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REVIEWS

A neglected complication of COVID-19: liver injury

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[Abstract] Coronavirus disease-2019 (COVID-19) not only causes substantial respiratory pathology, but also results in several extrapulmonary manifestations, including thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologicillnesses, ocular symptoms, and dermatologic complications. Given that ACE2, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in multiple extrapulmonary tissues, direct viral tissue damage is a plausible mechanism of injury. In addition, endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways might all contribute to these extrapulmonary manifestations of COVID-19. Recent reports showed about 2%-11% of patients with COVID-19 had underlying chronic liver diseases. Here we reviewed the liver-specific pathophysiology, presentations and management considerations for patients with COVID-19 to aid clinicians and scientists in recognizing and monitoring the spectrum of manifestations, and in developing research priorities and therapeutic strategies for liver injury in COVID-19.

[Key words] COVID-19; SARS-CoV-2; Liver injury; Pathophysiology; Therapy

1 Introduction

Since the first reported case of the novel coronavirus disease 2019 (COVID-19) in Huanan Seafood Market, Wuhan, China, at the end of 2019, COVID-19 has quickly becoming a global issue to control its spread[1-2]. This newly recognized strain of coronaviruses that have been found to be the etiologic agent of COVID-19 was called severe acute respiratory syndrome coronavirus 2(SARS-CoV-2)[3]. It was initially referred to as novel coronavirus 2019 (2019-nCoV) but was given the official name of COVID-19 by WHO on February 11, 2020.

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2 Epidemiology and manifestations of liver injury in COVID-19

The current pandemic coronavirus has been labelled as SARS-CoV-2, which is responsible for the COVID-19, has infected over 9.5 million people and has caused more than 480 000 deaths globally[4-5]. It is extremely contagious and the number of infections is difficult to control in the world. SARS-CoV-2 was found to have 80% homology with SARS-CoV (pandemic in 2003)[6], which suggested that we could make treatment options by referring to its transmission mode and mechanism. COVID-19 has a lower case-fatality rates but fast infection than SARS. The clinical symptoms of COVID-19 include cough, fever, sore throat, diarrhea, and loss of taste or smell[7]. Statistically, in addition to the obvious fever and respiratory diseases, a high proportion of patients were accompanied by acute myocardial injury, shock, acute renal injury and gastrointestinal reactions. Patients with endocrine system disorders, cardiovascular or cerebrovascular diseases were more susceptible to infection with SARS-CoV-2[8-10]. Most (81%) of infected individuals had a mild illness, 14% had serious and 5% have critical illness[11]. Older patients and those with medical co-morbidities were at risk of a severe disease course.

While SARS-CoV-2 is known to cause substantial pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), clinicians have observed many extrapulmonary manifestations of COVID-19. The severe comorbidity is one of the important causes of death in COVID-19 patients[12]. Timely diagnosis and early treatment are important for an effective COVID-19 control programme[9]. Previously with the SARS epidemic, around 60% of patients developed various degrees of liver damage[13]. Number of patients with complications of acute liver injury is accumulating[14-16], which should arouse our attention. The burden of chronic liver diseases including hepatitis B, hepatitis C, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD) has been increasing around the world[17]. Chronic liver disease has also been identified as an independent risk factor for COVID-19-related hospital mortality in recent studies[18-19]. In critically ill patients of COVID-19, hepatocellular injury is observed in 14%-53% of hospitalized patients[20]. More than half of the patients with of COVID-19 cases showed abnormal levels of AST and ALT[21]. AST elevation is more common than ALT, reflecting the contribution of AST from sources outside liver[22].

The liver pathology of COVID-19 patients showed moderate microvascular steatosis and mild lobular and portal activity, indicating the liver injury could be caused by either SARS-CoV-2 infection or drug-induced liver injury[23]. Another post-mortem liver tissue revealed overactivation of T cells, suggesting a collateral liver damage from virally induced cytotoxic T cells[24]. SARS-CoV-2 virus and Angiotensin Converting Enzyme 2 (ACE2) receptor are highly expressed in stool specimens of infected patients with gastrointestinal symptoms[25].The virus can induce vomiting, diarrhea and other reactions by infecting the gastrointestinal tract[25]. ACE2 is an important regulator of intestinal inflammation and highly expressed in cholangiocytes and the gastrointestinal tract[6]. It is speculated that SARS-CoV-2 virus attack bile duct and gut, and mediate the autoimmune inflammatory reaction to cause liver damage and failure[21, 25]. However, no experimental studies have provided direct evidence that SARS-CoV-2 directly attacks hepatocytes. Interestingly, COVID-19 patients with gastrointestinal symptoms were more likely to develop chronic liver diseases, with significantly increased ALT and AST levels[26]. Gastrointestinal reactions are often accompanied by liver disease, which suggests that we should consider the connection between gastrointestinal tract and liver in COVID-19 patients. Since there is no evidence that the liver can be directly attacked by SARS-

CoV-2, it is probably that the virus can indirectly cause liver damage by infecting the gastrointestinal tract. Therefore, ACE2 receptor may be an important factor for liver injury caused by SARS-CoV-2 virus. Intestinal and bile acid metabolism disorders can also damage the liver[27]. The possibility that SARS-CoV-2 induces liver injury by changing the composition of gut microbiota and affecting the normal operation of the enterohepatic axis[28] should be further explored.

3 Pathophysiology of liver injury in COVID-19

In case of autopsy, the main target of COVID-19 attack are the lungs and respiratory system, the damage to the liver will not be a lethal factor[29]. However, it is essential to identify the pattern of liver injury in COVID-19[21]. Hepatic involvement in COVID-19 could be multifactorial related to the direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis or drug-induced liver injury[13]. Pathology showed that the liver volume of COVID-19 patients were increased and liver cells were damaged.The liver histology revealed moderate microvesicular steatosis, mild inflammatory infiltrates of hepatic lobule and portal tract[30]. Other histopathologic changes in the liver included portal fibrosis, lymphocytic infiltrates and ductular proliferation, lobular cholestasis, and acute liver-cell necrosis, together with central-vein thrombosis[31]. Elevated transaminases in critically ill patients were associated and more serious with liver dysfunction[10,21]. CT scan is the main imaging diagnostic method of SARS-CoV-2, and biochemical of blood and feces is an important aided detection. Patients can be afebrile in the early stages of infection, with only chills and respiratory symptoms. High temperature is not a general presentation. Elevated C-reactive protein (CRP) is an important factor of COVID-19 and impaired immunity, characterized by lymphopenia[32]. Moreover, immunosuppressed patients with cirrhosis and liver injury are at higher risk of infection by COVID-19 and lesion development[21]. Patients with chronic diseases receiving immunomodulatory therapy are also need more screening to avoid deterioration of the patient condition[33]. If a patient needs liver transplantation, it is great degree of caution to evaluate the level of surgical risk[34]. Hepatitis or enteritis patients may increase the risk of infection. Non-alcoholic steatohepatitis (NASH) patients with diabetes or cardiovascular diseases are predicted to accelerate the disease process[35]. It is concluded that there is direct and indirect association between COVID-19 and liver injury.

4 Causes of liver injury in COVID-19

Key mechanisms that may lead to the pathophysiology of multi-organ injury secondary to infection with SARS-CoV-2 include direct viral toxicity, endothelial cell damage and thromboinflammation, dysregulation of the immune response, and dysregulation of the renin–angiotensin–aldosterone system (RAAS)[36]. While some of these mechanisms, including ACE2-mediated viral entry and tissue damage, and dysregulation of the RAAS, may be unique to COVID-19, the immune pathogenesis caused by the systemic release of cytokines and the microcirculation dysfunctions may also occur secondary to sepsis[37]. For the mechanism of liver injury in SARS patients, most scholars believe that it is directly related to SARS-CoV. Although SARS-CoV-2 has not been detected in liver biopsy of COVID-19 patients so far, we speculate that liver injury in COVID-19 patients may be directly caused by SARS-CoV-2 due to the many commonalities between SARS-CoV-2 and SARS-CoV.

Similar to SARS Co-V, ACE2 appears to be the susceptible receptor for SARS-CoV-2 and is expressed in more than 80% of alveolar cells in the lungs[13]. Given that ACE2 is also highly expressed in multiple extrapulmonary tissues,

direct viral tissue damage is a plausible mechanism of organ injury. In addition, endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways might all contribute to these extrapulmonary manifestations of COVID-19[36]. One of the key mechanisms suggested to explain liver injury secondary to COVID-19 include direct viral toxicity, viral entry through ACE2 can occur directly in the hepato-biliary system[38]. Several studies have indicated the enrichment of ACE2 in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6%). Thus, several authors to explain mechanisms of liver injury, suggested a major role of bile duct cells as crucial player in dysregulation of liver immune response[39]. This proposed us that up-regulation of ACE 2 expression due to compensatory proliferation of hepatocyte induced by bile duct cells[40].

Other causes of liver injury include the impairment of liver function before SARS-CoV-2 infection, the hepatotoxicity of viruses attacking liver cells, and therapeutic drugs[21]. Elevated transaminases were caused by inflammation induced by SARS-CoV-2 attack in the liver, or by systemic inflammation similar to severe influenza infection[41]. The ability of liver to metabolize drugs is also reduced, thus resulting in hepatotoxicity. SARS-CoV-2 infection triggers the systemic inflammatory response syndrome, leading to the activation of T lymphocytes, induction of a variety of pro-inflammatory signals causing second ary inflammatory responses[42]. This phenomenon has already been confirmed by high levels of inflammatory markers, suggesting a direct link between the presence of the cytokine storm syndrome and disease severity[43]. Thus, hyperinflammation induced by cytokine storm and hypoxia-associated metabolic derangements are other potential mechanisms of liver damage.

Since the liver is the major organ for drug metabolism, the reasons after treatment in patients with liver function index derangements can also be caused by drugs[29]. Drug-induced liver injury, particularly secondary to investigational agents such as remdesivir, lopinavir, and tocilizumab, may also occur[44-45]. Acetaminophen, used as antifebrile drug, is also recognized as a drug that causes severe liver damage[42]. Antibiotics and corticosteroids used to treat COVID-19 will take some adverse reactions. The commonly used antiviral drugs interferon and ribavirin will increase the burden of liver and cause certain hepatotoxicity. It is necessary to monitor if the liver function is abnormal[41, 46].

Chronic liver failure is more prone to developing hepatic complications in the presence of SARS-CoV-2 infection, chronic liver disorders (CLD) are well-known independent causative factors of severe COVID-19[47]. A group of research published survey of 2 780 persons with COVID-19, 250 patients with known CLD were at a higher risk of death. Of note, according to available data, it is difficult to predict which liver diseases are mostly dangerous. Thus,CLD patients require special supervision. To date, the pathway of liver injury during the course of SARS-CoV-2 infection mechanism is still not clear enough, such as systemic inflammatory storm, potentially hepatotoxic drugs, viral attack and multiple organ failure (Fig.1).

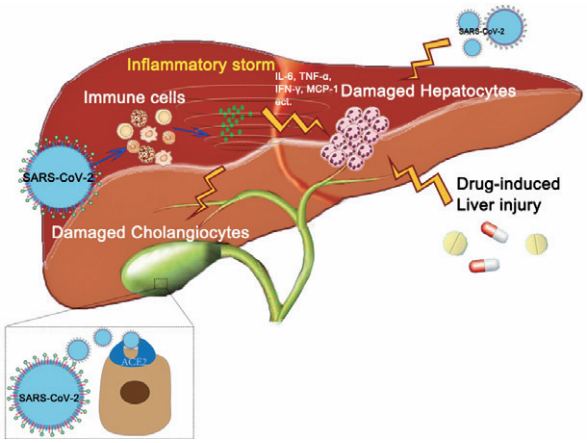

Fig. 1 Schematic diagram showing the COVID-19 patients with liver injury may be considered of secondary liver damage caused mainly by many factors

5 Treatment strategy and manage consideration

A common complication in COVID-19 patients is organ failure like the liver. Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment. However, when severe liver damage occurs, hepatoprotective drugs should be administrated to these patients[21]. Most COVID-19 patients were treated with antiviral drugs and the liver is subjected to a further insult. We should be considered the drug-drug interactions if the patients with underlying liver disease before COVID-19 infection and long-term medication use[48]. Moreover, long-term toxicity concerns are spurring the idea of moving treatment away from drug therapy. It is a challenge to develop new drug combinations with less toxicity and improved antiviral activity.

Although the evidence is less clear, the current treatment recommendations include antiviral drugs, antibiotics, intravenous fluids and corticosteroids[13]. Most patients with hepatocellular carcinoma have underlying chronic liver disease and therefore, they fall under this high-risk category and likely to have worse outcome[49]. Longitudinal monitoring of hepatic transaminases is recommended, particularly in patients receiving investigational treatments, including remdesivir, lopinavir, and tocilizumab, although low-level elevations should not necessarily be considered a contraindication to treatment with these agents[50].

Now, isolation, antiviral, and symptomatic treatments are still mainly adopted for COVID-19 treatment, the protocol of traditional Chinese medicine treatment is continuously updating. In fighting with COVID-19, three Chinese patent medicines (Lianhua Qingwen keli/jiaonang, Jinhua Qinggan keli and Xuebijing injection) were approved by the China National Medical Products Administration for COVID-19 treatment[51]. The major constituents of them are also play a protective role in the liver (Table 1). The current study by ZHONG Nanshan et al. found that Lianhua Qingwen capsules, which suppressed the increased inflammatory cytokines such as TNF-a, IL-6 and CCL-2/MCP-1[52]. Consequently, it has anti-inflammatory and immune-protective effect. More recent studies suggest that some traditional Chinese medicine inhibit virus-mediated inflammatory response, exhibit antiviral effects, such as *Lonicerae Japonicae Flos*[53], *Scutellaria baicalensis Georgi*[54] and *Isatidis Folium*[55]. These Chinese medicines and active ingredients (Table 2) provided reference for anti-SARS-CoV-2 drug screening and clinical treatment[51].

6 Summary and future directions

To date, the underlying mechanisms responsible for the severe form of the disease and death are not completely understood, and no specific therapies

Table 1 Traditional Chinese medicine formulas for COVID-19 treatment

Chinese patent medicines	Main component	Medication
Lianhua Qingwen jiaonang	*Forsythia suspensa*	Inhibit HSC activation induced by down-regulating inflammatory[56]
	Lonicera Japonica	Protect the mice with BCG+LPS-induced ILI obviously[57]
	Isatis tinctoria	Protective the liver function of diabetic rats[58]
Jinhua Qinggan keli	*Lonicera Japonica*	Id
	Scutellaria baicalensis Georgi	Increasing GSH level and anti-oxidantability of liver tissues[59]
	Arctii Fructus	Protect against LPS-induced hepatic injury in mice[60]
Xuebijing Injection	*Radix paeoniae rubra*	Reduce bile stasis plot, accelerate icteric subside[61]
	Radix Salviae Miltiorrhizae	Cholestatic liver damage, immune liver damage, liver fibrosis, liver cancer and drug-induced liver injury[62]
	Angelica sinensis	Enriching blood and promoting blood circulation, immuneoenhan-cement, antitumor, and antiradiation[63]

Table 2 Traditional Chinese medicine for liver injury

Mechanism of liver injury	Chinese medicine compositions	Medication
Chemical liver injury	*Sinensis Radix*	Antioxidative effect[64]
	Schisandra chinensis	Improved the activity of SOD, reduced the contents of MDA and HYP in liver[65]
Immune liver injury	*Aconitum carmichaeli Debx*	Possess a certain action of protecting liver and lowering transaminase[66]
	Sophorae	Reduce the infiltration of inflammatory cells[67]
Drug-induced liver injury	*Rhubarb*	Increasing the expression of TNF-α gene to decrease the damage[68]
	Radix Salviae Miltiorrhizae	Protective effects on the hepatic fibrosis of rats[69]
Alcoholic liver injury	*Pueraria lobata*	Improve SOD activity and reduce MDA content[70]
	Lonicera Japonica	Reduce the contents of GSH, MDA and TG[71]

have been demonstrated to be effective against COVID-19. Beyond the life-threatening pulmonary complications of SARS-CoV-2, the widespread organ-specific manifestations of COVID-19 are increasingly being appreciated. COVID-19 causes pneumonia, but hepatic dysfunction can occur in severe cases and were associated with fatal outcomes. Cases of severe acute liver injury has been reported with higher mortality.

Among the almost four million individuals diagnosed with COVID-19, many have been offered unproven treatments. We are now entering a new era of the pandemic, with many ongoing randomized controlled trials aimed at identifying patient-tailored drugs, and drugs better suited to the specific phase of the disease with improved precision. Nevertheless, clinical and scientific communities, and the pharmaceutical industry, supported by public and private funds, are making a tremendous effort to support an unprecedented number of pathophysiological studies and clinical trials to face this highly unexpected pandemic.

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