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Liver injury in COVID-19: A review

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Abstract

Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has escalated into a global tragedy afflicting human health, life and social governance. Through the increasing depth of research and a better understanding of this disease, it has been ascertained that, in addition to the lungs, SARS-CoV-2 can also induce injuries to other organs including the liver. Liver injury is a common clinical manifestation of COVID-19, particularly in severe cases, and is often associated with a poorer prognosis and a higher severity of COVID-19. This review focuses on the general existing information on liver injury caused by COVID-19, including risk factors and subpopulations of liver injury in COVID-19, the association between pre-existing liver diseases and the severity of COVID-19, and the potential mechanisms by which SARS-CoV-2 affects the liver. This review may provide some useful information for the development of therapeutic and preventive strategies for COVID-19-associated liver injury.

Key Words: Liver; SARS-CoV-2; Angiotensin-converting enzyme 2; Transmembrane serine protease 2; Chronic liver disease

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Core Tip: The global pandemic of coronavirus disease 2019 (COVID-19) has imposed a great threat to human health and become a medical and social challenge. Although

severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mainly affects the respiratory tract, it also frequently damages the liver especially in severe and critical cases. Direct hepatoxicity of SARS-CoV-2, or indirect hepatic injury caused by immune overactivation and systemic inflammation, drug-induced injury, ischemia/reperfusion and hypoxia/reoxygenation injuries, and worsening of pre-existing liver diseases, are potential contributing factors to liver damage in COVID-19.

INTRODUCTION

In December 2019, an outbreak of the novel coronavirus disease 2019 (COVID-19) was reported in Wuhan, Hubei Province, China, induced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 has evolved into a global health challenge[1], posing an enormous threat to human health and economic development. Severe COVID-19 patients may present symptoms of acute respiratory distress syndrome (ARDS), requiring admission to the intensive care unit (ICU) and oxygen ventilation therapy. The shortest time from admission to ARDS is approximately two days. At this stage, COVID-19 mortality is extremely high[2]. Global infection of SARS-CoV-2 are now widespread with confirmed 601189435 COVID-19 cases, including 6475346 deaths reported until September 3, 2022 by the WHO[3]. Most COVID-19 patients exhibit mild symptoms (fever, cough, shortness of breath, fatigue, vomiting, diarrhea, anosmia, and headache), whereas critical cases may develop into severe illness and even death due to severe lung injury and respiratory failure, liver injury, cardiac injury, septic shock, and even multi-organ failure[4].

Although COVID-19 mainly affects the respiratory tract, researchers have focused on the impacts of SARS-CoV-2 on other organs[5]. Liver injury is common in COVID-19 and is associated with poor prognoses. Liver test abnormalities, including higher levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are frequently observed in severe and critical COVID-19 cases compared to mild and moderate cases[6]. The most common manifestation of liver injury in COVID-19 is acute hepatitis with elevated AST, ALT, and total bilirubin levels[7]. Moderate microvesicular steatosis and

slight lobular activity are commonly observed in the liver biopsies[8]. Possible mechanisms include direct infection of the SARS-CoV-2 in hepatocytes or bile duct epithelial cells, excessive inflammation, drug-induced liver injury, ischemia/reperfusion syndrome, and liver injury associated with preexisting liver disease. Angiotensin-converting enzyme 2 (ACE2) is known to be the most important receptor for SARS-CoV-2 in contact with the host cell membrane, while transmembrane serine protease 2 (TMPRSS2) also plays an essential role in mediating viral entry. TMPRSS2 can prime the spike protein (S protein), and has been considered as a target for designing TMPRSS2 inhibitors to block virus entry as a new therapeutic approach[9]. When cells are infected by SARS-CoV-2, the spike protein of the viral particles must be cleaved by TMPRSS2 and then bound to ACE2, so that viral particles can fuse with the plasma membrane and enter host cells[10]. Lower ACE2 expression has been detected in hepatocytes, while biliary epithelial cells express abundant ACE2 and thus can serve as a binding site for SARS-CoV-2. It has also been shown that most viruses that infect the respiratory tract can damage hepatocytes by affecting the $CD8^+$ mediated immune response[11]. Common risk factors, such as older age, male sex, and a range of potential comorbidities, including hypertension, obesity, diabetes, and underlying liver diseases, can also lead to varying degrees of liver damage, critical illness and even death. However, the exact connection between comorbidities and liver injury caused by SARS-CoV-2 remains unclear. This review summarizes the pathophysiology, possible mechanisms, clinical manifestations, risk factors and special populations of liver injury in COVID-19 patients.

PATHOPHYSIOLOGY OF LIVER INJURY IN COVID-19

The mechanism of liver injury in COVID-19 remains largely unknown. SARS-CoV-2 may induce direct hepatoxicity after entering into the liver *via* bile duct cells which express high levels of the ACE2 receptor. SARS-CoV-2 may also indirectly injure the liver *via* immune overactivation, systemic inflammation, drug toxicity, and hepatic hypoxia/reoxygenation or ischemia/reperfusion due to respiratory failure and

endothelial damage (Figure 1). Liver is the main organ for detoxification and metabolism, and liver injury can reflect the severity and clinical course of COVID-19. Therefore, it is crucial to understand the mechanisms underlying liver injury in COVID-19 to develop effective treatments.

Direct effect of SARS-CoV-2 on the liver

Previous research has established that the ACE2 receptor can specifically bind to the S protein, which has a receptor binding domain (RBD) to mediate SARS-CoV-2 entry into host cells. Although the binding pattern of the SARS-CoV-2 RBD-ACE2 complex is greatly analogous to that of the SARS-CoV RBD-ACE2 complex, ACE2 has a higher affinity for the RBD of SARS-CoV-2 [12]. This may be one possible reason why the SARS-CoV-2 is more dangerous than the other emerging SARS-CoVs. However, the level of ACE2 in the liver tissue is much lower than that in the bile duct based on previous data analysis, which suggests that SARS-CoV-2 may bind to ACE2-positive bile duct cells, but not hepatocytes[13]. Another possibility is that ACE2 can sense viral entry and upregulate its expression in hepatocytes[14]. Current evidence indicates that bile duct cells are actively involved in immune defense, inflammatory response, and liver regeneration, which may be a possible explanation of virus-induced liver injury once these cells are damaged. Cholangiocytes can co-express ACE2 and TMPRSS2, and are susceptible to viral infections[13]. Elevated levels of gamma-glutamyl transpeptidase (GGT) andalkaline phosphatase (ALP) are caused by bile duct cell injury[15]. A previous study reported the histological, ultrastructural and immunohistochemical staining of liver biopsies performed on two patients who died of COVID-19. The researchers discovered a mass of viral particles of SARS-CoV-2 in the hepatocyte cytoplasm, and most of the viral particles had an intact coronoid envelope, indicating that SARS-CoV-2 can not only enter, but also replicate in the hepatocytes[14]. Another report also presented detailed liver histological results from two patients with acute COVID-19, and found extensive mitosis especially in the cholangiocytes, in addition to mixed inflammatory infiltrates in the portal region, endodermatitis, and severe bile duct

injury[16]. Another study of three patient cohorts provided evidence of SARS-CoV-2 Liver tropism. In autopsy reports from the third cohort of patients, viral RNA was detected in 69% of autopsy liver specimens and SARS-CoV-2 carrying infectiousness was detected in post-mortem liver tissues[17]. Regardless of whether SARS-CoV-2 directly affects cholangiocytes or hepatocytes, all the above studies support that the liver injury caused by SARS-CoV-2 is a direct cytopathic injury[16] (Figure 2A). Furthermore, obvious mitochondrial swelling, endoplasmic reticulum dilatation, and impaired cell membranes were also observed in two COVID-19 cases suggesting cytopathic damage. However, pathological changes including moderate microvascular steatosis and slight lobular and portal inflammatory infiltration are non-specific in viral infection and can be caused by drug-induced liver injury or chronic liver disease (CLD) such as non-alcoholic fatty liver disease (NAFLD)[18]. In addition, no viral inclusion bodies were observed in the liver tissue of COVID-19 patients. In summary, it is still unclear whether SARS-CoV-2 directly causes cytopathic changes in liver cells.

Systemic inflammatory response and cytokine storm in COVID-19

Severe COVID-19 is characterized by a systemic inflammatory response that may cause a cytokine storm leading to multiorgan failure. Current evidence has shown that serum inflammatory cytokine levels are positively correlated with the indicators of liver dysfunction in COVID-19 patients[19]. This suggests that systemic inflammatory response and cytokine storm are also involved in liver injury, with a possible underlying mechanism between them. A previous study has shown that the activation and dysregulation of $CD8^+$ T cells in severe patients may be an important factor for the pathogenesis of SARS-CoV-2 infection, as $CD8^+$ T cells in critically ill patients express high levels of cytotoxic molecules[20]. A cohort study of 133 COVID-19 patients with liver damage reported high levels of inflammatory cytokines [TNF-α, interleukin (IL)-2, IL-6, and IL-10] and low levels of T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$ T cells). IL-2, IL-6, IL-10, $CD4^+$, and $CD8^+$ T cells can be regarded as possible independent predictors of hepatic injury in COVID-19 patients[21]. This is consistent with an

alternative study, which also revealed that the elevated levels of IL-2, IL-6, and IL-10 in the serum of COVID-19 patients were associated with the progression of severe disease[22]. Notably, IL-6 is particularly important for liver injury, because IL-6-mediated procoagulant endotheliopathy with increased hepatic von Willebrand factor (vWF) expression and platelet accumulation are linked to liver injury and liver inflammation (elevated ALT and neutrophil infiltration). In addition, IL-6 plays a potential role in hepatic endothelial dysfunction and inflammation because its level is correlated with vWF level[23]. IL-6 is associated with elevated liver enzymes, but the relationship is not necessarily causal, as IL-6 can be used to accurately detect inflammatory responses to liver injury[24]. IL-6 is activated primarily by the pathway of JAK (Janus kinase)/STAT (signal transducer and activator of transcription). Baricitinib, an inhibitor of the JAK/STAT pathway, can improve the clinical outcomes of COVID-19[25]. JAK inhibition can affect the viral entry and inflammation of COVID-19[26]. Previous studies have established an association between increased levels of endotoxin, ILs and TNF-α in COVID-19 patients with liver function damage compared with those with normal liver function[27]. COVID-19 patients with elevated ALT levels also have increased IL-6, ferritin, lactate dehydrogenase, and C-reactive protein (CRP)[14]. Furthermore, significantly increased levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), and IP-10 (interferon-inducible protein-10) have been observed in severe patients compared with mild or moderate patients[22]. In conclusion, patients with severe COVID-19 may exhibit intense inflammation and cytokine storm syndrome leading to liver injury.

Drug-induced liver injury in COVID-19

An additional opinion is that liver injury in COVID-19 patients is related to hepatotoxicity. Drug-induced liver injury (DILI) cannot be overlooked, as it may contribute to abnormal liver function, such as elevated ALT and ALP levels, and subsequently affect drug metabolism and excretion[28]. In addition, histopathologic fingdings from liver biopsies of COVID-19 patients, such as microvesicular steatosis

and liver inflammation, may also be associated with DILI[18]. Recent evidence suggests that DILI may occur secondarily to the drugs commonly used for COVID-19 treatment, such as paracetamol, antiviral therapies, low molecular weight heparin, anti-IL-6 receptor agents, and antibiotic treatments[29]. This is consistent with another study, in which corticosteroids and immune modulators were also mentioned[18]. Notably, NAFLD patients are more likely to develop DILI, because NAFLD can increase the sensitivity of the liver to hepatotoxicants, such as acetaminophen[30]. Antibiotics and nonsteroidal anti-inflammatory drugs are considered one of the most common causes of DILI[31]. One previous study showed that, when receiving glucocorticoid therapy, more patients had a liver injury (58.1%) than those without (39%)[32], and, tocilizumab (TCZ)-induced liver injury was reported in one COVID-19 patient. TCZ, also known as an IL-6 inhibitor, is recommended for the treatment of COVID-19 due to its vital role in inducing cytokines, and increased IL-6 can predict the fatal outcome of COVID-19. In this case, when TCZ was administrated, serum aminotransferase levels increased by nearly 40-fold on the first day, and after 10 d of DILI formation, aminotransferase levels returned to normal. Therefore, it is no doubt that TCZ has positive effects on other clinical and laboratory parameters of cytokine storm, such as CRP, IL-6, fibrinogen, and D-dimer, resulting in transaminase levels close to the normal range[33]. In brief, it is necessary to emphasize the importance of drug-related liver damage in patients with COVID-19, especially in those with underlying liver diseases.

Hypoxia/reoxygenation and ischemia/reperfusion induced liver damage

COVID-19 is primarily characterized by respiratory failure, thus, severe cases of hypoxic hepatitis are commonly seen, and 10% of the cases suffer from a hypoxic liver injury in the ICU[34]. Hypoxic hepatitis, also known as ischemic hepatitis or shock liver[35], is accompanied by a rapid elevation of aminotransferases in cases of respiratory failure, shock, or heart failure. One possible reason is that the complex vascularization of the liver makes it susceptible to changes in circulation, resulting in decreased liver perfusion[31]. It has been shown that SARS-CoV-2 also causes liver damage by

producing diffuse endodermatitis. Viral inclusion structures can also be observed in endothelial cells. Liver ischemia/reperfusion, including ischemia-induced cell injury and reperfusion-induced inflammatory responses resulting from the activation of neutrophils, Kupffer cells, and platelets, can induce the generation of reactive oxygen species (ROS) and calcium overload. Endothelial cells are involved in liver ischemia/reperfusion damage, which can promote oxidative stress through ROS and derivatives of nitric oxide[18]. ROS and lipid peroxidation products can mediate the production of redox-sensitive transcription factors, which in turn induce the release of abundant pro-inflammatory factors, resulting in hepatic injury[31]. Furthermore, hepatic sinusoidal endothelial cell damage has been reported to further aggravate hepatic ischemia and hypoxia by disturbing microcirculation[36]. In addition, a high level of positive end-expiratory pressure may be a possible contributor to liver injury in COVID-19 patients, because it can increase right atrial pressure and obstruct venous return, leading to hepatic stasis[37]. These findings indicate that hepatic hypoxia/reoxygenation and ischemia/reperfusion may be potential etiologies of COVID-19-related liver injury.

The ACE2-independent pathway of liver injury

In addition to receptor-mediated viral entry, antibody dependent enhancement (ADE) may also partially associated with hepatic injury in COVID-19 patients. ADE is a pathway that can enhance the interaction of virus-based antibodies, and the CR and/or FC receptor complements allow the virus to easily come into contact with macrophages, granulocytes, and monocytes, This results in the virus multiplying and increasing production, causing the infection to worsen. It has been identified that ADE can be activated by SARS-CoV antibodies, thus, SARS-CoV can trigger ADE activity in immune cells, even though the immune cells do not express ACE receptors (Figure 2B). However, there is a lack of discussion concerning the ADE pathway of liver injury, thus the ACE2-independent mechanisms of liver damage in COVID-19 remain unclear and warrant further study[27].

There is alternative hypothesis that liver cells express two receptors, CD147 and L-SIGN, which have an affinity for the S protein of SARS-CoV-2, and thus may mediate the infection of liver cells by SARS-CoV-2. The presence of CD147 on the surface of host cells may be a new way for SARS-CoV-2 invasion[38]. It has been experimentally verified that CD147 directly interacts with SARS-CoV-2 and that bloking CD147 can prevent SARS-CoV-2 replication, whereas massive expression of CD147 can promote SARS-CoV-2 replication[39]. These findings suggest that CD147 mediates the entry of SARS-CoV-2 into liver cells. However, this requires further exploration (Figure 2C). Additionally, L-SIGN serves as a liver-specific membrane receptor associated with viral capture. Autopsy studies have shown that L-SIGN receptors were present in SARS-CoV-2-infected sinusoidal cells[40] (Figure 2D). Therefore, L-SIGN may provide an alternativer way for SARS-CoV-2 to invade the liver tissue.

Clinical manifestation of liver injury in COVID-19

Liver injury is common in severe COVID-19 cases, as shown by significant circulatory elevations in hepatocyte enzymes including ALT and AST, and a slight increase in cholangiocyte-related enzymes such as GGT and ALP. Mao *et al*[41] analyzed 35 studies involving 6686 COVID-19 patients, among which one in five patients developed liver function abnormalities, especially in severe cases. Therefore, paying close attention to liver function in COVID-19 patients before and during admission is necessary to control the severity of COVID-19. The main findings of the liver biopsy were moderate microvascular steatosis and mild lobular and portal activity. Other specific clinical manifestations of liver injury warrant further investigation.

Abnormal liver function tests

Liver test abnormalities are frequent in COVID-19 patients and often progress to severe illness. Liver function tests include hepatocyte injury markers ALT and AST, cholestasis or bile duct injury markers GGT and ALP, and measures of synthetic capacity [prothrombin time (PT) and albumin]. One comprehensive study has described the

results of liver tests from 417 patients with COVID-19 and found elevated levels of ALT and GGT (24%), AST and total bilirubin (TBIL, 12% and 15%), and no increase in ALP[42]. Such elevated GGT and normal ALP cannot be attributed to bile duct type but are possibly drug-induced liver injuries. GGT elevation is also considered to be a marker of substitution of excessive oxidative stress and increased inflammation due to acute inflammatory stress. However, by analyzing a small subset of COVID-19 patients with possible persistent abnormalities over 60 d, one study found that the predominant abnormality was a cholestatic pattern, as indicated by elevation of the ALP/GGT ratio[43]. Although GGT is not a specific marker of liver injury, liver damage may result from direct bile duct cell injury and cholestasis induced by SARS-CoV-2[43]. Many studies in China revealed that COVID-19 patients who used lopinavir/ritonavir during hospitalizations had liver injuries that influenced liver tests[44]. A cohort study including 1040 COVID-19 patients (mean age 38 years old, 54% men) revealed that drugs used for treatment, such as lopinavir-ritonavir, interferon beta, and/or corticosteroids, are correlated with an elevation in the ALT/AST ratio, a ratio of which acts as an independent contributor to worse clinical outcomes[45]. Using a random effect method and an inverse variance approach, a meta-analysis was conducted using 128 studies, identifying that the most common abnormalities were hypoalbuminemia [61.27% (48.24-72.87)], increased levels of GGT [27.94% (18.22-40.27)], ALT [23.28% (19.92-27.01)] and AST [23.41% (18.84-28.70)][46]. Notably, hypoalbuminemia is an independent risk predictor for liver dysfunction and mortality upon admission[47]. One previous study analyzed 2623 confirmed COVID-19 cases at different risk levels, including non-critically ill, critically ill, and deceased groups[48]. This study revealed that hypoalbuminemia may be due to hepatotoxicity of the cytokine storm. In addition, low-density lipoprotein (LDL) and high-DL (HDL) levels were significantly lower in the critically ill and dead groups than in the non-critically ill group. Furthermore, patients with abnormal liver function had higher inflammatory indices, such as a high level of CRP which is associated with disease severity. Patients with an increased level of ALP have significantly elevated CRP levels, and CRP levels are correlated with ALT

levels[49]. Notably, D-dimer, lactate dehydrogenase, creatine kinase, and troponin levels are also higher in patients with abnormal liver function tests than in those with normal liver function[50]. A retrospective study analyzed 216 patients diagnosed with COVID-19 and concluded that elevated LDH is an independent contributing factor to ICU admission and may require mechanical ventilation[51]. However, the increase in serum LDH does not specifically reflect cellular damage in the liver, because LDH is present in many organs.

In summary, abnormal liver function tests are frequent in COVID-19 patients, which are secondary to other injuries, mostly ischemia or drug-induced liver damage. Patients with abnormal liver tests have extended hospital stay and are at higher risk of developing severe disease, however, this does not directly leading to death[52].

Hepatic histopathological findings in COVID-19

Hepatic histopathological findings in patients who died from COVID-19 revealed moderate microvascular steatosis in addition to mild lobular and portal activity. This is consistent with other studies suggesting that the changes are non-specific, and liver injury may be due to SARS-Cov-2 or drugs, but not caused by cholestasis[8,53,54]. Some studies have found sinusoidal thrombosis, which is less common and is mostly observed in severe COVID-19, because COVID19 is a prothrombotic disease[55,56]. A case study of the liver autopsy of an elderly patient with COVID-19 found no obvious inflammation in the portal area, but observed a few hepatocytes with slight vesicular steatosis and watery degeneration, possibly associated with ischemia and hypoxia[42]. Inflammatory cells, including neutrophils, plasma cells, and Kupffer cells, were observed in the hepatic sinuses at a higher magnification. In addition, numerous scattered or apoptotic hepatocytes characterized by nuclear condensation or formation of apoptotic bodies were also observed in liver biopsy tissues, but no viral inclusions were observed[14], similar to the results of Wang *et al*[32]. Based on these studies, direct effect of SARS-CoV-2 on hepatocytes seems less convincing. Notably, a report on the histopathological findings of 40 patients who died from COVID-19 revealed that mild

lobular necroinflammation was present in 20 cases (50%), with few infiltrations of lymphocytes and histiocytes[55]. Hepatocyte degeneration with focal necrosis and low infiltrations of leukocytes in the lobular and portal areas have also been observed in an alternative liver biopsy study of deceased COVID-19 patients[57]. Liver biopsies from three patients and necropsies from three others revealed striking iron accumulation in hepatocytes, and an abundance of ferritin particles in damaged mitochondria[58], suggesting that hepatic iron overload could have a potential relationship with liver injury. Post-mortem wedge liver tissues from 48 deceased COVID-19 patients suggest that different degrees of liver injuries are present, including liver blood involvement and acute (thrombosis, lumen expansion) and chronic (fibrous thickening of vessel wall, portal vein fibrosis) liver injuries[59]. In conclusion, the most common seen in liver histopathological findings were hepatic steatosis, portal inflammation, and varying degrees of liver injury. However, related investigations into the mechanisms and etiologies of hepatic histopathological changes are still lacking.

Other special clinical manifestations

In addition to the elevated liver enzymes and histopathologic changes described above, other specific manifestations of liver damage in COVID-19 patients have also been reported, including a darkened face and pigmentation. Pigmentation may be a result of abnormal liver metabolism *via* the following mechanisms. Firstly, liver dysfunction can increase estrogen levels thereby damaging the inhibitory effect of thiamine on tyrosinase, so that more tyrosine is transformed into melanin. Secondly, abnormal liver function may result in hypofunction of adrenocortical hormones, and melanin secretion is increased due to the elevation of the melanocyte-stimulating hormone. In addition, more iron may enter into the blood vessels due to liver damage, increasing the ion level in the blood circulation to the facial skin and resulting in a darkened face[27].

COVID-19 INDUCED LIVER INJURY IN SPECIAL POPULATIONS

Risk factors of severe COVID-19 and liver injury

A growing body of studies suggests that male sex, older age, and potential comorbidities, such as hypertension, obesity, diabetes, cardiovascular diseases, and respiratory diseases, and particularly obesity and type 2 diabetes, are more likely to become critical COVID-19 after infection by SARS-CoV-2[60]. One study involving 174 consecutive COVID-19 patients shows that 24 of them had no other comorbidities but diabetes. By comparing the diabetic group with the non-diabetic group, it is found that COVID-19 patients with diabetes more easily experience an overactivated inflammatory response and a hypercoagulable state, resulting in a worse COVID-19. The mechanism could be that COVID-19 patients with diabetes are easily to develop inflammatory storm that rapidly worsens COVID-19 due to high blood levels of inflammatory factors, such as IL-6, CRP, serum ferritin, coagulation index, and D-dimer[61]. These proinflammatory cytokines were strongly correlated with liver injury, so it is worth paying attention to whether patients with a history of diabetes are more susceptible to liver injury. Age is by far the most associated risk factor of COVID-19, with the risk increasing gradually after 65 years[62]. This may be due to T cell and B cell functions which show age-dependent defects, as well as inadequate control of viral replication due to overproduction of type 2 cytokines and prolonged inflammatory responses[63]. Compared to infected adults, infected children usually present with mild clinical symptoms, and are mostly asymptomatic[64]. This may be because of their immature immune systems. Past reports have confirmed that children with abnormal liver function tests such as increased ALT usually have a pre-existing condition such as an immunocompromised state (including malignancy), or chronic liver disease (CLD)[65]. Patients with poor underlying liver conditions, such as cirrhosis, hyperplasia, non-alcoholic steatohepatitis, and mild steatosis, could have a high expression of ACE2 than those without liver diseases[66]. Preexisting liver disease and age ³ 60 years are risk factors for progressing to severe COVID-19[67]. Besides, male sex is linked to the severity of COVID-19 and has been identified as an important etiology of liver injury, possibly due to lack of the protective effect of estrogen on the liver[68], or the enhancement of male innate immunity and the activation of T cells[62].

Notably, patients with obesity represent a dysregulated hepatic innate immunity, adaptive immune response, and pro-inflammatory state, thus aggravating the cytokine storm caused by SARS-CoV-2 infection, resulting in worse prognoses of COVID-19[60]. To evaluate the relationship between obesity and COVID-19, a meta-analysis was conducted using 50 studies in total with a total of 18260378 eligible subjects. It was found that obesity increased the chance of contracting SARS-CoV-2 and developing critical COVID-19. In addition, patients with a body mass index (BMI) ^{3} 30 were 1.39 times more susceptible to SARS-CoV-2 infection compared with those with normal body weight, and the hospitalization rate of COVID-19 became higher with increasing BMI[69]. However, fatty liver is not a predisposing factor for hepatic injury after SARS-CoV-2 infection compared with the susceptibility rate of the general population[70].

In addition to the above risk factors, chronic heart disease, excessive inflammatory response, extended prothrombin time (PT), elevated liver enzymes, and high levels of bilirubin may also be related to severe COVID-19 and mortality[71]. In conclusion, the sex of the patient (males), older age, and comorbidities were independent risk factors for the rapid aggravation of COVID-19. Patients older than 60 years with a history of diabetes have an increased risk of mortality[72]. However, the exact association between liver injury and risk factors remains unclear.

Preexisting liver diseases and the severity of COVID-19

Chronic liver disease (CLD) is deemed to be a major burden of disease and a threat to human worldwide. CLD mainly includes cirrhosis, alcoholic liver disease, non-alcoholic fatty liver disease, and chronic hepatitis B, which affects nearly 300 million people in China. Because of this high burden, it is necessary to carefully assess the relationship between underlying liver disease and liver injury in patients with COVID-19[73]. However, the extent to which CLD affectes the liver function and the disease ending in COVID-19 is controversial. On the one hand, patients with CLD are thought to be more susceptible to viral infection and developing liver injury due to an altered immune status. On the other hand, previous studies reveal that CLD is rarely related to the

progression of liver injury or critical/fatal outcomes of COVID-19 (Table 1)[74]. Therefore, the connection between the underlying liver disease and COVID-19 requires further investigation.

Cirrhosis and COVID-19

Cirrhotic patients have complex immune disorders are more susceptible to infection, the leading causes of mortality are not only respiratory complications but also deterioration of liver function, leading to end-stage liver disease. Patients with cirrhosis are not only at risk of related immune dysfunction, but also are more likely to have comorbidities that predispose them to severe COVID-19, such as diabetes, chronic kidney disease, and heart disease[75]. However, there is a debate about the risk of cirrhosis on the clinical outcomes of COVID-19. A multicenter retrospective study revealed that cirrhotic patients infected with COVID-19 have a high 30-d mortality rate[76]. In this study, elevated transaminases may have had an adverse influence on the process of cirrhosis, and ALT levels in cirrhotic patients were affected by SARS-CoV-2. Additionally, nearly half of the patients who previously had normal transaminases developed to an acute liver injury. Indeed, patients with impaired liver function have a higher 30-d mortality rate and more studies suggested that cirrhotic patients are more susceptible to infection resulting from immune dysfunction. SARS-CoV-2 damages the lymphocytes, especially T cells, resulting in impaired immune function and increased sensitivity to the viruses. Moreover, an elevated neutrophil-to-lymphocyte ratio (NLR) increases the risk of bacterial infection, which is related to stress and sepsis, particularly in decompensated liver cirrhosis leading to a worse outcome[67]. In a study of 386 patients with cirrhosis, 32% had a growing risk of mortality after SARS-CoV-2 infection. Patients with CLD without cirrhosis just have a similar risk of mortality as patients without liver disease[77]. In addition, cirrhotic patients with SARS-CoV-2 infection appear to have a high risk of developing acute hepatic decompensation (46%), as well as a 2-fold increased rate of mortality. These studies suggest that cirrhosis is closely linked to the disease progression from COVID-19.

Contrary opinions argue that CLD and cirrhosis have little correlation with the critical and mortality rates of COVID-19. One study found that there was no increase in liver damage after SARS-CoV-2 infection in CLD patients[18]. However, the results may be relatively low persuasive, because only three patients with cirrhosis were studied.

Hepatitis B and COVID-19

Recent evidence suggests that liver injury in patients co-infected with SARS-CoV-2 and hepatitis B virus (HBV) leads to increased disease severity and worse clinical outcomes[78]. In addition, liver test abnormalities often appear in patients co-infected with SARS-CoV-2 and hepatitis B virus, with elevated levels of ALT, AST, ALP, and TBIL.

In addition, the largest multicenter retrospective study revealed several novel risk factors such as high levels of LDH, D-dimer, and reduced albumin (ALB) or ALB/globulin (GLO), which increase the risk of COVID-19 severity and mortality in patients with chronic hepatitis B (CHB)[79]. An alternative study showed similar results: high levels of LDH, D-dimer, and IL-6 were more likely to worsen liver function in COVID-19 patients following HBV coinfection. Two weeks after the onset of symptoms, serum LDH levels were increased only in patients with COVID-19 and HBV coinfection copmpared with patients without HBV coinfection[80]. The conditions of four chronic HBV-infected patients were further aggravated after SARS-CoV-2 coinfection, as presented by progressive jaundice elevation, coagulation disorders, ascites, and developed acute-on-chronic liver failure (ACLF)[78]. These findings suggest that SARS-CoV-2 and HBV coinfection are related to disease severity and poor clinical presentation, affect liver function tests and that HBV inactive carriers have more severe liver damage. This may be due to the altered immune status caused by SARS-CoV-2 coinfection. Other possible reasons include inactive HBV carriers, who are more prone to HBV reactivation and liver injury with ALT flares caused by SARS-CoV-2 coinfection, and these patients have increased sensitivity to hepatotoxic antiviral drugs used for COVID-19 treatment[80].

There are opposing opinions that chronic HBV coinfection is not a predictive factor for the disease severity or poor prognosis of COVID-19. A study using a prognostic model with a nomogram indicated that HBV infection was not linked to the mortality risk of COVID-19[81]. Several studies have supported this hypothesis. In a cohort study of 326 confirmed COVID-19 patients shows that 20 (6.1%) had HBV coinfection, and the outcomes of the 20 patients (including rates of severe/critically ill, mortality, and discharged and hospital stays) showed no difference from those without coinfection, and HBV coinfection did not increase the degree of liver injury[82]. This is consistent with the results of a previous review indicating that the degree of hepatic damage in patients with HBV and SARS-CoV-2 coinfection is not significantly different from that in patients with SARS-CoV-2 infection alone[83]. Therefore, whether or not HBV infection affects the clinical manifestations and outcomes of COVID-19, and how, requires further study.

Metabolic dysfunction-associated fatty liver disease and COVID-19

Metabolic dysfunction-associated fatty liver disease (MAFLD), previously defined as nonalcoholic fatty liver disease (NAFLD), has been reported to be associated with increased ICU admissions and the need for mechanical ventilation after infection with SARS-CoV-2. However, it was not a predictive factor of death in COVID-19[18]. MAFLD is the most frequently occurring chronic disease in the world, with a common incidence of 30%, and is regarded as a liver performance of the metabolic syndrome. There is a distinct lack of research regarding the history of liver disease in COVID-19 patients and the connection between MAFLD and COVID-19[84]. A meta-analysis of COVID-19 comorbidities showed upregulation of ACE2 receptor expression in NAFLD[85]. A cohort study of 202 consecutive COVID-19 patients showed that patients with NAFLD had prolonged virus-shedding time and increased risk of disease severity compared to non-NAFLD patients[86]. In addition, a previous study has shown that younger patients (age < 60 years) with MAFLD have increased disease severity, possibly due to the higher incidence of cytokine storm caused by MAFLD in younger patients[87]. This is

consistent with an alternative multicenter study that compared the risks of developing severe COVID-19 between younger and older patients with MAFLD. Results showed that 55.9% of the younger, and 24% of the elderly developed severe COVID-19 (P = 0.01)[88], suggesting that younger MAFLD patients have an higher risk of developing severe COVID-19, while older patients with MAFLD appear to have little association with disease severity.

The mechanism underlying age-related disease severity in COVID-19 remains unclear. Possible explanations include: (1) Younger MAFLD patients are more likely to exhibit liver and systemic immune responses, and thereby a cytokine storm after SARS-CoV-2 infection; (2) older MAFLD patients usually have a higher burden of comorbidities which may harm COVID-19 disease and mask the link among MAFLD and COVID-19 severity[88]; (3) cytokine storm have been shown to increase in obese patients, especially in those with preexisting MAFLD[89]; (4) BMI is much higher in patients with NAFLD than in those without NAFLD[90]; (5) MAFLD is also linked to abnormal levels of aminotransferases and gamma-glutamyl transpeptidase (GGT)[89]; and (6) the connection between MAFLD and the severity of COVID-19 may be related to the release of pro-inflammatory mediators, such as, tumor necrosis factor, factor-alpha, and IL-6[91]. Notably, one study reported that the prognosis of MAFLD is closely related to the degree of fibrosis, and thus could affect the outcomes of COVID-19[63]. When MAFLD is accompanied by severe advanced liver fibrosis, it may exacerbate the cytokine storm caused by the virus, thus the release of proinflammatory cytokines lead to more severe COVID-19. In conclusion, unhealthy lifestyles contribute to the high morbidity of MAFLD and high risk of severe COVID-19.

Alcoholic liver disease and COVID-19

A previous study reveals that an unprecedented increase in both ALD and liver transplant rates during the spread of COVID-19[92]. Therefore, more research focus should be placed on ALD, in relation to the COVID-19 pandemic. The mortality rate reported by the Centers for Disease Control and Prevention in the US has shown that

the mortality due to ALD has increased rapidly during the COVID-19 pandemic. One possible reason for this is the high consumption of alcohol and the increase in alcohol-related comorbidities before and during the COVID-19 pandemic. Other possible reasons include increased obesity/metabolic syndrome and nonalcoholic fatty liver disease, which also contribute to the risk of ALD development. In addition, a study found that females and young adults showed the highest relative increases in ALD-related mortality, while older adults over the age of 85 years presented a smaller increase in overall female mortality and even a decrease in male mortality[93]. A comprehensive study of 978 CLD patients with the infection of SARS-CoV-2 from 21 institutions in the United States revealed a novel association between ALD and poor survival or COVID-19 related mortality. It has been confirmed that patients with preexisting ALD may be more susceptible to contracting COVID-19 due to immune system dysregulation. ALD is associated with a sterile inflammatory state caused by an injury-related molecular pattern, resulting in the spread of pro-inflammatory cytokines throughout the body. In addition, SARS-CoV-2-induced cytokine storm may exacerbate inflammation in patients with ALD leading to worse clinical outcomes[94]. In a report on the trends in alcohol consumption and liver disease before and after COVID-19, more than a third of patients with CLD and 50% with ALD consumed alcohol daily, suggest that high alcohol consumption may indicate a relationship with poor prognosis of COVID-19. There are many possible reasons why alcohol abuse leads to poor outcomes. Alcohol abuse and related liver disease can disrupt the innate and acquired immune systems due to impaired immune cell function and survival, which participate in defending against viral infections.Another reason may be that patients with chronic alcohol consumption are more likely to develop ARDS, thus leading to a worse outcome[95].

Liver transplant and COVID-19

Liver transplant recipients are more likely to develop severe COVID-19, due to chronic immunosuppression and related comorbidities, which may lead to mortality[96]. A

systematic search of 15 studies consisting of 223 Liver transplant patients, among which 77.7% required hospitalization, found that 36% experienced more severe disease, with a mortality rate observed in the cohort compared with approximately 1%-4% in the general population. In addition, liver transplant recipients often present with fever and dyspnea which are similar to common COVID-19 manifestations, however, liver transplant recipients are more likely to have concurrent diarrhea symptoms. Furthermore, older liver transplant recipients (aged > 60 years) with diabetes are at an increased risk of mortality[72]. Another study compared 151 Liver transplant patients (68% male, median age of 60 years) with 627 non-transplanted patients (52% male, median age of 73 years), showing that groups of liver transplant patients tended to have ICU admission (28% *vs* 8%) and needed treatment with invasive ventilation (20% *vs* 5%), while mortality was lower in the liver transplant cohort than in the non-transplant cohort (19% *vs* 27%). Several statistical analyses have shown age-related mortality among liver transplant recipients[18]. Similarly, the first nationwide study comparing the morbidity and outcomes of 111 Liver transplant patients infected with SARS-CoV-2 with those of the general population, matched for age and sex[97]. Liver transplant recipients have a doubled risk of developing COVID-19, but have a lower standardized mortality rate compared to the general population. They conclude that chronic immunosuppression and increased comorbidity make the liver transplant recipients more likely to suffer from the infection of the virus and develop to COVID-19; whereaschronic immunosuppression can resist the most severe forms of COVID19 and play a protective role against the virus, resulting in reduced mortality rates.

DISCUSSION

COVID-19 caused by SARS-CoV-2 infection is a worldwide epidemic, which has had catastrophic impacts on healthcare systems and social management. Although SARS-CoV-2 mainly affects the respiratory tract, current studies have also focused on mutiorgan injury particularly liver injury, with liver test abnormalities identified as an important extrapulmonary manifestations related to SARS-CoV-2 infection[98]. As liver

dysfunction is associated with disease severity and poor clinical presentation, understanding the pathogenesis of liver injury and its associated risk factors is extremely important for the prognosis and treatment of the disease. This review briefly summarizes the onset, mechanism, risk factors, susceptible groups, and correlation between liver injury and the clinical outcomes of COVID-19.

According to previous studies, hypoalbuminemia and elevated AST and ALT levels are frequently observed in severe COVID-19 cases, indicating abnormal liver function. These elevations are usually accompanied by elevated lactate dehydrogenase (LDH). GGT levels were also generally elevated, but ALP elevation was not evident in most studies. Although it is debated whether the pattern of liver injury is hepatocellular or cholestatic, the vast majority of studies support the hepatocellular injury. However, because of the high expression of ACE2 receptors in cholangiocytes, the hypothesis that liver injury is results from the direct cytopathic effect of SARS-CoV-2 on hepatocytes seems unconvincing. Liver injuries likely reflects the severity of the disease. Liver histopathological studies predominantly showed moderate microvascular steatosis and slight lobular activity and inflammatory infiltration of the portal area in the biopsy and autopsy of COVID-19 cases. However, the exact mechanisms of liver injury in COVID-19 are still unclear, perhaps more cases are due to indirect liver injury.

Predisposing risk factors for liver damage in COVID-19 include male sex, older age, other comorbidities, and underlying CLDs. Men are more likely to develop liver injury than women because of the stronger innate immune system in men and estrogen protection in women. Patients aged > 65 years appear to exhibit a progressive increase in the risk of developing severe disease. Obesity is also a contributing factor to severe COVID-19, because dysregulated hepatic innate immunity, adaptive immune response, and pro-inflammatory state are usually present in fatty cases, which may aggravate the cytokine storms. Cytokine storms can be enhanced in patients with preexisting MAFLD. The contributions of other preexisting CLDs (including cirrhosis, ALD and chronic hepatitis B) to the progression of disease severity and liver injury in COVID-19 remain controversial. Most studies have emphasized that CLDs are more susceptible to severe

COVID-19 due to immune disorders, and CLDs are often associated with abnormal liver function tests. However, CLD is not a predictor of nor directly cause mortality. Liver transplant recipients have many potential risk factors for developing worse outcomes in COVID-19, but it appears that chronic immunosuppression can protect COVID-19 patients from developing severe disease and thus reduce the mortality. Older liver transplant recipients (aged > 60 years) with diabetes are at increased risk of mortality. The exact link between CLD and COVID-19 is unclear, whether CLD aggravates liver dysfunction and worsens the clinical outcomes of COVID-19 remains ambiguous.

CONCLUSION

Liver injury is frequent in patients with COVID-19 and abnormal liver function tests are more often observed in severe cases. Risk factors and populations for liver dysfunction in COVID-19 patients include male sex, older age, underlying comorbidities (particularly diabetes, hypertension and obesity) and preexisting liver diseases (chronic liver diseases and liver transplant). The mechanisms underlying liver injury in COVID-19 patients remain unclear, which is more likely due to the direct effect of the virus on hepatocytes or biliary epithelium, and the indirect effects of excessive inflammation, drugs, and ischemia/hypoxia syndromes. Collectively, liver injury in COVID-19 patients is associated with increased disease severity and requires additional attention and effective treatments. In addition, targeted therapy is needed for patients with preexisting liver diseases, especially older patients with comorbidities. Further research is needed to determine whether the underlying disease coexists with COVID-19 to cause severe diseases that causes liver damage, or whether the underlying conditions directly contributes to liver damage. Attention should also be paid to drug-induced liver injury during the treatment of COVID-19, especially the conventional and new drugs used for specific groups. The information discussed in this review may aid in establishing recommendations and guidance for the treatment of liver injury in COVID-19 to reduce liver burden.

Figure 1 Mechanisms of liver injury caused by SARS-CoV-2. The mechanisms include direct hepatoxicity (Severe acute respiratory syndrome coronavirus 2 affects cholangiocytes or hepatocytes) or indirect hepatic injury (drug-induced liver injury, excessive systemic inflammation and cytokine storm, deterioration of Pre-existing liver disease). SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2.

Figure 2 Possible pathways of SARS-CoV-2 entering into the liver. A: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells through angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors by its S protein. Direct SARS-CoV-2 infection targeted to hepatocytes or billiary epithelial cells results in hepatocyte injury or bile duct injury; B and C: CD147 (B) and L-SIGN (C) may be alternative receptors for SARS-CoV-2 entry into the liver; D: Antibody dependent enhancement is a pathway which can enhance interaction of virus-based antibody and the CR and/or FC receptor complements further making virus easily entry and infection. ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; LSECs: Liver sinusoidal endothelial cells; BECs: Biliary epithelial cells.

Table 1 Abnormal liver function with existing liver disease and effects of COVID-19

Ref.	Numbers included	Numbers with preexisting liver disease	Liver function markers	Impact on disease
Cirrhosis				
Iavaron *et al*[76], 2020	399	50	Bilirubin, ALT significantly increased, while albumin significantly decreased	Elevated transaminases may have an adverse impact on the process of cirrhosis and the 30-d mortality rate was higher in those patients who had impaired liver function
Marjot *et al*[77], 2021	745	386	-	SARS-CoV-2 infection in patients with cirrhosis appear to have high rates of acute hepatic decompensation (46%) and patients would have a 2-fold increased rate of mortality
Hepatitis B				

Zou *et al*[78], 2021	105	105	Elevated levels of ALT (22,20.95%), AST (29,27.62%), Total bilirubin (7, 6.67%), GST(7, 6.67%), ALP (1, 0.95%)	Liver injury in patients with SARS-CoV-2 and chronic HBV co-infection was associated with disease severity
Chen *et al*[82], 2020	376	20	No significant increase	Coinfection with SARS-CoV-2 and HBV slightly affect liver function and had no effect on COVID-19 outcomes
MAFLD				
Zhou *et al*[88], 2020	327	93	-	Among younger COVID-19 patients (aged < 60 years) with MAFLD have a more than 2-fold higher prevalence of severe COVID-19 while older MAFLD patients who appear no relation to the severity of the disease
Tripon *et al*[89], 2022	719	445	-	SARS-CoV-2-induced cytokine storm can be enhanced in patients with a preexisting liver disease like NAFLD

ALD				
Kim *et al*[94], 2021	367	94	-	Patients with ALD were at higher risk of contracting COVID-19 due to their immune system dysregulation and SARS-CoV-2-induced cytokine storm may exacerbate inflammation in ALD patients
Liver transplant				
Fraser *et al*[72], 2020	223	223	-	In liver transplant recipients with COVID-19, 77.7% required hospitalization, 36% experienced more severe disease,and the mortality rate observed in the cohort was 19.3%
Colmenero *et al*[97], 2021	111	111	-	In liver transplant patients, chronic immune-suppression increases the risk of developing COVID-19 but it could reduce disease severity and the mortality

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GST: Gamma-glutamyl transpeptidase; MAFLD: Metabolic dysfunction-associated fatty liver disease; ALD: Alcoholic liver disease.

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