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MINIREVIEWS

Hepatic manifestations of coronavirus disease 2019 infection: Clinical and laboratory perspective

Farina M Hanif, Zain Majid, Shoaib Ahmed, Nasir H Luck, Muhammed Mubarak

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Farina M Hanif, Zain Majid, Shoaib Ahmed, Nasir H Luck, Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi 74200, Sindh, Pakistan

Muhammed Mubarak, Department of Pathology, Sindh Institute of Urology and Transplantation, Karachi 74200, Sindh, Pakistan

Corresponding author: Muhammed Mubarak, FCPS, Professor, Department of Pathology, Sindh Institute of Urology and Transplantation, Dewan Farooque Medical Complex, Chand Bibi Road, Karachi 74200, Sindh, Pakistan. drmubaraksiut@yahoo.com

Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become a global challenge of unprecedented nature since December 2019. Although most patients with COVID-19 exhibit mild clinical manifestations and upper respiratory tract involvement, in approximately 5%-10% of patients, the disease is severe and involves multiple organs, leading to multi-organ dysfunction and failure. The liver and gastrointestinal tract are also frequently involved in COVID-19. In the context of liver involvement in patients with COVID-19, many key aspects need to be addressed in both native and transplanted organs. This review focuses on the clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 with no prior liver disease, patients with pre-existing liver diseases and liver transplant recipients. A brief overview of the history of COVID-19 and etiopathogenesis of the liver injury will also be described as a prelude to better understanding the above aspects.

Key Words: COVID-19; Liver injury; SARS-CoV-2; Clinical manifestations; Liver function tests; Cirrhosis

Core Tip: The novel coronavirus disease 2019 (COVID-19) has affected the entire globe with devastating consequences on the health and economy of all countries. Primarily a disease of the upper respiratory tract, it may involve multiple organs in severe cases, which are fortunately rare. The liver and gastrointestinal tract are also frequently involved in COVID-19. Involvement of the liver is multifaceted and may be asymptomatic or may lead to acute liver failure. This review article focused on various clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19. This will help in creating awareness among the general physicians, gastroenterologists, hepatologists and infectious disease consultants regarding this important complication.

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INTRODUCTION

During the past 20 years, three major outbreaks by coronaviruses have occurred. These include severe acute respiratory distress syndrome (SARS), Middle East respiratory syndrome and coronavirus disease 2019 (COVID-19)[1]. Among these, COVID-19, caused by SARS coronavirus 2 (SARS-CoV-2) was reported for the first time in Wuhan, China in December 2019, which later spread in pandemic form throughout the world[2]. In patients with COVID-19 infection, upper and lower respiratory tract involvement, *e.g.*, common cold, bronchiolitis, and pneumonia, are the dominant manifestations. Primary clinical symptoms of COVID-19 patients are fever, dry cough, fatigue and myalgia. However, in many cases, SARS-CoV-2 affects other organs such as the heart, gastrointestinal tract, liver and kidneys with organ-specific symptoms (Table 1). Many patients with severe disease may die from multiorgan failure. In this review, we described liver involvement in COVID-19, which can be studied from many aspects. The focus of this review, however, was on clinical and laboratory manifestations of liver disease in COVID-19 patients, in the native healthy liver, native diseased liver and in the transplanted liver.

For this narrative review, we searched the electronic databases of Web of Science, Scopus, Embase, PubMed and Google Scholar. The search terms used were: COVID-19, combined with the following terms; acute liver injury (ALI), acute-on-chronic liver failure (ACLF), chronic liver disease (CLD), cirrhosis of liver, hepatitis, deranged liver function tests (LFTs), liver failure, SARS-CoV-2, angiotensin-converting enzyme 2, hepatocellular carcinoma (HCC), liver transplantation, autoimmune liver disease, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV). The search was carried out within the time frame of January 1, 2020 to May 2022. We found 4758 records and used 85 (mainly original articles or guidelines) for extracting information to be presented in this review.

PATHOGENESIS OF LIVER INJURY

COVID-19 causes liver damage that is mostly hepatocellular in nature as demonstrated by increased transaminase levels. It is often asymptomatic and manifests with derangement in liver functions on laboratory testing. COVID-19-induced liver injury is due to a multitude of reasons, which possibly differ from case to case according to various clinical scenarios[1]. Various mechanisms have been proposed including the direct cytopathic effect of the virus itself, immune dysfunction, systemic inflammatory response syndrome, cytokine storm, sepsis, vascular thrombosis, hypoxia and ischemia-reperfusion injury, as shown in Figure 1. Additionally, drug-induced liver injury has also been implicated as a possible secondary mechanism of liver impairment in patients with COVID-19[3].

The entry of SARS-CoV-2 into human host cells with resultant injury is primarily mediated *via* a metalloproteinase enzyme, called angiotensin-converting enzyme 2 (ACE2) receptor, located in various tissues, including the lungs, liver and gastrointestinal tract[4]. The previous RNA-seq data in the Human Protein Atlas database (www.proteinatlas.org) has demonstrated relatively low expression of ACE2 in the liver that, in all respects, could be considered a potential target. In particular, ACE2 expression is limited to the cholangiocytes of normal hepatic tissue and, to a minimal extent, in the hepatocytes[4]. A low throughput study of ACE2 protein expression in selected cell types of multiple organs showed a low frequency of ACE2 occurrence in cholangiocytes but not in hepatocytes, Kupffer cells and endothelial cells[5]. However, the antibody detection might be subjected to nonspecificity and sensitivity issues. Neither data sources could provide a definitive conclusion of cell type specific expression of the *ACE2* gene in the liver.

Table 1 Major clinical manifestations and laboratory abnormalities in coronavirus disease 2019

Signs/symptoms
Systemic and respiratory system manifestations
Fever, cough, malaise, dyspnea, fatigue, sputum
Cardiovascular system manifestations
Heart failure, arrhythmia, shock, tight chest, acute myocarditis
Gastrointestinal manifestations
Anorexia, diarrhea, loss of appetite, loss of taste, gastrointestinal bleeding, nausea and vomiting, abdominal pain, mild pancreatitis, mild colitis
Hepatobiliary manifestations
Abnormal liver function tests, jaundice, hypoalbuminemia, new-onset decompensation, acute-on-chronic liver failure, cholangiopathy, acalculous cholecystitis
Kidney manifestations
Acute kidney injury, proteinuria, hematuria
Neurological manifestations
Dizziness, headache, skeletal muscle injury, acute cerebrovascular disease, seizures

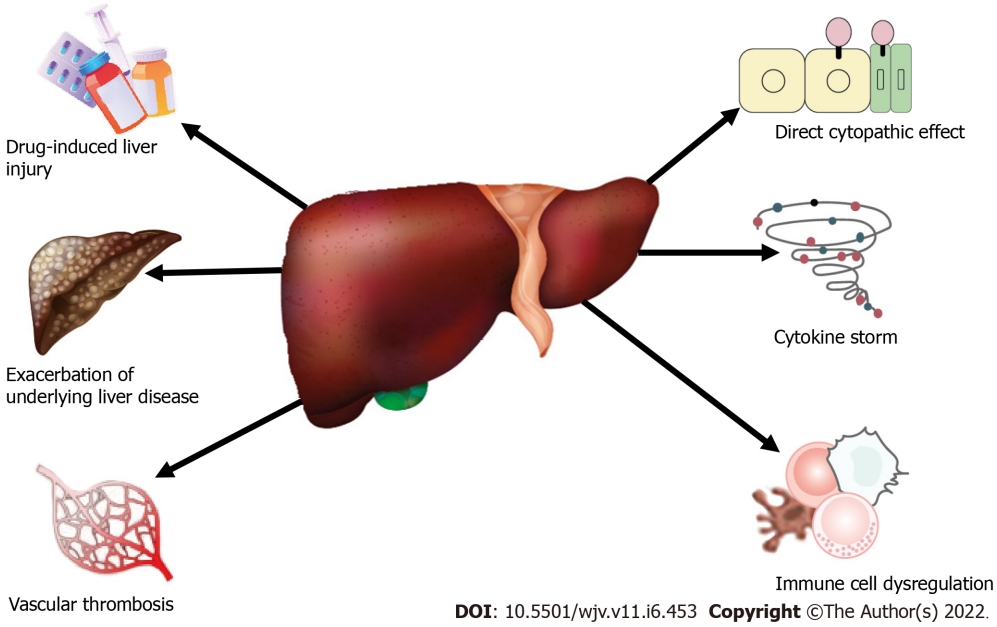

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Figure 1 Schematic illustration of possible mechanisms of liver injury in coronavirus disease 2019. Other mechanisms (not shown) may be involved.

Recent advances of single cell technologies allow unbiased profiling of all cell types in given tissues at an unparalleled scale. Chai *et al*[5] performed an unbiased evaluation of cell type specific expression of ACE2 in healthy hepatic tissues employing scRNA-seq data of two independent cohorts. This study revealed significant enrichment of ACE2 expression in cholangiocyte clusters (59.7% of cells) compared to hepatocytes (2.6% of cells) suggesting that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes, and the liver abnormalities of COVID-19 patients may not be due to a direct hepatocyte damage but, probably, to cholangiocyte dysfunction. It is well established that cholangiocytes play an essential role in liver regeneration and immune response; hence, their dysfunction may contribute to liver damage (Figure 2). Overexpression of the ACE2 receptor on hepatocytes has been observed in patients with liver fibrosis/cirrhosis and in cases of hypoxia. This might explain the high probability of liver injury in these populations[6]. Since liver biopsies of COVID-19 patients show focal hepatic necrosis without significant surrounding inflammatory infiltration, this points toward direct viral injury. However, considering high receptor levels in cholangiocytes rather than hepatocytes and as most of the COVID-19 patients manifest with elevated transaminases, the possibility of direct viral attack is less likely[7]. Other possible pathways of virus entry in hepatocytes have also been suggested to play a

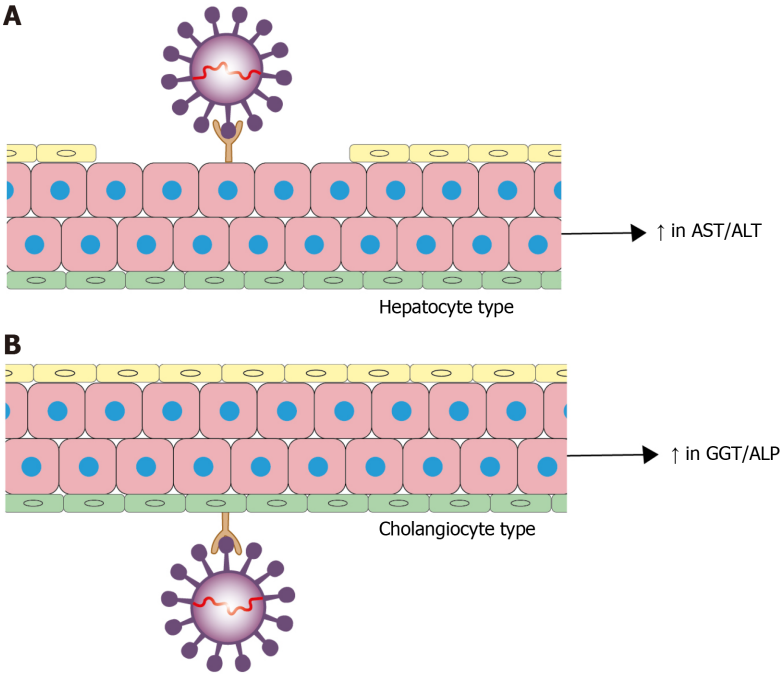

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Figure 2 Two principal types of severe acute respiratory syndrome coronavirus 2 infection of the liver parenchyma. A: Direct severe acute respiratory syndrome coronavirus 2 infection targeted to hepatocytes is designated as hepatocellular type; B: Direct viral entry into biliary epithelial cells is known as the cholangiocyte type. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-Glutamyltransferase; ALP: Alkaline phosphatase.

role in liver involvement in COVID-19 (Figure 3).

Another mechanism potentially associated with hepatic injury is the cytokine storm generated by the coronavirus infection. Excess inflammatory burden and potential immune-mediated damage lead to increased vascular permeability, multiorgan failure and death[1,3]. Similarly, studies have documented a correlation between high levels of interleukins, a group of cytokines, and severity of COVID-19[8].

In addition, COVID-19-related vascular thrombotic complications with consequent hypoxia and shock can lead to liver injury mediated by the ischemia-reperfusion injury mechanism. Ischemia-reperfusion injury involves a biphasic process of ischemia-induced cell injury and reperfusion-induced inflammatory response. Thus, an activated proinflammatory immune cascade due to the aforementioned processes can be a possible mechanism of liver injury in COVID-19 patients[3,6,9].

Finally, studies have also reported variable degrees of hepatotoxicity with medications used in the treatment of COVID-19[10,11]. Hundt *et al*[12] reported the use of medications needed to treat COVID-19 virus (remdesivir, hydroxychloroquine, lopinavir/ritonavir and tocilizumab) as a significant predictor of raised transaminases [> 5 × upper limit of normal (ULN)] during hospitalization for COVID-19. Cai *et al*[13] described lopinavir/ritonavir as a risk factor for liver injury in COVID-19 patients [odds ratio (OR): 4.44; 95% confidence interval: 1.50-13.17]. However, these authors did not report significant risk with the use of antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, herbal medications and interferon.

Muhović *et al*[14] reported severe drug-induced liver injury with tocilizumab in patients previously treated with chloroquine and lopinavir/ritonavir. As interleukin-6 is known to be associated with liver regeneration and metabolism, it is postulated that inhibition of interleukin-6 by tocilizumab may be the potential cause of liver enzyme derangement[11,15]. Hepatotoxicity can be expected in COVID-19 patients as the liver metabolizes nearly all medications used in COVID-19. Several mechanisms, like upregulation of ACE2 receptors and downregulation of cytochrome p450, sensitize the hepatocytes to the SARS-CoV-2 virus or therapeutic agents. While on the other hand, the pharmacological features of medications may increase susceptibility to liver injury[11].

In summary, the progression of COVID-19 from a mild to severe form is associated with a dysregulated immune response, which leads to uncontrolled viral replication and cellular damage, thus further exacerbating the immune-mediated damage, which includes liver damage[16].

CLINICAL MANIFESTATIONS

The SARS-CoV-2 genomic sequence has shown similarity with the SARS coronavirus and Middle East respiratory syndrome coronavirus. Like these viruses, respiratory symptoms along with gastrointestinal

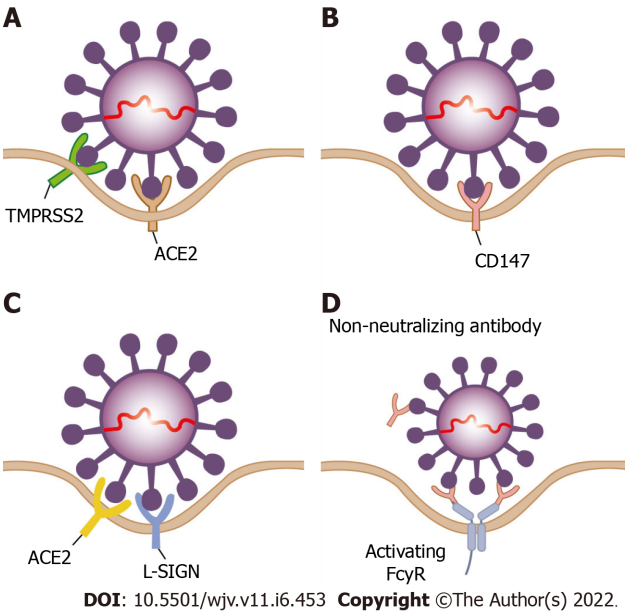

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Figure 3 Possible pathways of virus entry in hepatocytes. A: The angiotensin converting enzyme-2 in conjunction with transmembrane protease serine protease 2 is considered the predominant receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells; B: CD147 is another possible receptor for SARS-CoV-2 entry into hepatocytes. CD147 is highly expressed in tumor tissues, inflamed tissues and pathogen-infected cells including hepatocytes; C: L-SIGN (CD209L) may serve as a liver-specific cell receptor for SARS-CoV-2 infection of hepatocytes; D: Antibody-dependent enhancement may also facilitate SARS-CoV-2 infection of hepatocytes. During antibody-dependent enhancement of infection, suboptimal non-neutralizing antibodies cannot completely neutralize the virus; instead, they bind with the Fc receptors expressed on hepatocytes, leading to virus entry and infection. ACE2: Angiotensin-converting enzyme 2.

and liver involvement have been reported in SARS-CoV-2[17]. Clinical manifestations in COVID-19 infected patients with no previous liver comorbidities may range from asymptomatic liver function abnormalities to liver failure, as shown in Table 1[1,18].

ABNORMAL LIVER FUNCTIONS

The reported prevalence of liver injury in COVID-19 varies widely from 10.5% to 58.0% depending on many factors[4,19]. Various studies have reported a slight derangement of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin levels[19,20]. The reported figures of complications in COVID-19 are slightly lower as compared to SARS-CoV and Middle East respiratory syndrome-CoV infections, as shown in Table 2. A systemic review reported a 15.0% elevation of AST and ALT, while a 16.7% elevation of bilirubin was reported[21]. Similarly, a meta-analysis pooled 13251 COVID-19 patients and reported a mild decrease in albumin in 39.8% cases, with a mild increase in AST in 22.8% and ALT levels in 20.6%[19]. Parohan *et al*[22] reported older age, male sex, obesity and underlying liver disease as commonly associated risk factors for deranged LFTs.

Furthermore, the extent of liver enzyme derangement has been associated with the severity of COVID-19 infection and its prognosis. Marjot *et al*[23] and Wang *et al*[24] reported higher levels of AST in intensive care unit (ICU) admitted COVID-19 patients. Similarly, Guan *et al*[25] reported 18.2% liver enzyme derangement in non-severe disease as compared to 39.4% with severe disease in 1099 Chinese patients affected by COVID-19 infection. The authors also described higher bilirubin, ALT and AST levels in COVID-19 patients that had either passed away or required ICU admission and/or the need for mechanical ventilation as compared to those patients who did not[25].

Different studies have reported different prognoses of deranged LFTs in COVID-19 patients. Moreover, different studies have used different definitions of liver injury. Ding *et al*[26] labeled liver injury as a 3 × ULN increase in ALT or AST or 2 × ULN increase in total bilirubin, direct bilirubin or alkaline phosphatase. The authors documented ALI in 0.5% of the COVID-19 patients without underlying liver disease. In addition, all patients had concomitant debilitating conditions like acute respiratory distress syndrome, septic shock, kidney injury, *etc*. Hajifathalian *et al*[27] defined ALI as elevation of any parameter of a liver biochemistry panel and demonstrated a higher risk of ICU admission and death in patients with ALI. Phipps *et al*[28] retrospectively studied a large cohort of in-hospital patients based on raised ALT levels, graded liver injury into no/mild (< 2 × ULN), moderate (2-5 × ULN) or severe (> 5 × ULN) forms. Although only 6.4% of the study population developed severe injury, it was significantly associated with severe clinical outcomes including death. The authors also proposed that severe liver injury can be used as a prognostic factor in hospitalized patients. Considering

Table 2 Rates of hepatic complications in different clinically significant human coronavirus infectious diseases

Hepatic complications	SARS-CoV-2, %	SARS-CoV, %	MERS-CoV, %
Increase in ALT	13.3-28.0	52.5-8.07	11.0-56.3
Increase in AST	22.0-58.0	37.1-86.9	15.0-86.8
Increase in TB	10.5-18.0	30.0	NA
Decrease in serum albumin	36.8	40.4-72.0	NA
Co-morbidity with liver disease	HBV-positive patients were more prone to develop severe disease (32.9%) *vs* HBV-negative patients (15.3%)	HBV infection was not associated with worse clinical outcomes	NA

ALT: Alanine transaminase; AST: Aspartate transaminase; HBV: Hepatitis B virus; MERS: Middle east respiratory syndrome; NA: Not applicable; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SARS-CoV: Severe acute respiratory distress syndrome; TB: Total bilirubin.

the association of deranged LFTs with disease severity and prognosis, Tian and Ye[17] suggested that changes in LFTs should be vigilantly monitored for early identification and management.

Although, the majority of studies have reported higher levels of liver enzymes with the severity of COVID-19, a few case reports also documented liver failure in patients without underlying liver disease. Gurala *et al*[18] and Weber *et al*[29] documented acute liver failure in patients without comorbidities and presenting with worsening pulmonary symptoms. However, Orandi *et al*[30] reported acute liver failure documented by replicating SARS-COV-2 RNA in hepatocytes in a young female with COVID-19 presenting with non-respiratory symptoms. Moreover, Busani *et al*[31] reported two fatal cases of acute liver failure in patients with COVID-19 secondary to herpes simplex virus 1 infection. Both patients were treated with tocilizumab.

The resolution of liver injury post-COVID-19 hospitalization is not well studied. A large retrospective study demonstrated persistent deranged LFTs post-discharge in 31.7% of the study population. Thus, it was suggested that recovery from liver injury after resolution of COVID-19 symptoms could be delayed [26]. Hence, the European Association for the Study of the Liver (EASL) position paper recommends monitoring LFTs not only during hospitalization but also post-discharge in COVID-19 patients with persistent deranged laboratory parameters[32].

CHRONIC LIVER DISEASE

CLD, an immunocompromised state, makes the patient susceptible to various diseases including COVID-19 virus[4]. The reported prevalence of CLD amongst COVID-19 patients ranges between 2%-11%[23]. Studies have reported contradictory outcomes for CLD patients with COVID-19. Some have documented higher mortality rates while others negated these findings.

An international registry study between March 2020 and July 2020 documented 745 CLD patients from 29 countries infected with COVID-19 virus. Of the total study population, 386 (51.8%) had cirrhosis, 345 were hospitalized, 108 required ICU admission, and 71 required mechanical ventilation. Among these, 123 (32%) cirrhotic patients died mainly due to pulmonary complications (64%). Moreover, in comparison with non-cirrhotic CLD patients, multivariate analysis documented age, higher Child-Turcotte-Pugh (CTP) score and ALD as significant prognostic factors. Additionally, increased morbidity and mortality were observed with an incremental increase in CTP score[33]. Similarly, a preliminary report of 152 CLD patients documented 39.8% mortality in patients with cirrhosis with CTP B and CTP C scores serving as significant predictors of mortality (P = 0.03 and < 0.001, respectively)[34].

A large National COVID Cohort Collaborative dataset study reported 220727 COVID-19 patients with CLD. Among which, 8941 were patients with cirrhosis, out of which, 8.8% required mechanical ventilation, while 8.9% of patients died at 30 d. In contrast, amongst 29446 non-cirrhotic patients, 2.0% required mechanical ventilation while 30 d mortality was documented in 1.7% of patients. The multivariate analysis documented higher odds of mortality among patients with cirrhosis compared to patients without cirrhosis with COVID-19 (adjusted hazard ratio: 3.31)[35]. However, a pooled analysis of six studies documented no significant association between the severity of COVID-19 and death in patients with CLD[36].

Similarly, in a nationwide Swedish cohort, a nonsignificant association was documented between mortality and COVID-19 in CLD patients. In addition, the presence or absence of cirrhosis did not have an impact on this association. However, the authors did document a slightly higher risk of hospitalization and development of severe COVID-19 in CLD patients as compared to matched controls (adjusted hazard ratio: 1.08 and 1.23, respectively)[37].

ALI at the admission of COVID-19-affected patients was documented in 14 (32.6%) patients, while (39.5%) developed ALI during the hospital stay. Acute decompensation was reported in 9.1%, while 11.6% developed acute-on-chronic liver failure. Further analysis documented higher mortality and complications (liver-related and overall) in decompensated cirrhotic patients with COVID-19. In non-cirrhotic patients with liver injury there was a higher propensity of ICU admission, but the recovery, hospital stay and mortality were comparable to those without liver injury[38]. In another study of 179 patients with cirrhosis with acute decompensation, 50% developed acute-on-chronic liver failure, and this complication was associated with a higher rate of mortality ($P < 0.001$)[33]. Thus, it may be concluded that not only the underlying liver disease but also the existing liver reserve may predict a patient's outcomes with COVID-19 infection. Hence, active and dynamic management of these patients should be done considering their high associated risk of morbidity and mortality.

Recognizing high-risk groups and those predisposed to the severe clinical courses are of utmost importance to plan preventive strategies and management. A limited number of studies have documented the variable impact of etiology on the severity of COVID-19 infection[37].

In a nationwide cohort of 42320 CLD patients, underlying etiology was not associated with a significant risk of hospitalization or development of severe COVID-19. In this study, 32.7% had viral hepatitis, 15.0% had NAFLD, 2.1% had ALD, and 44.0% had other etiologies. However, an international registry of 745 CLD patients with COVID-19 documented ALD as a predictor of mortality ($P = 0.04$). However, no significant association was documented with NAFLD, hepatitis B and C[33]. Similarly, a United States multicenter study also documented ALD along with decompensated cirrhosis and HCC as a liver-specific predictor of mortality in COVID-19 patients[39]. The authors suggested that the added cytokine storm of the SARS-CoV-2 virus to the already heightened inflammatory state in alcoholics could be the cause of the detrimental outcomes. Moreover, increased use of alcohol due to economic and social burdens during the COVID-19 era could be a contributing factor[39,40]. Wang *et al*[41], in a large case-control study, documented that patients with CLD secondary to alcohol-related liver damage and alcoholic liver cirrhosis have odds of 7.05 and 7.00, respectively, of developing COVID-19.

Viral hepatitides, mainly hepatitis B and C, have infected millions of people worldwide. A case-control study of electronic health records documented that adjusted odds of developing COVID-19 were 8.93 and 4.37 with chronic hepatitis C and chronic hepatitis B, respectively[41].

A higher prevalence of hepatitis B has been reported in COVID-19 patients in Asian studies, ranging from 0.8%-6.3%, while a lower prevalence rate of 0.1% has been reported in a United States-based study [41-43]. Although, the pathogenesis is unclear, studies have documented the variable associations of HBV on clinical outcomes of patients with COVID-19. In 105 COVID-19 and HBV co-infected patients, Zhang *et al*[44] reported 23 cases of HBV-related CLD patients with COVID-19. Among which, two patients with cirrhosis (8.7%) became critically ill. Yet, no mortality was reported.

Chen *et al*[45] retrospectively analyzed 20 HBV-positive patients amongst 326 COVID-19 patients. Authors reported three deaths in hepatitis B surface antigen-negative patients, while no patients in the hepatitis B surface antigen-positive group died. Moreover, no statistically significant difference was noted in LFTs, hospital stay and disease severity[45]. In another retrospective analysis of 5639 chronic hepatitis B patients with COVID-19, the authors concluded that current or past hepatitis B infection is not associated with increased mortality[46]. However, another Chinese study documented higher COVID-19 severity and mortality in HBV-infected patients[47]. Zou *et al*[48] observed liver injury as a significant cause of disease severity and mortality in chronic hepatitis B patients with COVID-19.

A chronic immunosuppressed state potentiates the risk of HBV reactivation in patients with chronic or resolved hepatitis B. Moreover, HBV reactivation is associated with high morbidity and mortality [49]. Few case reports have documented HBV reactivation in patients with COVID-19. Aldhaleei *et al*[50] reported a case of HBV reactivation in a patient with COVID-19 presenting with an altered level of consciousness and deranged LFTs. However, high HBV DNA levels were interpreted as reactivation without prior DNA levels.

It is postulated that the immunosuppressive therapy used in COVID-19 can attenuate the host immunity against HBV, thus leading to increased HBV replication. Moreover, with the later withdrawal of immunosuppressants, the reconstituted immune system might mount a heightened immune response against HBV antigen-laden hepatocytes, thus leading to liver injury[51]. Sagnelli *et al*[52] reported HBV reactivation in a patient with COVID-19 pneumonia 7 d after stopping corticosteroid therapy. Wu *et al* [53] also documented HBV reactivation in a COVID-19 patient on entecavir treated with recombinant interferon-alpha-2b, lopinavir/ritonavir and subsequently with methylprednisolone. However, Yip *et al* [46] did not document HBV reactivation in 10 patients on no treatment treated with corticosteroids for severe COVID-19. Nevertheless, the detrimental risk of hepatitis B reactivation persists with COVID-19 treatment. Thus, the Asian Pacific Association for the Study of the Liver (APASL) COVID-19 Taskforce recommends screening all COVID-19 patients for hepatitis B surface antigen. Moreover, antiviral treatment should be prescribed to hepatitis B-positive patients especially treated with interleukin-6 monoclonal antibodies or other immunosuppressive therapy[3].

The prevalence of HCV in COVID-19 is not well reported. A case series from the United States of 5700 hospitalized patients with COVID-19 reported < 0.1% incidence of HCV infection[54]. However, a retrospective single-center study reported a higher incidence of 4.1%. In the latter study, the authors also reported HCV, age, D-dimers and serum ferritin as predictors of in-hospital mortality[55]. The

authors suggested that vascular endothelial dysfunction, elevated cytokine levels and the role of overexpressed transmembrane protease serine 2 could be the potential cause of morbidity and mortality of COVID-19 in HCV-infected patients.

Lensen *et al*[56] reported reactivation of HCV leading to patient mortality in an elderly patient following COVID-19 vaccination. However, the patient had multiple comorbidities along with HBV and HCV co-infection-related cirrhosis[56]. Although, a large veteran database study of HCV-positive patients documented a higher rate of hospitalization, the rates of ICU admission and mortality were similar to negative patients. Moreover, the rate of hospitalization increased with higher fibrosis[57]. The American Association for the Study of Liver Diseases recommends continuing therapy for HBV and HCV if patients are already on treatment when infected with COVID-19. In addition, HBV treatment should be considered in patients with a risk of HBV flare[58].

With the increasing prevalence of NAFLD, it is not surprising that a higher incidence of NAFLD is noted among COVID-19 patients. The prevalence varies from 30% to 55%. The range may be an overestimate, as most of the studies were concentrated on hospitalized patients[59]. NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease) is associated with factors like diabetes and obesity, which are known to aggravate COVID-19 severity[60]. An electronic health records-based study reported that CLD patients have an increased risk of acquiring COVID-19 with the highest odds in patients with NAFLD (adjusted OR: 13.11), nonalcoholic cirrhosis (adjusted OR: 11.5) and chronic hepatitis C (adjusted OR: 8.7)[41]. A systemic review and meta-analysis of 14 studies reported an increased risk of COVID-19 severity and ICU admission in patients with NAFLD. However, no difference in mortality was observed in comparison to non-NAFLD patients[61]. Similar findings have also been reported in other studies[60,62,63]. However, a single-center study from India reported a nonsignificant difference in hospital stay and mortality in COVID-19 patients with or without NAFLD [64]. Similarly, Madan *et al*[65] also documented no association of fatty liver with COVID-19 morbidity and mortality.

Thromboembolism risk is high in COVID-19 patients and is associated with high mortality[66]. A prospective cohort documented a statistically significant association of NAFLD with the development of pulmonary thrombosis in COVID-19 patients. Increased levels of proinflammatory proteins and cytokines may be the contributing factor in this debilitating disease process[59].

Like hepatitis B and C, the underlying liver fibrosis plays an important role in COVID-19 outcomes. Targher *et al*[67] determined the impact of non-invasive fibrosis scores, FIB-4 or NAFLD fibrosis score on COVID-19 severity. After adjustment for sex, obesity and diabetes, the authors documented a significant association of severe COVID-19 with high/intermediate FIB-4 or NAFLD fibrosis score[67].

Regarding autoimmune hepatitis (AIH), a database study of three large registries with 70 AIH patients documented no differences in rates of hospitalization, ICU admission and death between patients with and without AIH-related CLD. However, a higher risk of mortality was observed in the AIH cohort with CTP B and C. Interestingly, the use of immunosuppression was not associated with mortality[68]. Another case series reported uneventful clinical course of 10 AIH patients on immunosuppression[69].

Thus, liver disease etiology may play a role, but the underlying liver fibrosis is the cornerstone to determining susceptibility to COVID-19 and its outcomes. Furthermore, no studies have documented increased predisposition to COVID-19 infection or adverse outcomes in patients with CLD secondary to AIH, primary biliary cholangitis or primary sclerosing cholangitis[70].

HEPATOCELLULAR CARCINOMA

Studies amongst oncological patients have reported a higher risk of acquiring COVID-19 infection along with a greater risk of morbidity and mortality. Moreover, recent cancer treatment may also worsen the outcomes[71,72]. The reported mortality in cancer patients with COVID-19 ranges from 11% to 28%. Nevertheless, concomitant comorbidities, functional class and cancer activity status are associated with a poorer prognosis. Hence, the immunodeficient status of cancer patients determines clinical outcomes [72].

It is estimated that more than 70% of HCC patients have underlying CLD or cirrhosis[73]. It has been shown that the SARS-CoV-2 virus can aggravate liver damage in patients with underlying disease, thus making patients with HCC more susceptible to COVID-19-related morbid complications[74]. Yet, data on the outcomes of HCC with COVID-19 is scarce. A large United States-based multicenter study involving CLD patients infected with COVID-19 reported 52% mortality among patients with HCC (n = 22). Additionally, the authors concluded that decompensated cirrhosis, ALD and HCC were independent liver-related risk factors of mortality[75].

HCC is an aggressive tumor with a tumor volume doubling time of nearly 70 to 120 d[76]. A monthly ultrasound for 6 mo for HCC surveillance is thus recommended under normal circumstances. However, during the pandemic, the delay of 2-3 mo in surveillance has been considered acceptable[58,77]. Inchingolo *et al*[78] suggested prioritizing patients who are at high risk of incidence and/or recurrence of HCC and patients eligible for liver transplantation.

Since the majority of resources were diverted in managing and treating COVID-19 patients during the COVID-19 pandemic, various hepatological associations and societies drafted recommendations for the management of patients with HCC in these times[58,77,79].

Regarding the treatment of HCC, hepatology societies have recommended tailoring the treatment on a case-by-case basis. The American Association for the Study of Liver Diseases proposes that during the COVID-19 pandemic, HCC treatment with curative intent should not be delayed[58]. In addition, APASL recommends postponing surgical treatment and suspending vascular intervention if there is high risk of decompensation or comorbidities since it increases the risk of severe COVID-19. Moreover, ablation therapy could be considered an alternative therapy during this time[77]. Like APASL, EASL guidelines recommend postponing locoregional therapies as these are mostly for the purpose of cytoreduction[77,79]. Similarly, radiation therapy should only be considered in case of functional or life-threatening situations[77].

Although, APASL suggests a preference for oral tyrosine kinase inhibitors over intravenous therapy, EASL proposes dose reduction based on the individual patients[77,79]. Moreover, EASL recommends temporary withdrawal of immune-checkpoint inhibitor therapy in patients with HCC[79].

In general, in all patients with HCC, it is of utmost importance to screen patients for the SARS-CoV-2 virus prior to diagnosis or intervention. Assessment and/or treatment should be postponed until noninfective status is achieved in COVID-19-positive patients. Limited staff with protective gear along with hygienic measures should always be followed during each intervention to curtail the spread of the novel viruses[77].

SOLID ORGAN TRANSPLANTS

Globally, solid organ transplantation has been profoundly affected by the COVID-19 pandemic, resulting in decreased rates of organ procurement and transplantation[80,81]. Liver is the second most common solid organ transplanted in the world after kidney[82]. Although prolonged immunocompromised status and post-transplant associated comorbidities theoretically increase the susceptibility to COVID-19 severity, the data on liver transplant recipients is scarce. Contradictory to the initial reports, a recent multicenter and large database studies have reported similar outcomes in transplanted and non-transplanted COVID-19 populations[80,83,84]. The studies were performed on only hospitalized patients, so it could not be concluded that transplanted patients are prone to be hospitalized due to COVID-19[80]. Centers for Medicare and Medicaid Services has labelled transplant surgery in Tier 3b that is not to be postponed[85]. Owing to diverted and limited resources amidst the pandemic, hepatology societies have restricted liver transplants to urgent transplants only. Table 3 describes a summary of recommendations from various societies regarding liver transplantation activities during the COVID-19 pandemic.

LIMITATIONS

There are certain limitations to this study. We addressed the clinical presentation and laboratory abnormalities primarily, and pathogenesis and particularly pathology were not described. We also did not cover management and prognostic aspects of this infection in detail. New variants of COVID-19 virus were also not discussed nor the vaccination of patients with liver diseases.

FUTURE DIRECTIONS

There is a need for international collaboration for carrying out basic research for better understanding the pathogenesis of hepatobiliary injury in COVID-19 as it can pave the path for the development of targeted therapy and personalized medicine. The role of direct virus infection of the liver with consequent cytopathic effects *vs* indirect liver injury needs to be explored further. Expression profiles of various SARS-CoV-2 entry receptors vary across different *in vitro* and *in vivo* liver models; however, evidence of specific viral hepatotropism of SARS-CoV-2 is inadequate. Abnormal LFT values are common in patients with COVID-19; both the prognostic significance of these derangements and whether they are directly attributable to hepatic SARS-CoV-2 infection remain to be explored in future focused research.

CONCLUSION

In conclusion, liver involvement is common in patients with COVID-19 infection, particularly in those

Table 3 Summary of recommendations from various hepatology societies regarding liver transplantation during the coronavirus disease 2019 pandemic

Step	AASLD	EASL	APASL	Indian Transplant Society
Indications	Develop a hospital-specific policy for organ acceptance in consideration to community incidence of COVID-19 infection	Restrict transplant with poor short-term prognosis like ALF, ACLF, high MELD score and HCC at upper limit of Milan criteria	Can limit transplant to urgent cases (ALF, high MELD, high risk of HCC progression) according to resources and infection status of country	Until April 2020, elective transplants were withheld. However, in ALF and ACLF transplant could proceed
Pre- transplant evaluation	Test all recipients and donors for SARS-CoV-2 before transplantation. In case of COVID-19 infection in potential recipient, transplant can be considered after at least 14-21 d if symptoms are resolved and repeat SARS-CoV-2 test is negative. Vaccination of potential recipient is encouraged	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Reduction of hospital stay for transplant evaluation and consultation	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Donor should also be evaluated for evidence of COVID-19 infection on chest CT	All recipients and donors should be tested for SARS-CoV-2 before transplantation
Post-transplant management without COVID-19	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage COVID-19 vaccination at least 6 wk post-transplant if partially vaccinated pretransplant than vaccination can be completed 1 mo after transplant	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in new transplant recipient. In cases of long-term transplant dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in post-transplant period
Post-transplant management with COVID-19	Consider lowering immunosuppression levels especially antimetabolite drugs (*e.g.*, azathioprine or MMF). Dose adjustment of immunosuppression should be based on severity of COVID-19. Monitor kidney function and calcineurin inhibitor levels	Dose adjustment of calcineurin- and/or mTOR- inhibitors may be required to avoid drug interactions with anti-viral therapy	Consider lowering immunosuppression levels in patients with moderate COVID-19 infection. Immunosuppression should be reduced in recipients with lymphopenia, fever or worsening pneumonia. Severe COVID-19 should be treated as per local protocol. Drug-to-drug interaction should be considered with anti-viral therapy	

AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on chronic liver failure; ALF: Acute liver failure; APASL: Asian Pacific Association for the Study of the Liver; COVID-19: Coronavirus disease 2019; CT: Computed tomography; EASL: European Association for the Study of the Liver; MELD: Model For End-Stage Liver Disease; HCC: Hepatocellular carcinoma; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

with moderate to severe disease. It is mostly asymptomatic or mild in nature. Conversely, patients with pre-existing liver disease are prone to serious COVID-19. Data on the impact of COVID-19 infection on patients with pre-existing diseases or liver transplants is either conflicting or scarce. Hence, large collaborative studies with prolonged follow-up are needed to fully comprehend the impact of this challenging infection on patients with liver diseases.

FOOTNOTES

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Country/Territory of origin: Pakistan

ORCID number: Farina M Hanif 0000-0002-2011-4721; Zain Majid 0000-0002-6961-3011; Shoaib Ahmed 0000-0003-2536-8197; Nasir H Luck 0000-0002-4752-4157; Muhammed Mubarak 0000-0001-6120-5884.

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