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An overview of SARS-COV-2-related hepatic injury

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of coronavirus disease 2019 (COVID-19), is highly contagious and has a variety of clinical manifestations, including liver injury. There have been a few reports indicating acute-on chronic liver failure among COVID-19 patients, however, patients with COVID-19-related liver injury are generally asymptomatic and present with a mild to moderate elevation in serum hepatic enzymes. Severe COVID-19 patients have high rates of liver injury with poorer outcomes. The pattern of abnormalities in liver biochemical indicators may be hepatocellular, cholestatic, or mixed. Although the pathogenesis of hepatic injury is not yet completely understood, causes of liver damage include systemic inflammatory response syndrome, ischemia-reperfusion injury, side effects of medications, and underlying chronic liver disease. While viral RNA has been detected in hepatocytes, it remains unknown if the coronavirus has the capacity to cause cytopathic effects in hepatic tissue. Additionally, it is important to remember that the current upheaval to daily life and access to healthcare caused by the COVID-19 pandemic has had a significant and negative effect on other patients with chronic liver disease. The objective of this review was to summarize the current literature on COVID-19-related hepatic injury with an examination of clinical features, potential pathogenesis, and histopathological findings of this entity.

Keywords: COVID-19; drug-induced liver injury; hepatic injury; hepatotoxicity; liver; SARS-CoV-2.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 led to a global pandemic and a significant medical crisis. As of January 25, 2021, the total number of cases of the disease caused by infection with SARS-CoV-2, coronavirus disease 2019 (COVID-19), was some 100 million worldwide, and the US led with approximately 25 million cases.[1] While patients with COVID-19 typically present with a fever, cough, and shortness of breath, mounting evidence shows that patients might also have extra-pulmonary involvement, including the liver. A growing body of evidence has shown that patients with COVID-19 may develop different degrees of liver dysfunction, primarily characterized by elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) accompanied by slightly increased bilirubin levels.[2–6] Liver involvement was also reported with SARS-CoV[7] and Middle East respiratory syndrome (MERS-CoV).[8]

The reasons for liver injury in COVID-19 patients may be multifactorial and can be delineated according to several mechanisms. It has been established that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor and the co-receptor (neuropilin-1) to enter host cells, and this entry is regulated by transmembrane protease serine 2 (TMPRSS2).[9–11] ACE-2 expression occurs at different densities. Cholangiocytes, and to a lesser extent, hepatocytes, can express ACE-2 receptors on the cell surface.[12,13] Therefore, theoretically, one mechanism for liver injury might be viral-induced cytopathic effects. Other potentially contributing effects are systemic inflammatory response syndrome,[14] ischemia-reperfusion injury,[15] drug-induced liver injury,[6] or underlying chronic liver disease.[16]

This review is based on a literature search of English-language articles published in the PubMed and MEDLINE databases as of December 2020.

Clinical Features of Hepatic Involvement in COVID-19

The prevalence of abnormal hepatic biochemical indicators in hospitalized patients with symptomatic COVID-19 ranges from 14% to 53%. The prevalence of hepatic injury among asymptomatic patients infected with SARS-CoV-2 is largely unknown. The most common abnormalities are mild elevation of transaminases, hypoalbuminemia, elevated gamma-glutamyltransferase (GGT), and hyperbilirubinemia.[17–21] Many studies have demonstrated high rates of liver function test (LFT) abnormalities in severe COVID-19 patients, such as intensive care unit patients and those requiring mechanical ventilation.[5,22] The pattern of LFT abnormality is generally hepatocellular, rather than cholestatic.[23,24] A high bilirubin level and liver stiffness observed with transient elastography has been reported to be correlated with more severe outcomes.[25,26] Although LFT abnormalities have been frequently encountered in COVID-19 patients, and may be associated with mortality, acute liver failure has been demonstrated in only a few patients with underlying chronic liver disease and multi-organ dysfunction.[27,28]

Another important point is that the hepatic injury in COVID-19 patients is usually assessed with LFT abnormalities in the current literature; elevated ALT and AST levels are the most frequent biomarker measures of hepatic parenchymal injury. Based on the available data, patients infected with SARS-CoV-2 generally have mildly to moderately elevated aminotransferase levels in the early stages of the disease, accompanied

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by a slight increase in bilirubin level.[29–31] In a study of 5700 individuals with COVID-19, ALT and AST abnormalities were detected in 39.0% (n=2176) and 58.4% (n=3263), respectively.[32] A meta-analysis of 108 studies encompassing 17,776 patients found abnormal aminotransferase levels in 24% of the patients (95% confidence interval [CI]: 17-31).[33] Consistent with those findings, another meta-analysis reported that the AST level was elevated in 15% of 2514 individuals in 16 studies and the ALT level was higher than the accepted normal level in 15% of 2711 patients in 17 studies (95% CI: 13.6-16.5 and 13.6-16.4, respectively).[34] Patients with high aminotransferase levels tended to have a higher body mass index and underlying chronic liver disease and were generally male and elderly.[29] Additionally, the prevalence of elevated transaminase and bilirubin levels has been reported to be at least double in cases of severe COVID-19.[35] However, myositis can produce elevated aminotransferases without the presence of a concomitant hepatic injury, and the level of creatinine kinase, a muscle damage marker, was reported to be elevated in 14% of patients with COVID-19 in a cohort from China.[4]

Evaluation of the albumin level and prothrombin time are standard tests to assess function of the liver. Zhang et al.[36] reported hypoalbuminemia in 55% of hospitalized COVID-19 patients. It was also found to be a factor associated with greater disease severity and an independent predictor of mortality.[37,38] Given the high inflammatory activity in COVID-19 patients, the level of albumin may decrease as a result of increased capillary permeability.[39] Higher catabolic activity and malnutrition may be additional factors that could result in hypoalbuminemia in severe COVID-19 cases. Alkaline phosphatase (ALP) and GGT are markers for biliary injury and cholestasis. The bilirubin level also provides important clues regarding hepatic clearance and biliary secretion capacity. However, none of these markers are sufficiently specific for liver functions.

Potential Pathogenesis of Hepatic Injury in COVID-19

The ACE-2 receptor is not only expressed in type-2 alveolar cells; abundant expression of ACE-2 has been found in cholangiocytes.[11] Hepatocytes can express ACE-2 receptors on the cell surface with less enrichment than cholangiocytes.[40,41] In addition, TMPRSS2 mRNA expression has been demonstrated in a subset of hepatocytes and cholangiocytes.[42]

There are 3 proposed mechanisms responsible for abnormality in LFTs among COVID-19 patients.

i. Viral Cytopathic Effects

Although SARS-CoV-2 particles and RNA have been identified in liver biopsy specimens of patients with COVID-19, productive infection of hepatocytes has yet to be demonstrated. Similarly, the low rate of clinically significant hepatic injury and ALP elevation in patients without pre-existing chronic liver disease or multi-organ failure suggests that direct infection of hepatocytes or cholangiocytes is not a main mechanism of hepatic injury. According to the available data, we may conclude that liver injury in COVID-19 most likely originates from systemic inflammation, underlying chronic liver disease, or multi-organ dysfunction, rather than a direct cytopathic effect of viral infection of liver cells.

ii. Immune-Mediated Hepatic Injury

As previously mentioned, COVID-19-related hepatic injury is more common in severe forms of COVID-19. It has been established that the antiviral response is mediated by joint action of the innate and adaptive immune systems. In brief, the immune system of human beings characteristically recognizes pathogen-associated molecular patterns (PAMPs) along with special viral antigens and expresses inflammatory molecules, such as cytokines and chemokines, in response. These molecules stimulate macrophages and T-cells to kill the virus and virus-infected cells.[43] Early elevation of several inflammatory cytokines (e.g., interleukin [IL] 6, IL-10, IL-2, interferon lambda [IFNλ]) have been found in the vast majority of COVID-19 patients.[44,45] This excessive cytokine response against the virus remains high and becomes a cytokine storm over the course of the disease in severe COVID-19 cases.[44,46] Patients with severe outcomes had increased levels of the inflammatory cytokines IFNλ, transforming growth factor alpha, thymic stromal lymphopoietin, IL-16, IL-23, IL-33, and coagulopathy-related mediators, such as thrombopoietin.[44] This kind of overreaction is called "cytokine storm syndrome," which can be associated with multi-organ failure and disseminated intravascular coagulation due to a dysregulated release of pro-inflammatory cytokines.[47,48] This uncontrolled inflammatory reaction can also result in endotheliitis, which has been identified in the hepatic tissue samples of the patients with COVID-19.[48] In a study that assessed liver samples taken at autopsy, the authors reported massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis, and microthrombi in the sinusoids.[49] Additionally, patients with severe COVID-19 have been found to have lower levels of stromal growth factors, such as epidermal growth factor, which mediate tissue healing and repair.[44]

The available evidence suggests that an exaggerated systemic immune response can be considered a major contributory factor to liver injury in COVID-19 patients.

iii. Drug-Induced Liver Injury

Many drugs, such as acetaminophen, antivirals, antibiotics, corticosteroids, and immune-modulators, utilized for symptom relief, treatment of accompanied bacterial infections, or COVID-19 itself, are potentially hepatotoxic. A meta-analysis reported a pooled incidence of drug-induced hepatic injury in 25.4% of COVID-19 patients.[19] Cai et al.[50] found that lopinavir-ritonavir use was associated with a 7-times higher odds of LFT alterations during the course of treatment. In contrast, a clinical trial of 199 patients with severe COVID-19 reported that LFT abnormalities were not more frequent in patients treated with lopinavir-ritonavir compared with those who received standard care.[51] It is necessary to note that a lopinavir-ritonavir regimen has now been almost abandoned in COVID-19 treatment, as has hydroxychloroquine.[52]

Remdesivir was found to significantly shorten the recovery time of hospitalized patients with COVID-19 and has been used as a standard of care therapy in some countries.[52,53] In a randomized controlled trial, the rate of abnormalities in aminotransferase levels among patients treated with remdesivir was 5% to 8% and 1% to 2% of all patients experienced significant increases in ALT/AST levels that would warrant discontinuation of therapy.[54] In a smaller double-blinded placebo-controlled trial in China, 155 patients treated with remdesivir were compared with 78 patients who received a placebo. In this study, 15 patients (10%) had an increased total bilirubin level, and severe hyperbilirubinemia was seen in only 1 patient. Similar to other studies, an AST abnormality was detected in 5% of patients, and no patient had grade 3 or 4 level adverse events related to elevation in AST level. Remdesivir treatment was discontinued in 18 patients (12%) because of severe adverse events. However, hepatic toxicity was not the cause of the event in any of these cases.[55] Furthermore, certain immunomodulator drugs, such as tocilizumab and dexamethasone, used to tame an uncontrolled immune response in severe COVID-19, can potentially lead to hepatic injury

by reactivating hepatitis B virus in patients with occult infections.[56,57] Other drugs, including baricitinib[58] and favipiravir,[59] are notoriously known to have the potential to cause hepatic injury.

Acetaminophen is frequently used to relieve COVID-19 symptoms of fever and body ache. Acetaminophen is the most common cause of drug-induced liver failure worldwide. However, no studies have so far specifically addressed its role in observed LFT abnormalities among COVID-19 patients.

Histopathological Findings of COVID-19-Related Hepatic Injury

Histopathological examinations of liver biopsies taken from patients with COVID-19 revealed that the most common findings were moderate macrovacuolar steatosis, and mild lobular and portal inflammation.[60,61] Findings suggesting acute hepatitis were detected in almost 50% of cases. The bile ducts were generally unaffected. However, changes may be related to baseline comorbidities and a variable degree of acute congestion may be seen. Additionally, SARS-CoV-2 RNA has been be identified in up to 55% of biopsy specimens.[61,62] Partial or complete sinusoidal thrombosis has been another important finding observed in histopathological examinations of postmortem wedge biopsies.[49] Another report of postmortem whole-body autopsy and macroscopic inspection study of 22 patients (18 patients with comorbidities and 4 patients without any comorbidity) conducted in Italy noted that liver parenchymal congestion was typically observed. Similar to previous reports, microscopic changes seen included sinusoidal congestion, red blood cell extravasation into the space of Disse, congestion of small veins, hepatocyte necrosis, and macrovacuolar and microvacuolar steatosis.[63] The available data suggest that most of pathological findings appear to originate from underlying co-morbidities and a systemic inflammatory response, rather than as direct SARS-CoV-2-related cytopathic effects.

The Impact of Underlying Chronic Liver Disease on Clinical Outcome in COVID-19 Patients

The prevalence rate of underlying chronic liver disease in patients with COVID-19 has been reported to range from 1% to 11%.[64–66] The liver is a well-known regulator of immune homeostasis. Therefore, patients suffering from chronic liver diseases, especially those with cirrhosis, may be at higher risk of acquiring SARS-COV-2 and COVID-19-related complications.[67] However, the current evidence shows no tendency towards increased susceptibility to SARS-CoV-2 infection in patients with chronic liver disease.[66] A large-scale study of 2780 COVID-19 patients reported that the patients with chronic liver disease had a 3-fold higher risk of mortality compared with patients without chronic liver disease, and this risk was substantially (~5-fold) higher in patients with cirrhosis.[68] Similarly, Sarin et al.[69] confirmed a higher rate of severe liver injury and death in patients with more advanced stages of liver disease following SARS-CoV-2 infection, particularly in patients with a Child-Pugh score of ≥9. However, the current literature is inconsistent in this regard, since no association was observed between pre-existing liver disease and COVID-19 severity or mortality in another study.[70] It should be kept in mind that chronic liver disease includes a spectrum of diseases that may have the potential to change outcomes. For instance, liver transplant recipients and patients with autoimmune liver disease who use immunosuppressive drugs merit special concern with regard to COVID-19-related outcomes. However, the current literature is not yet sufficient to indicate that these patients have a higher risk of infection or a higher likelihood of serious complications compared with the general population.[71–74]

The other important type of chronic liver disease that should be noted is non-alcoholic fatty liver disease (NAFLD). Patients with NAFLD have exhibited more rapid disease progression and a longer duration of viral shedding compared with those without NAFLD.[16] Similarly, a higher risk of severe disease has been reported when NAFLD was found with co-existing obesity, in younger patients and in patients with high hepatic fibrosis scores.[75–77] Given the profound immunological changes seen in obesity, such as low-grade inflammation and macrophage activation, it is likely that similar changes in the immune system of patients with NAFLD play an important role in the higher rate of severe COVID-19 in these patients.[77,78] In addition, NAFLD significantly increases the hepatotoxic potential of some drugs, including acetaminophen, which may result in a higher incidence of the LFT abnormalities in NAFLD patients during the course of COVID-19.[79] As most studies have not stratified patients with NAFLD according to the presence of non-alcoholic steatohepatitis (NASH), it is still unknown whether more severe outcomes stem from the presence of NASH rather than NAFLD.

In addition to patients with NAFLD, patients with alcohol-associated liver disease (ALD) may be at particular risk of severe COVID-19. Excessive alcohol use weakens the anti-infective defense mechanisms of the human body by disrupting both the innate and adaptive immune systems.[80] Moreover, accompanying comorbidities, such as obesity and use of corticosteroid therapy for alcoholic hepatitis, may increase the risk of severe COVID-19. Likewise, concurrent smoking, which is frequent among patients with ALD, makes these patients vulnerable to COVID-19-related mortality and morbidity. At the time of writing, there are not enough data regarding the impact of COVID-19 on ALD. Nevertheless, SARS-CoV-2 infection, particularly a severe infection, can act as a significant decompensating factor in patients with ALD.

The current pandemic has created unbearable difficulties for healthcare services around the world. Limited access to healthcare centers and the deferral of all non-urgent diagnostic and screening tests or treatments have led to an unprecedented upheaval in the care of patients with chronic liver disease.[81] For instance, postponement of prophylactic screening and treatment of esophageal varices, insufficient hepatocellular carcinoma screening in cirrhotic patients, and a significant decrease in organ donation and liver transplantation will have long-term adverse outcomes that cannot be compensated for with future interventions.[82] In addition, measures to control the spread of the virus, including social distancing and curfews, have resulted in negative influences on the mental health of patients and provoked alcohol addiction relapse and abuse, which can aggravate ALD.[83]

Conclusion

LFT abnormalities are commonly seen in COVID-19 patients on admission or during follow-up. Although the underlying pathogenesis of hepatic injury in COVID-19 is not fully understood, a direct viral cytopathic effect seems unlikely at this time. Hepatic injury associated with COVID-19 seems to correlate with the severity of inflammatory response and ensuing multi-organ dysfunction, the presence of pre-existing chronic liver disease, or exposure to hepatotoxic drugs. Additionally, patients with NAFLD and cirrhosis have an increased risk of severe disease independent of other concomitant comorbidities. Last, but not least, healthcare professionals should be aware that restrictions on access to healthcare can have serious short- and long-term effects on morbidity and mortality associated with chronic liver disease.

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