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Review Article

Mechanism of SARS-CoV-2 Invasion into the Liver and Hepatic Injury in Patients with COVID-19

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Abstract. Many studies have shown that patients with Coronavirus disease 2019 (COVID-19) have different degrees of liver injury. However, the mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invasion into the liver are still not fully understood. This review mainly summarizes the recently published works on the abnormal liver biochemical indicators and the mechanism of viral invasion with liver injury in COVID-19 patients. Generally, SARS-CoV-2 infection of the liver was caused by blood circulation or retrograde infection of the digestive tract, which led to the liver injury through direct cytopathic effect induced by virus or immunopathological effect caused by excessive inflammation. Besides these, hypoxia, endothelial injury and drug-induced jury were also the main reasons of liver injury in COVID-19 patients. In the liver function indicators, elevated alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and lactate dehydrogenase levels with reduced albumin levels were observed in COVID-19 patients.

Keywords: SARS-CoV-2; COVID-19; Liver injury; Viral invasion; Biochemical indicator.

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Introduction. The coronavirus disease 2019 (COVID-19) outbreak, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global public health problem. As of July 15, 2021, SARS-CoV-2 infection had led to a total of 189,219,660 confirmed cases and 4,071,640 deaths documented in 219 countries. SARS-CoV-2 mainly comprises four structural proteins: the spike (S), the membrane, the envelope, and the nucleocapsid protein.[1] The S protein recognizes the receptor on the host cell surface and has pivotal roles in viral infection and pathogenesis.

It is well established that most individuals with

COVID-19 present with fever and typical respiratory symptoms. However, abnormal liver function is often found in patients with COVID-19. With the increase in cases and further research, clinical studies suggest that liver biochemical indicators, such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were significantly increased in COVID-19 patients, which suggests hepatocellular and cholangiocellular damage.[2] Patients with liver damage are at higher risk of developing severe disease.[3] Therefore, clinicians should be alert to the possibility of liver injury in COVID-19 patients.

The major pathophysiological features of liver injury include enlargement of liver volume, liver cell focal necrosis with neutrophil infiltration, hepatocyte steatosis, lobular and portal inflammation, hepatic sinus congestion, microthrombosis, and high filling of the gallbladder.[4] These pathological changes in the liver suggested that the degree of liver injury in most COVID-19 patients was mild and that abnormal liver function might be caused by a viral infection, drug-induced or immune-mediated liver injury. However, it is still unknown how does the virus invade the liver and whether increased serum liver biochemistry is caused by hepatic injury or systemic progression of the disease. Therefore, it is crucial to understand the routes and mechanism of viral invasion to the liver and the effect of liver biochemistry abnormalities on the progression and prognosis of COVID-19. This review will highlight the process of virus invasion in the liver and the pathogenesis of liver injury, explain the changes in liver biochemistry after COVID-19 infection, and provide a theoretical basis for clinical evaluation of liver injury in COVID-19 patients.

Routes of Viral Invasion to Liver.

Receptors of SARS-CoV-2 in Liver. ACE2 (angiotensin-converting enzyme 2) receptor, an important part of the renin-angiotensin-aldosterone system, is the gateway for SARS-CoV-2 to enter host cells. SARS-CoV-2 binds to the ACE2 receptor through its surface S protein,[5] which is similar to SARS-CoV, but the binding affinity of SARS-CoV-2 to ACE2 receptor is 10-20 times higher than that of SARS-CoV.[6] Many studies analyzed the distribution of ACE2 receptors in different tissues and cell types of the human body using immunohistochemistry, RNA sequencing and other methods. The results showed that the tissues with the highest expression of ACE2 receptor were: small intestine, colon, duodenum, kidney, testis, gallbladder. On the other hand, the distribution of receptors in the liver is low, mainly expressed in bile duct cells.[7-9]

Interestingly, the expression of ACE2 in the lung is lower than that in liver,[7] mainly in alveolar type 2 epithelial cells, but the lung is recognized as the primary site of viral invasion. Thus, the distribution of ACE2 receptors is not completely consistent with the load of virus in organs. Studies also suggest that ACE2 is abundant in endothelial cells and smooth muscle cells of almost all organs.[10] Therefore, once the virus enters the blood circulation, it is easy to spread in the body. Generally, the presence of virus particles in the liver confirmed the possibility of direct virus infection in the liver, but it is not clear whether the virus directly invades the liver through the ACE2 receptor.

Blood Circulation Transmission of SARS-Cov-2. With a large number of viral SARS-CoV-2 replication and an accumulation of a variety of pro-inflammatory cytokines and chemokines, the alveolar epithelial cells were damaged, and the integrity of the air-blood barrier was seriously interrupted.[11] In addition to alveolar epithelial cells, SARS-CoV-2 can also invade pulmonary capillary endothelial cells, resulting in a large amount of plasma components exudate in the alveolar cavity; as shown in **Figure 1**. Since the alveoli are located at the end of the respiratory tract and contain an abundant capillary network, SARS-CoV-2 can diffuse from the damaged alveoli into the capillaries and spread through the blood circulation. In clinical cases, sepsis and septic shock were found in many COVID-19 patients with a severe and critical illness. However, bacterial and fungal cultures in blood and lower respiratory tract specimens of 76% of septicemia patients were negative in 76% of septicemia patients,[12] suggesting that the clinical manifestations of septicemia were caused by viral infection. The liver has a double and abundant blood flow, so it is easily affected by COVID-19 in circulating blood. It has been found that SARS-CoV-2 virus particles exist in the portal vein lumen and endothelial cells of liver samples from patients with COVID-19,[13] which confirmed that the virus might infect the liver with blood circulation.

Retrograde Infection of the Digestive Tract in COVID-19 Patients. In addition to the blood circulation, the spread of the virus in the digestive tract has gradually attracted people's attention. Since the ACE2 receptor is most widely distributed in the small intestine, colon and duodenum, it provides convenience for SARS-CoV-2 infection. About 50% of the patients had fecal excretion of virus and could isolate infectious SARS-CoV-2 particles from it. Moreover, viral nucleic acid in feces remained positive for more than two weeks after the respiratory system nucleic acid test turned negative.[14] At present, many studies have confirmed that COVID-19 can directly lead to gastrointestinal infection [15-17] through biopsy of the duodenum and rectum, and that suggests that the gastrointestinal tract is also the main site of SARS-CoV-2 infection.

Some patients with intestinal injury were more likely

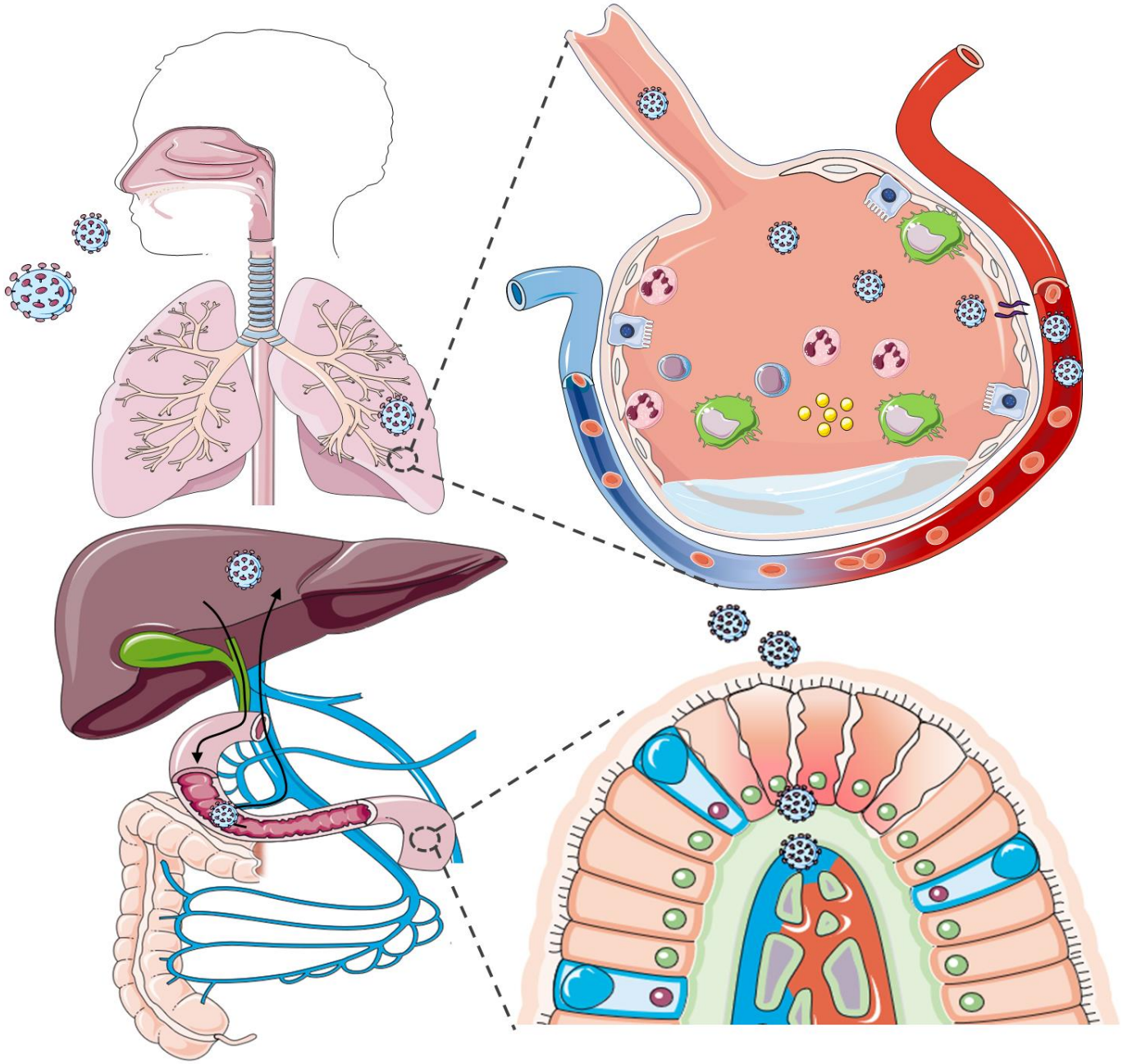

Figure 1. Routes of SARS-CoV-2 infecting liver. SARS-CoV-2 entered the airway epithelial cells and alveoli. Due to a large number of viral replication and the accumulation of a variety of pro-inflammatory cytokines and chemokines, the alveolar epithelial cells were damaged with reactive proliferation, shedding. SARS-CoV-2 can diffuse from the damaged alveoli into the capillaries and spread through the blood circulation. After SARS-CoV-2 invades the intestinal tract, it can damage the intestinal mucosal epithelium and vascular barrier, and enters the liver through the portal vein. Then SARS-CoV-2 can reach bile through intercellular vesicle pathway after the virus infects hepatocytes. SARS-CoV-2 may reach and infect the intestine through the bile, and then cause the secondary infection of the intestine.

to have a severe liver injury than those with normal intestinal tract.[18] Similarly, people with underlying liver diseases are at a higher risk of developing intestinal manifestations after SARS-CoV-2 infection, suggesting a relationship between gastrointestinal and liver injury. Actually, there is a very important two-way communication pathway between the intestine and the liver, called the "gut-liver axis".[19] The liver secretes synthetic bile acids and other active substances into the intestine, and the bacterial metabolites and nutrients in the intestine can be absorbed into the blood through the portal vein and then flow back to the liver.[20] Therefore, it is speculated that there is a possibility of retrograde infection of the liver after SARS-CoV-2 infection of the intestinal tract. After SARS-CoV-2 invades the intestinal tract can damage the intestinal mucosal epithelium and vascular barrier and carry out retrograde infection through the portal vein. In addition, SARS-CoV-2 virus particles can reach bile through the intercellular vesicle pathway after the virus infects hepatocytes. Therefore, bile duct cells may also contact and infect SARS-CoV-2. Because the biliary tract provides a direct connection between the liver and the intestine, SARS-CoV-2 may reach and infect the intestine through the bile and then

cause the secondary infection of the intestine, as shown in **Figure 1**.

Molecular Mechanism of Liver Injury in COVID-19 Infection. Many COVID-19 patients have been found to have different degrees of liver injury, but the mechanism of liver injury remains unclear. The liver plays an important role in host defense against microorganisms, and some viruses can directly cause cytopathic effects on hepatocytes and bile duct cells. In addition, hypoxia, vascular endothelial injury, drug-induced and immunoinflammatory play a key role in the pathophysiological mechanisms of liver injury in COVID-19.

Direct Action of The Virus. Although ACE2 expression levels are very low in the liver, the distribution of the ACE2 receptor is not consistent with that of organ infection.[10,21,22] A number of studies have been conducted on liver samples from postmortem cases of COVID-19 deaths. It was found that SARS-CoV-2 RNA can be detected in the liver of COVID-19 patients.[23] Wang et al.[4] performed liver biopsies on two dead COVID-19 patients with elevated transaminase. Through transmission electron microscopy, immunohistochemistry and pathological studies, it was found that there were a large number of SARS-CoV-2 virus particles in the cytoplasm of liver cells of the two COVID-19 patients. Most virus particles have an intact envelope with a coronal process, suggesting that SARS-CoV-2 can enter liver cells and replicate in them.

A series of studies showed that SARS-CoV-2 infection in the liver directly contributes to hepatic impairment in patients with COVID-19. The mitochondria of liver cells infected with SARS-CoV-2 were swollen, the endoplasmic reticulum was expanded, and the glycogen granules were reduced. Histologically, a large amount of hepatocyte apoptosis and some binuclear hepatocytes were observed. Ultrastructural and histological evidence shows a typical viral infection lesion, and SARS-CoV-2 can directly damage the liver and cause abnormal liver transaminase.[4] In addition, in situ hybridizations of liver samples revealed that SARS-CoV-2 virions were present in the vascular lumen and portal vein endothelial cells of liver samples from COVID-19 patients.[13] Approximately 2-10% of COVID-19 patients develop symptoms of diarrhea. Nucleic acid of SARS-CoV-2 was detected in their stool and blood samples, suggesting that the virus may invade the liver through the digestive tract or the circulation.[24] However, the mechanisms of how infection with SARS-CoV-2 can directly lead to liver injury remains unclear.

ACE2 is lowly expressed in the liver, but it is highly expressed in the bile duct. Thus, liver injury caused by SARS-CoV-2 infection may also derive from the biliary tract system. Furthermore, studies have shown that ACE2 can be expressed in bile duct endothelial cells with a specificity of up to 59.7%, which is 20 times higher than the expression in liver cells, suggesting that SARS-CoV-2 may further affect liver function and bile excretion by directly binding to bile duct epithelial cells.[25] Using a system of human stem cells grown in vitro, Zhao's team[26] constructed "liver ductal organoids". A large number of ACE2 receptors were found in this organ, and it was highly susceptible to the SARS-CoV-2 virus. Moreover, SARS-CoV-2 infection can reduce the expression of the Claudin1 gene, leading to the destruction of the barrier function of bile duct cells, resulting in bile duct cell damage and the corresponding accumulation of bile acid and thus the symptoms of liver injury.

Hypoxia and Vascular Endothelial Injury. The liver is an important organ responsible for digestion and metabolism. It has a complex dual blood supply system and is a highly aerobic tissue and organ. An oxygen partial pressure gradient phenomenon exists, and it is extremely sensitive to hypoxia. Patients with COVID-19 have different degrees of hypoxemia, and hypoxia is a typical feature of the disease cases. In addition, severe patients can also be complicated with systemic inflammatory response syndrome, respiratory distress syndrome, and multiple organ failure, worsening liver tissue ischemia and hypoxia. Hepatic ischemia and hypoxia can activate Kupffer cells, neutrophils, and platelets, causing a series of destructive cellular responses and leading to inflammation and cell damage.[27] Meanwhile, the microcirculation disturbance caused by hepatic sinusoidal endothelial cell injury can further aggravate hepatic ischemia and hypoxia. Hypoxia is an important regulator of ACE2 and can upregulate its expression in hepatocytes.[28] The high expression of ACE2 in hepatocytes and bile duct endothelial cells may promote the entry of novel coronavirus.[29,30,31] These may explain why extrapulmonary transmission of SARS-COV-2 is mainly seen in ARDS and other hypoxic patients.

The current view is that COVID-19 is a vascular disease with clotting disorders and thrombosis. SARS-COV-2 can infect endothelial cells and cause diffuse endothelitis. Subsequent microvascular dysfunction leads to hypercoagulation, tissue edema, and organ ischemia.[32,33] Diffuse intravascular coagulation caused by vascular endothelial cell injury can also affect the blood supply to the liver, resulting in hepatic microcirculation disorder and liver function impairment. In addition, recent studies have found that the glycolytic pathway is significantly enhanced to provide energy for virus survival and replication after the virus infects host cells, thus mediating the production of a large number of reactive oxygen species.[34] Excessive reactive oxygen species can cause oxidative stress and lipid peroxidation

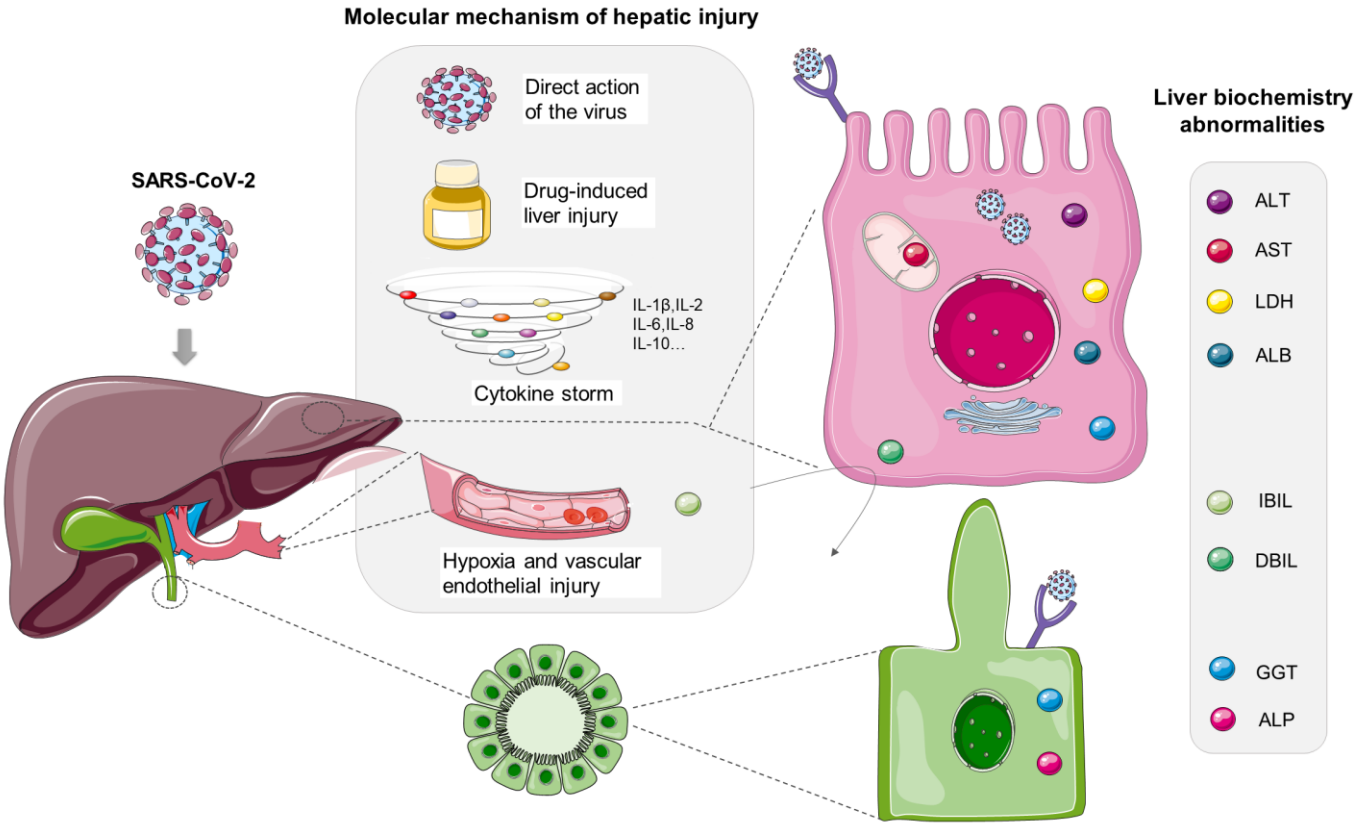

Figure 2. Liver biochemistry abnormalities and molecular mechanism of hepatic injury in COVID-19 infection. SARS-CoV-2 invade the liver through the digestive tract or the circulation. The main mechanisms of liver injury include: direct action of the virus, hypoxia and vascular endothelial injury, drug-induced liver injury and immunoinflammatory injury caused by cytokine storm. SARS-CoV-2 can directly cause hepatocyte damage, showing swelling of mitochondria and expansion of endoplasmic reticulum, and cause abnormal liver transaminase, mainly manifested as increased levels of ALT, AST, LDH, TBIL, GGT and ALP and decreased levels of ALB.

in liver cells, thus damaging the function of liver cells.[35]

Drug-Induced Liver Injury. The liver is an important organ for drug transformation and metabolism. These metabolites can lead to apoptosis or necrosis of liver cells through cellular stress, destruction of mitochondrial membrane permeability and specific immune responses.[36] At present, common drugs such as antiviral, antibiotics and immunoregulatory factors, glucocorticoid, sedative and other proprietary Chinese medicines are used to treat COVID-19 patients, leading to possible liver injuries.

A study found that ritonavir led to a mild to moderate increase in transaminase expression in 44% of COVID-19 patients. The main manifestation is cytolysis, but cholestasis, steatosis, and fibrosis may also occur.[37,38] The drug is mainly metabolized by the liver cytochrome P4503A4 (CYP3A4) enzyme and can lead to elevated serum transaminase.[39] Hydroxychloroquine caused mild to moderate transaminase elevation in 11% of COVID-19 patients: however, acute liver injury is rare and sometimes accompanied by jaundice.[38,40] Azithromycin causes mild to moderate transaminase elevation in 40% of COVID-19 patients. A rare case of severe hepatotoxicity with hepatocyte injury and jaundice or chronic cholestatic liver failure was reported.[41] Tocilizumab can cause transaminase elevation and acute liver injury in COVID-19 patients.[42] Glucocorticoids have also been shown to be associated with steatosis or glycogenic diseases.[43] The mechanism of drug-induced hepatotoxicity mainly involves mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, lipid dystrophy and insulin resistance.[44] Zhan et al.[45] found that lopinavir/ritonavir was an independent risk factor for severe liver injury in COVID-19 patients. Therefore, for patients with decreased liver function, hepatotoxic drugs should be used with caution. Cai et al. also found that lopinavir/ritonavir were the most important risk factors for liver damage by analyzing the clinical case characteristics and medication of 417 patients with COVID-19 after admission. The use of lopinavir/ritonavir increased the risk of liver damage by four times.[2] Yip's team analyzed liver biochemistry data from 1040 COVID-19 patients at admission and during hospitalization and found that the use of lopinavir/ritonavir, ribavirin, interferon and

glucocorticoids was independently associated with increased ALT/AST in COVID-19 patients. Glucocorticoid use was also associated with acute liver injury.[46] Thus, cautious use of antiviral agents in COVID-19 patients with decompensated liver disease should be considered.

Immunoinflammatory Injury. With the increasing number of COVID-19 patients, it was found that the clinical characteristics of some COVID-19 patients, not serious in the early stage, could suddenly deteriorate rapidly and enter the state of multiple organ failure, related to cytokine storms caused by excessive immune responses in the body.[47] Cytokine storm refers to the overactivation of the immune system caused by severe stimulation, such as infection, which rapidly produces a large number of cytokines, leading to a systemic inflammatory reaction with mycrothrombosis,[48] which can induce hypoxia in the body, leading to cell damage and necrosis. This process not only leads to lung damage but also can involve the liver, heart, and kidney. Current studies show that cytokine storm is an important node in the transition from mild to severe and critical COVID-19 disease and an important reason for the death of patients.[47] Serum levels of pro-inflammatory cytokines, including interferon-α (IFN-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-18 (IL-18), interleukin-33 (IL-33), tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-inducible protein-10 (IP-10), and C-reactive protein (CRP), were significantly increased in patients with severe COVID-19,[49] as shown in **Figure 2**. Huang et al.[47] conducted a clinical summary of COVID-19 patients and found that 63% of the patients had lymphocytopenia, and the plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1A (MIP1A) and TNF-α were higher in critically ill patients. It is speculated that excessive cytokine secretion may activate Th1 cells, and the viral-induced cytokine storm determines the severity of the disease. Notably, cytokine storms may directly cause immune cell death, tissue damage, and respiratory arrest. The study found that the number of immune cells in COVID-19 patients changed, and pathological changes such as spleen atrophy and necrosis, lymph node necrosis, renal hemorrhage, hepatomegaly, and degeneration of neurons in the central nervous system were observed.[50] Studies have also found a correlation between lymphocyte reduction and liver injury in patients with COVID-19, and increased IL-6 and IL-10 and decreased CD4+ T cells are independent risk factors for severe liver injury.[45,51]

Liver Biochemistry Abnormalities in COVID-19 Patients. Liver function impairment will seriously affect the synthesis and metabolism of the body. The risk of hepatic injury in COVID-19 patients during hospitalization was

Table 1. Liver biochemical of COVID-19 patients at admission or during hospitalization.

References	Countries and regions	Sample size (n)	Abnormal liver biochemical indicators No. (%)						
			ALT	AST	GTT	ALP	LDH	ALB	TBIL
Zhou et al.[12]	Wuhan, China	191	59 (31%)	NA	NA	NA	123 (67%)	NA	NA
Zhang et al.[59]	Wuhan, China	82	22 (30.6%)	44 (61.1%)	NA	NA	68 (93.2%)	56 (77.8%)	22 (30.6%)
Cai et al.[2]	Shenzhen, China	417	54 (14.9%)	76(18.2%)	68 (16.3%)	16(4.8%)	NA	NA	96 (23.1%)
Chen et al.[67]	Wuhan, China	99	28 (28.3%)	35 (35.4%)	NA	NA	75 (76%)	97 (98%)	18 (18.2%)
Wang et al.[51]	Beijing. China	105	17 (16.2%)	9 (18%)	NA	NA	NA	NA	2(4%)
Chen et al.[68]	Wuhan, China	274	60 (22%)	84 (31%)	NA	NA	116 (42%)	96 (35%)	NA
Zhao et al.[69]	Jingzhou, China	91	10 (11.0%)	18 (19.8%)	NA	NA	NA	NA	NA
Yang et al.[70]	Wenzhou, China	149	18 (12.1%)	27 (18.1%)	NA	NA	45 (30.2%)	9 (6%)	4 (2.7%)
Zheng et al.[71]	Changsha, China	161	13 (8.1%)	22 (13.7%)	NA	NA	38 (23.6%)	NA	9 (5.6%)
Zhang et al.[58]	Wuhan, China	115	11 (9.6%)	17 (14.8%)	15 (13%)	6 (5.2%)	23%	63 (54.78%)	8 (7.0%)
Pan et al.[18]	Hubei, China	204	27 (13.2%)	22 (10.8%)	NA	NA	NA	NA	NA
Fan et al.[65]	Shanghai, China	148	27 (18.2%)	32 (21.6%)	26 (17.6%)	6 (4.1%)	NA	NA	9 (6.1%)
Qian et al.[72]	Shanghai, China	324	51 (15.7%)	53 (16.4%)	NA	4 (1.2%)	NA	136 (42%)	21 (6.5%)
Wu et al.[66]	Jiangsu, China	80	3 (3.75%)	3 (3.75%)	NA	NA	17 (21.3%)	2 (2.5%)	1(1.3%)
Yip et al.[44]	Hong Kong, China	1040	184 (22.5%)	184 (22.5%)	NA	NA	NA	NA	NA
Sun et al.[73]	Nanyang, China	150	24 (16%)	15 (10%)	NA	NA	47 (31%)	NA	3 (2%)
Wu et al.[56]	Wuhan, China	157	12 (7.6%)	25 (16.9%)	NA	NA	32 (21.6%)	NA	NA
Du et al.[60]	Wuhan, China	85	14 (16.5%)	28 (32.9%)	NA	NA	70 (82.4%)	67 (78.8%)	30 (35.3%)
Guan et al.[74]	30 provinces, China	1099	158 (21.3%)	168(22.2%)	NA	NA	277 (41.0%)	NA	76 (10.5%)
Cai et al.[50]	Shenzhen, China	298	39 (13.1%)	25 (8.4%)	51 (17.1%)	1 (0.3%)	23 (8.4%)	NA	24 (8.1%)
Zhang et al.[55]	Wuhan, China	95	52 (54.7%)	45 (47.4%)	NA	NA	74(77.9%)	NA	NA
Richardson et al.[4]	New York, USA	5700	2176 (39.0%)	3263 (58.4%)	NA	NA	NA	NA	NA

NA not available**,** ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; ALB, albumin; TBIL, total bilirubin abnormal.

Table 2. Liver biochemical of COVID-19 patients at different disease severity.

References	Country	Group	Patients (*n*)	ALT (U/L)	AST (U/L)	GGT (U/L)	ALP (U/L)	LDH (U/L)	ALB (g/L)	TBIL (μmol/L)
Du et al.[75]	Wuhan, China	Survivors	158	22 (14–41)	28 (19–42)	29 (17–55)	NA	NA	33 (31–38)	9 (7–12)
		Deceased	21	27 (20–37)	40 (27–62)*	23 (17–42)	NA	NA	33(31–36)	10 (8–16)
Zhou et al.[12]	Wuhan, China	Survivor	137	27(15–40)	NA	NA	NA	254 (219–318)	34 (31–36)	NA
		Non-survivor	54	40(24–51)*	NA	NA	NA	521 (363–669)*	29 (27–31)*	NA
Lei et al.[54]	China	Non-severe	4585	23(15-38)	22(17-31)	NA	65(51-83)	NA	38(35-41)	10(8-14)
		Severe	1186	26(17-45)*	31(21-46)*	NA	63(50-84)	NA	36(32-39)*	11(8-15)
Wang et al.[57]	Wuhan, China	Non-ICU	102	23 (15–36)	29 (21–38)	NA	NA	212 (171-291)	NA	9 (8–13)
		ICU	36	35 (19–57)*	52 (30–70)*	NA	NA	435 (302-596)*	NA	12 (10–19)*
Wang et al.[76]	Wuhan, China	Survivors	274	28 (17–43)	29 (22–43)	NA	NA	286 (220–355)	NA	NA
		Deaths	65	24 (19–49)	43 (30–68)*	NA	NA	439 (360–643)*	NA	NA
Mo et al.[77]	Wuhan, China	General	70	20 (15–33)	32 (23–38)	NA	NA	241 (198-338)	39 (36-42)	NA
		Refractory	85	28 (17–42)	37 (25–56)*	NA	NA	293 (193-434)*	36 (32-40)*	NA
Cai et al.[50]	Shenzhen, China	Non-severe	240	30 (22-38)	28 (19-37)	34 (23-44)	82 (49-98)	168 (124.8-261.5)	NA	14 (8-18)
		Severe	58	42 (28-78)*	38 (23-66)*	47 (31-152)*	87 (54-106)	227 (173-312)*	NA	21 (13-25)*
Cai et al.[2]	Shenzhen, China	Non-severe	233	41 (23–65)	34 (27–45)	40 (25–61)	69 (57–89)	NA	NA	19 (13–26)
		Severe	85	67 (47–100)*	58 (41–93)*	92 (53–161)*	79 (62–101)	NA	NA	22 (18–28)*
Zheng et al.[71]	Changsha, China	Non-severe	131	19(15-18)	23 (19-29)	NA	NA	162(134-209)	NA	11 (8-15)
		Severe	30	24 (18-35)	32 (26-49)*	NA	NA	226(194-315)*	NA	13(9-17)
Zhang et al.[58]	Wuhan, China	Mild	84	21 (13)	24 (10)	29 (25)	72(24)	177(55)	40(3)	10 (4)
		Severe	31	38 (32)*	39 (23)*	57 (73)*	80 (25)	346 (257)*	34 (4)*	14 (6)*
Wu et al.[78]	Jiangsu, China	Mild	197	20 (16–38)	26 (21–34)	NA	NA	184 (155–262)	42 (39–45)	7 (5–12)
		Severe	83	24 (18–38)	26 (23–39)	NA	NA	235 (170–355)*	38 (33–39)*	7 (6–13)
Qian et al.[72]	Shanghai, China	Non-severe	298	22(15-32)	23(18-31)	24(15-41)	57(48-67)	NA	41(4)	8(7-11)
		Severe	26	26(19-35)	34(25-52)*	28(21-63)	59(48-70)	NA	36(5)*	11(9-15)*
Huang et al.[61]	Jiangsu, China	Non-severe	179	25(18-35)	NA	NA	NA	226(174-357)	41(38-45)	10 (7-14)
		Severe	23	31(25-51)*	NA	NA	NA	369(248-638)*	38(34-41)*	10(7-15)
Wan et al.[79]	Chongqing, China	Mild	95	22(15-37)	22(17-31)	NA	NA	212 (180-259)	50 (37-44)	9 (6-14)
		Severe	40	27 (154.5-33)	34(26-44)*	NA	NA	309 (254-408)*	36(33-39)*	10(8-16)
Chen et al.[68]	China	Recovered	161	20 (14.8–32)	25 (20–33.3)	28 (19–45.3)	64 (51–77)	268(214-317)	36 (34-40)	8 (6–11)
		Deaths	113	28 (18–47)	45 (31–67)	42 (27–70)	76 (60–118)	565(431-716)	30 (28-33)	13 (9–16)

NA not available**,** ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; ALB, albumin; TBIL, total bilirubin abnormal. *P<0.05 compared to the other group.

8.4-58.4%,[52,53] mainly manifested as increased levels of ALT, AST, GGT, ALP, lactate dehydrogenase (LDH), and total bilirubin (TBIL) and decreased levels of albumin (ALB). The changes of liver biochemical indexes in COVID-19 patients mainly reflected liver injury and bile duct injury. We integrated the liver biochemical indexes of COVID-19 patients in multiple studies, and their variations are shown in **Table 1**.

Biochemical Indexes of Liver Injury. The main indexes of liver injury were ALT, AST, LDH and ALB. Elevated ALT and/or AST on admission was found in 3.75% to 61.1% of COVID-19 patients. The rate of change during hospital treatment ranged from 8.4% to 58.4% (**Table 1**). The elevation of ALT and AST in most patients was between 1 and 2 times the upper reference limit, suggesting that mild liver injury was the main result of COVID-19.[2,54] The patients with abnormal liver biochemical test results, especially hepatocytic or mixed type, had a significantly higher risk of developing severe pneumonia and higher mortality than patients with normal liver biochemical tests at admission (**Table 2**).[2,46] An elevated AST/ALT ratio on admission was an independent risk factor for poor prognosis[55]. Qin et al. found that COVID-19 patients with AST/ALT ≥1.38 had more severe chest CT findings, poorer laboratory examination results, more severe disease scores, and worse prognosis.[56] Lei et al. reported a significantly increased mortality risk for patients with AST ranging from >40 U/L.[57]

LDH levels were significantly increased in COVID-19 patients.[58,59] Patients with severe ICU and refractory COVID-19 had higher LDH levels.[47,60,61] In two retrospective studies of COVID-19 deaths, elevated LDH levels were as high as 82.4% to 93.2%.[62,63] LDH was positively correlated with COVID-19 severity and was higher in patients with abnormal liver function than in those with normal liver function, and it is a good predictor of severe disease.[62,63]

Abnormal protein metabolism occurs when liver

function is impaired, depending on liver injury type, severity, and duration. Most patients with COVID-19 have decreased albumin after hospitalization, and in some patients, the decrease is progressive and lower than the pretreatment level (**Table 1**). The decrease in ALB levels was most pronounced in severe COVID-19 patients.[61,64] Patients with COVID-19 have gastrointestinal symptoms such as nausea and vomiting, resulting in reduced nutrient intake and ALB production. Patients also have a fever, shortness of breath, dyspnea, and diarrhea, which can lead to increased consumption of ALB. In addition, the virus-induced release of inflammatory cytokines alters vascular permeability, leading to extravascular leakage of ALB. Finally, patients with liver injury have an impaired ability to synthesize ALB, decreasing ALB levels.

Biochemical Indexes of Bile Duct Injury. ALP is closely bound to the lipid membrane in liver cells and is not easily released. While bile acids, by their surface activation, can dissociate ALP from the lipid membrane, resulting in a significant increase in serum ALP during cholestasis. Therefore, ALP is a bile duct cell-related enzyme. The increase in ALP is not obvious in liver injury but bile duct injury. Generally, ALP is not significantly elevated on admission in patients with COVID-19, and during the hospitalization, the rate of elevation of ALP increased to 8.5-11.0%.[46]

Nevertheless, the elevated rate of ALP was low, and there was no significant difference in ALP levels between severe COVID-19 patients and milder COVID-19 patients (**Tables 1** and **2**). Like GGT, ALP is considered a bile duct cell-related enzyme, but ALP is more sensitive to bile duct injury than GGT. Usually, patients with elevated GGT levels and normal ALP may have drug-induced liver injury.[2,65,66]

Biochemical Indexes of Both Liver and Bile Duct Injury. GGT and bilirubin were biochemical indexes that could reflect the injury of the liver and bile duct. GGT is considered as one kind of "bile duct cell-related enzyme", and its level was significantly increased in COVID-19 patients.[61,67,68] During hospitalization and in patients with COVID-19 liver injury, GGT increased by 75.6-82.2%.[2,46] Studies have found that GGT levels are significantly higher in severe COVID-19 patients than in mild COVID-19 patients.[61] Although GGT is also considered a bile duct cell-related enzyme, GGT is not sensitive to ALP in bile duct injury.

Direct bilirubin elevation indicates that the excretion of bilirubin from the biliary tract after metabolism by liver cells is obstructed. However, the indirect elevation of bilirubin is usually due to damage to normal liver cells and disorder of bilirubin metabolism and/or excretion in the liver, which indicates liver lesions. Abnormal bilirubin in COVID-19 patients were mainly associated with an increase in indirect bilirubin.[63,69] Total bilirubin (TBIL) and direct bilirubin values of COVID-19 patients increased from the first week compared with baseline levels, suggesting abnormal bile metabolism in COVID-19 patients in the early stage of the disease. Studies have found that the levels of TBIL are significantly higher in severe COVID-19 patients than in mild COVID-19 patients.[47,57]

Conclusions. Liver injury in COVID-19 patients is common, especially in critically ill patients. SARS-CoV-2 infected the liver through blood circulation or retrograde infection of the digestive tract. Liver injury in COVID-19 patients was mainly related to viral infection, hypoxia and endothelial injury, drug injury and immune injury. Patients generally have elevations of ALT, AST, GGT, ALP, LDH, bilirubin, and ALB reduction. Patients with abnormal liver tests are at increased risk of developing serious disease. In conclusion, more monitoring of liver biochemical examination in patients with COVID-19 should be carried out, and liver-protecting therapy should be given based on the active treatment of the primary disease to reduce liver injury.

Abbreviations. COVID-19, coronavirus disease 2019; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; TBIL, total bilirubin; ALB, albumin; ACE, angiotensin-converting enzyme; ICU, intensive care unit.

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