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REVIEW

Liver injury in COVID-19: Clinical features, potential mechanisms, risk factors and clinical treatments

Shu-Wu Zhao, Yi-Ming Li, Yi-Lin Li, Chen Su

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has been a serious threat to global health for nearly 3 years. In addition to pulmonary complications, liver injury is not uncommon in patients with novel COVID-19. Although the prevalence of liver injury varies widely among COVID-19 patients, its incidence is significantly increased in severe cases. Hence, there is an urgent need to understand liver injury caused by COVID-19. Clinical features of liver injury include detectable liver function abnormalities and liver imaging changes. Liver function tests, computed tomography scans, and ultrasound can help evaluate liver injury. Risk factors for liver injury in patients with COVID-19 include male sex, preexisting liver disease including liver transplantation and chronic liver disease, diabetes, obesity, and hypertension. To date, the mechanism of COVID-19-related liver injury is not fully understood. Its pathophysiological basis can generally be explained by systemic inflammatory response, hypoxic damage, ischemia-reperfusion injury, and drug side effects. In this review, we systematically summarize the existing literature on liver injury caused by COVID-19, including clinical features, underlying mechanisms, and potential risk factors. Finally, we discuss clinical management and provide recommendations for the care of patients with liver injury.

Key Words: Liver injury; COVID-19; Clinical feature; Risk factor; Treatment and

management strategy

Core Tip: A growing body of evidence suggests that patients with coronavirus disease 2019 (COVID-19) may experience varying degrees of liver injury. The characteristics and mechanisms of liver injury associated with COVID-19 are not fully understood. In this review, we summarized the clinical features, mechanisms, and management strategies of liver injury associated with COVID-19. Moreover, we collected all the information about high risk factors for liver injury from COVID-19, which is of significance and help for further study of liver damage related to severe acute respiratory syndrome coronavirus 2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Since the first outbreak in late December 2019 in China, it has unleashed a matchless public health crisis worldwide. The COVID pandemic has been going on for nearly 3 years, and there is still no end in sight. Initially, it was considered solely an atypical pneumonia until patients started to show signs of multiorgan involvement[1]. Now we know that the effects of COVID-19 on the body are extensive. In addition to the respiratory system, almost all systems in the body, including the circulatory system, cardiovascular system, urinary system, gastrointestinal and hepatobiliary system, endocrine system, nervous system, ophthalmic system, and skin system can be affected[2,3]. SARS-CoV-2 virus mainly affects the respiratory system, causing common symptoms such as fever, fatigue, cough, and dyspnea. Relatively, diarrhea, myalgia, hemoptysis, and sore throat are less common[4]. Other reports show that liver dysfunction is a common manifestation of COVID-19 and is associated with higher mortality[5]. It is worth mentioning that the incidence of liver injury in severe COVID-19 cases can reach 93%[6]. However, the exact mechanism of how COVID-19 impairs liver function remains unclear. This comprehensive literature review is aimed at providing useful guidance for diagnosis, risk factor identification, and management of liver injury associated with COVID-19.

CLINICAL FEATURES OF LIVER INJURY IN COVID-19

Liver injury is mainly manifested as abnormal liver function (ALF) indexes. Alterations in hepatocyte damage biomarkers (HDBs), such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), are commonly used to evaluate COVID-19-related liver injury[6,7]. In some cases, elevated lactate dehydrogenase (LDH), hypoproteinemia, prolonged prothrombin time, total bilirubin (TBil), and direct bilirubin (DBiL) are also used to assess liver function in COVID-19 patients[8-10].

In COVID-19 patients, transaminase elevations are usually mild [1-2 times the upper limit of normal (ULN)][9]. These changes in laboratory values may persist for a long time, even after hospital discharge. ALF was defined as at least one test HDB exceeding the ULN. Xu *et al*[10] evaluated the proportion of patients with abnormal HDBs, and found on admission ALT 13.2%, AST 8.5%, ALP 2.0%, GGT 7.4%, LDH 37.6%, TBiL 4.0%, DBiL 7.8%, and albumin 10.1%, and peak during the hospitalization ALT 29.4%, AST 17.5%, ALP 2.6%, GGT 13.4%, LDH 49.4%, TBiL 10.1%, DBiL 18.0%, and albumin 30.6%. In another study, the proportion of patients with at least one of the HDBs and TBil exceeding the ULN for the first time immediately after hospitalization, before discharge, a median of 14.0 d after discharge, and 1 year after discharge was 32.2%, 45.8%, 54.8%, and 28.8%, respectively[11]. In addition, a single-center prospective cohort study found that the proportion of patients with any ALF was 25.1% at 1 mo, 13.2% at 3 mo, 16.7% at 6 mo, and 13.2% at 12 mo after discharge[12]. Based on these data, long-term monitoring of liver enzymes may be warranted in patients with a history of COVID-19.

AST is generally considered to be less specific for liver injury than ALT due to additional extra-hepatic production[13,14]. Nevertheless, in liver damage, elevated AST levels appear earlier, and the increase in AST levels at admission is usually more pronounced than ALT levels. In cases of severe

COVID-19, however, ALT levels typically rise rapidly, exceed the ULN value and peak within 10-15 d of admission. Subsequently, ALT levels remained stable in all patients with liver injury and then gradually decreased with longer hospital stay. ALT is a more effective indicator of liver injury in COVID-19 patients with severe manifestations[15]. However, if serum AST and LDH levels are elevated but ALT levels remain normal, other causes of elevated liver biochemical responses rather than liver injury should be considered, such as myositis (especially AST > ALT), cardiac injury, ischemia, and cytokine release syndrome (CRS)[16].

The reported prevalence of liver injury in COVID-19 patients varied widely across studies, ranging from 4.8% to 78%[17]. This is mainly due to a variety of factors, including dynamic changes in liver function, small sample sizes, different admission criteria, lack of adjustment for baseline chronic liver disease (CLD), use of different HDBs, and inconsistent definitions of "liver injury"[10,18-20]. Notably, almost all studies were conducted on hospitalized patients, ignoring non-hospitalized patients, thus resulting in unclear overall morbidity (Table 1).

LIVER INJURY AND PROGNOSIS

COVID-19 patients with moderate or severe liver injury (SLI) have an increased risk of admission to the intensive care unit (ICU), disease progression, and death compared with patients without elevated liver chemistries[9,19,23]. Cai *et al*[6] have reported that patients with liver injury have a 9-fold greater risk for developing severe COVID-19. In a retrospective cohort study, when compared with moderate liver injury (2-5 ULN) and no/mild liver injury (< 2 ULN), COVID-19 patients with SLI (ALT > 5 ULN) had more severe clinical outcomes, including higher ICU admission rates (69% *vs* 42% *vs* 16%), intubation (65% *vs* 38% *vs* 13%), renal replacement therapy (33% *vs* 15% *vs* 7.5%), and mortality (42% *vs* 23% *vs* 21%). Among SLI patients, 70% required vasopressors, 12% received inotropes, 39% were paralyzed, 10% were proned, and 2.8% required extracorporeal membrane oxygenation[19].

Changes in liver function are predictors of severity and mortality in patients with COVID-19[5,23]. Abnormal liver biochemical parameters are closely related to an increased risk of mortality in critically ill patients with COVID-19. The levels of ALT, AST, GGT, LDH, TBil, and DBil in severe patients were significantly higher than those in mild-moderate patients. Conversely, severe patients had significantly lower albumin levels than non-severe patients[5,20]. In a study of 151 hospitalized patients, 5 liver injury parameters, ALT, AST, TBil, DBil, and indirect bilirubin, were identified as notable prognostic factors, while total protein, albumin, ALP, GGT, and total bile acid appeared to be less related to prognosis[25]. In other studies, low albumin is also a marker of severe infection and poor prognosis[10,26]. Lei *et al*[15] emphasized the association of ALF tests, especially AST and TBil, with higher mortality. They observed that AST was more frequently elevated than ALT in severe patients. However, elevated ALP and peak ALT were significantly associated with discharge to hospice and death[19,27].

ABDOMINAL IMAGING FINDINGS

Possible imaging signs of liver damage on computed tomography (CT) scans of the hepatobiliary system include hepatomegaly, decreased liver density, periportal edema, fat stranding around the gallbladder, portal lymphadenopathy, and dilated gallbladder and bile ducts[28,29]. Portal venous gas can be seen in patients with mesenteric ischemia, especially in critically ill patients[30]. CT-quantified liver density can be assessed by the liver-spleen attenuation ratio, which correlates with the severity of liver injury. A common manifestation of liver damage caused by COVID-19 is homogeneous or heterogeneous low density of the liver. Liver hypodensity is more common in critically ill cases[28]. Ultrasound can be easily performed in COVID-19 patients to help identify liver damage quickly and effectively. The most frequent sonographic finding is hepatomegaly with increased parenchymal echogenicity, followed by biliary disease, including gallbladder sludge and distention, gallbladder wall thickening, mural hyperemia, intraluminal mud, and pericholecystic fluid[29-31]. Portal venous gas suggests mesenteric ischemia. Further, gallbladder cholestasis is common in critically ill patients of COVID-19[30]. Collectively, imaging of liver injury can reveal changes in liver density, gallbladder and bile duct dilation, portal pneumatosis and/or mesenteric ischemia.

PROPOSED MECHANISMS OF LIVER INJURY

The pathological basis of liver injury following COVID-19 infection is puzzling and not fully understood. Studies suggest that direct cytotoxicity, hypoxic hepatitis, cytokine storm syndrome, exacerbation of preexisting liver disease, and drug-induced liver injury (DILI) may be major mechanisms of COVID-19-related liver injury.

Table 1 Criteria, grading, and incidence of abnormal liver function or injury

Ref.	Sample size	Study type	Criteria and grading of ALF or injury	Comments
Salık *et al*[5]	533	Retrospective study	Liver biochemical parameters: ALT, AST, and TBiL > ULN. Liver injury: ALT and/or AST > 3 ULN, and/or TBiL > 3 ULN	NA
Cai *et al*[6]	417	Retrospective, single-center study	ALF: > ULN. Liver injury: ALT and/or AST > 3 ULN, ALP, GGT, and/or TBiL > 2 ULN	76.3% had ALF and 21.5% had liver injury during hospitalization
Fan *et al*[8]	148	Retrospective, single-center study	Increased levels of ALT, AST, GGT, ALP, and total bilirubin	37.2% had ALF at hospital admission
Kulkarni *et al*[9]	20874	Meta-analysis	ELC: AST or ALT > ULN. SLI: Any elevation of enzymes > ULN and bilirubin over 2 ULN	ELC: 23.1% at initial presentation. 24.4% developed ELC during the illness
Xu *et al*[10]	1003	Retrospective cohort study	Mild liver injury: 1-2 ULN. Moderate liver injury: 2-5 ULN. Significant liver injury: > 5 ULN	Most patients with abnormal liver function parameters had mild elevations (1-2 ULN) at admission and peak hospitalization
Hundt *et al*[13]	1827	Retrospective observational cohort study	ELC: AST, ALT, ALP, TBiL, albumin: > ULN	ELC at pre-hospitalization (AST 25.9%, ALT 38.0%, ALP 56.8%, and TBiL 44.4%). Admission (AST 66.9%, ALT 41.6%, ALP 13.5%, and TBiL 4.3%). Peak hospitalization (AST 83.4%, ALT 61.6%, ALP 22.7%, and TBiL 16.1%)
Balderramo *et al*[14]	298	Multicenter study	ALEx2: The elevation of at least one of the following: TBil, ALT, AST, GGT, or ALP > 2 ULN	During admission, 29.2% out of 298 patients presented ALEx2
Phipps *et al*[19]	6913	Retrospective cohort study	Mild: ALT 1-2 ULN. Moderate: ALT between 2-5 ULN. Severe: ALT > 5 ULN	Among patients who tested positive, 45% had mild, 21% moderate, and 6.4% SLI
Wang *et al*[21]	156	Retrospective, 2-centers study	Elevated aminotransferases	41.0% patients with elevated aminotransferases
Liu *et al*[22]	245	Retrospective, single-center study	Mild liver dysfunction: AST ≥ ULN. Moderate liver dysfunction: AST ≥ ULN combined with any parameter being greater than the ULN values of ALT, GGT, and TBiL. Severe liver dysfunction: AST ≥ ULN combined with ALT ≥ 3 ULN and/or GGT, TBiL ≥ 2 ULN	43.7% experienced mild liver dysfunction, 40.4% experienced moderate liver dysfunction, and 20.4% experienced severe liver dysfunction
Chaibi *et al*[23]	281	Retrospective cohort study	ALF: AST, ALT, GGT, ALP or TBil > ULN	36.3 % had liver dysfunctions. Only a minority of patients (6.4%) had perturbations above 5 times the ULN
Shousha *et al*[24]	547	Multicenter cohort study	Liver injury: Transaminase > 3 ULN	26% and 32% of patients had elevated ALT and AST, respectively. 4.91 and 3.70%patients, respectively, had AST or ALT elevation > 3 ULN

ALEx2: Abnormal liver enzymes over twice the upper limit of normal; ALF: Abnormal liver function; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ELC: Elevated liver chemistries; DBiL: Direct bilirubin; GGT: Gamma-glutamyl transferase; NA: Not available; TBil: Total bilirubin; ULN: Upper limit of normal.

Direct cytotoxicity

The dual blood supply to the liver may be a route of infection. It is speculated that retrograde liver infection occurs after intestinal infection with SARS-CoV-2[32,33]. It is known that the S protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to facilitate virus entry into host cells. ACE2 receptors are widely expressed in multiple organs, including the liver[34]. Although the expression of ACE2 is much lower in hepatocytes compared to type 2 pneumocytes, its expression levels are similar in cholangiocytes and type 2 pneumocytes[35], indicating that the hepatobiliary system is a potential target organ of SARS-CoV-2.

SARS-CoV-2 RNA has been reported to be detectable in the liver of COVID-19 patients. Electron microscopy also revealed larger numbers of coronavirus particles in the livers of these patients[21,36]. Postmortem liver biopsies showed typical coronavirus particles in the cytoplasm and typical viral infection lesions, such as mitochondrial swelling, endoplasmic reticulum dilation, and decreased glycogen granules. Besides, massive hepatocyte apoptosis and some binuclear hepatocytes were also observed[21].

Cytokine storm syndrome

Cytokine storm refers to the rapid and massive production of various cytokines in body fluids, which plays an important role in acute respiratory distress syndrome and multiple organ failure. The liver

cannot escape the cytokine storm. The pathogenesis of cytokine-mediated liver injury may stem from inflammation, altered coagulation, and activation of the renin-angiotensin-aldosterone system, culminating in microvascular insult, hepatocyte damage, and perpetuation of inflammation[37]. It has been reported that plasma levels of interleukin (IL)-2, IL-6, IL-7, IL-10, interferon (IFN)-γ, granulocyte colony-stimulating factor, IFN-inducible protein-10, monocyte chemoattractant protein-1, recombinant macrophage inflammatory protein 1 alpha, and tumor necrosis factor alpha (TNF-α) were higher in severe COVID-19 patients than in mild and moderate cases[38,39].

The IL-6 signaling complex causes deleterious changes in hepatic sinusoidal endothelial cells and may promote blood clotting. This may be a possible mechanism behind liver injury in these patients [40]. Animal experiments have demonstrated that TNF-α has a moderate contribution to ALT elevation, necroinflammation, and apoptosis[41]. The role of other cytokines in liver injury in COVID-19 patients still requires further study.

Hypoxia, endotheliitis, and coagulation dysfunction

Patients with COVID-19, especially with severe manifestations, may have varying degrees of hypoxemia. Interestingly, some of them have no experience with breathing difficulties[42]. *In vivo* and *in vitro* studies have observed the occurrence of hepatic ischemia and hypoxia, hepatic cell death, and inflammatory cell infiltration[43]. Moreover, studies have found that SARS-CoV-2 enters endothelial cells, destroys vascular endothelium, and causes diffuse endothelial inflammation that can rapidly induce vasoconstriction and procoagulant tendency[44,45].

Spiezia *et al*[46] found that COVID-19 patients with acute respiratory failure presented with severe hypercoagulability rather than consumptive coagulopathy. In these patients, plasma levels of fibrinogen and D-dimer were significantly elevated and a marked hypercoagulable thromboelastometry profile was observed. Rampotas and Pavord[47] examined 20 random blood films from COVID-19 patients receiving invasive ventilation and observed the presence of platelet aggregates and macrothrombocytes, indicating increased platelet activity.

Reactivation of pre-existing liver disease

Liu *et al*[48] evaluated hepatitis B virus (HBV)-DNA viral load in 19 hospitalized patients with COVID-19. They found that three patients had HBV reactivation (HBVr) and one patient had a high HBV-DNA viral load throughout the hospital stay. This study suggests that COVID-19 patients with pre-existing chronic HBV infection, with or without corticosteroids use, may be at risk for hepatitis B reactivation. In a review, Perrillo *et al*[49] divided the drugs that induce HBVr into three categories. High-risk drugs are anticipated to induce HBVr in > 10% of cases, moderate-risk drugs are anticipated to induce HBVr in 1%-10% of cases, and low-risk drugs are anticipated to induce HBVr in < 1% of cases. Moderate/high-dose corticosteroid therapy for ≥ 4 wk is a high-risk factor for HBVr. Anthracycline derivatives are moderate/high-risk drugs. Moderate-risk drugs include TNF-α and other cytokine inhibitors, integrin inhibitors, tyrosine kinase inhibitors, and ≥ 4 wk of low-dose corticosteroid therapy. Therefore, patients receiving any of these drugs for COVID-19 are at risk of inducing HBVr and its complications.

DILI

Various potentially hepatotoxic drugs such as remdesivir, lopinavir, azithromycin, hydroxychloroquine, acetaminophen, antibiotics, and corticosteroids are thought to induce liver injury[50,51]. In some cases, the extent of liver damage depends on the dose[52]. Antiviral drugs have been used against SARS-CoV-2, examples of such antivirals are remdesivir, lopinavir-ritonavir, and others. They have all been documented to be potentially hepatotoxic. Although some small-scale trials have reported ALT/AST elevations with remdesivir, most clinical trials have not shown significant hepatotoxicity in the treatment of COVID-19[53]. Lopinavir/ritonavir and remdesivir have similar hepatotoxicity profiles [54].

Dexamethasone, used for hypoxic respiratory failure in patients with COVID-19, is known to induce the elevation of liver enzymes, increase hepatic lipid peroxidation, and decrease antioxidant activity [55]. The liver-damaging effects of azithromycin and acetaminophen have been proven for many years [56,57]. Acetaminophen, an analgesic and antipyretic drug widely used for mild-to-moderate pain and fever, may cause dose-dependent hepatotoxicity[52].

RISK FACTORS FOR LIVER INJURY

Studies have shown that the incidence of liver injury in severe/critically ill patients is much higher than the incidence in moderate cases[17,58]. Apparently, male sex, older age, and higher body mass index are also associated with liver damage from COVID-19[6,17,58,59]. Besides, coexisting diseases such as hypertension, diabetes, cardiovascular disease, malignancy, and some liver diseases may all be risk factors for liver damage[60,61]. Currently, the susceptibility of children and pregnant women to liver injury is not fully understood.

Male sex

Multiple studies show that men with COVID-19 have an increased risk of liver damage[6,17,59,62]. Among younger patients, men also have higher odds of severe pneumonia, acute kidney injury, and acute liver injury than women. However, among elderly patients, there was no difference in the likelihood of poor outcomes between men and women[62].

Possible mechanisms are attributed to the activity of sex hormones and X-linked genes and differential regulation of innate and adaptive immune responses to viral infection. Compared with women, men have higher circulating levels of ACE2 and ACE2 levels in the lungs. Moreover, testes have much higher levels of ACE2 than ovaries. Additionally, men have lower expression of protective cytokines but higher levels of pro-inflammatory cytokines and chemokines[62].

Elderly

In a study of 900 patients with COVID-19, those aged 40-69 were at particularly high risk of liver injury and liver-related death. COVID-19-related deaths were more frequent in patients 40-69 years and ≥ 70 years of age with elevated AST levels. Although only a small proportion (1.7%) of patients without prior liver disease also died from liver-related causes, severe liver impairment and acute liver failure are rare but important complications of COVID-19[63]. Liver dysfunction is associated with poor prognosis in elderly patients with higher mortality due to liver cell damage[64].

Liver transplant

According to recent reports, liver transplant (LT) patients have a higher incidence of COVID-19, possibly due to long-term immunosuppression. Despite the increased risk of acquiring COVID-19, LT patients have lower mortality rates than matched general individuals[65]. In another study, the prevalence of COVID-19 in LT patients was 6.05%, twice that of the general population of the same age, possibly due to higher susceptibility to the virus[66]. Verbeek *et al*[67] suggested that organ transplantation should be avoided in patients with active infection and respiratory symptoms because of the risk of COVID-19 progression and subsequent organ failure, as well as the risk of exposure to the virus for transplant operators.

Furthermore, patients with LT are at high risk for hepatic decompensation and increased mortality, and may suffer from severe extrahepatic sequelae of COVID-19[68,69]. Due to lack of evidence that LT children are at a greater risk of contracting COVID-19, routine withdrawal of immunosuppressive drugs is not recommended for LT children or patients with autoimmune liver disease[70]. Generally, LT recipients do not appear to have an increased risk of death following COVID-19 infection compared to the matched general population[71].

CLD

The most common cause of CLD is nonalcoholic fatty liver disease (NAFLD), followed by HBV infection, alcohol-related liver disease, and hepatitis C virus infection[72]. Liver injury and pre-existing CLD are significantly associated with disease severity and mortality in COVID-19 patients[73,74]. Yang *et al*[75] found that CLD is independently associated with COVID-19 severity and mortality, especially in a male-dominated elderly population. However, some studies believe that liver injury is indeed an independent predictor of key outcomes, but CLD and HBV infection status are not significant comorbidities of COVID-19[73,74,76].

Similar to other CLDs, metabolically associated fatty liver disease (MAFLD) has been shown to have longer viral shedding, a higher risk of disease progression, a higher all-cause mortality, and higher COVID-19-related mortality than patients without MAFLD[72,77]. Compared with other causes of CLD, patients with autoimmune hepatitis have a worse prognosis for COVID-19[78,79].

In adult studies, certain populations, such as those with cirrhosis, nonalcoholic steatohepatitis, and liver cancer, have been found to have an increased risk of severe COVID-19 and a poorer prognosis[69,80-82]. In adults with COVID-19, cirrhosis is a risk factor associated with worse outcomes. A large survey of 220727 patients found that COVID-19 infection in patients with cirrhosis was associated with a 2.38-fold risk of death, while cirrhosis in CLD patients with COVID-19 was associated with a 3.31-fold risk of death[83]. These results suggest that cirrhotic patients with COVID-19 infection are associated with an increased risk of all-cause mortality. Zecher *et al*[84] concluded that there were no differences in age, sex, autoimmune liver disease, and cirrhotic status between COVID-19 and non-COVID-19 cases.

Children with CLD, including obese children with suspected or confirmed NAFLD, may be at an increased risk for COVID-19 infection and severe COVID-19[70,85]. Children with CLD may experience decompensation of end-stage liver disease during COVID-19 infection[70]. Compared with LT recipients, children with CLD, including children with end-stage liver disease, are more likely to be hospitalized and require intensive care[86]. However, in the study by Di Giorgio *et al*[87], the susceptibility of different pediatric patient groups to COVID-19 infection was similar, and underlying liver disease may not increase the risk of severe COVID-19. The inconsistency between these findings may be related to the different sample sizes collected.

Obesity

Cumulative evidence support obesity as a risk factor for severe COVID-19 and related death, directly or indirectly increasing inflammation, hypercoagulability, and mechanical obstruction[88]. Obesity has emerged as a strong independent determinant of increased risk of morbidity and mortality in patients infected with COVID-19. In addition, data suggest that visceral obesity and hyperglycemia in non-diabetic and diabetic patients may also be significant independent risk factors for severe COVID-19[89]. In another study, patients aged 40-69 had a higher prevalence of obesity (44.4%), suggesting that a certain proportion of patients with hepatic steatosis in this age group may be predisposed to COVID-19-related liver damage[63,78,90]. Furthermore, one study showed that > 50% of COVID-19 cases in patients with underlying hepatic steatosis were severe, with a mortality rate of 17%[91].

Diabetes mellitus

Diabetes mellitus, whether due to insufficient pancreatic beta cells or peripheral insulin resistance, is considered a risk factor for COVID-19 infection. Numerous studies have shown that new-onset hyperglycemia, ketoacidosis, and diabetes are frequently observed in patients with COVID-19[88,89,92,93]. Individuals with diabetes often have associated comorbidities, such as obesity, hypertension, and cardiovascular disease, as well as diabetic complications, including chronic kidney disease, vascular disease, and related immune dysfunction, all of which put them at risk for infectious complications[94]. In a study of 458 patients with COVID-19 and diabetes, those with liver injury and chronic kidney disease had significantly higher mortality rates than other complications[95]. In other words, chronic kidney disease and liver disease are the two main contributors to the rise in mortality among patients with diabetes and COVID-19.

Malignancy

Hepatocellular carcinoma (HCC) has been identified as a predictor of poor prognosis in COVID-19 patients[72,76]. HCC is often associated with cirrhosis, suggesting that decreased immunity may increase the risk of severe COVID-19, and that infection with COVID-19 can exacerbate pre-existing liver disease, complicating cancer management[96]. Furthermore, COVID-19 vaccination is recommended for LT candidates and patients with CLD or HCC as they are susceptible to severe COVID-19[68]. Overall, cancer patients are considered to be at high risk of developing severe COVID-19 due to comorbidities and immunosuppressive status, especially among those who have recently received chemotherapy or had surgery within a month[96,97].

Hypertension

In a study of 300 patients with COVID-19, 33.2% were diagnosed with hypertension at admission. These hypertensive patients displayed higher levels of Troponin T and creatinine near hospital discharge[93]. Notably, the proportion of hypertensive patients in severe COVID-19 was significantly higher, and the mortality rate of severe patients was higher[93]. In addition, high blood pressure may increase the risk of liver damage following COVID-19 infection in elderly patients without pre-existing CLD[73].

It has been reported that hypertensive patients have a higher probability of liver damage and a poorer prognosis. The underlying mechanism may be related to the activation of the renin-angiotensin system and the damage of ACE2-positive cholangiocytes and hepatocytes, which further lead to cholangiocyte and hepatocyte-associated disorders[69,81,98,99]. ACE2-stimulating drugs for high blood pressure have been hypothesized to increase the risk of fatal COVID-19. Fang *et al*[100] reported that patients using ACE2-elevating drugs for hypertension, diabetes or heart disease are at increased risk of COVID-19 infection.

Pregnancy

Pregnant woman with COVID-19 have significantly decreased blood lymphocytes, increased neutrophils, and elevated C-reactive protein and TBil levels[101]. In the study by Deng *et al*[102], the incidence of liver injury in pregnant women infected with COVID-19 was 29.7%. Despite a higher frequency of ICU admissions, in-hospital mortality was lower among pregnant patients compared with non-pregnant patients with COVID-19 viral pneumonia, at 1.1% for pregnant women and 3.5% for non-pregnant women. Pregnancy is not an independent risk factor for in-hospital mortality in COVID-19 patients[103]. In the study by Tunç *et al*[104], COVID-19-related hospitalization rates were 24.1% in the first trimester, 36% in the second trimester, and 57.3% in the third trimester; there was no significant relationship between pregnancy duration and the need for ICU admission.

However, pregnant women may have many comorbidities, including hypertension, chronic lung disease, diabetes, and obesity, compared with non-pregnant women[103]. Pregnant patients with COVID-19 and chronic complications such as hypertension and diabetes have an increased risk of developing inflammation and liver damage[101]. Pregnant women taking antiviral drugs have several options, including continuing treatment, stopping or switching to safer drugs. Patients with high pretreatment ALT or less than 1 year of treatment prior to pregnancy have a high risk of severe hepatitis flares after cessation of antiviral agents[105].

The perinatal outcomes of all reported cases were reassuring, with 98% live births, 78% full-term births without neonatal complications, and a 20% neonatal ICU admission rate. The stillbirth rate was as low as 1.7%, and the neonatal mortality rate was 0.8%. No vertical transmission was found in 98.4% of neonates[106,107].

Children

Children with COVID-19 infection often have minimal or no increase in liver enzymes[60]. COVID-19 may impair liver function, usually resulting in transient and moderate elevations in liver markers without significant impairment of hepatic synthesis. COVID-19-infected patients with elevated ALT are at risk for a more severe disease course, including longer hospital stay and ICU stay[85]. Compared with adult patients, pediatric patients have relatively lower rates of lymphopenia, higher inflammatory markers, and possible thrombocytopenia[108].

MANAGEMENT OF LIVER INJURY IN PATIENTS WITH COVID-19

Liver injury in mild cases of COVID-19 is usually transient, self-limiting, and reversible without treatment. However, some COVID-19 patients who present with liver injury may become critically ill and require medical attention[16]. The cause of liver injury should be analyzed and judged in all patients. Initial screening includes careful review of preexisting liver disease, exposure to hepatotoxins (alcohol, drugs, herbs, and chemicals), hypoxia, and circulation status (Table 2). Liver function indicators including ALT, AST, TBil, DBiL, albumin, prothrombin activity, and international normalized ratio should be closely monitored[109,110].

Prophylactic use of hepatoprotective and enzyme-lowering drugs is not recommended[109]. Theoretically, reducing viral load with antiviral therapy is the most effective way to reduce organ damage. However, there is currently a lack of clinical data to support it, and more attention is paid to antiviral drug-related liver injury. This may be one reason for the lack of particularly effective antiviral drugs until recently.

The management of liver injury from COVID-19 is largely empirical and mainly supportive. Patients with severe liver damage associated with COVID-19 should be treated with hepatoprotective, anti-inflammatory, and jaundice-reducing agents such as glycyrrhizic acid, polyene phosphatidyl choline (PPC), bicyclol, and vitamin E[111,112]. Glycyrrhizic acid can effectively inhibit the replication and cytopathic effect of coronavirus without obvious cytotoxicity to host cells[113]. Glycyrrhizin has anti-inflammatory properties that may offer protection against liver disease[109]. PPC may be a drug that enhances the hepatoprotective function through glutathione and magnesium isoglycyrrhizinate[114].

Currently, there is no specific treatment for critically ill patients with COVID-19. Effective suppression of the host's uncontrolled immune response during cytokine storm may be a critical step in preventing disease progression and reducing mortality[115,116]. Anakinra is an IL-1 receptor antagonist that blocks the release of IL-β. A study concluded that early anakinra treatment is associated with significantly lower ICU admissions and mortality in patients with moderate/severe COVID-19[117]. Successful anakinra therapy includes treatment duration ≥ 10 d, dose ≥ 100 mg, intravenous administration, and early initiation of therapy[118]. Canakinumab is a human monoclonal anti-IL-1β specific antibody. Studies have shown that canakinumab therapy provides rapid and durable improvement in oxygenation levels, reduced proinflammatory markers and reduced need for mechanical ventilation resulting in better outcomes[119,120].

IL-6 is one of the key mediators of cytokine storm-induced damage[121]. Currently, there are two main types of IL-6 inhibitors that target IL-6 itself (siltuximab) or its receptors (tocilizumab and sarilumab)[115]. IL-6 levels drop after administration of siltuximab, suggesting that the inhibitor may reduce CRS and mortality[122]. The literature supports the early use of tocilizumab as it has been observed to lower mortality in adults with COVID-19 pneumonia[123,124] and achieve better clinical recovery at day 28[125]. In another study, clinical improvement and mortality were not statistically different between tocilizumab and standard treatment[125]. The reason may be a higher risk of bacterial or fungal infection in patients within tocilizumab application[123,124,126]. Sarilumab is a high-affinity anti-IL-6 receptor antibody. In a phase II, open-label, randomized, controlled clinical trial of hospitalized patients with COVID-19, early use of sarilumab was safe and associated with a trend for better outcomes[127]. However, in some other studies, the efficacy of sarilumab in hospitalized patients with moderate-to-severe COVID-19 has not been established[128-130]. Inhibition of IL-6-mediated signaling may not be sufficient to reduce CRS, and the answer may lie in combination therapy and interfere with other related pathways. So far, conflicting results hinder efforts to use IL inhibitors to combat COVID-19 infection[131].

Anti-TNF therapy has also shown conflicting results. In a case-cohort study, patients treated with anti-TNF-α inhibitors were hospitalized less frequently[132]. This was a systematic review and meta-analysis of COVID-19 and outcomes in patients with inflammatory bowel diseases (IBD). Compared with patients on corticosteroids, those on anti-TNF-α therapy had a lower risk of hospitalization and ICU admission. Moreover, similar results were seen in patients treated with anti-TNF-α compared to

Table 2 Treatments of liver injury in coronavirus disease 2019

Mechanisms of liver damage	Treatments	Caution	Ref.
Hepatocellular injury	Hepatoprotective, anti-inflammatory, and jaundice-reducing agents	Preventive administration is not recommended	[109, 111, 112]
Cytokine storm syndrome	Continuous renal replacement therapy. IL-1 inhibitor, IL-6 inhibitor, TNF inhibitor	IL-1 or IL-6 inhibitors could reduce inflammation; however, they have a potential to cause DILI and worsen clinical conditions	[109, 139, 140]
DILI	Prompt discontinuation or reduction of doses of suspected triggers. Medication reconciliation is important. Discontinue all non-vital therapy, redundant types/doses, modify course duration	Requires a trade-off between therapeutic effects and side effects	[109]
Reactivation of pre-existing liver disease	Continue treatment for hepatitis B and hepatitis C if already on treatment	Difficulty distinguishing between new-onset liver injury and reactivation of pre-existing liver disease	[16, 109]
Hypoxic hepatitis	Circulation and respiratory support	Higher PEEP, which may be needed to improve oxygenation, may affect cardiac output, decreasing hepatic arterial flow, thus enhancing arterial dysfunction	[139, 140]

DILI: Drug-induced liver injury; IL: Interleukin; PEEP: Positive end-expiratory pressure; TNF: Tumor necrosis factor alpha.

patients treated with mesalamine[133]. Colonic ACE2 expression was downregulated after anti-TNF-α therapy in IBD patients[134], but no liver-related data have been reported. In another meta-analysis and systematic review of 84 studies, no difference was found in the risk of hospitalization in patients receiving anti-TNF-α therapy compared to patients not receiving anti-TNF-α therapy[135]. Foods rich in vitamins, minerals, polyphenols, and other bioactive compounds may decrease inflammatory pathway activity and prevent liver damage in COVID-19 patients[136].

Corticosteroids have a dual effect. They have been associated with DILI, especially at high doses, however they are used to treat drug-induced cholestatic hepatitis and DILI associated with hypersensitivity reactions[137,138]. The only specific antidote for acute DILI remains N-acetylcysteine for acetaminophen poisoning. Glycyrrhizin, ursodeoxycholic acid, and silymarin have been used for decades to treat DILI, but success remains anecdotal[138]. The most effective treatment for suspected DILI is to discontinue drug therapy before progression to irreversible liver failure, which results in spontaneous recovery in approximately 90% of cases[139].

CONCLUSION

Nearly 3 years later, there is still no sign that the COVID-19 pandemic is over. COVID has long-term devastating effects involving multiple organs. Particular attention should be given to liver injury associated with COVID-19. There is growing evidence that liver injury is a typical long-term effect of COVID-19, especially in critically ill cases, and may require monitoring after the patient is discharged. The exact incidence and underlying mechanism of liver damage are not well known. Fortunately, most patients with mild liver damage recover without special treatment. However, SLI is believed to worsen the prognosis and increase mortality from COVID-19. Increased research efforts are needed to identify those patients at higher risk of complications, better definition of liver injury, better understanding of the pathophysiology, and effective therapies.

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