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Association between COVID-19 and chronic liver disease: Mechanism, diagnosis, damage and treatment

Qi RB *et al*. COVID-19 and CLD

Abstract

As the outbreak evolves, our understanding of the consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) on the liver has grown. In this review, we discuss the hepatotropic nature of SARS-CoV-2 and describe the distribution of receptors for SARS-CoV-2 (*e.g.,* angiotensin-converting enzyme 2) in the vascular endothelium and cholangiocytes of the liver. Also, we propose mechanisms for possible viral entry that mediate liver injury, such as liver fibrosis. Due to SARS-CoV-2-induced liver damage, many COVID-19 patients develop liver dysfunction, mainly characterized by moderately elevated serum aminotransferase levels. Patients with chronic liver disease (CLD), such as cirrhosis, hepatocellular carcinoma, nonalcoholic fatty liver disease, and viral hepatitis, are also sensitive to SARS-CoV-2 infection. We discuss the longer disease duration and higher mortality following SARS-CoV-2 infection in CLD patients. Correspondingly, relevant risk factors and possible mechanisms are proposed, including cirrhosis-related immune dysfunction and liver decompensation. Finally, we discuss the potential hepatotoxicity of COVID-19-related vaccines and drugs, which influenced the treatment of CLD patients with SARS-CoV-2 infection. In addition, we suggest that COVID-19 vaccines in terms of immunogenicity, duration of protection, and long-term safety for CLD patients need to be further researched. What's more, the diagnosis and treatment for liver injury caused by COVID-19 are also analyzed in this review. Here is a summary of each paragraph of the article.

Key Words: SARS-CoV-2; COVID-19; Chronic liver disease; Angiotensin-converting enzyme 2; Hepatotoxicity; Calcineurin inhibitors

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Core Tip: In this review, we discuss the hepatotropic nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and describe the distribution of receptors for SARS-CoV-2 (*e.g.*, angiotensin-converting enzyme 2) in the vascular endothelium and cholangiocytes of the liver. Also, we propose mechanisms for possible viral entry that mediate liver injury, such as liver fibrosis. Due to SARS-CoV-2-induced liver damage, many coronavirus disease 2019 (COVID-19) patients develop liver dysfunction. We discuss the longer disease duration and higher mortality following SARS-CoV-2 infection in chronic liver disease patients. Correspondingly, relevant risk factors and possible mechanisms are proposed. Finally, we discuss the potential hepatotoxicity of COVID-19-related vaccines and drugs.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 31 December 2019, World Health Organization first learned about this new virus from a set of cases of viral pneumonia reported in Wuhan, People's Republic of China. The most common symptoms of COVID-19 are: Fever, dry cough, fatigue. In particular, symptoms of severe COVID-19 often present with dyspnea, loss of appetite, confusion, and high fever. Of those who develop symptoms, the majority (about 80%) do not require hospitalization to recover. About 15% of patients are severely ill and require oxygen. And 5% of patients are critically ill and require intensive care.

Complications of death from COVID-19 may include respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiple organ failure, including heart, liver, or kidney damage. In particular, people aged 60 and older, as well as those with underlying medical conditions such as high blood pressure, cardiorespiratory problems, diabetes, obesity, or cancer, are at higher risk of developing severe COVID-19.

Currently, individual COVID-19 vaccines have been licensed for use by regulatory agencies in some countries, and many potential COVID-19 vaccine candidates are under

development. And this article analyzes and summarizes the COVID-19 from four aspects: Mechanism, diagnosis, damage and treatment.

MECHANISM

Our understanding of the hepatic consequences of SARS-CoV-2 infection and the resulting COVID-19 has evolved rapidly since the beginning of the pandemic[1]. Many reports showed that many COVID-19 patients had chronic liver disease (CLD) of varying degrees. In particular, COVID-19-related liver injury refers to any liver injury that occurs in patients with COVID-19 during the course and treatment of the disease, regardless of pre-existing liver disease[2-8].

Several studies have shown that SARS-CoV-2 can bind to the host angiotensin-converting enzyme 2 (ACE2) receptor, allowing the virus to enter cells and actively replicate in the liver[9-11]. Notably, severe disease outcomes depend on the high affinity of the virus to ACE2[12]. ACE2 expresses in multiple organs, such as the lung, gastrointestinal tract, and liver[13-15]. In the liver, ACE2 is expressed at a low level in hepatocytes, with a positive rate as low as 2.6%[16]. However, it is highly enriched (59.7%) in cholangiocytes, similar to the expression levels in the type II alveolar cells (primary target cells of SARS-CoV-2 in the lung)[17,18]. Therefore, the virus may directly infect bile duct cells but not hepatocytes[13]. Viral infection could lead to cholangiocytes apoptosis accompanied by mitochondrial swelling, endoplasmic reticulum expansion, reduction of glycogen granules, and extensive necrosis[19,20].

Besides, SARS-CoV-2 infection can lead to severe host hyper immunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. Cytokine storm syndrome may induce a massive release of multiple pro-inflammatory cytokines and inflammatory markers[23], leading to tissue damage and multiple organ damage or failure, including the liver[24]. Cytokine storms caused by virus-induced excessive immune response may be one of the pathways of the CLD[25,26].

In addition, liver disease worsens because of COVID-19 complications, including coagulation disorders and cardiac and respiratory failure. These complications induced diffuse intravascular coagulation, ischemia, and hypoxia in the liver. All of these can lead to upregulation of fibrotic pathways, fatty acid oxidation, oxidative phosphorylation, and dysregulation of markers of immune activation. And these are also the potential pathological mechanisms of extensive liver injury[27].

DIAGNOSIS

Liver biochemical abnormalities are common in COVID-19-related CLD patients, occurring in approximately 15%-65% of SARS-CoV-2 infected individuals[28-35]. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated lactate dehydrogenase (LDH) levels[12,16,36-40]. However, COVID-19 may cause damage to multiple other organs, including cardiac, skeletal, and kidneys. Skeletal muscle and myocardial injury can also lead to elevated serum transaminases and LDH levels. In addition, hypoalbuminemia was reported to be a nonspecific marker of disease severity associated with poor COVID-19 prognosis[39]. Therefore, the severity of CLD during the COVID-19 course can be effectively judged by detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations.

DAMAGE

Invasion of SARS-CoV-2 may lead to significant systemic disease involving the gastrointestinal tract, liver, biliary tract, and pancreas[12]. Most patients with SARS-CoV-2 infection are asymptomatic or have mild symptoms, including fever, cough, loss of smell, and headache[1]. However, approximately 15% of patients would develop severe lung disease within ten days, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death[41-43].

COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases, including hypertension, cardiovascular disease, type 2 diabetes, chronic lung

disease, and metabolic syndrome[44,45]. In particular, people at high risk for severe COVID-19 are usually the elderly and those with comorbidities[36]. In addition, obese patients who frequently develop the metabolic dysfunction-associated fatty liver disease are also at high risk of developing severe COVID-19 due to the role of acutely active inflammatory pathways[19,37]. Infection with SARS-CoV-2 can increase the severity of viral hepatitis, and its clearance in patients is delayed. For those underlying undetected liver diseases, especially nonalcoholic fatty liver disease and cirrhosis, the prevalence of COVID-19 is significantly increased, and the prognosis will be worse[46]. For CLD patients, especially those with advanced liver disease, SARS-CoV-2 infection may seriously jeopardize survival and exacerbate liver failure in the case of the diminished liver reserve[47,48].

In conclusion, SARS-CoV-2 can cause CLD in the following aspects, including direct cytopathies (SARS-CoV-2 invades liver cells and causes cytopathic effects leading to liver dysfunction in COVID-19 patients); immune-mediated (SARS-CoV-2 infection leads to a disordered inflammatory response and increased pro-inflammatory cytokines, which in turn triggers severe liver dysfunction); hypoxia/ischemia (in severe COVID-19, multiple organ dysfunction can lead to hypoxia-related acute respiratory distress syndrome[49], hypotension[50] or congestive heart failure, which in turn leads to liver dysfunction); microvascular thrombosis.

TREATMENT

CLD is common worldwide. The rapid spread of COVID-19 has resulted in infections in many patients with underlying CLD. Immunosuppression therapy is meaningful for both COVID-19 and CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders. First, calcineurin inhibitors (CNIs), including cyclosporine or tacrolimus, are considered the basic drugs for immunosuppression in treating CLD[51]. They are often used with mycophenolate mofetil (MMF) or everolimus to reduce plasma levels. Their use avoids the adverse effects of cyclosporin A binding to the intracellular receptor cyclosporine to form an

active complex. This may inhibit the phosphatase activity of calcineurin. Second, immunosuppressants such as MMF and CNIs have been shown to have antiviral activity against coronaviruses[52]. There is evidence that CNIs have direct antiviral effects. Cyclosporine can block replication of all coronavirus genera, including SARS-CoV. Similarly, mTOR inhibitors (*e.g.*, tacrolimus) have antiviral properties in addition to their immunosuppressive and antiproliferative effects. And glucocorticoids for COVID-19 have been shown to prevent the disturbances in the immune response that lead to the poor prognosis of COVID-19[53].

The side effect can't be ignored, despite the indispensable role of immunosuppression therapy in COVID-19-related CLD. Immunosuppression induced by these drugs may increase susceptibility to SARS-CoV-2 infection[54] and secondary bacterial or fungal infection. Besides, it may also prolong viral clearance time[55]. Related research shows that patients using immunosuppressive drugs have an increased average risk of SARS-CoV-2 infection. Therefore, experience suggests that reducing MMF or mTOR inhibitors remains beneficial for managing immunosuppression during SARS-CoV-2 infection. What's more, patients who received thiopurines and glucocorticoids before the onset of COVID-19 have a higher risk of severe COVID-19 than CLD patients who were not receiving immunosuppressive therapy[56]. In particular, patients with severe COVID-19 infection may need to consider dose adjustment of steroids, CNIs, or mycophenolate to reduce the effect of liver injury.

In addition, currently prescribed drugs for COVID-19 (*e.g.*, oseltamivir, lopinavir/ritonavir, and chloroquine) are all metabolized in the liver. Although there is currently no recognized effective antiviral drug for COVID-19, nearly half of the critically ill patients were prescribed antiviral drugs such as oseltamivir, abidol, lopinavir, and ritonavir[57]. These antiviral drugs may cause abnormal liver function. In particular, patients with CLD, such as hepatitis B or C, may have elevated aminotransferase levels before treatment, which may increase the risk of drug-induced liver injury (DILI)[46]. Therefore, attention should be paid to abnormal liver test indicators during the treatment process to reduce DILI[58].

In summary, the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 must be balanced. The effects of drugs on liver toxicity, steatosis, necroinflammation, fibrosis, and biological metabolism should be comprehensively considered when treating COVID-19. This is beneficial to avoiding serious DILI while exerting a sufficient immune response and antiviral effect[12].

Finally, although these patients have compromised immune responses, immediate and long-term protective responses through immunization may not be complete for the protective measure of vaccination. However, early vaccination against various pathogens, including SARS-CoV-2 in patients with CLD remains essential and effective[59]. And a small number of patients have mild jaundice (slightly elevated bilirubin levels).

CONCLUSION

Above all, SARS-CoV-2 can bind to the host ACE2 receptor, allowing the virus to enter cells and actively replicate in the liver. And severe disease outcomes depend on the high affinity of the virus to ACE2. Besides, SARS-CoV-2 infection can lead to severe host hyper immunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. This leads to tissue damage and multiple organ damage or failure. In addition, symptoms due to COVID-19 complications are also underlying pathological mechanisms of extensive liver injury.

Liver biochemical abnormalities are common in COVID-19-related CLD patients. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated LDH levels. And the severity of CLD during the COVID-19 course can be effectively judged by detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations.

Invasion of SARS-CoV-2 may lead to significant systemic disease, some can even develop severe lung disease, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death. Typically, COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases. Besides,

SARS-CoV-2 can cause CLD in four aspects, including direct cytopathies, immune-mediated, hypoxia/ischemia and microvascular thrombosis.

Immunosuppression therapy is meaningful for both COVID-19 and CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders. Common immunosuppressive drugs include CNIs and mTOR inhibitors. Medication side effects need to be considered during treatment, including increasing susceptibility to SARS-CoV-2 infection and secondary bacterial or fungal infection and prolonged viral clearance. In addition, currently prescribed drugs for COVID-19 are all metabolized in the liver, and these antiviral drugs may lead to abnormal liver function. Therefore, it is necessary to balance the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19, and minimize the use and dosage of immunosuppressants to reduce the impact of liver damage.

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