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MINIREVIEWS

Impact of COVID-19 on liver

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Abstract

The incidence of liver injury after coronavirus disease 2019 (COVID-19) infection ranged from 15%-53%. The mechanism includes direct viral cytopathic effect, cytokinesis, and treatment drug-induced liver injury. The symptoms include nausea, vomiting, diarrhea, and loss of appetite. The laboratory results include increased liver enzyme levels, decreased monocyte count, and longer prothrombin time. The most common imaging findings are hepatomegaly on ultrasound, ground-glass opacity on chest computed tomography (CT), and liver hypodensity and pericholecystic fat stranding on abdominal CT. Patients may also have different presentations and poor outcomes of different liver diseases concomitant with COVID-19 infection. Liver function test (LFT) results should be monitored, and all factors known to cause or predispose liver injury should be investigated while managing the patients. The risks of transfer to an intensive care unit, need for mechanical ventilator support, and acute kidney injury is higher in COVID-19 patients with than without abnormal LFTs. Increased mortality and length of hospital stay are both observed.

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Core Tip: The main cause of mortality in coronavirus disease 2019 (COVID-19) infection is a respiratory complication, but the liver is one of the most affected organs after the respiratory system. The incidence of liver injury after COVID-19 infection ranges from 15%-53%. COVID-19-infected patients with liver injury may have higher liver enzyme levels, lower monocyte count and longer prothrombin time than those without liver injury. The risks of transfer to an intensive care unit, need of mechanical ventilator support, and acute kidney injury are higher in COVID-19 patients with, than in those without, abnormal liver function tests. Increased mortality and longer length of hospital stay are both observed.

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INTRODUCTION

Two coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), which caused relatively recent epidemics in 2003 and 2012 share genome sequence similarity and sequence homology[1]. Since December 8, 2019 in Wuhan, Hubei province, China, several novel and atypical pneumonia cases were found, the pathogen was identified by the Chinese Center for Disease Control and Prevention, and it was named SARS-CoV-2 by the World Health Organization on 11 February 2020. The virus spread rapidly by human-to-human transmission, and by March 3, 2021, the coronavirus disease 2019 (COVID-19) pandemic had spread to 223 countries and regions causing 11517155 confirmed cases, and 2554207 deaths (https://www.worldometers.info/coronavirus/?). SARS-CoV-2 affects more men than women, and common presentations include cough, fever, flu symptoms, rhinorrhea, muscle aches, sore throat, dysgeusia, anosmia, vascular thrombosis, and shortness of breath[2-4]. COVID-19 patients with a history of heart failure, renal insufficiency, male gender, older age, higher lactate dehydrogenase, and thrombocytopenia have poor outcomes with higher mortality and in-hospital complications[5,6].

During the previous SARS epidemic, around 60% of patients developed various degrees of liver damage, and MERS-CoV caused pathological changes including lymphocytic portal inflammation, perivenular congestion, hemorrhage, and loss of hepatocyte[7,8]. Based on genome sequence homology it is possible that COVID-19 also causes liver injury. It is well known, the main cause of mortality in COVID-19 infection is upper and lower respiratory tract infection-related respiratory failure. But there is still some extrapulmonary involvement of SARS-CoV-2 infection in organs such as the liver, kidneys, or heart[9,10]. The liver is one of the most affected organs other than the respiratory system in COVID-19 infection[11].

According to a study from México, the incidence of liver injury after COVID-19 infection ranged from 15%-53%. Those who had liver injury caused by COVID-19 infection had higher levels of alanine aminotransferase (ALT) and aspartate transaminase (AST), total bilirubin, and lower serum albumin[12]. Another study reported that mortality and the severity of COVID-19 infections were significantly related to liver dysfunction and increased AST levels[13]. In addition, that COVID-19 patients with preexisting liver disease are at higher risk for hospitalization and death[14]. Herein we performed a comprehensive review of liver injury caused by COVID-19 infection, including prevalence, pathophysiology, mechanism, symptoms and signs, laboratory data, image presentation, the situation with concomitant liver diseases (viral hepatitis, fatty liver, liver cirrhosis, hepatoma), management, outcome, and prognosis.

PREVALENCE OF LIVER DYSFUNCTION AFTER COVID-19 INFECTION

Liver injury can be multifactorial and heterogeneous in nature, therefore extensive workup and continuous surveillance during the disease course is required to evaluate their clinical relevance. Most important, we need to determine whether liver injury is related to an underlying liver disease, drugs used for treatment or the direct effect of the virus, or dysregulation innate immune response[15]. A report from United States disclosed that 25% of COVID-19 patients had hepatic injury[11]. In such patients, the elevation of liver enzymes (AST and ALT) were usually less than five-fold above the upper reference limit and increased inflammatory markers were seen in severe cases [16]. The median age of liver dysfunction after COVID-19 infection was 50 years, with a male predominance (56%)[17]. Only 2% of cases had preexisting liver diseases. There was no correlation between the presence of acute liver injury (ALI) and gastrointestinal symptoms, but increases AST and ALT levels caused increasing rates of admission to intensive care units (ICU)[17].

PATHOPHYSIOLOGY

COVID-19 infection causing liver injury and gastrointestinal dysfunction lead to presentation of extrapulmonary symptoms such as nausea, vomiting, diarrhea, and loss of appetite. The pathophysiology of ALI after COVID-19 infection includes direct invasion of SARS-CoV-2 Leading to destruction of hepatocytes, endotheliitis-related vascular coagulopathy or thrombosis, inflammatory cytokine storm, hypoxia/ischemia reperfusion injury and drug-induced liver injury (DILI) caused by the use of acetaminophen, lopinavir/ritonavir, and remdesivir[16,18].

MECHANISM

Direct viral cytopathic effect

In most cases, viruses exert have a direct cytopathic effect on hepatocytes and cholangiocytes. The postulated mechanism of viral entry is through the host angiotensin-converting enzyme 2 receptors expressed in the gastrointestinal tract, vascular endothelium, and liver cholangiocytes. Furthermore, approximately 10% of patients with COVID-19 present with diarrhea[19], and SARS-CoV-2 RNA has been detected in stool and blood samples. Gamma-glutamyl transferase (GGT) released by injured cholangiocytes, indicates the likelihood of viral exposure in the liver. GGT was found to be elevated in 30 (54%) of 56 patients with COVID-19 during hospitalization[20].

Additional evidence of direct cytopathic liver injury by SARS-CoV comes from autopsy studies that detected SARS-CoV in 41% of the liver tissue samples, with a maximum viral load of 1.6×10^{6} copies/g[21,22]. A recent autopsy analysis of liver tissue from a patient with COVID-19 found microvesicular steatosis and inflammation in the lobular and portal area. However, that is not specific for COVID-19 and histological injury can also be observed during sepsis or a variety of DILI[23]. COVID-19 can also directly lead to presentation of acute hepatitis[24].

Cytokinesis

Activation of the immune system and dysregulation of the innate immune response can occur in the context of liver injury during COVID-19 infection. Pneumonia-associated hypoxia may also contribute to ischemic liver injury which frequently develops in critically ill patients with COVID-19 infection. Patients with COVID-19 frequently exhibited marked activation of C-reactive protein, lymphocytes, neutrophils, and cytokines, in particular interleukin-6[20]. Not many clinical studies have investigated the release of cytokines from the gastrointestinal mucosa of COVID-19 patients, but it is possible that hepatic dysfunction may result from cytokine storm rather than only by direct cytopathic effects of the virus. If that is the case, control of cytokine dysregulation at an early stage would help to curb disease progression.

TREATED MEDICINE RELATED DILI

DILI is an important consideration in patients with COVID-19 because the liver is involved in the metabolism of nucleoside analogs and protease inhibitors that are well

known for their hepatotoxicity. A recent randomized controlled trial of lopinavir and ritonavir in severe COVID-19 reported adverse liver effects in some patients[25]. A case series from Wuhan reported that 55.4% in 99 patients experienced liver injuries after treatment with lopinavir and ritonavir[26]. Azithromycin may cause cholestatic hepatitis within 1–3 wk after starting treatment and has also been associated with hepatocellular injury. Interferon β has been shown to cause hepatic injury, most often appearing as transient with mild elevations in serum aminotransferase levels. Imatinib has been reported associated with rare instances of clinically apparent ALI with jaundice[27]. Tocilizumab, an interleukin-6 receptor antagonist, has been used to treat COVID-19, and first reported adverse reaction, 40-fold elevation of serum transaminase level, resolved in 10 d[28].

The results of ongoing studies, especially randomized clinical trials, could resolve the current uncertainties around remdesivir. New clinical trials using a combination of inhaled and intravenous remdesivir improved the efficacy of antiviral therapy against SARS-CoV-2[29]. The most common adverse reactions, those with an incidence of 5% of all grades, observed with remdesivir treatment were nausea and increased ALT and AST increased[30]. Hepatotoxic antiviral medications require careful monitoring of adverse effects.

SYMPTOMS AND SIGNS OF LIVER DYSFUNCTION IN COVID-19 INFECTION

Symptoms of liver dysfunction can include fever, fatigue, anorexia, nausea, vomiting, diarrhea, abdominal pain, dark urine, and jaundice. However, except for tea colored urine and jaundice, most symptoms are nonspecific. Manifestations of COVID-19 range from no symptoms to severe illness and mortality. Most manifestations of COVID-19 are respiratory and systemic, such as fever (65.9%), cough (23.5), malaise (23.5%), and sore throat (12.9%)[31]. The most common digestive manifestations are loss of appetite (98%), nausea (73%), vomiting (65%), and diarrhea (37%)[32]. Although abnormal liver function is mentioned in many studies, symptoms/signs of liver-related complications such as jaundice or dark urine of COVID-19 are rarely described [31-35]. A case report of 59-year-old woman initially presenting with dark urine and acute hepatitis included a diagnosis of COVID-19. However, her clinical condition was complicated with a medical history of human immunodeficiency virus infection, hypertension, hyperlipidemia, Graves' disease, and left facial paralysis. The evidence of the relationship between acute hepatitis and COVID-19 was not strong[36].

LABORATORY FINDINGS IN LIVER DYSFUNCTION AFTER COVID-19 INFECTION

Serum aminotransferases are sensitive markers of hepatocellular injury[37]. Although elevations in aminotransferases are most often mild *i.e.* one or two times the upper limit of normal (ULN), severe liver injury has been reported[34]. COVID-19 patients with digestive symptoms may have increased liver enzyme levels, lower monocyte counts, and longer prothrombin times[38]. In a study of 417 patients with COVID-19, 76.3% had abnormal liver tests and 21.5% had liver injury during hospitalization[39]. In a large United States cohort, 45% of COVID-19 patients had mild, 21% had moderate, and 6.4% had severe liver injury, mild if ALT was elevated but less than two times ULN, moderate if it was between two and five times the ULN, and severe if it was more than five times the ULN[34]. In a meta-analysis of 64 studies with 11,245 COVID-19 patients, the prevalence of elevated AST was 23.2%, and it was 21.2% for ALT, 9.7% for total bilirubin, 15.0% for GGT, and 4.0% for ALP[40].

IMAGING FINDINGS IN LIVER DYSFUNCTION AFTER COVID-19 INFECTION

A study of critically ill COVID-19 patients reported ultrasound ultrasound findings of hepatomegaly in 56% of patients (23/41). Biliary problems, such as cholecystitis, the thickness of gall bladder wall, and prominent common bile duct were found in 41.4% of patients (17/41)[41]. Sonographic findings of ALI, including signs of acute hepatitis

(*e.g.*, thickening of the gall bladder wall, hepatomegaly, and decreased echogenicity of the liver parenchyma) and vascular complications, appeared in 48.7% of COVID-19 ICU patients and 37.3% of COVID-19 patients[42]. In COVID-19 patients, ground-glass opacity was the most common finding (56.4%) on chest computed tomography (CT) on admission[43]. Abdominal CT scan findings were rarely mentioned. One retrospective cohort study included 115 patients with COVID-19. The findings of upper abdominal CT scans were liver hypodensity (26.09%) and pericholecystic fat stranding (21.27%). Liver hypodensity was more frequently found in critical cases (58.82%)[44].

LIVER DYSFUNCTION IN LIVER DISEASE CONCOMITANT WITH COVID-19 INFECTION

Viral hepatitis

In a large United States cohort, 5% of patients had chronic liver disease. The most common etiologies were HBV (0.7%), HCV (1.9%), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (1.9%), and alcohol-related liver disease (ALD) (0.5%)[34]. A large study enrolling 5700 COVID-19 patients from the New York area reported that 0.1% were coinfected with either HBV or HCV patients[45]. A study of 253 patients in China found that 20.2% had liver diseases prior to acquiring COVID-19, 5.9% had hepatitis B, 8.7% had fatty liver, 5,5% had hepatic cysts, and 2.0% had cholecystopathy[46]. Underlying liver diseases such as chronic HBV or HCV could have contributed to elevated liver enzyme abnormalities. Previous studies have shown that SARS patients with HBV or HCV infection were more likely to develop severe hepatitis[35]. In a study from China, 2.1% patients had HBV infection. Patients infected with HBV were more likely to have severe illness (2.4%) than those without severe illness (0.6%)[35,43]. In an electronically retrieved cohort of COVID-19 patients with or without HCV infection from a veterans database, the mean FIB-4 score was higher in those with HCV (1.9 ± 2.1 *vs* 1.2 ± 0.9; $P < 0.0001$) and a larger proportion of those with HCV had cirrhosis (8.1% *vs* 1.4%; $P < 0.0001$). However, mortality was not increased in CODIV-19 infected persons with HCV infection (6.6% *vs* 6.5%; $P = 0.9$)[47].

Fatty liver

The presence of metabolic-associated fatty liver disease (MAFLD), a new term used to describe NAFLD, had a 6.3- to 6.8-fold increased risk of respiratory disease progression compared with its absence. MAFLD is diagnosed by evidence of hepatic steatosis and one of the following three criteria: overweight or obesity; type 2 diabetes mellitus; or metabolic dysregulation. Obesity is of greater risk for respiratory infection factors, and diabetes mellitus patients have a three-fold increased risk of developing critical illness[48,49]. The duration of viral shedding was reported to be longer in COVID-19 patients with MAFLD (12.1 d) than in those without MAFLD (5.4 d)[48]. During COVID-19 treatment, MAFLD might enhance the risk of DILI. Some drugs might be hepatotoxic when use in obese patients with MAFLD compared with lean individuals[50].

Liver cirrhosis

A large study of 5700 hospitalized patients in the New York area reported cirrhosis in 0.4% of the COVID-19 patients[45]. The rate was lower than in a previous study in Korea in 2020, which reported that 1.4% of COVID-19 patients ($n = 1005$) had liver cirrhosis, and 4.7% had had liver-related comorbidities[51]. People with both COVID-19 infection and liver cirrhosis had a 5-fold increased risk of pneumonia; increases of 4.1-fold for acute kidney injury (AKI); 4-fold for mortality; 3.8-fold for ICU admission; 3.3-fold for acute respiratory distress syndrome; 3.5-fold for the use of high flow oxygen therapy; and 2-fold oxygen therapy compared with those without cirrhosis[51,52]. Liver cirrhosis is an independent predictor of developing severe COVID-19 and of worse liver-related outcomes, including increased hospitalization and mortality compared with those with noncirrhotic liver disease[53,54]. A report from United States in 2020, COVID-19 Patients with liver cirrhosis had 2.3-fold greater mortality compared with COVID-19 patients without liver cirrhosis, with mortality reaching 30%[55].

Hepatoma

In September 2020, a report from California disclosed that hepatocellular carcinoma (HCC), had a higher hazard ratio (3.31) than decompensated cirrhosis (2.91) and ALD

(2.42) as independent risks of overall mortality in COVID-19 infection concomitant with liver-specific diseases[56]. Inevitably, during the COVID-19 pandemic, people may experience decreased availability of health care. A study in France reported that during the first 6 wk of the COVID-19 pandemic in 2020, 21.5% of HCC patients experienced a treatment delay of more than 1 mo compared with 9.5% in the same period in 2019[57].

MANAGEMENT

In addition to treating the respiratory syndrome in COVID-19, liver function tests (LFTs) should be done and all factors known to cause or predispose to liver injury should be investigated while managing the patient[58]. In patients with mild liver test abnormalities of one or two times the ULN, close observation and flow-up is necessary. Test results more than three times the ULN, during hospitalization indicate more severe liver injury. Patients with abnormal liver function test (LFT) results have been found more likely to develop severe COVID-19[46].

Medications known to insult the liver must be used carefully and LFTs should be performed at regular intervals. To resolve the symptoms of COVID-19, acetaminophen 500 mg every 6 h daily, or nonsteroidal anti-inflammatory drugs are all acceptable to manage fever and discomfort. It is well known that remdesivir can shorten the time to recovery from COVID-19 infection but elevations in transaminase levels have been observed with remdesivir use in clinical trials. Consequently, remdesivir should not be prescribed in patients with transaminase that are five times or more the ULN at baseline[59]. Patients who do not require oxygen or ventilator support do not benefit from dexamethasone, which has a role as a treatment of cytokine storm by regulating the immune system to prevent debilitative inflammation seen in critically ill patients, especially those who need oxygen or mechanical ventilator support[59].

SEQUELAE, OUTCOME, AND PROGNOSIS

COVID-19 patients with abnormal LFTs had 2.5-fold increased rate of transfer to the ICU; and increases of 2.3-fold for need of mechanical ventilator support and 1.7-fold for AKI. The mortality rate was 21%, or 1.9-fold higher than COVID-19 patients without abnormal LFTs[60]. That is, in COVID-19 patients, liver injury is associated with systemic inflammation and organ dysfunction and is an independent predictor of transfer to the ICU or death[60]. COVID-19 patients with abnormal LFTs were also found to have a 2.3 d longer length of stay (15.1 d *vs* 12.8 d) than COVID-19 patients whose LFTs were normal[61]. Patients with COVID-19 infection and were HBV carriers had a 32.9% rate of severe illness, which was 2.2-fold higher than that in COVID-19 patients who were not HBV carriers[62]. There was no significantly difference in the length of stay of COVID-19 patients with or without HBV infection (15.9 *vs* 15.7 d)[62].

Extrapulmonary insults in COVID-19 patients, like liver or renal injury may indicate extensive, severe inflammatory responses and might have a role in increasing mortality. A mortality rate 28.6% has been reported in cirrhotic COVID-19 patients, which was 2.9-fold higher than the mortality of COVID-19 patients without liver cirrhosis[51]. In decompensated cirrhosis with COVID-19 infection, liver injury was progressive in 57% of the patients and mortality was 43%[63]. Prevention of viral entry into the body reduces transmission and avoids infection. Keeping suitable social distancing, frequent washing of hands with water and soap for at least 20 s, wearing masks while in public areas, staying home as much as possible, cleaning and disinfecting surfaces at home, and avoiding contact with those who might be infected are all practical strategies that should performed by everyone.

CONCLUSION

The main cause of mortality in COVID-19 infection respiratory failure caused by infection of the upper and lower respiratory tract. The liver is one of the most affected organs other than the respiratory system. Evaluation of patients suspected of having COVID-19 infection, should pay careful attention to symptoms and signs of digestive manifestations in addition to the main pulmonary presentations. If liver dysfunction is

ruled in, then liver enzyme levels, monocyte count, and prothrombin time should be checked. Abdominal ultrasound and CT of the chest and abdomen should be depending on different case conditions. The concomitant liver disease, (*e.g.*, viral hepatitis, fatty liver, liver cirrhosis, or hepatoma), needs to be confirmed. As for management, medications known to insult the liver must be used carefully and LFTs should be monitored at regular intervals.

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