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SARS-CoV-2-induced liver injury: A review article on the high-risk populations, manifestations, mechanisms, pathological changes, management, and outcomes

Payus AO *et al*. SARS-CoV-2 induced liver injury

Abstract

The novel coronavirus disease 2019 is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was declared a global pandemic with more than 500 million reported cases and more than six million deaths worldwide to date. Although it has transited into the endemic phase in many countries, the disease's mortality rate and overall prognosis are still abysmal and need further improvement. There has been evidence that shows the significance of SARS-CoV-2-related liver injury. Here, we review the literature on the various spectrum of SARS-CoV-2 infections-induced liver injury and the possible mechanisms of damage to the hepatobiliary system. This review aims to illustrate the latest understanding regarding SARS-CoV-2-induced liver injury including the high-risk prone populations, the characteristic clinical manifestations, the possible pathogenic mechanism, the pathological changes, current suggestions for clinical treatment for various spectrum of populations and the prognosis of the condition. In conclusion, SARS-CoV-2 patients with a liver injury warrant close monitoring as it is associated with the more severe and poorer outcome of the infections.

Key Words: COVID-19; SARS-CoV-2; Pandemic; Liver injury; Pandemics; Prognosis

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Core Tip: There are several reviews in the literature that discussed on the pathophysiology, management and outcomes of liver injury in coronavirus disease 2019 (COVID-19). Here, we review to report the current understanding on the various aspect of COVID-19-related liver injury, including the high-risk prone populations, the characteristic clinical manifestations, the possible pathogenic mechanism, the

pathological changes, current suggestions for clinical treatment for various spectrum of populations and the prognosis of the condition.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a name given to the newly emerged zoonotic virus that causes the coronavirus disease 2019 (COVID-19)[1]. It was first reported in Wuhan, China, on 29th December 2019 and was declared a global pandemic on 11th March 2020[2]. SARS-CoV-2 is an enveloped, single-stranded positive-sense ribonucleic acid (RNA) genome virus, which harbours the largest genome among currently known RNA viruses, with a genome length of around 26 to 32 kb. It has an oval shape and an average size of 100 nm in diameter. Large club-shaped spikes of glycoprotein membrane on the viral surface make the viral particles appear like a typical crown-like shape in an electron microscope[3].

COVID-19 is a syndrome with various systemic and respiratory symptoms such as fever, fatigue, dry cough, and breathing difficulty. It can be critical, causing severe pneumonia and cardiorespiratory failure that requires specialized management in intensive care units[4]. SARS-CoV-2 can also affect other systems, namely the nervous system causing headache, anosmia, paraesthesia, and altered consciousness[5]. Abnormal liver function parameters are commonly found in patients with SARS-CoV-2 infection, indicating that SARS-COV-2 infection is associated with liver injury and even failure. Apart from that, several studies suggested that liver injury has a significant role in determining the severity and mortality rate of the disease. Considering the ongoing global threat of SARS-CoV-2 infection and the necessity to improve the prognosis of the disease, the treating physicians need to be aware of the association and significance of SARS-CoV-2 infections-related liver injury not only to the severity of the disease but also to the mortality rate and prognosis as a whole. Therefore, this review aims to elucidate the importance of hepatobiliary involvement in SARS-CoV-2 infections and hopefully provide helpful information for managing the condition and improving the disease's overall prognosis.

SARS-COV-2 INDUCED LIVER INJURY PRONE POPULATIONS

Since the beginning of the pandemic, it was reported that patients with severe SARS-CoV-2 infection tend to develop liver injury compared to mild infection. Apart from that, Cai *et al*[6] reported that male patient of older age and has higher body mass index (BMI) have a higher tendency to develop liver injury during the course of the disease. A similar finding was seen in a study on 79 non-hospitalized SARS-CoV-2 patients by Xie *et al*[7], who reported that liver injury is more common among male patients. The authors also said that patients with an underlying severe chronic lung disease have a higher rate of liver injury which was then also reported by Zhang *et al*[8]. Cai *et al*[6] and Singh and Khan[9] both found that liver injury is more common among patients with underlying liver disease. According to Da *et al*[10], the common aetiology of chronic liver disease that is prone to developing worsening liver injury during the infection is alcohol-related liver disease. Apart from that, patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are usually associated with additional metabolic risk factors, such as obesity which can increase the susceptibility to the infection and is commonly associated with a more severe presentation[11].

There has been significant concern about the increased susceptibility to SARS-CoV-2 infection among solid organ transplant recipients. In a systematic review by Piedade and Pereira[12], patient with liver transplant was not associated with an increased risk of SARS-CoV-2 infection. The risk is highly dependent on the gender, age, BMI, history of hepatocellular carcinoma, and also the immunosuppression drug dose of the patient. However, the prevalence of severe infection is higher among liver transplanted patients. A study by Becchetti *et al*[13] found that alteration in liver enzymes among liver transplanted patients with SARS-CoV-2 occurs more commonly among hospitalized patients. In addition, Ali Malekhosseini *et al*[14] showed that the admission rate of liver transplanted patients to the intensive care unit was as high as 33.3%.

No evidence shows that pregnancy increases susceptibility to SARS-CoV-2-induced liver injury. Nevertheless, a retrospective cohort study involving 122 pregnant patients

with confirmed SARS-CoV-2 infection by Can *et al*[15] found that 13.9% developed an abnormal liver function which was generally mild, where most of them were critically ill and had a longer stay in the hospital compared to the normal liver function group.

THE CHARACTERISTIC MANIFESTATIONS OF SARS-COV-2 INDUCED LIVER INJURY

The most common manifestations of SARS-CoV-2 induced liver injury was the elevation of liver enzymes, such as the alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). In a meta-analysis done in the first few months of the pandemic by Cai *et al*[6], about 25% of SARS-CoV-2 patients developed raised liver enzymes, which it shows a direct association with the disease activity. The prevalence of raised AST was higher than ALT levels and was positively correlated with the severity of cases, where the level was higher in patients with severe cases[7,8,15]. Lei *et al*[16] reported a significant association between inpatient mortality in SARS-CoV-2 infected patients and liver injury based on the liver enzymes, specifically the AST elevation. In a study on 417 SARS-CoV-2 infected patients by Cai *et al*[6], 41% of patients had abnormal liver tests, and 5% had a liver injury upon presentation to the hospital. Throughout hospitalization, 76.3% developed some form of abnormal liver function, and 21.5% was high enough to be considered a liver injury. A similar finding was reported by Fan *et al*[17], who conducted a retrospective single-center study on 148 patients with SARS-CoV-2 infection, where 37.2% had an abnormal liver function at hospital admission. Patient with the abnormal liver function was also found to have a more extended hospital stays. A retrospective study on 79 patients with SARS-CoV-2 by Xie *et al*[7] found that patients with an abnormal liver test had a more extended stay in hospital. Phipps *et al*[18] reported that 21% out of 2273 patients with SARS-CoV-2 infection had a moderate liver injury which was defined as elevated liver enzymes two to five times above the upper limit of normal, and 6.4% had a severe liver injury which defined as liver enzymes raised more than five times the upper limit of normal. 69% of the patients with liver injury required intensive care unit care. The

reports also mentioned that severe liver injury was associated with elevated inflammation markers, including ferritin and interleukin 6 (IL-6).

PROPOSED PATHOPHYSIOLOGICAL MECHANISM OF SARS-COV-2 INDUCED LIVER INJURY

The exact pathophysiological mechanism of SARS-CoV-2-induced liver injury is still poorly understood, but evidence has shown it to be multifactorial (as shown in Figure 1). One of the factors is a direct invasion of the SARS-CoV-2, which has been suggested in several studies. The primary receptor for SARS-CoV-2 cellular entry is the angiotensin-converting enzyme 2 (ACE2) receptors which are found not only in the lung parenchyma but also in the other parts of the body[19], such as the brain[5], gastrointestinal tract, biliary tree and liver epithelia[20]. Zhou *et al*[21] said that SARS-CoV-2 patients with gastrointestinal symptoms had higher AST and ALT levels, which reflect that ACE2 receptor is expressed within the gastrointestinal tract and the biliary tree. However, even though the ACE2 receptor is expressed more within the biliary tree than the liver parenchyma, most studies showed a predominant pattern of parenchymal liver injury based on the elevated level of AST and ALT rather than the damage to the bile ducts, which reflected by raised GGT and ALP[22]. Wu *et al*[23] found that almost 50% of SARS-CoV-2 infected patients recovered from the disease had persistent virus shedding in their faecal specimens for more than ten days after the viral detection in respiratory tract samples became negative. This may further support the possibility of viral replication in the hepatobiliary system. Similarly, the previous SARS-CoV-2 strains have caused the outbreak from 2002 to 2004 have also been shown to directly injure the liver parenchyma causing lobular inflammation and apoptosis of hepatocytes[24].

Apart from the direct viral-induced hepatocytopathic hypothesis, autoinflammatory mediated injury to the liver is another plausible explanation. Immune dysregulation can occur in severe SARS-CoV-2 infection, which in the extreme condition, the overactivation of the immune system will lead to systemic hyperinflammation. This condition is called 'cytokine storm syndrome', which is a phenomenon that will not

only cause pulmonary inflammation but also multi-organ involvement, including the nervous system causing encephalitis[25] and peripheral neuritis[26], and the liver causing acute hepatitis and even failure[27,28].

Drug-induced liver injury is also common in SARS-CoV-2 patients, as the medications used to treat the infection can be hepatotoxic. These include lopinavir/ritonavir, remdesivir, tocilizumab, and others[29]. A study on 148 cases of SARS-CoV-2 infected patients in Shanghai by Li *et al*[30] found that the utilization rate of lopinavir/ritonavir among patients with abnormal liver function is higher than the patients with normal liver function. There was no significant difference in the pre-hospital medication between the two groups of patients. The exact mechanism of how lopinavir/ritonavir induces liver injury is still uncertain, but here is evidence that it activates the endoplasmic reticulum stress pathway in the liver and induces hepatocytes apoptosis[31]. Ritonavir is also widely metabolized by the liver through the cytochrome P450 system, where the production of toxic intermediate of any drugs that are metabolized by the system will have the potential of causing liver injury[32]. Tocilizumab, which is an IL-6 inhibitor that is used to reduce overactive inflammation, has been reported to cause drug-induced liver injury and liver failure, which in some cases requires a liver transplant[33]. The exact mechanism is still unknown but may be due to its inhibitory effect on the IL-6 pathway, which is essential for liver regeneration.

SARS-CoV-2 patients with underlying chronic liver diseases are more likely to suffer from liver injury. This may suggest that SARS-CoV-2 infection can aggravate underlying liver diseases. In addition, there is a possibility that the liver damage may be caused by the viral reactivation of existing liver diseases in SARS-CoV-2 infection. Apart from that, some biological medications such as tocilizumab and baricitinib may cause reactivation of viral hepatitis B, which causes deterioration of liver function[34].

Another simpler hypothesis is that prolonged hypoxia and tissue ischemia in critically ill SARS-CoV-2 patients who suffers severe pneumonia and acute respiratory distress syndrome can also be one of the mechanisms of liver injury and even failure[35]. This occurs due to prolonged tissue hypoperfusion leading to ischemia, including in the

liver. The anaerobic metabolism and lactic acidosis will further depress the cardiorespiratory effort, which will cause the continuation of the vicious circle[36].

PATHOLOGICAL CHANGES IN SARS-COV-2 INDUCED LIVER INJURY

The first post-mortem autopsy on a patient who succumbed to SARS-CoV-2 infection was reported by Xu *et al*[37]. The liver histology showed a moderate degree of microvesicular steatosis with mild lobular and portal vein activity in the study. Ji *et al*[38] reported overactivation of T-cells, suggesting viral-induced cytotoxic T-cell liver damage. Liu *et al*[39] described various hepatic lesions, including focal lobular necrosis, lobular lymphocytic and monocytic infiltration, ballooning degeneration of liver cells, and sinusoidal congestion with microthrombosis. A study on 48 liver autopsies by Sonzogni *et al*[40] reported a focal portal and lobular lymphocytic infiltrates with multiple vascular changes, which are suggestive of hepatic vascular involvement. Tian *et al*[41] also reported a similar autopsy finding of mild lobular lymphocytic infiltration, with a sinusoidal expansion of central lobule and patchy necrosis in the periportal and centrilobular areas. There was no significant inflammatory cell infiltration around the portal tracts, which is consistent with the mode of acute liver injury. An autopsies report on seven SARS-CoV-2 infected patients who died by Rapkiewicz AV *et al*[42] noted multiple platelet-fibrin microthrombi in the hepatic sinusoids. Wang *et al*[43] and Wang *et al*[44] reported massive hepatic apoptosis, microvesicular steatosis, and inflammatory cell infiltration over the portal systems. Apart from that, there was a high amount of viral SARS-CoV-2 ribonucleic acid (RNA) titres detected in the liver *via* reverse transcriptase-polymerase chain reaction[41,45].

CURRENT MANAGEMENT OF SARS-COV-2 INDUCED LIVER INJURY IN VARIOUS SPECTRUM OF POPULATIONS

Liver injury is a severe complication of SARS-CoV-2 infection and can significantly affect the outcome of the patients. Multiple studies have suggested regular monitoring of liver function parameters in SARS-CoV-2 infected patients. Based on the consensus

statement of the American Association for the Study of Liver Diseases[46], it is recommended to consider aetiologies outside SARS-CoV-2, such as other viral hepatitis. This has been proven in a case reported by Hambali *et al*[47], where a patient with SARS-CoV-2 infection presented with abnormal liver function and high IL-6 was due to hepatocellular carcinoma. Apart from that, it is also essential to consider other indirect causes of liver injury such as myositis, cardiac injury, ischemia, and cytokine release syndrome. Patients with liver enzymes that raised more than five times over the upper limit of normal may be excluded but not contraindicated from using medications such as Remdesivir, Tocilizumab, and hydroxychloroquine. Every patient receiving the medications, especially Remdesivir and Tocilizumab should be regularly monitored for liver biochemical indicators regardless of baseline values. Patients with autoimmune hepatitis and liver transplantation should not be assumed to have a sudden onset of disease or acute cellular rejection without biopsy confirmation. Apart from that, patients who are immunocompromised or are treated with immunosuppressive drugs should be considered at increased risk for SARS-CoV-2 infection and should be prioritized for testing[46].

SARS-CoV-2 infected patients with ongoing antiviral treatment for hepatitis B or C should be continued, but the initiation of antiviral treatment for hepatitis C may need to be delayed. Patients with an underlying liver disease requiring immunosuppressants should be continued in cases of mild infection, but in moderate to severe infection, the treatment dosage of calcineurin inhibitors should be reduced. The position statement in the European Association for the Study of the Liver - European Society of Clinical Microbiology and Infectious Diseases recommended that the dose of immunosuppressant drugs can be adjusted according to antiviral treatment regimens because the drugs in both regimens will likely to interact with each other[48].

THE OUTCOME OF SARS-COV-2 INDUCED LIVER INJURY AND PREDICTORS OF INFECTIONS SEVERITY

The biomarkers of liver injury were significantly higher in severe cases of SARS-CoV-2 infection. In a meta-analysis by Henry *et al*[49], the severity and mortality rate of SARS-CoV-2 infection was related to the biomarkers of liver functions, which suggests that liver injury has a strong correlation with the severity of SARS-CoV-2 infection. A retrospective study that compares the clinical spectrum between patients with and without liver injury by Xie *et al*[7] found the hospitalization time was significantly longer in patients with liver injury. Lei *et al*[16] reported that abnormal AST in SARS-CoV-2 infection was associated with a higher risk of death during hospitalization than other indicators of liver injury. Kulkarni *et al*[50] said that the severity of elevated liver enzyme markers determines the outcome of SARS-CoV-2 infection, with the incidence of liver injury is as high as 58%-78% among the death cases. A multicenter study involving 2780 SARS-CoV-2 infected patients by Singh and Khan[9] found that patients with underlying liver disease had higher mortality and hospitalization. In addition to the abnormal liver biochemistry, hypoalbuminemia during the illness is also an important indicator of the severity of the SARS-CoV-2 infection. Both studies by Gong *et al*[51] and Huang *et al*[52] showed that hypoalbuminemia was associated with severe infection and an independent risk factor for death.

CONCLUSION

In conclusion, this review aims to illuminate the significance of liver injury in SARS-CoV-2 infection based on the descriptions from the scientific literature. Although it is common and mild in the majority of cases, it is a strong predictor of the severity and a significant risk factor for the mortality rate of the disease, especially if it is associated with male gender, older age, the presence of other comorbidities or underlying chronic liver disease, and in severe respiratory symptoms. Therefore, it is prudent to monitor SARS-CoV-2 infected patients with a liver injury and to individualize treatment for patients with an underlying disease who developed liver injury to improve the prognosis by delivering the appropriate management timely.

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