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MINIREVIEWS

Liver and COVID-19: From care of patients with liver diseases to liver injury

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Abstract

The global pandemic of coronavirus disease 2019 (COVID-19) changed dramatically all priorities on medical society and created several challenges for clinicians caring for patients with liver diseases. We performed a comprehensive review about how COVID-19 can affect the liver, the influence of liver diseases on the risk of developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 severity and also some strategies to overcome all the challenges clinicians have to face in the management of patients with liver diseases in a period of time when all the focus turned on COVID-19. We analyze the relationship between COVID-19 and non-alcoholic fatty liver disease, alcoholic liver disease, viral hepatitis, autoimmune liver disease, cirrhosis, hepatocellular carcinoma and liver transplantation, as well as the approach to SARS-CoV-2 vaccination.

Key Words: COVID-19; Liver diseases; Vaccination; SARS-CoV-2

Core Tip: Coronavirus disease 2019 (COVID-19) has become a major health problem worldwide in the last few months, affecting the health system dramatically. Apart from the respiratory system, associated liver injury is one of the main concerns in severe acute respiratory syndrome coronavirus 2 infection and several mechanisms could explain liver abnormalities. In this mini-review, and different from other papers, we not only analyze liver injury by COVID-19, the effect of COVID-19 in liver diseases, its pathophysiology and strategies to keep an adequate care of liver patients, but also

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highlight the potential higher risk of severe disease or risk of infection in patients with different etiologies of liver disease. We also analyze the recent recommendations and prioritization regarding vaccination in patients with liver disease.

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INTRODUCTION

Coronaviruses are single-stranded RNA viruses that mainly cause upper respiratory tract infections in humans. Two coronaviruses were previously described, severe acute respiratory syndrome coronavirus (SARS-CoV), causing an epidemic in 2003, and middle eastern respiratory syndrome coronavirus (MERS-CoV), causing an epidemic in 2012[1].

The new SARS-CoV-2 is responsible for one of the most important and devastating pandemic in the human history - the first case of severe pneumonia caused by SARS-CoV-2 was described on 3rd January 2020 in Wuhan, China, the first epicenter of the disease[2]. Since then, SARS-CoV-2 have widespread across the world, causing a global pandemic - in the beginning of May 2021, World Health Organization reported more than 150000000 infected patients and more than 3000000 deaths[3].

Coronavirus disease 2019 (COVID-19) has a variety of clinical presentations, with the majority of patients remaining asymptomatic or with mild symptoms, such as cough, anosmia, fatigue, diarrhea, headache or fever. However, 10%-15% will present acute hypoxemia or respiratory distress syndrome that might progress to multi-organ failure and death[4-7].

The respiratory tract is the main target of SARS-CoV-2 but several reports revealed a systemic involvement of the disease, including liver and the gastrointestinal tract[8].

In this review, we will highlight the relationship between COVID-19 and the liver.

LIVER INJURY IN COVID-19

It is well established that the respiratory tract is involved in the majority cases of SARS-CoV-2 infections but several studies reported COVID-19 associated liver injury, defined as liver damage during disease progression or treatment[9].

Elevated serum liver biochemistries in patients with COVID-19 was first described by Chen *et al*[10] in Wuhan where 43.9% of patients had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Overall, the incidence of liver injury ranged from 14.8% to 78% and the most common changes are mild elevations of AST and/or ALT (mainly within 3 times the upper limit of normal)[11-13]. The wide range of incidence could be explained by the different cut-off values of upper limit of normal and geographical variability in prevalence and type of underlying chronic liver disease[7,14].

It was also described a possible relationship between liver injury and severity of the disease: Abnormalities in liver function were significantly higher in critically ill patients and associated with poorer outcome. One large Chinese study showed that 18% of non-severe COVID-19 patients had elevated ALT *vs* 56% in the group of severe COVID-19[1,15,16].

Liver biopsies in COVID-19 patients did not show any typical pattern of hepatic lesions and liver injury is probably associated with multiple mechanisms (Table 1)[1,7,9,17-26]: (1) Direct cytotoxicity by active replication of SARS-CoV-2 in hepatic cells due to abundance of its receptor in cholangiocytes - however, the major COVID-19 induced liver function abnormalities are in aminotransferases that might be explained by others factors such as mitochondrial dysfunction, SARS-CoV-2 induced hepatic steatosis, transaminase release due to breakdown of skeletal and cardiac muscle and venous and arterial thromboses; (2) Hyper-inflammatory reaction to COVID-19: Substantial elevations in serum ALT are usually associated with high levels of C reactive protein, D-dimer, ferritin and interleucin-6 and result from the development of the cytokine

Table 1 Mechanisms of coronavirus disease 2019 liver injury

Mechanisms	Pathophysiology
Direct cytotoxicity	Active replication of SARS-CoV-2 in hepatic cells
Hyper-inflammatory reaction	Cytokine storm and activation of immune system
Systemic hypoxia	COVID-19 cardiomyopathy
Drug-induced liver injury	Liver toxicity to medication used to treat COVID-19

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

storm and activation of the innate and adaptive immune system; (3) Systemic hypoxia and hepatic congestion related to cardiomyopathy (hypoxia hepatitis is frequent in the severe cases); and (4) Drug-induced liver injury: Mainly with lopinavir-ritonavir, tocilizumab and remdesivir.

COVID-19 AND LIVER DISEASES

The presence of previous liver disease could influence the prognosis of COVID-19 and SARS-CoV-2 could also pose some difficult challenges in care of liver diseases' patients (Table 2).

Non-alcoholic fatty liver disease and metabolic associated fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is one of the most common etiologies of liver disease in the world and the most emerging cause in developed countries, being expected to become the leading cause of liver transplantation worldwide[27,28]. Recently, a new concept has merged, metabolic associated fatty liver disease (MAFLD), diagnosed in the presence of hepatic steatosis and any of the following metabolic conditions: Diabetes mellitus, obesity/overweight or evidence of metabolic dysregulation in lean patients[29].

Several studies investigated the possible relationship between NAFLD/MAFLD and the outcome of COVID-19. Ji *et al*[30] reported liver abnormalities in 50% at admission of COVID-19 and NAFLD patients and in 75% during hospitalization and NAFLD was an independent risk factor for COVID-19 progression[27]. Another study, a meta-analysis by Pan *et al*[31], showed that NAFLD increased the risk of disease progression among patients with COVID-19.

NAFLD patients may also suffer from comorbidities known to be important risk factors for severity of COVID-19 and that could negatively influence prognosis, such as hypertension, obesity or diabetes[27]. However, Zhou *et al*[32] established a synergic effect of NAFLD for severe COVID-19 in patients less than 60 years-old and independent of other comorbidities, showing that NAFLD alone could be an important prognostic factor. This might be explained by metabolically active fat, which is associated with[17,33]: (1) Chronic inflammatory changes and higher cytokine levels, making NAFLD patients more vulnerable to cytokine storm in COVID-19; and (2) Imbalance in host inflammatory and tolerance response to SARS-CoV-2. On the other hand, it was also demonstrated that COVID-19 patients exhibited higher levels of monocyte chemoattractant protein-1 that is associated with steatohepatitis exacerbation, increasing the risk of NAFLD progression[34].

Therefore, it is of paramount importance to carefully follow NAFLD and COVID-19 patients due to the higher risk of poorer outcomes in both diseases.

Alcoholic liver disease: Alcoholic liver disease is one of the main causes of liver disease and its patients were considered one of the most affected groups during the pandemic as they present[35-37]: (1) Higher risk of developing SARS-CoV-2 infection due to reduced immunity to bacterial and viral infection (due to heavy alcohol consumption) and also willingness to adopt prevention measures; (2) Worse COVID-19 outcomes with a study reporting to be the only liver disease with a significant odds ratio for death; and (3) Higher alcohol consumption during the time of social isolation, increasing the risk of decompensation.

Strategies to overcome all these difficulties should be implemented and include social and psychological support (locally or *via* telemedicine), educational sessions to deal with the risk of COVID-19 as well as regular appointments with hepatologists.

Table 2 Influence of liver diseases in risk of infection or outcome of coronavirus disease 2019

Higher risk of infection or severe outcome of COVID-19	Apparently non-higher risk of infection or severe outcome of COVID-19
Non-alcoholic fatty liver disease	Hemochromatosis
Alcoholic liver disease	Wilson's disease
Alpha-1 antitrypsin deficiency	Autoimmune liver disease
Cirrhosis	Hepatitis B infection
Hepatocellular carcinoma	

COVID-19: Coronavirus disease 2019.

A debatable question is the use of corticosteroids in alcoholic hepatitis: There are some recommendations suggesting to avoid steroids in this situation as it may delay viral clearance but benefits must be weighed against risks and there are some reports showing that prednisolone might be an effective and safe treatment in patients with SARS-CoV-2 infection and alcoholic hepatitis[38,39].

Other metabolic liver diseases: There is no data on the risk of infection and severity of COVID-19 in patients with hemochromatosis and Wilson's disease. It is always important to search for iron overload in patients with SARS-CoV-2 and abnormal liver tests as elevated ferritin levels could be associated to viral infection and mask an underlying hemochromatosis[40].

Alpha-1 antitrypsin might inhibit infection by SARS-CoV-2, has anticoagulation effects and protect against inflammation[41]. Therefore, patients with alpha-1 antitrypsin deficiency seems to have increased risk of infection and COVID-19 severity, mainly Pi*ZZ and/or low alpha-1 antitrypsin levels.

Autoimmune liver diseases: Autoimmune liver diseases are a group of diseases that include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

The management of autoimmune liver diseases was one of the main concerns of hepatologists during COVID-19 pandemic due to the use of immunosuppressive therapy. Previous reports with other coronaviruses (SARS-CoV or MERS-CoV) did not show worse outcomes in patients who were undergoing transplantation, chemotherapy or other immunosuppressive treatments and there was also some evidence that imunossupressive therapy might have a protective effect against severe COVID-19[42,43]. Therefore, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) were against stopping immunosupressive therapy as it may lead to disease flares that will need high doses of steroids, which will increase the susceptibility for SARS-CoV-2 infection. More recently, a multicenter study evaluated the outcomes of COVID-19 in patients with AIH and showed that the overall outcome of SARS-CoV-2 disease was favorable in patients without cirrhosis and that ongoing immunosuppression was not associated with increased risk of severe COVID-19[44]. Efe *et al*[44] also described that the risk of AIH relapse may be related with hyperstimulation of the immune system by COVID-19[45]. There is scarce information about COVID-19 and PBC or PSC - an Italian study found an incidence of SARS-CoV-2 infection of 5.6% in AIH patients but only 1.5% in PBC patients - the higher incidence in AIH might be related with the use of immunosuppressive therapy (not used in PBC)[46]. Another important finding, also described in other autoimmune and inflammatory conditions, is the development of new-onset PBC after COVID-19, where SARS-CoV-2 triggered the development of PBC in a genetically predisposed individual[45,47,48].

Viral hepatitis: COVID-19 did not seem to influence the course of hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. A meta-analysis by Mantovani *et al*[49] reported an incidence in COVID-19 patients of only less than 0.1% HCV infection and 0.1% of HBV infection. In fact, the major effect of COVID-19 is the impact in HCV elimination efforts. A Spanish study showed that the interruption of HCV screening, linkage to care and harm reduction programs, would substantially decrease HCV diagnosis and treatment, consequently, increase the number of HCV liver-related deaths, hepatocellular carcinoma (HCC) and decompensated cirrhosis[50]. Thus, it is of paramount importance to keep HCV elimination a major health priority through

innovative programs as telehealth or home-delivery HCV drugs[50].

Akin to HBV infection, one of the largest cohorts of patients with COVID-19 and past or current HBV infection did not show an association with acute liver injury. Patients that fulfill the criteria for HBV treatment or under corticosteroid therapy should receive antiviral treatment but it may not be necessary in all patients with COVID-19 and current or past HBV infection[51]. A study by Liu *et al*[52] also reported that HBV infection did not predispose COVID-19 patients to more severe outcomes. There is also a report of COVID-19 accompanied by HBV infection causing a fulminant hepatitis[53].

Cirrhosis: Cirrhosis is one of the major causes of morbidity and mortality in the entire world and the second leading cause of digestive disease mortality[54].

Patients with cirrhosis have multiple mechanisms of immune dysfunction and are more susceptible to infection, not only to severe bacterial infection but also to viral and fungal-related disease[7,22,55]. However, data about risk of COVID-19 in this population is controversial, with Richardson *et al*[56] not suggesting a higher prevalence of cirrhotic patients in COVID-19 population while Kushner *et al*[57] reporting higher risk of infection, severity of the disease and hepatic decompensation. In cirrhotic patients, there is also a relationship between severity of liver disease and SARS-CoV-2 morbidity and mortality, with Child-Pugh C patients presenting higher frequency of Intensive Care Unit admission, renal replacement therapy and mortality [58].

Bajaj *et al*[59] showed that cirrhotic patients hospitalized with COVID-19 had similar mortality rates of patients admitted with cirrhosis alone but higher than patients with COVID-19 alone. An Italian study also demonstrated that cirrhotic patients that develop COVID-19 present a worse prognosis due to respiratory complications but also worsening of liver function leading to end-stage liver disease. They also found that the 30-d mortality in non-cirrhotic patients was significantly lower[60].

A very interesting finding in a multicenter cohort is that COVID-19 is associated with hepatic decompensation and, in this study, 24.3% had no respiratory symptoms at the time of diagnosis[4]. As so, testing to SARS-CoV-2 infection is advisable in patients with hepatic decompensation and early admission should be considered due to high rates of mortality.

SARS-CoV-2 infection can also cause acute-on-chronic liver failure characterized by hepatic decompensation events, extrahepatic organ failure and high rates of mortality.

EASL and World Gastroenterology Organization recommend that care should be maintained as this fragile population have a very high risk of decompensation. Prophylaxis of spontaneous bacterial peritonitis and encephalopathy, therapeutic paracentesis and variceal banding in high risk patients should be always performed in a COVID-19 free environment and following all the protective measures, as this will reduce the risk of further decompensation and hospitalization[37,61].

Cancer and hepatocellular carcinoma: Patients with COVID-19 and cancer are at increased risk of infection and worse outcomes[62]. A nationwide Chinese study that included 1590 patients (18% with history of cancer) reported higher risk of adverse events in patients with active or past history of cancer. This might be explained as cancer patients are more susceptible to infection (due to their systemic immunosuppressive state associated with malignancy but also with its treatment) and have increased risk of COVID-19 related serious events[63,64].

HCC is the sixth most commonly diagnosed and the fourth leading cause of cancer-related death in the world, being one of the major health challenges in liver clinic[65,66]. There is scarce information on the impact of COVID-19 in patients with HCC - in a small study, Zhang *et al*[67] reported poorer outcomes in patients with HCC but also with other malignancies when compared to the general population.

The major impact of COVID-19 on HCC is related to the delay on the proper management of HCC. A French multicenter study reported a significant decrease in the rate of HCC patients referred for first diagnosis or treatment[68]. Several interpretations could be made but may be related to the increase delay of referral by other professionals, patients' fear to search for healthcare services, delay in the Hepatology appointments and limited assessment to diagnostic and therapeutic tools. They also found a higher rate of treatment delay longer than one month when compared 2019 to 2020[68].

Currently, AASLD and EASL recommend to continue HCC surveillance and treatment with an acceptable delay of a maximum of two months to reduce the number of patients presenting with HCC not amenable to curative treatment[43,69]. Whenever possible, telemedicine could replace clinic visits and multidisciplinary team

meetings, and all diagnostic and therapeutic procedures should be performed according to the COVID-19 prophylactic measures to avoid nosocomial spread on infection[60].

The real effect of COVID-19 on HCC management is still undetermined and only the middle-term follow-up will clarify the pandemic impact on HCC morbidity and mortality.

Liver transplantation: The risk and severity of COVID-19 in liver transplant patients is still unclear[70]. A multinational cohort reported a similar risk to the general population of contracting infection with SARS-CoV-2[71]. The proportion of liver transplant recipients hospitalized with COVID-19 was 82% and 19% died and advanced age, presence of non-liver cancer and elevated baseline creatinine were associated with higher mortality rates, while the type of immunosuppression and time since transplantation were not associated[71]. However, the European Liver and Intestine Transplantation Association established a registry and suggested that longer time of transplantation might have higher rates of mortality[72].

Liver transplantation programmes were heavily affected by COVID-19 pandemic by several reasons: Limited access to intensive care unit (ICU) due to the number of COVID-19 patients needing ventilation support, reduced number of organs because all major guidelines recommended against using organs from donors with SARS-CoV-2 infection and also limited access of patients to liver transplant centers[58].

It is crucial to maintain liver transplant programs to reduce liver diseases mortality, facing all the new challenges through innovative tools, in which telemedicine might play a key role.

The postoperative period is also a challenge and should follow a SARS-CoV-2 free pathway, with proper free-SARS-CoV-2 ICU to ensure high transplant success rates and preventing nosocomial infection[5]. In the perioperative period, patients' follow-up should be preferably through telemedicine and, in case of symptoms, the threshold for testing for SARS-CoV-2 infection should be low[5]. In case of COVID-19, patients should always present to the hospital for medical evaluation[5].

Regarding immunosuppression after liver transplants, all liver associations recommend to maintain medication as there is no data suggesting a higher risk of COVID-19 severity, while stopping will increase the risk of graft rejection[43,61,73]. However, in case of COVID-19, immunosuppression should be reduced, particularly antimetabolite dosages[43].

Vaccination: The development of SARS-CoV-2 vaccine is one of the major advances to mitigate all the health and economic issues. This development started in January 2020 and progressed very rapidly, being now available more than 5 vaccines. The process of vaccination is moving forward worldwide in order to achieve herd immunity as soon as possible.

Despite some concerns about vaccines' adverse events, the safety profile is excellent and, based on current knowledge, there is no contra-indication for vaccination of liver disease patients, as the potential benefits are higher than the risks[74]. However, there is a report of auto-immune hepatitis developing post-COVID-19 vaccination[75].

Vaccination should also be prioritized in[74]: (1) Cirrhotic patients or with liver decompensation; (2) Hepatobiliary malignancies patients; (3) Chronic liver disease patients and risk factors for severe COVID-19; (4) Liver transplant recipients (prior to liver transplant whenever possible or 3-6 mo after transplantation); and (5) Healthcare professionals caring for these patients.

CONCLUSION

Liver abnormalities in COVID-19 patients are common and may result from direct cytotoxicity, hyper-inflammatory status or DILI. In addition, a direct relationship between grade of liver injury and severity of the disease was also established.

The existence of previous liver disease could influence the prognosis, with patients with NAFLD, cirrhosis and HCC presenting higher risk of severe COVID-19 and death (Table 2). In this population, vaccination should be considered a priority. On the other hand, the focus on SARS-CoV-2 infection lead to reduced access to care for patients with liver disease that must be reestablished to improve the outcome of these diseases.

In conclusion, the consequences of COVID-19 on liver ranges from its direct liver injury to the profound negative effect on liver disease patients' care which might increase liver disease burden and negatively influence prognosis.

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