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Correlation between COVID-19 and hepatitis B: A systematic review

He YF *et al.* Correlation between COVID-19 and hepatitis B

Abstract

BACKGROUND

There is growing evidence that patients with coronavirus disease 2019 (COVID-19) frequently present with liver impairment. Hepatitis B virus (HBV) remains a major public health threat in current society. Both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and HBV can cause liver damage, and current findings on whether HBV infection increases disease severity in COVID-19 patients are inconsistent, and whether SARS-CoV-2 infection accelerates hepatitis B progression or leads to a worse prognosis in hepatitis B patients has not been adequately elucidated.

AIM

To explore the complex relationship between COVID-19 and hepatitis B in order to inform the research and management of patients co-infected with SARS-CoV-2 and HBV.

METHODS

An experienced information specialist searched literature in the following online databases: PubMed, China National Knowledge Infrastructure, Google Scholar, Scopus, WileyWeb of Science, Cochrane and ScienceDirect. Literature published from December 2019 to September 1, 2022 was included in the search. We also searched medRxiv and bioRxiv for gray literature and manually scanned references of included articles. Articles conducted in humans discussing hepatitis B and COVID-19 were included in the criteria. Articles that met the criteria in the *Reference Citation Analysis* (<https://www.referencecitationanalysis.com>) were also included in this review. We excluded duplicate publications. News reports, reports and other gray literature were included if they contained quantifiable evidence (case reports, findings, qualitative analysis). Some topics that included HBV or COVID-19 samples but did not have quantitative evidence were excluded from the review.

RESULTS

A total of 57 studies were eligible and included in this review. They were from 11 countries, of which 33 (57.9%) were from China. Forty-two of the 57 studies reported abnormalities in liver enzymes, three mainly reported abnormalities in blood parameters, four indicated no significant liver function alterations, and another eight studies did not provide data on changes in liver function. Fifty-seven studies were retrospective and the total number of co-infections was 1932, the largest sample size was 7723, and the largest number of co-infections was 353. Most of the studies suggested an interaction between hepatitis B and COVID-19, while 12 studies clearly indicated no effect between hepatitis B and COVID-19. Six of the 57 studies clearly reported HBV activation. Six studies were related to liver transplant patients.

CONCLUSION

There is some association between COVID-19 and hepatitis B. Future high-quality randomized trials are needed to further elucidate the interaction between COVID-19 and hepatitis B.

Key Words: COVID-19; SARS-CoV-2; Hepatitis B virus; Chronic hepatitis B; Liver injury; Co-infection

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Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hepatitis B virus (HBV) infection are two major current global public health crises. Both infection with SARS-CoV-2 and infection with HBV can cause liver damage. There are conflicting views on whether HBV infection aggravates the prognosis of patients with coronavirus disease 2019 (COVID-19). There is a potential association between COVID-19 and

hepatitis B. Clarification of this association could benefit these special patients with SARS-CoV-2 co-infection with HBV.

INTRODUCTION

Since the outbreak of coronavirus disease 2019 (COVID-19), there has been increasing evidence that patients with COVID-19 frequently present with hepatic impairment^[1-3]. This may be caused by pre-existing liver disease, viral infection of hepatocytes, and certain medications. Hepatitis B virus (HBV) remains a major current public health threat to society, with approximately 300 million people chronically infected worldwide^[4]. Since both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and HBV can cause liver damage, current findings on whether HBV infection increases disease severity in patients with COVID-19 are inconsistent, with some reports suggesting that co-infection with SARS-CoV-2 and HBV has no effect on the course and prognosis of COVID-19^[5,6], while several studies have shown that patients with SARS-CoV-2 and HBV co-infection are more likely to have serious outcomes^[7-9]. Does pre-existing HBV infection increase susceptibility to SARS-CoV-2 infection, leading to more severe disease and a worse prognosis? Conversely, does SARS-CoV-2 infection accelerate the progression of hepatitis B or lead to worse outcomes? The potential association between hepatitis B and COVID-19 has not been fully elucidated, so it is important and interesting to understand how COVID-19 and hepatitis B interact with each other. In order to elucidate this complexity, we summarize almost all current clinical studies to provide a detailed description of the interaction between COVID-19 and hepatitis B, possible mechanisms, and clinical interventions to provide a reference for the clinical management of these special patients.

MATERIALS AND METHODS

Identify research question

Does SARS-CoV-2 and HBV co-infection have any effect on the course and prognosis of COVID-19? And vice versa, does COVID-19 accelerate the progression of hepatitis B and lead to a severe prognosis?

Identify relevant types of evidence

Literature published from December 2019 to September 1st, 2022 was included in the search. To avoid missing any relevant and important literature, we used an inclusive search strategy. An experienced information specialist searched literature in the following online databases: PubMed, China National Knowledge Infrastructure, Google Scholar, Scopus, WileyWeb of Science, Cochrane and ScienceDirect. we also searched medRxiv and bioRxiv for gray literature and manually searched the references of included studies to further ensure the comprehensiveness of the search. Articles were included if they met the following criteria: Performed in humans, discussing SARS-CoV-2 in patients with hepatitis B and HBV in COVID-19 patients. For detailed search strategies, see Supplementary material.

Study selection

Several articles were included after our initial search, including case reports, case series, qualitative studies, systematic and scoping reviews. We excluded repetitive publications. Articles containing more complete descriptions of the data were used for data charting. News articles, case reports, survey results, qualitative analyses, and other gray literature were also included in our review if they contained quantifiable evidence. We read the full text, synthesized relevant evidence, and organized the literature thematically. All five authors participated in the discussion and decided on a theme. Some topics that included HBV or COVID-19 samples but did not have quantitative evidence were also excluded from the review. See Figure 1 for a visual representation of inclusion workflow.

Data charting

As of September 1, 2022, we retrieved 1136 publications, adding six manually retrieved papers for a total of 1142. We tested 139 full-text articles for eligibility after being screened by the above inclusion criteria, and 57 were finally included in this review (Figure 1). Two independent reviewers extracted data from the full-text papers of eligible studies, including the name of the first author, publication month and year, country of the study, number of included patients, number of SARS-CoV-2 and HBV co-infection, main biochemical characteristics of co-infected patients, their clinical outcome (death or survival) and main conclusion of each study. A summary of information on the included studies is presented in Table 1, and details of important parameters are presented in Table 2 and Supplementary material. This systematic review has been registered on the PROSPERO platform: <https://www.crd.york.ac.uk/prospero/#recordDetails>.

RESULTS

A total of 57 studies were eligible and included in this review. They were from 11 countries, of which 33 (57.9%) were from China (Figure 2). Forty-two of the 57 studies reported abnormalities in liver enzymes^[2,5,7-46], three mainly reported abnormalities in blood parameters^[47-49], four indicated no significant liver function alterations^[6,50-52], and another eight studies did not provide data on changes in liver function^[53-60]. Fifty-seven studies were retrospective, and the total number of co-infections was 1932, the largest sample size was 7723^[54], and the largest number of co-infections was 353^[16]. Most of the studies suggested an interaction between hepatitis B and COVID-19, while 12 studies clearly indicated no effect between hepatitis B and COVID-19^[5,11,16,18,21,25,28,50,51,54-56]. Six of the 57 studies clearly reported HBV activation^[23,29,41,43,46,52]. Six studies were related to liver transplant patients^[36,38,39,49,57,58].

Interpretation of 'no effect' results

As previously mentioned, the possible reasons why HBV infection was not associated with clinical outcomes of COVID-19, despite the fact that some patients had high liver

enzyme levels, are as follows: (1) The infection rate was not affected. The main consideration is the positive effect of nucleoside analogues on resistance to SARS-CoV-2^[59]. In the included studies, some hepatitis B patients received long-term treatment with nucleoside analogues, such as tenofovir, which binds tightly to RNA-dependent RNA polymerase and terminates SARS-CoV-2 RNA synthesis^[61,62], resulting in a low rate of SARS-CoV-2 infection in chronic hepatitis B (CHB) patients treated with anti-HBV; (2) The severity of the disease is not affected. The main consideration is the key role played by immune dysfunction in SARS-CoV-2 co-infected HBV patients. The cytokine storm caused by SARS-CoV-2 infection leads to ¹² overproduction of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6, and IL-2, while HBV infection with persistent viral antigens leads to virus-specific CD4⁺ and CD8⁺ T cell depletion, resulting in impaired cytokine secretion, especially IL-2 and TNF- α , in which the depleted and immunosuppressed state of HBV-specific T lymphocytes may attenuate or avoid the excessive host immune response to SARS-CoV-2 and reduce the cytokine storm, resulting in a less severe disease^[63-65]; and (3) Prognosis is not affected. Previous studies have demonstrated that hepatitis C virus infection can limit the replication of HBV^[66], a phenomenon in which one virus in the host prevents the replication of another co-infected virus by competitive inhibition rather than by the action of immune antibodies is called viral interference. Impaired type I interferon activity has been found to be a major feature of patients with severe COVID-19^[67-69]. When co-infected, HBV can inhibit the replication and proliferation of co-infected SARS-CoV-2 by enhancing type I interferon signaling, thereby reducing viral load and prolonging survival. In addition to this, the small number of HBV co-infected patients in the 57 studies we included may have influenced the results.

Interpretation of altered liver enzymes and other biochemical abnormalities

Explanation of enzyme system abnormalities: Many studies have suggested that elevated liver enzyme systems are associated with drug therapy (Table 2). Corticosteroids have been widely used to treat and benefit COVID-19^[70]. Systemic

corticosteroids are also associated with an increased risk of aspartate aminotransferase (AST) elevation^[71]. Several studies have reported that elevated liver enzyme systems are associated with antiviral therapy medication^[72-74]. The results of these studies showed that liver enzyme levels in patients dropped to near normal within a few days after discontinuation of medication. In addition, a study by Lei *et al*^[71] showed that elevated AST and alkaline phosphatase levels were associated with the use of antifungal drugs. Another explanation is that some enzymes reflecting liver function, such as glutamic aminotransferase, are nonspecific and are expressed in a wide range of tissues, including heart, skeletal muscle, red blood cells and liver, and can originate from other sites^[75,76].

Explanation for the decrease in albumin: Patients with SARS-CoV-2 co-infection with HBV show a decrease in albumin, especially in heavy and critically ill patients, which may be due to the high catabolic state of the patient's body, poor nutritional status, negative nitrogen balance, and insufficient raw materials for synthesizing albumin, as well as impaired hepatic synthesis of albumin due to hepatocyte damage. Corticosteroid treatment can also cause a decrease in albumin during the treatment process^[21]. COVID-19 patients co-infected with HBV have lower prealbumin levels due to weaker hepatic reserve capacity, which also contributes to the decrease in albumin. With the resolution of the disease, most of the patients' liver function will return to normal.

Explanation for lymphocytopenia and thrombocytopenia: Patients with SARS-CoV-2 and HBV co-infection have significantly lower white blood cell counts, mainly due to reduced lymphocyte counts and significantly lower monocyte levels. The mechanism leading to lymphocytopenia remains unclear. Since low lymphocyte counts are associated with increased disease severity and mortality in COVID-19^[77,78], patients with SARS-CoV-2 and HBV co-infection may be in greater need of increased clinical surveillance. Thrombocytopenia is common in liver disease caused by HBV infection.

The mechanism of thrombocytopenia in COVID-19 may be that SARS-CoV-2 reduces platelet production, increases platelet destruction, or increases platelet consumption^[79]. Specifically, the lung is one of the organs where megakaryocytes dynamically release platelets^[80], and SARS-CoV-2 damages the lungs of COVID-19 patients through angiotensin-converting enzyme 2 (ACE2), leading to increased destruction of megakaryocytes in the lung and resulting in decreased platelet production. In addition, SARS-CoV-2 may directly invade hematopoietic cells or infect bone marrow stromal cells by binding to CD13 or CD66a receptors, etc damaging megakaryocytes and platelets and exacerbating apoptosis^[81]. Cytokine storm leads to immune hyperactivation, causing cellular damage and increased platelet destruction through autoantibody or immune complex activation of complement; at the same time, immune hyperactivation releases large amounts of inflammatory factors that promote excessive platelet activation and platelet-monocyte aggregation formation^[82], forming thrombi at the site of injury and further leading to increased platelet depletion and destruction.

DISCUSSION

The impact of COVID-19 on hepatitis B

We mainly describe the effects of COVID-19 on hepatitis B from the aspects of HBV reactivation, abnormal liver enzyme system, mortality, and liver histopathological changes.

HBV reactivation: Six of the 57 included studies reported COVID-19-induced HBV reactivation (Table 2), which primarily refers to the re-detection of HBV DNA in patients who previously had HBV DNA below the lower limit of detection or a sudden and substantial increase in HBV DNA levels in individuals with detectable HBV DNA^[83]. In some cases, it may also evolve into fulminant liver failure. The mechanism of HBV reactivation after SARS-CoV-2 infection is mainly due to a disruption of the balance between the immune status of the host and viral replication. The intensity of glucocorticoid or immunosuppressive therapy is a major risk factor for HBV

reactivation during COVID-19 treatment^[29,41,84]. Age, male sex, and severe comorbidities (such as hypertension, diabetes, hypercholesterolemia, and chronic kidney disease) are considered risk factors for HBV reactivation^[29]. In addition, SARS-CoV-2 infection causes significant lymphopenia, which may increase the likelihood of HBV reactivation.

Although there is a risk of HBV reactivation with SARS-CoV-2 infection, studies have shown that the overall risk is low. In a study by Rodríguez-Tajes *et al*^[29], 61 patients with severe COVID-19 on immunosuppressive therapy were followed up for at least one month and no cases of hepatitis B surface antigen (HBsAg) reversal were found, with only two (3%) patients having detectable serum HBV-DNA.

Considering the risk of reactivation, it is recommended that HBV patients should start or continue anti-HBV therapy once COVID-19 is diagnosed^[85], and some scholars recommend treatment with the nucleoside analogs entecavir and tenofovir^[83], and closely monitor HBV virological indicators and indicators related to liver injury. It has been suggested that the use of IL-6 receptor antagonists can reduce the risk of HBV reactivation, and in Watanabe *et al*^[86]'s study, 152 patients who recovered from HBV infection treated with disease-modifying antirheumatic drugs had a very low risk of HBV reactivation (<5%).

Abnormalities in liver enzymes: Most studies have evaluated the effects of COVID-19 in HBV patients mainly manifesting as abnormalities in liver enzymes, dominated by elevated levels of alanine aminotransferase (ALT), AST and total bilirubin (TBIL), especially in severely ill patients (Table 2)^[2,5,7-46]. Several studies have shown a predominance of AST elevations in COVID-19 patients^[14,17,71,87], reflecting the severity of the disease. A large study including 5700 subjects showed elevated levels of AST (58%) and ALT (39%) in hospitalized COVID-19 patients^[17]. Sixty-two percent of critically ill patients had elevated AST levels^[88]. Abnormal liver function tests ranged from 37% to 69%, ALT and AST increased by 18.2% to 31.6% and 14.8% to 35.4%, respectively^[14,52,89,90], and several studies have reported elevated TBIL elevation (5.1% to 11.5%)^[89,91]. It is worth noting that AST alone does not prove with certainty that more

liver damage occurred, as other tissues, including heart or muscle tissue, can also release glutathione^[75,76].

Zhao *et al*^[92] also noted that COVID-19 patients had significantly higher levels of γ -glutamyl transpeptidase, lactate dehydrogenase (LDH), and α -hydroxybutyric dehydrogenase than non-COVID-19 patients. A study by Chen *et al*^[27] including 113 deceased patients (five of whom were SARS-CoV-2 co-infected with HBV) showed that the deceased patients had creatinine, creatine kinase (CK), LDH, cardiac troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer, IL-2 receptor (IL2R), IL-6, IL-8, IL-10, and TNF- α concentrations that were significantly higher compared to those in recovered patients. Among these, several studies have confirmed that NT-proBNP is strongly and independently associated with mortality in COVID-19 patients^[93-95]. In addition, serum albumin was below the normal range, and prothrombin time was prolonged due to the compromised synthetic function of the liver.

Mortality: Several reports have suggested that pre-existing liver disease may be associated with high mortality in patients with COVID-19^[96-99]. Studies have noted that the risk of mortality is associated with pre-existing liver disease status and not with age, race, body mass index, hypertension, or diabetes^[96]. Several studies have evaluated the relationship between the severity of abnormal liver tests and mortality in patients with COVID-19^[1,14,96,97]. A study from the United States showed that among 2780 patients with COVID-19, the mortality rate was 12% in patients with chronic liver disease (10 out of 250 patients with chronic liver disease have CHB, compared to 4% in patients without liver disease^[99]). Another study of 152 consecutively submitted COVID-19 cases in patients with chronic liver disease found a higher mortality rate in COVID-19 patients with combined chronic liver disease, 11.8% of whom were hepatitis B patients^[96]. These studies support that SARS-CoV-2 affects the immune response exacerbating HBV replication during the acute and chronic phases of hepatitis B infection^[12]. Iavarone *et al*^[45] also concluded that COVID-19 is associated with increased

mortality in patients with deteriorating liver function. The cause of death may be related to the failure of patients to receive timely specialist care, inadequate hepatoprotective therapy, and hepatitis B infection complicated by SARS-CoV-2. Leading to fulminant hepatitis and multi-organ failure.

Histopathological changes of the liver: Histopathology-specific manifestations of the liver in patients with COVID-19 include binucleated or multinucleated hepatocytes, swollen mitochondria, and reduced glycogen granules^[47]. Macrovesicular steatosis is one of the common nonspecific manifestations^[72], in addition to mild portal lymphocytic infiltration, mild sinusoidal dilatation, inflammatory cells in the sinusoids, and portal vein inflammation, with electron microscopy also showing the presence of viral particles^[100-103].

Effect of hepatitis B on COVID-19

We will describe the effect of hepatitis B on COVID-19 in terms of the rate of infection in patients with hepatitis B, changes in biochemical indicators and cytokines, and the prognosis of hepatitis B on COVID-19 (including mortality, complications, and severe COVID-19).

The rate of infection: An important indicator of the impact of hepatitis B on COVID-19 is the rate of infection. It has been shown that hepatitis virus infection reduces the chance of COVID-19 infection to some extent in people with hepatitis B^[15]. Antiviral drugs also reduce susceptibility to COVID-19 infection. Data from Naderi *et al*^[15] showed that the risk of COVID-19 in healthy individuals was 2.3 times higher than in patients with CHB. Antiviral therapy in patients with CHB, including tenofovir and entecavir, resulted in a decreased incidence of SARS-CoV-2 positivity. Kang *et al*^[54] reported that the occurrence of CHB resulted in a lower rate of SARS-CoV-2 positivity. A recently published survey of a larger cohort in Spain showed a reduced incidence of COVID-19 infection in CHB patients given tenofovir, suggesting a positive effect of

tenofovir on SARS-CoV-2^[59]. A large study in the United States including 5700 in patients with COVID-19 showed that 14% (13/93) of CHB patients and 32.25% (20/62) of controls were infected with COVID-19, respectively, and ¹ the risk of developing COVID-19 was 2.3 times higher in healthy controls than in CHB patients, suggesting that antiviral drugs also reduced the susceptibility to SARS-CoV-2 infection^[17].

Cytokines and biochemical indicators: As with the effects of COVID-19 on hepatitis B, SARS-CoV-2 and HBV co-infection aggravate liver injury in COVID-19 patients^[5,24], leading to abnormalities in the liver enzyme system. In addition to ALT, AST, alkaline phosphatase and TBIL described previously^[30,32,37], IL-6, LDH, D-dimer TNF- α , CK and other inflammatory factors levels are elevated^[14,27,104,105].

Among the cytokines in co-infected patients, IL-6 was most significantly elevated. IL-6 is the result of SARS-CoV-2 activation of the immune system leading to massive cytokine release^[106]. IL-6 plays a role as a pro-inflammatory factor in the regulation of vascular leakage, complement activation, and coagulation pathways. The coagulation biomarker D-dimer is derived from the formation and cleavage of cross-linked fibrin, and the systemic pro-inflammatory cytokine response following viral infection may induce endothelial cell dysfunction, leading to overproduction of thrombin, which activates platelets and stimulates fibrinolysis, resulting in elevated D-dimer^[107,108]. D-dimer has also been found in COVID-19 patients to be associated with poor outcome and abnormally dysregulated in CHB patients^[109]. LDH not only ⁴ plays an important role in glucose metabolism by catalyzing the conversion of pyruvate to lactate, but also regulates the immune response by inducing T cell activation and enhancing immunosuppressive cells through lactate production^[110]. Serum CK levels are the most sensitive indicator of muscle damage^[111]. Hypovolemia occurring in dehydrated patients with severe COVID-19 may lead to renal failure, which may increase CK levels^[25]. Two recent studies suggest that high CK, IL-6, and D-dimer levels may be early warning indicators of serious disease and monitoring these indicators may help in the early detection of adverse events^[25,112].

Mortality, complications, or serious prognosis: Patients with SARS-CoV-2 and HBV co-infection are more likely to have severe disease and a worse prognosis, including higher mortality and complications^[44,55,60]. Two recent studies have shown that patients with COVID-19 who have pre-existing liver disease have a higher mortality rate compared to patients without liver disease^[96,97]. Mirzaie *et al*^[113] found that of the reported SARS-CoV-2-HBV co-infection cases, the mortality rate was 4.7%, 14.1% were transferred to the intensive care unit (ICU), and 38.8% reported severe COVID-19. In a study by Chen *et al*^[9], seven of 15 HBV-infected patients (46.7%) developed severe disease, compared with 24.1% of severe cases in COVID-19 patients without HBV infection. In a study of 436 patients with COVID-19, more patients with CHB developed a severe status compared to non-CHB patients [30/109 (27.52% vs 5.20%) 17/327], with mortality rates of 13/109 (11.93%) and 8/327 (2.45%), respectively^[8]. Another recent study by Wu *et al*^[44] involving 70 co-infections showed a higher proportion of severe patients and critical patients in the COVID-19 and HBV co-infected group than in the non-HBV infected group (32.86% vs 15.27%). Data from a study by Yang *et al*^[30] showed that patients with COVID-19 combined with CHB had a higher risk of death and ICU admission than patients without CHB. These data support the hypothesis that patients with liver disease may be associated with serious outcomes in patients with COVID-19. However, it is unclear whether these results reflect the severity of the patient's pre-existing liver disease or the severe prognosis caused by SARS-CoV-2 itself. However, it has also been reported to the contrary, that is, the incidence of ICU admission or death may be lower in patients with observed pre-existing HBV infection [none (0%) vs 36 (6.47%)] compared to 556 of 571 COVID-19 cases without HBV infection^[20]. These findings suggest that the immune status of the host is influenced to some extent by CHB, which may affect the consequences of infection by SARS-CoV-2.

COVID-19 has no effect on hepatitis B

Yu *et al*^[6] included 7 HBsAg(+) and 60 HBsAg(-) (a total of 67) COVID-19 patients and found no extensive fluctuations in markers of HBV replication during the acute course of SARS-CoV-2 infection, indicating that SARS-CoV-2 had no effect on HBV kinetics, and that co-infection did not prolong viral shedding or latency cycles in COVID-19 patients, and it did not trigger reactivation or seroconversion of CHB. Therefore, they concluded that SARS-CoV-2 infection would not be a source of HBV reactivation. Ding *et al*^[28] conducted a study in which 204 of 2073 patients with COVID-19 had pre-existing liver disease, including 134 patients with hepatitis B and five patients with CHB cirrhosis, and after adjusting for baseline characteristics by matching propensity scores between groups, the in-hospital mortality rate in patients with hepatitis B was similar to that in patients without liver disease. These results suggest that SARS-CoV-2 infection may not increase the risk of severe liver injury in patients with hepatitis B and in patients with compensated liver function.

Hepatitis B has no effect on COVID-19

In a study by Wen *et al*^[21], patients with COVID-19 combined with hepatitis B had no significant increase in the probability of abnormal ALT, AST, and albumin compared to patients without combined hepatitis B. No differences were found in various adverse clinical outcomes in patients with CHB compared to HBsAg negative patients. Chen *et al*^[5] divided 326 COVID-19 confirmed cases into 20 patients with co-infection with HBV and 306 patients without HBV infection for observation and found no significant differences in the levels of liver function parameters, discharge rates, length of stay and mortality between the two groups. Similarly, a study by Yu *et al*^[6] showed that co-infection with HBV did not increase the severity of COVID-19 or prolong the length of hospital stay. There was also no significant difference between the two groups in terms of disease recovery at discharge. Zou *et al*^[7] and Zhang *et al*^[22] showed that the proportion of organ damage in patients co-infected with HBV was not significantly different from that in patients infected with SARS-CoV-2 alone. Liu *et al*^[23] matched 21 patients with COVID-19 and HBV co-infection to 51 patients with COVID-19 without

HBV, and found that HBV did not prolong the shedding of SARS-CoV-2, nor did it add to the progression of COVID-19 or increase the risk of poor prognosis. Similarly, Li *et al*^[18] and He *et al*^[20] had similar conclusions. Hepatic biochemistry (ALT, AST, TBIL) was similarly dynamic and insignificantly different between the two groups of patients at each time point. In addition, HBV antiviral therapy has been reported to have a limited impact on the incidence and outcome of COVID-19^[114]. The analysis by Zhu *et al*^[115] also supports the view that HBV is not a significant risk factor for serious adverse outcomes among hospitalized patients with COVID-19.

Data from several studies have shown that co-infection did not negatively affect the course of COVID-19, although the SARS-CoV-2/HBV co-infection group had higher results in terms of liver function index levels^[16,25,28]. Guardigni *et al*^[56] in a study of 606 subjects found no statistical difference in mortality between the two groups, despite the higher rate of admission to the ICU in HBV-positive individuals. Pre-existing viral liver infections had no impact on the clinical and virological evolution of COVID-19. A study by Liu *et al*^[48] found that although patients co-infected with SARS-CoV-2 and HBV exhibited more severe monocytopenia, thrombocytopenia, and hepatic dysfunction in albumin production and lipid metabolism, no differences in inflammatory cytokine levels were observed between patients co-infected with SARS-CoV-2 and HBV and those co-infected with SARS-CoV-2 alone. ²³ Most of the disturbances could be reversed with recovery from COVID-19, and HBV co-infection had no significant effect on the outcome of COVID-19.

Possible mechanisms between COVID-19 and liver injury

The mechanisms underlying liver dysfunction in patients with SARS-CoV-2 co-infection with HBV are not fully understood and may include direct injury, immune injury, drug injury, ischemia and hypoxia, and reactivation of HBV with immunosuppressive drugs^[8-11], or may be the result of a combination of factors.

2
Direct injury: SARS-CoV-2 replication directly causes liver damage. There is increasing evidence that SARS-CoV-2 can directly cause liver damage in patients with COVID-19. ACE2 is widely present in human organ tissues, with the highest expression in the small intestine and also in the spleen, brain, muscle, heart and liver^[116]. It has been shown that SARS-CoV-2 can use ACE2 as a receptor for cell entry^[117,118]. Dipeptidyl peptidase 4 and transmembrane serine protease 2 can also act as receptors to mediate SARS-CoV-2 virus entry into host cells^[119,120]. **11** Pre-existing liver disease is associated with increased expression of ACE2 in hepatocytes, thereby increasing the likelihood of SARS-CoV-2 entry into hepatocytes^[121,122]. Recent data have shown higher ACE2 expression in bile duct cells than in hepatocytes, suggesting that the virus may bind directly to ACE2 expressed in bile duct cells, leading to hepatic impairment^[117,123]. These findings suggest that abnormal liver function may be caused by the preferential binding of SARS-CoV-2 to bile duct cells^[124]. SARS-CoV-2 granules in the cytoplasm of COVID-19 patients' hepatocytes, mitochondrial swelling and structural damage, and massive apoptosis of hepatocytes were shown by electron microscopy, strongly suggesting direct cytopathy of SARS-CoV-2 in hepatocytes^[125,126].

Immune impairment: Currently, the most discussed immune injury is the 'cytokine storm'. During the immune activation phase, the replication and proliferation of SARS-CoV-2 leads to cellular inflammatory necrosis and release of pro-inflammatory cytokines^[127], activating of T and B cells, and recruiting macrophages^[128-130], which in turn produce additional inflammatory factors, such as C-reactive protein, IL-6, IL-1, IL-8, and IL2R, leading to **14** a cytokine storm that causes severe immune damage to the lung as well as the liver^[131,132]. IL-6 is a potential risk factor for severe liver injury in patients with COVID-19^[133,134]. IL-6 is produced *via* classical cis-signaling or trans-signaling two different pathways that lead to a systemic cytokine storm^[135].

Drug-induced liver injury: The liver is an important organ for the metabolism of these drugs, and antivirals are one of the main measures for the treatment of COVID-19. The

drugs currently used for treatment, including antibacterial drugs, nonsteroidal anti-inflammatory drugs, traditional Chinese medicine, antiviral drugs, and other drugs used in clinical trials, such as chloroquine, hydroxychloroquine and tocilizumab, may produce hepatotoxicity^[72,96]. Cai *et al*^[72] observed that lopinavir and ritonavir contributed significantly to liver injury in patients with COVID-19. Antifungal drugs and systemic corticosteroids have also shown a positive association with liver injury^[71]. Traditional Chinese medicine plays a crucial role in the treatment of COVID-19, but it can also contribute to liver injury^[136]. The mechanisms of liver injury are variable and it is generally believed that the pathogenesis of liver injury with antiviral drugs is related to mitochondrial toxicity, hypersensitivity/induced autoimmune hepatitis, and secondary bacterial infections^[124,137]. In addition to this, HBV reactivation is also considered to be one of the manifestations of drug-induced liver injury, as HBV reactivation occurs at an increased rate in patients treated with high doses of long-term corticosteroids or immunomodulators^[43].

Ischemia and hypoxia of the liver

Ischemia and hypoxia in the tissues and organs of COVID-19 patients after SARS-CoV-2 infection is a common pathophysiological phenomenon^[78]. The consequences of progressive hypoxia may include viral proliferation, cytokine release, inflammation, and intravascular coagulation^[78], leading to hypoxic injury in several organs, including the liver, and in severe cases, hypoxic hepatitis^[138]. Cellular damage caused by hepatic ischemia and inflammatory response caused by reperfusion both lead to hepatocyte apoptosis and elevation of liver enzymes^[139,140]. In addition, patients' prior underlying diseases, such as chronic lung disease^[91], diabetes^[105], and gastrointestinal disease^[141] have been predicted as possible mechanisms of liver injury in the context of viral infection. Interestingly, being male has also been reported to be associated with a high risk of liver injury^[71,142].

Drug treatment and alternative therapies

² COVID-19 combined with chronic liver disease has become a very prominent clinical problem, and the treatment and prevention of COVID-19 combined with liver injury is particularly important. In the treatment of COVID-19 combined with hepatitis B, the first priority is to treat the cause, followed by a comprehensive treatment plan of antiviral therapy, use of antibiotics, liver protection and nutritional support, as well as aggressive treatment of comorbidities, such as hypertension and diabetes. Corticosteroids are now widely used to treat COVID-19, antiviral therapy is a basic treatment, and in China, traditional Chinese medicine is also used to treat SARS-CoV-2 infection^[143]. Nucleoside (acid) analogues are used in the treatment of CHB. These drugs are effective in inhibiting HBV replication, reducing viral load, and improving liver histological lesions. Some studies have shown that in patients with SARS-CoV-2 co-infection with HBV, the use of nucleoside analogs is safe and does not lead to exacerbation of the disease due to drug administration. However, antiviral drugs may also cause liver damage, and ²⁰ corticosteroids may increase the risk of hepatitis exacerbation in patients with chronic HBV infection, especially when combined with other immunosuppressive drugs^[144]. Therefore, the use of hepatoprotective drugs and close monitoring of changes in liver function are recommended in clinical work to minimize the risk of liver injury and HBV reactivation.

Interestingly, some authors have suggested that hemoperfusion can delay the progression of the hyperinflammatory process of COVID-19 and remove the toxins involved in acute liver failure and could be an alternative option to mitigate disease progression in patients with COVID-19^[26]. In addition, plasma therapy in recovering patients has been reported to be very effective in patients who still have the virus in their system^[145,146].

Care monitoring and social management

During the COVID-19 pandemic, delays in the care of patients other than those with COVID-19 may result in negative outcomes for CHB patients due to discontinuation of antiviral therapy. Patients with hepatitis B, especially those in the decompensated phase

of cirrhosis, many of whom have a decline in blood cells associated with hypersplenism, will frequently present with pulmonary and abdominal infections due to their reduced immune function, and this is a particularly important situation to screen and identify. For patients with HBV combined with SARS-CoV-2 infection, it is recommended not to discontinue anti-HBV drugs and to strengthen the dynamic monitoring of the patient's liver function. The diagnosis and treatment of chronic diseases is long-term, and a variety of problems may still be faced in the post-pandemic era. Therefore, it is important to emphasize the importance of network hospitals, strengthen the use of network cloud platforms, increase network consultation and follow-up, provide online assistance to these patients, and reduce unnecessary hospital visits. Avoid large gatherings during a pandemic, and be careful to wear masks and wash your hands more often in public places.

Vaccination

The already licensed COVID-19 vaccine is immunogenic and has a good short-term safety record^[147-151]. Given the potential for SARS-CoV-2 infection to have serious health consequences in patients with hepatitis B, patients with liver disease should be considered a priority population for receiving the vaccine. The potential interactions between the COVID-19 vaccine and other vaccines have not been well studied, and the few data available is limited to the concurrent use of the COVID-19 vaccine and influenza vaccine, with studies showing that antibody responses to both vaccines were maintained, and no safety issues were reported^[137]. Future clinical studies on the interaction between the COVID-19 vaccine and hepatitis B vaccine are urgently needed.

Limitations

The present review has several limitations. First, most of the current research papers on SARS-CoV-2 co-infection with HBV were retrospectively designed, and no randomized controlled studies were found, which means that a selection bias must be acknowledged. Second, some studies do not distinguish the clinical stage of HBV

infection and do not clarify the immune stage of the patient. Clinical outcomes may be different in patients with chronic HBV infection or acute HBV infection, and the prognosis of COVID-19 may be influenced by the status of the patient's immune system, which may affect the interpretation of the results. Third, the results related to hepatitis B were derived from a limited sample size of observational and case studies, some of which were not classical studies on hepatitis B. The participation of patients with hepatitis B may have partially contributed to these studies, and thus the overall analysis may have overstated its role in COVID-19. Finally, because different countries have different institutions, policies, and economic conditions regarding COVID-19, the 57 studies extracted for our review were distributed across 11 countries, and it is necessary to carefully interpret whether there is regional or population bias in these results (Figure 2) and whether they are representative of the entire population.

CONCLUSION

In conclusion, both SARS-CoV-2 and HBV are globally pathogenic viruses, and there are currently few and conflicting data on the potential association between COVID-19 and hepatitis B. In the future, high-quality randomized trials are needed to further elucidate the interaction between COVID-19 and hepatitis B. To our knowledge, our review is the most comprehensive report to date describing the association between COVID-19 and hepatitis B. By reviewing these studies, we provide direct evidence of some association between COVID-19 and hepatitis B, explain the clinical phenomena they exhibit, explore the possible mechanisms of the interaction between COVID-19 combined with hepatitis B, and provide management measures for co-infected patients, and therefore, our review can provide a reference for future scientific studies and clinical management.

ARTICLE HIGHLIGHTS

Research background

7 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hepatitis B virus (HBV) are two major current global public health crises. Both SARS-CoV-2 and HBV can cause liver damage. It is unclear whether HBV itself makes patients more susceptible to coronavirus disease 2019 (COVID-19), or whether COVID-19 leads to worse outcomes in patients with HBV infection. There are few and conflicting data on the association between COVID-19 and hepatitis B.

Research motivation

All current studies on patients with COVID-19 co-infection with hepatitis B will be searched to explore the complex relationship between COVID-19 and hepatitis B in order to inform the research and management of patients co-infected with SARS-CoV-2 and HBV.

Research objectives

We searched almost all current clinical studies on COVID-19 combined with hepatitis B to describe the interaction between COVID-19 and hepatitis B, possible mechanisms and clinical interventions to inform the clinical management of this special population with SARS-CoV-2 and HBV co-infection.

Research methods

An experienced information specialist searched literature in the following online databases: PubMed, China National Knowledge Infrastructure, Google Scholar, Scopus, WileyWeb of Science, Cochrane and ScienceDirect. Literature published from December 2019 to September 1, 2022 was included in the search. We also searched medRxiv and bioRxiv for gray literature and manually scanned references of included articles. Articles conducted in humans discussing hepatitis B and COVID-19 were included in the criteria. Articles that met the criteria in the *Reference Citation Analysis* (<https://www.referencecitationanalysis.com>) were also included in this review. 13 we excluded duplicate publications. News reports, reports and other gray literature were

included if they contained quantifiable evidence (case reports, findings, qualitative analysis). Some topics that included HBV or COVID-19 samples but did not have quantitative evidence were excluded from the review.

Research results

A total of 57 studies were eligible and included in this review. They were from 11 countries, of which 33 (57.9%) were from China. Forty-two of the 57 studies reported abnormalities in liver enzymes, three mainly reported abnormalities in blood parameters, four indicated no significant liver function alterations, and another eight studies did not provide data on changes in liver function. Fifty-seven studies were retrospective and the total number of co-infections was 1932, the largest sample size was 7723, and the largest number of co-infections was 353. Most of the studies suggested an interaction between hepatitis B and COVID-19, while 12 studies clearly indicated no effect between hepatitis B and COVID-19. Six of the 57 studies clearly reported HBV activation. Six studies were related to liver transplant patients.

Research conclusions

Both SARS-CoV-2 and HBV are both globally pathogenic viruses, and there are few and conflicting data on the potential association between COVID-19 and hepatitis B. Our review provides direct evidence for some association between COVID-19 and hepatitis B, explains the clinical phenomena they exhibit, explores the possible mechanisms of the interaction between COVID-19 combined with hepatitis B, and provides management measures for co-infected patients.

Research perspectives

To our knowledge, our review is the most comprehensive report to date describing the association between COVID-19 and hepatitis B. In the future, high-quality randomized trials are needed to further elucidate the interaction between COVID-19 and hepatitis B.

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