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Liver injury in COVID-19: Known and unknown

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Abstract

Since the first report of the coronavirus disease 2019 (COVID-19) in December 2019 in Wuhan, China, the outbreak of the disease is currently continuously evolving. Previous studies have shown varying degrees of liver damage in patients with COVID-19. However, the exact causes of liver injury and the relationship between COVID-19 and liver injury is unclear. This article describes liver injury induced by COVID-19, analyzes its causes, and discusses the treatment and prognosis of liver damage in patients with COVID-19.

Key Words: SARS-CoV-2; COVID-19; Liver injury; Prognosis; Treatment

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Core Tip: This review describes the causes of liver injury in patients with coronavirus disease 2019 (COVID-19), including inflammatory storms, hypoxia, drug factors, and viral damage to liver cells, and discusses the treatment of liver injury with COVID-19, which we believe to be beneficial to manage COVID-19 patients with liver injury well and improve their prognosis.

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INTRODUCTION

Since the pandemic of coronavirus disease 2019 (COVID-19) in November 2019 in Wuhan, more than 70 million people have been diagnosed with COVID-19 and over 1.6 million have died. According to the report of the World Health Organization, people with COVID-19 have spread to 220 countries and regions on December 17, 2020. How to control the spread of COVID-19 has become the most urgent problem that we are facing. Some vaccines have been launched in many countries. But we still need to take effective measures to cure the infected and reduce the mortality.

Besides the lung, the liver is one of the main target organs of COVID-19[1]. Previous studies found that the incidence of liver injury in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is 14%-53%[2-6] and that liver injury increases the ventilator risk and mortality of patients with COVID-19. The relationship between COVID-19 and liver injury is unclear. Thus, this article reviews the relationship between these concepts.

LIVER INJURY INDUCED BY COVID-19

Liver injury caused by SARS-CoV-2 can be classified into hepatocyte type, cholangiocyte type, and mixed liver injury[7,8]. Transaminases, bilirubin (Bili), alkaline phosphatase, lactate dehydrogenase (LDH), and albumin (Alb) can be used as the biochemical indicators of liver injury[9-11]. Liver injury was defined as increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in Fan *et al*'s research[12]. However, liver injury was identified when the levels of ALT and AST are three-fold higher than normal and Bili two-fold higher[13], which is one possible reason of different incidence rates of liver injury in COVID-19 patients. Only three (3.75%) patients showed liver dysfunction of the 80 patients with COVID-19 since most of the cases in this study were mild and moderate, with a median age of 46.1 years[14]. Wang *et al*[15]'s meta-analysis showed that 2.6%-53% of patients had abnormal levels of ALT, AST, and total bilirubin (TB), and 6%-98% had abnormal levels of Alb in COVID-19. Transient increases in AST and ALT are commonly seen in mild and moderate COVID-19 patients[16]. Peak aminotransferases were about six to nine-fold higher, while peak total bilirubin was about two-fold higher in severe COVID-19 patients. Peak ALT correlated with peak AST levels[17]. While the values of ALT, AST, and Bili in severe COVID-19 patients are higher than those in non-severe patients, the value of Alb was significantly lower in severe cases[9]. Severe patients also displayed a markedly prolonged activated partial thromboplastin time (APTT), which reflected coagulopathy[17,18].

Critically ill patients were more likely to be older male individuals with a higher prevalence of coronary heart disease, diabetes mellitus, hypertension, malignancy, and chronic obstructive pulmonary disease, compared to non-critically ill patients[10]. Inactive HBV carriers with mild SARS-CoV-2 co-infection are at a higher risk of enhanced liver injury, which was identified as the hepatocyte type rather than the cholangiocyte type[19]. Complications including acute-on-chronic liver failure (ACLF), acute cardiac injury, and shock happened more frequently in patients with severe COVID-19 and chronic HBV co-infection, and the mortality rate was higher in individuals with liver injury[20]. In 202 patients with confirmed COVID-19 and information relating to non-alcoholic fatty liver disease (NAFLD), the elevated ALT level was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization, respectively, which was significantly higher than that of patients without NAFLD[21]. In COVID-19 patients with chronic liver disease, 43% of non-cirrhotic patients presented with acute liver injury and 20% cirrhosis presented with either acute-on-chronic liver failure or acute liver decompensation[22]. Mortality was significantly higher in patients with cirrhosis and COVID-19 than in those with bacterial infections[23] (Table 1).

LIVER DAMAGE IN ASYMPTOMATIC COVID-19 PATIENTS

Asymptomatic COVID-19 patients do not present specific symptoms and signs. As such, they are often diagnosed *via* nucleic acid monitoring. Currently, asymptomatic infected patients account for 17.9%-30.8% of all COVID-19 cases[24,25]. However, asymptomatic and symptomatic patients with COVID-19 have the same virus load[26] and thus likely play major roles in virus transmission[27,28]. To prevent virus trans-

Table 1 Overview of included papers regarding coronavirus disease 2019

Ref.	Country	City	Sample size (n)	Male, n (%)	History of liver disease (%)	Abnormal liver bio-chemical indicators at admission or during hospitalization, n (%)
Chu <i>et al</i> [7]	China	Wuhan	838	464 (55.3)	NA	Elevated ALT 429 (51.1);Elevated AST 429 (51.1); Elevated TBIL 429 (51.1)
Piano <i>et al</i> [8]	Italy	NA	565	357 (63.1)	31 (6)	Elevated ALT 329 (58);Elevated AST 329 (58); Elevated TBIL 329 (58)
Huang <i>et al</i> [10]	China	Jiangsu	2623	1312 (50)	NA	Decreased albumin levels: 1230 (46.9) on the first laboratory test; 1435 (54.7) on the second test after hospitalization
Huang <i>et al</i> [11]	China	Shenzhen	417	198 (47.5)	21 (5.04)	318 (76.3) had abnormal liver test results;90 (21.5) had liver injury during hospitalization.
Fan <i>et al</i> [12]	China	Shanghai	148	75 (50.7)	NA	55 (37.2) with abnormal liver function tests on admission;45 (48.4) developed liver functional abnormality 7 d after admission
Wu <i>et al</i> [14]	China	YanchengWuxi	80	39 (48.7)	NA	Abnormal ALT 3 (3.75); Abnormal AST 3 (3.75); Abnormal Alb 2 (2.50)
Da <i>et al</i> [16]	United States	New York	5	3 (60)	NA	Abnormal ALT 5 (3.75); Abnormal AST 5 (3.75); Abnormal Alb 4 (2.50)
Da <i>et al</i> [17]	United States	New York	176	103 (58.5)	NA	Abnormal ALT 109 (61.9);Abnormal AST 109 (61.0),
Fu <i>et al</i> [18]	China	Wuhan Fuyang	355	190 (53.5)	16 (4.5)	151 (42.5) with cholestasis;101 (28.5) with hepato-cellular injury
Lin <i>et al</i> [19]	China	Chongqing	133	72 (54.1)	17 (12.7)	Elevated ALT 31 (23.3);Elevated AST 27 (20.3);
Zou <i>et al</i> [20]	China	Wuhan	105	55 (52.3)	105 (100)	Elevated ALT 22 (20.95); Elevated AST 29 (27.62);
Ji <i>et al</i> [21]	China	NA	202	113 (55.9)	NA	Elevated ALT 101 (50.0);Elevated AST 34 (16.8); Elevated TBIL 17 (8.4)
Sarin <i>et al</i> [22]	NA	NA	228	132 (57.8)	132 (100)	NA
Iavarone <i>et al</i> [23]	Italy	Lombardy	50	35 (70)	50 (100)	Elevated ALT 29 (58);Elevated AST 32 (67)

NA: Not available; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin.

mission, scientists have been studying the characteristics of patients with asymptomatic SARS-CoV-2 infection, but they have yet to perform large clinical studies on the characteristics of the liver function of asymptomatic COVID-19 patients.

Uhm *et al*[29] compared the liver function of asymptomatic and non-severe patients with COVID-19; they found that their ALT and AST levels are within the normal range and have no significant differences between the two groups. This finding may be related to the severity of the selected patients. Another study has conducted liver function tests on nine patients among 34 asymptomatic COVID-19 patients at early stages and showed that the ALT, AST, and Alb are all within their normal ranges[30]. Similarly, the liver function tests of 50 asymptomatic patients among 648 patients with COVID-19 from 25 hospitals in Jiangsu Province have shown that the Alb, AST, and ALT levels of symptomatic patients are within their normal ranges[31]. Han *et al*[32] analyzed the ALT, AST, ALP, TP, ALB, and total bilirubin (TBIL) levels of 25 asymptomatic COVID-19 patients. They observed that the AST and ALT levels of symptomatic patients are significantly higher than those of asymptomatic patients. Conversely, the albumin and total protein levels of asymptomatic patients are lower than those of symptomatic patients. The bilirubin levels of the two groups are not significantly different. Another study has monitored the liver function of 15 patients among 342 symptomatic COVID-19 patients before and during hospitalization. Its results have revealed the following: Increased ALT levels in three patients, increased LDH levels in six, and decreased ALB levels in two. During treatment, the following findings have been noted: Increased ALT levels in four patients, with the highest value of 106 U/L; decreased albumin levels in three patients, with the lowest value of 31.6 g/L; and increased LDH levels in six patients, with the highest value of 504 U/L. This result has also indicated that the liver function of asymptomatic patients may be damaged[33]. However, further studies should be conducted to analyze the character-

istics of changes in the liver function of asymptomatic COVID-19 patients.

CAUSES OF LIVER DAMAGE IN COVID-19 PATIENTS

The causes of liver damage are multifold. The inflammatory reaction damages the liver. COVID-19 leads to local inflammation in the affected area of the lung and induces the production of pro-inflammatory cytokines and chemokines, such as IL-6, IFN- γ , M-CSF, and MCP1. IL-6 induces acute inflammation by recruiting neutrophils, which can cause liver injury and increase transaminase levels[34]. The inflammatory storm induced by severe COVID-19 causes the release of a large number of inflammatory mediators into the blood circulation, thereby damaging the liver function. Disease-related inflammatory reactions and disease exacerbation may explain the death of some critical patients[10,35,36]. The markers ferritin, IL-8, IL-6, and TNF- α significantly increase in the acute inflammatory phase. IL-6 is positively correlated with increased AST, TBIL, and ALP. IL-8 is positively correlated with increased AST, and TNF- α is positively correlated with increased ALT, AST, and GGT[37,38]. Although IL-6 is significantly increased in patients with liver injury, no causal relationship between this cytokine and liver injury has yet been confirmed. Other scholars have reported that IL-8, TNF- α , and IL-1 β may not have a significant relationship with liver injury. Severe patients are more prone to liver damage and show significantly increased levels of inflammatory cytokines [e.g., C-reactive protein (CRP), IL-6, IL-10, and IL-17A] compared with mild patients. IL-2 and IL-17A have been suggested to be key inflammatory factors causing liver injury in COVID-19 patients[39,40]. The early increase in AST level and its correlation with disease severity indicate that immune-mediated inflammation plays an important role in liver injury in severe COVID-19 patients[41].

Hepatotoxic drugs damage the liver function. COVID-19 patients are often prescribed with antiviral drugs, antibiotics, antifungal drugs, and systemic glucocorticoid drugs. These drugs could result in the elevation of liver transaminase levels. Some antiviral drugs may have potential hepatotoxicity. For example, lopinavir/ritonavir is mainly affected by cytochrome p450 3A4 in the liver[42]. Patients treated with lopinavir/ritonavir combined with arbidol often show liver damage, and the incidence of liver injury in this group may be up to 3.58 times greater than that in patients who did not receive the same treatment. Drug treatment increases the likelihood of liver damage by 12.1%[43]. Some patients may be given symptomatic treatment with acetaminophen and other drugs during hospitalization. Large doses or combinations of these drugs with other medications can cause liver toxicity and even liver failure[44]. In a study of seven COVID-19 patients who were administered with tocilizumab treatment, the drug increased transaminase levels in all patients by up to fivefold compared with normal levels, but the CRP levels and liver function returned to normal within 3 wk. However, Campochiaro *et al*[45] reported that tocilizumab treatment does not significantly reduce mortality in patients with COVID-19. These contradictory findings suggest that great care should be taken when providing tocilizumab treatment. Patients treated with remdesivir also showed liver transaminase elevation, which indicates that the antiviral drug may cause liver cell injury[46, 47].

Hypoxia may be another cause of liver injury. The release of a large number of inflammatory cytokines induces acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) and causes hypoxia, which leads to lung, liver, myocardial, and kidney damage. Microthrombi and hemophagocytes have been noted in the liver biopsy of patients with COVID-19, suggesting that ischemia may be a potential cause of liver injury[48]. Liver biopsy of COVID-19 patients revealed moderate microvascular steatosis and mild liver lobule and portal lesions[49, 50]. Hypoxia caused by COVID-19-related complications, such as respiratory distress syndrome or multiple organ failure, can also cause liver ischemia and hypoxia-reperfusion dysfunction, which is more severe in serious cases than in mild COVID-19 patients.

Studies have found that ACE2 is the key receptor through which SARS-CoV-2 cells are able to enter cells[51]. The expression of ACE2 in liver cells is very low and occurs mainly in bile duct cells; this finding indicates that hepatic bile duct cells may be the site of direct assault of the novel virus. Eleven patients were found to be PCR positive in 20 deceased COVID-19 patients; moreover, although the results were not statistically significant, the AST peak of PCR-positive patients was higher than that of PCR-negative patients[52]. The liver pathology of one deceased patient showed no bile duct

injury or virus infiltration, and LDH and GGT, which reflect bile duct damage, were not significantly increased[36].

IMPACT OF LIVER INJURY ON PATIENT PROGNOSIS

Abnormal liver function indices can be used to judge the severity of COVID-19. Compared with other indicators of liver injury, COVID-19 patients with abnormal AST have a greater mortality[53]. A high ratio of white blood cells to lymphocytes indicates that the systemic inflammatory response is activated. Liver steatosis and the ratio of neutrophils to lymphocytes are related to disease severity[54]. The ratio of white blood cells to lymphocytes is an independent risk factor influencing the mortality of patients with COVID-19 and liver injury. Patients with chronic liver disease generally experience longer hospital stays than those without. Unfortunately, prolonged hospital stays increase the risk of nosocomial infection, which contributes to a poor patient prognosis[55]. Some studies revealed no obvious correlation between chronic liver disease and the severity of COVID-19[56]. Hepatic steatosis (HS) is associated with elevated transaminases and the need for intubation, dialysis, and vasopressors. No connection between HS and jaundice or portal hypertension complications has been reported[57]. Liver steatosis can be used to predict COVID-19-related complications [58,59]. These previous findings indicate that males and elderly patients, as well as more severely ill patients, are highly likely to develop liver damage. COVID-19 patients with liver injury are more likely to be diagnosed with previous hypertension, coronary heart disease, and malignant tumors than patients without liver injury, and patients with liver abnormalities tend to have a higher incidence of heart injury, kidney injury, and SIRS. These findings indicate that liver biochemical abnormalities are closely related to heart damage, kidney damage, and SIRS and play an important role in COVID-19[7]. Increased bilirubin and AST/ALT ratios could predict the mortality of patients with liver cirrhosis[22]. Compared with the normal liver function group, patients with liver injury showed 3-fold greater AST levels, 19.27-fold greater risk of mechanical ventilation, and 116.7-fold greater risk of death. Factors significantly associated with liver damage included leukocytosis, lymphopenia, and male sex[60].

MANAGEMENT AND TREATMENT OF LIVER INJURY IN COVID-19 PATIENTS

A consistent treatment recommendation for liver function abnormalities in patients with COVID-19 has yet to be established. Liver function could provide clinicians with valuable information. Abnormal liver function could be used as an indicator to evaluate the prognosis of patients with COVID-19. Mishra *et al*[61] reviewed 348 patients diagnosed with COVID-19 and treated in a nursing center. Their liver injury is related to inflammation caused by COVID-19. Early and continuous monitoring of liver enzymes in patients with COVID-19 helps identify the changes in these patients in early disease stages. Another study found that the bilirubin level of dead patients with COVID-19 is significantly higher than that of patients discharged from hospitals. Early bilirubin monitoring can help detect severe and critical patients in early stages [40]. We can evaluate liver function to assess whether changes in the same in critical patients will influence their prognosis after identifying critical and non-critical patients [9]. The management of patients with COVID-19 and liver transplantation is complex, but strict prevention strategies are widely believed to be among the most important measures[62]. Dynamic changes in liver function may be significantly related to the severity and prognosis of COVID-19. Therefore, the relevant indicators should be closely monitored during hospitalization. Strengthening monitoring or individualized treatment in severe COVID-19 patients with previous liver disease and other pathological conditions is necessary. Compared with patients with normal liver function, patients with liver damage generally experience longer hospital stays and greater mortality[12].

Li *et al*[63] proposed that ALT, ALP, GT ALB, Pt, bilirubin, pre-ALB, blood cholesterol, and cholinesterase can contribute to the determination of the severity of liver injury and the evaluation of the regeneration ability of the liver. Therefore, an HBV DNA or HCV RNA nuclear acid test should be performed, and the status of patients should be determined to decide whether an antiviral treatment is needed. Albumin supplement and other necessary nutritional treatments should be given

because of the close relationship between hypoalbuminemia and prognosis of patients with COVID-19[10]. Circulating albumin levels should also be maintained above 35 g/L, which is beneficial to the prognosis of patients[63]. AASLD Expert Panel Consensus Statement has pointed out that patients with cirrhosis, patients who have autoimmune hepatitis and are taking immune agents, and patients with a liver transplant are more susceptible to COVID-19 and develop severe symptoms and complications. As such, their liver function should be monitored[64]. For patients with liver injury, glycyrrhizic acid drugs, reduced glutathione levels, ω -3 unsaturated fatty acids, and other drugs can be administered. Inhalation of interferon α -2b can reduce the elevation of ALT in patients during hospitalization. Nebulized inhalation of interferon α -2b can also inhibit SARS-CoV-2 and reduce the liver damage caused by this novel virus. The liver function of patients treated with drugs such as Rheticvir, Lopinavir, and Etaracizumab should also be monitored continuously. If their liver function is abnormal, the administration of the related drugs should be stopped as soon as possible[11].

These findings suggest that effective control of COVID-19 could have protective effects in alleviating liver damage. COVID-19 patients with liver damage, especially severe patients, require rigorous liver function monitoring. In addition, appropriate drugs should be selected according to the patient's condition, and medications that could damage liver function should be avoided.

CONCLUSION

The mechanism of liver injury caused by COVID-19 remains unclear. Inflammatory storms, hypoxia, drug factors, and viral damage to liver cells are known to participate in liver damage. However, the mechanisms through which these factors contribute to liver damage, the dynamic factors contributing specifically to liver damage, and which factors exacerbate liver damage remain unclear. More research is needed to clarify these issues. At present, no clear report on how to use drugs against liver damage for patients with COVID-19 is yet available. Whether patients with COVID-19 must be administered with treatment to protect their liver function at the onset of the disease or only after the relevant indicators become abnormal is unknown. However, reasonable treatment should be taken to avoid the failure of the liver and multiple organs in patients with liver damage. Such a strategy could decrease mortality in COVID-19 patients.

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