%) COVID-19; there was a significant increase in the proportion of patients with UGIB 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 a 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%)[51]. 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 after COVID-19[51]. Thus, the patients with variceal bleed in COVID-19 have similar management principles as pre COVID-19 era.

Hepatocellular carcinoma

The major impact of the COVID-19 pandemic on patients with Hepatocellular carcinoma (HCC) were multifactorial. A decline of 26.7% in new HCC cases was reported during the pandemic compared to the pre-pandemic [52]. Advanced BCLC stage and higher tumor burden at diagnosis was due to resource limitation and lack of physical appointments, and with a higher incidence of spontaneous tumoral hemorrhage [53]. Delayed treatment initiation longer than 1 month (21.5% *vs* 9.5%; $P < 0.001$) due to re allocation of services for pandemic was reported [54]. Muñoz-Martínez *et al* [55] 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. Second wave was predominantly caused by delta variant [56]. Nawghare *et al* [57] showed that second wave had more number of acute decompensations and the factors predicting outcomes were renal dysfunction and elevated d-dimer. Elhence *et al* [23] compared outcomes in first wave to 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 was similar with no significant differences.

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CONCLUSION

COVID-19 had a major impact on patients with pre-existing chronic liver disease in the form of severe COVID infections and worsening of underlying hepatic disease. The predictors of poor outcomes of patients infected with COVID-19 with underlying CLD are multiple and have been different in numerous studies across the globe. 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 is the severity of COVID-19 infection is cytokine storm and may even lead to multiorgan failure with liver being one of the organs involved. Other predictors include the presence of comorbidities which 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. COVID-19 pandemic also adversely affected routine services for patients with hepatitis B, 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.

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