



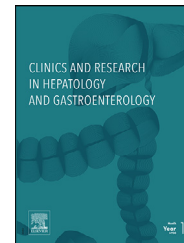
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REVIEW

COVID-19 and liver dysfunction: Epidemiology, association and potential mechanisms



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Available online 21 August 2021

KEYWORDS

Liver dysfunction;
 COVID-19;
 Systematic review

Abstract

Currently, there have been more than one hundred million confirmed cases of coronavirus disease 2019 (COVID-19), with two million deaths worldwide. This has caused a huge medical burden. Severe COVID-19 patients can experience multi-organ damage, including cardiac injury, kidney injury, and liver injury. About 2.0%–4.9% of COVID-19 cases involve patients with preexisting liver diseases. Additionally, preexisting liver diseases were reported and associated with severity (odds ratio (OR) or risk ratio (RR) = 1.48–1.70) and mortality (OR or RR = 1.08–2.65) among COVID-19 patients. Furthermore, the prevalence of liver injury was 16%–29% in COVID-19 patients. Higher prevalence of liver injury may worsen prognosis in patients (severity: OR or RR = 1.9–2.6; mortality: OR or RR = 1.1–4.0). The mechanisms of this association between liver injury and severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection are complex, including direct cholangiocyte damage induced by SARS-COV-2, cytokine storm, and drug-induced liver injury. In particular, drug-induced liver injury may be the most important reason. This review discusses the epidemiology of COVID-19 and liver dysfunction as well as potential mechanisms underlying the association between COVID-19 and liver dysfunction or other preexisting liver diseases. However, the association between preexisting liver diseases and COVID-19 prognosis and potential mechanisms underlying these associations require further prospective studies.

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Introduction

Coronavirus disease 2019 (COVID-19) has become a major public health problem. According to the World Health Organization (WHO), there have been more than one hundred

COVID-19 and Liver Dysfunction: Epidemiology, Association, and Potential Mechanisms

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<https://doi.org/10.1016/j.clinre.2021.101793>

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million confirmed cases of COVID-19, with two million deaths worldwide [1]. The COVID-19 pandemic is a major threat to public health, and its common symptoms include fever and dry cough, which are secondary to lung involvement [2]. Severe patients may present a systemic and multi-organ disease [2].

Current studies have shown that COVID-19 patients may present with gastrointestinal symptoms including diarrhea, nausea, and vomiting [3-5]. Additionally, growing evidence shows that hepatic dysfunction is common among COVID-19 patients, which should be of concern [6]. One meta-analysis found that the rate of liver dysfunction among COVID-19 patients was 27.4% [7]. Severe patients may present with higher rates of liver dysfunction, and patients with abnormal liver function may have higher risks of progressing to severe disease [8]. This review introduces epidemiological aspects of COVID-19 and discusses its underlying mechanisms. Finally, associations between COVID-19 prognosis and liver dysfunction/preexisting liver diseases are discussed to provide a reference for better patient management according to recent available information.

COVID-19

According to the World Health Organization (WHO) dashboard (as of March 5, 2021), there were 115,289,961 cumulative reported cases of COVID-19 globally, with the vast majority from the Americas (44%), Europe (34%), and Southeast Asia (12%) as of [1]. Meta-analysis showed that a higher proportion of infected patients were male 53.3%–57.8% [9-12]. Until March 5, 2021, nearly half of the deaths occurred in the Americas (1,227,085; 48%), followed by Europe (878,731; 34%) and Southeast Asia (209,729; 8%) [1]. The prevalence rate of mortality among hospitalized COVID-19 patients was 18.88% [13]. It was reported that men were more likely to have severe pneumonia than women [13,14]. Additionally, older age, obesity, and preexisting diseases were risk factors for mortality among hospitalized COVID-19 patients [13]. For example, a population study found that patients who were diagnosed with nonalcoholic steatohepatitis were at higher risk to infection with COVID-19 [15]. Although there have been relative reductions in case incidences in several countries recently, the ongoing and prolonged high rates of new infections continue to strain health systems in countries around the world [1].

COVID-19 patients can be asymptomatic or present with multiple clinical symptoms. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be transmitted by asymptomatic patients [16]. There were 1.2% asymptomatic cases among 44,672 patients with COVID-19 in China [17]. From April 1, 2020 to May 14, 2020, a total of 1,303 asymptomatic infections from the Chinese mainland were reported, 3.3% of which progressed to symptomatic cases during this period [18]. Approximately 97.5% of people infected with COVID-19 will develop symptoms within 11.5 days [19].

COVID-19 infection, which has various clinical manifestations, can be classified into three stages: stage I (early infection), stage II (pulmonary phase), and stage III (hyperinflammation phase)[20]. Patients may have mild and non-specific symptoms (e.g., malaise, fever, and dry cough),

and then develop viral pneumonia with cough, fever, and possibly hypoxia. Finally, the disease may manifest as shock, respiratory failure, and even cardiopulmonary collapse [20]. In a study of 44,672 patients with COVID-19 in China, 81% of patients had mild manifestations, 14% had severe manifestations, and 5% had critical manifestations (defined by respiratory failure, septic shock, and/or multiple organ dysfunction) [17]. Children with COVID-19 usually have mild symptoms limited to the upper respiratory tract, except for patients younger than one year of age [21]. In contrast, older patients with underlying comorbidities may progress to severe cases more often [22,23]. Polymerase chain reaction testing via nasal swab is a typical diagnosis method for COVID-19 infection, and clinical, laboratory, and imaging findings may also be used to make a presumptive diagnosis [23].

Pathogenic mechanisms mainly include two steps. (1) Direct invasion: during early infection, SARS-CoV-2 enters target cells through the viral structural spike (S) protein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor [24]. This receptor is present in nasal and bronchial epithelial cells, pneumocytes, epithelia of the gastrointestinal tract, vascular endothelium, and the liver [25]. Additionally, the type 2 transmembrane serine protease (TMPRSS2), which exists in host target cells (particularly alveolar epithelial type II cells) promotes viral uptake [24]. (2) Cytokine storm: a minority of infected patients may experience extrapulmonary systemic hyperinflammation syndrome [8]. Levels of several cytokine types increase, including interleukin (IL)-2, IL-6, IL-7, IL-10, and tumor necrosis factor (TNF) α [5]. Other inflammatory biomarkers, including granulocyte-colony stimulating factor, interferon (IFN)- γ inducible protein 10, and monocyte chemoattractant protein 1, also increase [26]. Importantly, severe disease will present with significantly elevated cytokine levels [27]. A meta-analysis found that IL-6 and IL-10 and serum ferritin are strong discriminators for severe COVID-19 disease [28].

COVID-19 and the liver

Relationship between preexisting liver diseases and prognosis of COVID-19 patients

According to previous studies, preexisting liver diseases in COVID-19 patients are usually comprised of chronic hepatitis B, chronic hepatitis C, metabolic associated fatty liver disease (MAFLD), alcohol related liver disease (ALD), autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [29-31]. The prevalence of baseline preexisting liver diseases is low (ranging from 1%–11%) [32-34]. However, the prevalence of preexisting liver diseases among COVID-19 patients is 2.0%–4.9% based on recent meta-analysis [7,29-31,35-45]. Furthermore, Kumar et al. found that the prevalence of hepatitis B and MAFLD was 1.76% and 3.78%, respectively, in China [29]. Richardson et al. reported that there were three (0.1%) and eight (0.1%) cases of chronic hepatitis C and B among 5,700 patients hospitalized with COVID-19 in the New York City area [46]. Additionally, there were two COVID-19 patients reported to have liver cancer [47]. Mallet et al. reported that 820 (0.32%) patients with chronic

hepatitis B, 711 (2.74%) patients with chronic hepatitis C, 719 (0.28%) patients with primary liver cancer among 259,110 adult patients with COVID-19 in France [34].

Preexisting liver diseases may have adverse effects on COVID-19 prognosis, including severity, death, and mechanical ventilation. Zhou et al. demonstrated that in patients aged less than 60 years with COVID-19, MAFLD was associated with an approximately four-fold increase in the probability for severe disease after adjusting for confounders [48]. Wu et al. [39], Kumar et al. [29], Kovalic et al. [31], Dorjee et al. [43], and Berek et al. [49] all found that preexisting liver diseases were associated with severity (odds ratio (OR) or risk ratio (RR) = 1.48–1.70). Kumar et al. [29] further reported that the risk of severity among COVID-19 patients with MAFLD was 1.33 times higher than those without MAFLD (RR = 1.33, 95% CI: 0.51–3.45). A large However, most meta-analyses showed that there was no association between preexisting liver diseases and the severity of COVID-19 [29,30,35,36,50-54].

Similarly, results regarding the relationship between preexisting liver diseases and COVID-19 mortality are inconsistent [12,31,40,43,55]. Some studies showed that there was an association between preexisting liver diseases and number of COVID-19 deaths (OR/RR = 1.08–2.65) [31,40,43], while others did not [12,55]. A French national retrospective cohort study reported that patients with mild liver disease, compensated cirrhosis were not at risk for COVID-19 mortality, while patients with decompensated cirrhosis or primary liver cancer were at high risk for COVID-19 mortality [34]. These differences may be related to the included studies and different definitions of outcomes [31,53].

Currently, based on available evidence, the proportion of COVID-19 patients with baseline preexisting liver diseases is lower than other comorbidities (e.g., diabetes, hypertension, and chronic kidney disease) [44,56]. However, preexisting liver diseases may still have an impact on COVID-19 prognosis. The underlying mechanisms may be related to the fact that MAFLD is a proinflammatory hypercoagulable state that is associated with severe disease and thrombosis in COVID-19 [57]. Nevertheless, the prevalence of preexisting liver diseases was similar in populations with and without COVID-19 ($p = 0.10$) [31]. Given the small number of patients with preexisting liver diseases analyzed, the effects of preexisting liver diseases on COVID-19 severity require further study [51].

Additionally, liver transplantation (LT) is considered the ultimate solution for patients with end-stage chronic liver disease or acute liver failure [58,59]. Mallet et al. reported that 329 (1.27%) patients with a liver transplant among 259,110 adult patients with COVID-19 in France [34]. However, patients needed LT may be at risk of wait list mortality due to COVID-19 infection [58, 59]. The other important issue was the outcomes of LT recipient with COVID-19. A prospective Spanish study of 111 LT recipients with COVID-19 showed 18% mortality, but the mortality is similar or even lower to population without liver transplantation [60]. Another study also found that 28 (19%) recipients died, while higher mortality in the patients who had not undergone liver transplantation 167 (27%) [61]. Transplanted patients have to receive immunosuppressive therapy which may be protective against cytokine storm induced by COVID-19 [58,59]. Hence, the outcome of this population is a complex interplay

of comorbidities and immunosuppression [59]. In addition, LT recipients especially COVID-19 asymptomatic recipients on immunosuppression who had more intense and prolonged shedding of the virus may have had the higher risk of transmission to contacts including healthcare worker [58,59]. There should have an attention on the care of people with liver disease, especially for those after liver transplantation, the management including exposure to medical staff, appropriate immunosuppressive therapy should be cautious [58,62].

Relationship between liver injury and prognosis of COVID-19 patients

COVID-19 patients with gastrointestinal symptoms may have an increased risk of liver injury (OR=2.71, 95% CI: 1.52–4.83) [63]. Liver injury diagnosis mainly depends on biochemical indicators including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), and prothrombin time (PT) [64].

Most meta-analysis showed that the prevalence of liver injury was about 16%–29% [7,9,10,38,45,53,63,65-68]. Additionally, the prevalence of liver injury during hospitalization was higher than that at admission [30,69]. Older patients experienced liver injury at a higher prevalence [30,63,68], while meta regression showed that the prevalence of acute liver injury had no relationship with age (coefficient = 0.012, $P = 0.110$) [68]. For specific biochemical indicators, AST, ALT, and TBIL were common indicators. The levels of AST, ALT, TBIL, globulin, GGT, ALP, and PT increased, while levels of ALB decreased among COVID-19 patients with liver injury during COVID-19 progression. The proportion of increased AST was 15%–34% [7,29,30,35,37,63,67,70-75]. Labenz et al. [72] reported that the mean AST value was 33 U/L among COVID-19 patients, and Bansal et al. [76] reported that the mean AST value was 27.28 IU/L among COVID-19 patients. The proportion of increased ALT was 15%–28% [7,29,30,35,37,63,67,70-75].

Additionally, Labenz et al. [72] reported that the mean ALT value was 31 unit/ liter (U/L), and Bansal et al. [76] reported that the mean ALT value was 24.44 liter international unit/ liter (IU/L). Liu et al. also found that Western populations showed abnormal indicators, including AST and ALT levels, more clearly than Eastern populations [67]. Abnormal levels of AST and ALT were reported more commonly in studies than other indicators. Additionally, some studies reported changes in biochemical indicators at admission and during hospitalization [69] as well as changes in biochemical indicators among different age populations [30,68]. Although evidence showed that there were no differences in ALT and AST abnormalities between COVID-19 patients and non-COVID-19 patients [29], considering the aforementioned information, the prevalence of liver injury and abnormal biochemical indicators were high among COVID-19 patients.

Liver dysfunction was associated with poor outcomes, including severity (OR/RR = 1.9–2.6) [11,29,38,63] and death (OR/RR = 1.1–4.0) among COVID-19 patients [38,77-79]. Vánca et al. [78] found that liver failure was associated with mortality (OR = 7.59, 95% CI: 1.84–31.30). Sharma et al. [53] reported that acute liver injury (ALI) was associated with poor outcome, defined by intensive care unit (ICU)

admission, oxygen saturation of <90%, invasive mechanical ventilation (IMV) utilization, severe disease, and in-hospital mortality. Additionally, Kulkarni et al. [30] found that elevated liver chemistries at initial presentation were associated with death and severe disease, while the relationship between elevated liver chemistries and death was not significant for elevated liver chemistries that developed during the illness.

Cai et al. found that 14.8% of COVID-19 patients had liver injury, which was more common among severe patients than non-severe patients (36.2% vs. 9.6%) [56]. Moreover, elevated liver enzymes were more frequent in males (OR: 1.52; 95% CI: 1.26, 1.83) with severe COVID-19 than in females [80]. Regarding specific liver biochemical indicators, AST and ALT levels were commonly reported, followed by TBIL and other indicators. Most meta-analysis showed that increased AST levels were associated with severity (OR/RR = 2.3–4.5) [7,29,32,35,50,69,73,77,78,81] and mortality (OR/RR = 4.4–10.4) [73,78,82], except for one study that found no association between increased AST and severity [82]. Furthermore, increased ALT levels were also associated with severity (OR/RR = 1.8–2.5) [7,29,32,35,69,73,78,81] and mortality (OR/RR = 1.4–2.4) [73,78,82].

While there are still contrary results [69,77,82]. Cai et al. found that serum biochemical indexes of the liver (e.g., ALT, AST, ALP, and GGT) were significantly increased among severe patients at admission and during hospitalization. Peak values of ALT, AST, TBIL, and GGT were also increased significantly among severe patients compared with non-severe patients [56]. Wang et al. [83] found that abnormalities in two or more liver function indexes were low in patients with COVID-19, but this was more likely to occur in the severe group (in this study, among 105 adult patients). According to existing evidence, liver injury and abnormal liver biochemical indicators are associated with poor prognosis among COVID-19 patients.

Mechanisms of liver damage in COVID-19 patients (Fig. 1)

Previous studies explored the mechanisms of liver damage in COVID-19 patients. The mechanisms are complex and mainly include direct cholangiocyte damage induced by SARS-COV-2, cytokine storm, and drug-induced liver injury. Drug-induced liver injury may be the most important reason (Fig. 1).

Direct cholangiocyte damage of SARS-COV-2

Qi et al. found that bile duct epithelial cells highly express the ACE2 receptor, and its expression in bile duct cells is 20 times higher than in liver cells [84,85]. This suggests that SARS-COV-2 may directly infect bile duct cells, injure bile duct cells, and further lead to bile duct dysfunction. Furthermore, bile duct epithelial cells play a key role in liver regeneration and immune response. Therefore, SARS-COV-2 may invade liver cells and cause liver injury by infecting bile duct cells and causing cholestasis [84,85].

Elevated levels of ALP and GGT are sensitive indicators of bile duct epithelial cell injury [69]. Wu et al. [69] reported that the prevalence of abnormal GGT levels at admission was 35.8%. However, most studies showed that abnormal

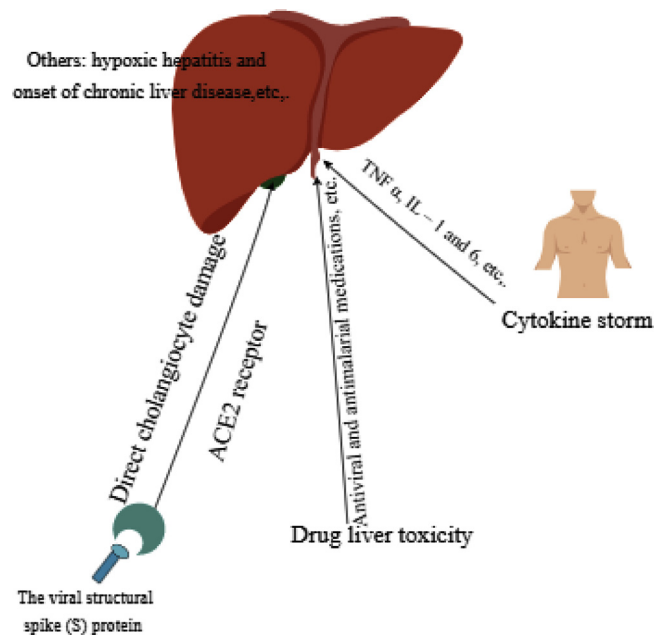


Fig. 1 Possible mechanisms of liver damage in COVID-19 patients. ACE2: angiotensin-converting enzyme 2; IL: interleukin; TNF: tumor necrosis factor.

AST and ALT levels were more common than abnormal GGT and ALP levels [29,30,70,73]. Therefore, the suggestion that damage to bile duct cells caused by SARS-COV-2 further damages liver cells warrants more research. Researchers have speculated that the compensatory hyperplasia of hepatic parenchymal cells derived from bile duct epithelial cells induce the upregulation of receptor ACE2 expression in liver tissue, which may be a possible mechanism of liver injury caused by SARS-COV-2 infection of liver cells [86].

Cytokine storm

COVID-19 patients may experience extrapulmonary systemic hyperinflammation syndrome [8]. Cytokine levels and inflammatory biomarkers [e.g., IL-2, IL-6, IL-7, IL-10, interferon (IFN)- γ inducible protein 10, and tumor necrosis factor (TNF)] α increase [5,26], especially in severe cases [27]. A meta-analysis reported that IL-6 and IL-10 and serum ferritin are strong discriminators for severe disease [28,56]. However, the liver is an important immune function organ and contains a large number of cells related to the immune response. It can promote immune activity after virus infection by activating immune cells, such as Kupffer cells [87].

Furthermore, cytokine storm, including elevated TNF α , IL-1, and IL-6 levels, can be prompted nonspecific inflammation of the liver and cause extensive damage (e.g., hepatomegaly, elevated serum transaminase, hyperbilirubin, hepatic encephalopathy, or even liver failure). If the inflammatory response syndrome progresses without further control, it can develop into multiple organ function failure and death in COVID-19 patients [2,5]. Patients with severe COVID-19 had significantly higher levels of C reactive protein (CRP), TNF α , and IL-6, which suggests that enhanced inflammation may be associated with COVID-19-related liver damage [88]. However, one meta-analysis showed significantly

lower absolute lymphocyte counts in the liver injury group compared with the non-liver injury group and no remarkable differences in CRP between the groups [38]. Therefore, hyperinflammation may be harmful to liver function, but liver damage may not necessarily be caused by hyperinflammation.

Drug-induced liver injury

The liver is the main organ responsible for drug metabolism in the human body. Drugs used by COVID-19 patients during the treatment process may cause liver damage. Kulkarni et al. reported that the prevalence of drug-induced liver injury was 25.4% [30]. Antimalarial medications, including chloroquine and hydroxychloroquine, have an emergency authorization for use in COVID-19 in the United States. Hydroxychloroquine is known to concentrate in the liver; thus, patients with hepatitis or other hepatic diseases or those taking other known hepatotoxic drugs, should be cautious [75].

Additionally, antiviral medications, including remdesivir, lopinavir–ritonavir, and favipiravir have been used in COVID-19 patients. One case series found that patients who were administered remdesivir had the most common hepatotoxicity, 23% of which reported elevations in hepatic enzymes associated with remdesivir [89]. Kulkarni et al. reported that the prevalence of remdesivir-induced liver injury was 15.2% [30]. The antiviral drugs lopinavir–ritonavir, which are mainly metabolized by the liver, can induce liver inflammation and lipid metabolism disorders by activating endoplasmic reticulum stress pathways in the liver. Additionally, they can cause hepatocyte apoptosis through the caspase system [90,91]. The proportion of subjects using lopinavir–ritonavir (ranging from 14%–100%) was reported in 12 studies [32].

Cai and colleagues found that compared to patients who were not administered the abovementioned drugs that may lead to liver dysfunction, patients who used lopinavir–ritonavir had a higher risk of liver injury (OR 4.44; 95% CI: 1.50–13.17) and showed much higher levels of TBIL and GGT during hospitalization [92]. Fan et al. reported that a significantly higher proportion of patients with abnormal liver function (57.8%) received lopinavir–ritonavir after admission compared with patients with normal liver function (31.3%) [90]. Yadav et al. found that the liver injury group was more frequently given lopinavir–ritonavir than the group without liver injury (OR: 4.15, 95% CI 2.36 to 7.29) [38].

Favipiravir, used in conjunction with interferon- α for COVID-19 treatment, was reported with a prevalence of liver injury of 2.9% in a random controlled trial [93]. Ibuprofen is one of the most commonly used nonsteroidal antiinflammatory drugs (NSAIDs) in the clinical setting, and it can induce abnormal liver function (and even acute vanishing duct syndrome) in patients [94,95]. However, Cai et al. and Yadav et al. found no significant evidence showing that the use of such drugs, including antibiotics, NSAIDs, ribavirin, herbal medications, and interferon, led to a higher risk of liver injury, except for lopinavir–ritonavir [38,92].

Additionally, the rate of abnormal liver function in the combined medication group was higher than that in the single medication group [96]. One study [39] compared the proportion of drug products ≥ 3 kinds between patients with liver injury and those with normal liver biochemistry. It

demonstrated that the proportion of drug products ≥ 3 kinds was significantly higher in patients with liver injury than in those with normal liver biochemistry (RR = 9.00, 95% CI 1.28–63.26) [69]. Wong et al. [32] found that lopinavir–ritonavir at high dosages induced higher risks of ALT elevation and hyperbilirubinemia compared with lower dosages. Mixed medications and longer durations of medication administration induced greater risk of liver damage. Therefore, it is believed that drug-induced liver injury is an important mechanism leading to liver injury in COVID-19 patients.

Considering the aforementioned information, lopinavir–ritonavir should be administered with caution. Additionally, it is necessary to take the liver injury caused by certain drugs into consideration to avoid unnecessary liver injury and clinical treatment burden, especially in severe patients with underlying liver disease [11]. Hence, lopinavir–ritonavir as a routine treatment option for patients with a history of liver dysfunction is not recommended. Clinicians should closely monitor liver function indicators, even in patients with baseline normal liver function, if they are being treated with lopinavir–ritonavir [39]. There are other possible mechanisms that affect COVID-19 prognosis, such as hypoxic hepatitis [97,98] and onset of chronic liver disease [42].

Conclusions

About 2.0%–4.9% of COVID-19 patients have preexisting liver disease. Additionally, limited evidence has shown that there is an association between preexisting liver diseases and adverse outcomes, while most evidence has not. Liver involvement during COVID-19 infection may affect about 16%–29% of patients, with higher prevalence in adult and elderly patients. The manifestations of liver damage mainly include elevated AST and ALT levels. Thus, the appearance of liver involvement during COVID-19 requires attention. While most related original studies were retrospective designs [54], they did not clearly define acute liver injury and chronic liver diseases [79].

Evidence from prospective cohort studies is still lacking. However, the underlying mechanisms are complex, including direct cholangiocyte damage induced by SARS-COV-2, cytokine storm, and drug-induced liver toxicity. Drug-induced liver toxicity may be the most likely reason; therefore, it is necessary to take the liver injury caused by certain drugs into consideration in order to avoid unnecessary liver injury, especially in severe patients with underlying liver disease.

Furthermore, liver injury and specific liver biochemical markers are associated with COVID-19 mortality and severity, so scientific management of patients with liver injury is needed. Additionally, the association between preexisting liver diseases and prognosis, as well as potential mechanisms underlying the association between COVID-19 infection and liver dysfunction/preexisting liver diseases, require further study. As this study mainly collected and analyzed epidemiological data from meta-analyses, the included original studies may have effects on the estimated results.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Author Contributions

Liu J conceived and designed the review study; Du M conducted the literature search and wrote the manuscript. Liu J, Liu M, Yang S and Du M revised the manuscript.

Funding

Supported by the National Natural Science Foundation of China (72122001, 71934002), National Key Research and Development Project of China (2020YFC0846300, 2019YFC1710301, 2018YFC1704400), and National Science and Technology Key Projects on Prevention and Treatment of Major Infectious Diseases of China (2020ZX10001002).

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