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MINIREVIEWS

Interaction between hepatitis B virus and SARS-CoV-2 infections

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Abstract

Coronavirus disease 2019 (COVID-19) has become a global pandemic and garnered international attention. The causative pathogen of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel, highly contagious coronavirus. Numerous studies have reported that liver injury is quite common in patients with COVID-19. Hepatitis B has a worldwide distribution as well as in China. At present, hepatitis B virus (HBV) remains a leading cause of cirrhosis, liver failure, and hepatocellular carcinoma. Because both viruses challenge liver physiology, it raises questions as to how coinfection with HBV and SARS-CoV-2 affect disease progression and mortality. Is there an increased risk of COVID-19 in patients with HBV infection? In this review, we summarize the current reports of SARS-CoV-2 and HBV coinfection and elaborate the interaction of the two diseases. The emphasis was placed on evaluating the impact of HBV infection on disease severity and clinical outcomes in patients with COVID-19 and discussing the potential mechanism behind this effect.

Key Words: COVID-19; Hepatitis B virus; Liver injury; SARS-CoV-2; Coinfection; Immune exhaustion

Core Tip: Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a global public health crisis. Liver impairment is frequent in COVID-19 regardless of whether it is combined with hepatitis B virus (HBV) infection. Currently, there is no evidence to suggest that HBV increases susceptibility to SARS-CoV-2. HBV and SARS-CoV-2 coinfection does not increase the risk of severity and outcome of COVID-19. Nucleoside analogs are recommended due to the risk of HBV reactivation in COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has become a global pandemic and a major public health threat[1-3]. The disease mainly involves the respiratory system, causing flu-like symptoms such as fever, dry cough, and dyspnea, and severe cases may deteriorate to acute respiratory distress syndrome[4]. Apart from respiratory disorder, SARS-CoV-2 can also contribute to multiorgan dysfunction such as acute cardiac injury, acute renal insufficiency, and liver damage[5-7]. According to the previous reports, the incidence of abnormal liver function ranges from 14.8% to 53% in patients with COVID-19[8-10].

Hepatitis B virus (HBV), a prototypical member of the Hepadnaviridae family, has a worldwide distribution, especially in China[11]. Currently, 3.5% of the global population is chronically infected with HBV and 5%-6% (70 million) of the Chinese population are carriers of hepatitis B surface antigen (HBsAg)[12-14]. Although new infection with HBV is decreasing due to vaccination, HBV is still the primary cause of liver cirrhosis and hepatocellular carcinoma (HCC), resulting in many deaths each year[15,16].

Because SARS-CoV-2 and HBV can both cause abnormal liver function, one of the major concerns is whether people with pre-existing HBV infection have increased susceptibility to and severity of COVID-19, thus leading to a worse prognosis. Another concern is whether SARS-CoV-2 infection accelerates the course of hepatitis B progression and leads to active viral replication. It is important to figure out the interaction between the two diseases. To elucidate this complexity, we summarize the limited clinical research to compare the severity of organ injury and clinical outcome between coinfected patients and those with COVID-19 alone, to provide insights into early risk stratification, and follow-up disease management.

IMPACT OF HBV ON COVID-19

Liver injury

According to the data from two large cohorts, which enrolled 5700 and 1099 COVID-19 patients, respectively, 0.1%-2.1% of patients had HBV coinfection[6,17]. The first issue that attracts widespread attention is whether there is more serious liver damage in chronic hepatitis B patients after coinfection with SARS-CoV-2.

Based on the currently available research, the pattern and degree of liver injury in patients with HBV and SARS-CoV-2 coinfection are like those with SARS-CoV-2 alone. We know from previous studies that liver injury has a prevalence of 14.8%-53.0% in COVID-19. The characteristics of liver injury mainly manifest as different degrees of elevation in alanine aminotransferase (ALT, 2.5%-50.0%), aspartate aminotransferase (AST, 2.5%-61.1%), γ-glutamyl transferase, and total bilirubin (0%-35.3%), and patients with severe disease may also show reduced albumin[8,10,18-20]. In a retrospective study by Zou *et al*[21], 105 patients with COVID-19 and HBV coinfection were studied. Liver injury was observed in a small proportion of patients (14, 13.33%), which is within the range of incidence in patients with COVID-19 alone, and four (28.57%) patients with liver dysfunction progressed to acute-on-chronic liver failure. Moreover, other retrospective studies have shown that liver injury in COVID-19 patients with HBV coinfection also presents with varying degrees of elevated transaminases (such as ALT, AST, γ-glutamyl transferase, and total bilirubin), but most studies have found no significant difference in the degree of liver damage compared to that in patients with COVID-19 alone[22-26]. The characteristics of liver injury in patients with SARS-CoV-2 and HBV coinfection are listed in Table 1.

Although liver injury is common in COVID-19, severe liver damage is rare. With recovery of the disease, liver function in most patients gradually recover back to normal. Guo *et al*[27] recently showed that males, COVID-19 severity, low liver computed tomography density, and medication are risk factors closely related to liver injury. The possible mechanism of liver injury for individuals infected with SARS-

Table 1 Characteristics of liver injury in patients with coronavirus disease 2019 and hepatitis B virus coinfection

Reference	Number of analyzed cases	HBV cases, *n* (%)	HBV status	Anti-HBV therapy, *n* (%)	ALT (U/L)[1]	AST (U/L)[1]	TBil (μmol/L)[1]	GGT (U/L)[1]	Note
Zou *et al*[21]	105	105 (100)	HBsAg(+), 94% HBeAg (–)	13 (12.38); entecavir (9, 8.75); tenofovir (3, 2.86); lamivudine/defovir (1, 0.95)	23 (15-33)	28 (19-43)	8.3 (6.6-12.8)	24 (16-36)	Four patients developed ACLF and liver injury was associated with disease severity and worse prognosis
Chen *et al*[22]	326	20 (6.1)	HBsAg(+); HBeAg(–); HBV DNA < 100 IU/mL	NA	28.00 (16.25-42.25)	27.50 (22.00-42.25)	10.55 (6.83-15.73)	23.50 (15.50-35.25)	No differences in the level of liver function (HBV *vs* non-HBV)
Liu *et al*[23]	347	21 (6.4)	HBsAg(+); 95% HBeAg(–)	1 (4.8) tenofovir	30.40 (22.00-36.85)	34.15 (27.00-39.58	12.60 (10.50-16.43)	28.50 (17.25-43.42)	Three patients had HBV reactivation
Li *et al*[24]	342	7 (2)	HBsAg(+); 14% HBeAg(+)	2 (28.6)	31 (29-38)	31 (29-38)	12.7 (11.1-16.6)	NA	Liver injury was common but mild with no severe liver-related complications
[2]Chen *et al*[39]	123	15 (12.2)	HBsAg(+) 6.7% HBeAg(+); 67% HBV DNA; > 20 IU/mL	3 (20) entecavir	25 (16-44)	28 (19-58)	13.2 (10.0-17.4)	20 (14-28)	The level of TBil was higher in patients with HBV infection ($P < 0.05$)
Wu *et al*[40]	620	70 (11.3)	NA	NA	50 (28-69)	40 (25-54)	NA	NA	33% of patients had abnormal ALT and AST; ALT/AST levels were higher in patients with HBV ($P < 0.05$)
He *et al*[25]	571	15 (2.63)	NA	3 (20) entecavir	NA	NA	NA	NA	HBV infection was observed to have a lower risk of severe events ($P < 0.05$)
Zhang *et al*[26]	23	23 (100)	65.2% HBV carriers; 30.4% CHB; 4.3% cirrhosis	NA	38.6 (17.0-42.0)	31.6 (15.0-36.8)	24.9 (7.2-13.9)	32.3 (13.5-41.0)	26% of patients had abnormal liver function test results at admission

[1]Data are expressed as median and interval interquartile.
[2]Another person whose family name is Chen. ACLF: Acute-on-chronic liver failure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transferase; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; NA: Not available; TBil: Total bilirubin.

CoV-2 includes the following: (1) Direct damage caused by SARS-CoV-2 particles; (2) Immune-mediated organ damage; (3) Hypoxic-ischemic liver injury; (4) Drug-induced liver injury; and (5) Reactivation of pre-existing liver disease[28-31]. These factors may participate together to cause abnormal physiological function of the liver.

Disease severity and clinical outcome

A meta-analysis reported that 3% of patients with COVID-19 have underlying chronic liver disease (CLD)[32]. In addition, disease progression is higher in COVID-19 patients with CLD[33]. Metabolic-associated fatty liver disease, one of the etiologies of CLD, has been reported to increase the severity of COVID-19[34-37]. Although most studies have shown that HBV coinfection does not aggravate the liver injury, whether it affects disease severity and outcomes remains controversial.

Some studies have suggested that HBV coinfection does not aggravate the disease in patients with COVID-19. In an analysis of several large studies[4-6,38], the major complications in COVID-19 included acute respiratory distress syndrome (3.4%-29.0%), acute cardiac injury (4%-12%), acute kidney injury (0.5%-7.0%), and shock (1.1%-8.7%). Zou *et al*[21] and Zhang *et al*[26] showed that 8.7%-44.8% of patients had acute respiratory distress syndrome, 13.3% of patients had an acute cardiac injury, 3.81%-4.30% of patients had acute kidney injury, 2.81% patients had a shock, and 4.3% had deep venous thrombosis and upper gastrointestinal hemorrhage in patients with SARS-CoV-2 and HBV coinfection. According to these data, the percentage of organ

injury in patients with HBV coinfection was roughly parallel to that in patients with COVID-19 alone. It seems that SARS-CoV-2 and HBV coinfection does not exacerbate organ impairment in COVID-19.

Additionally, in a cohort of 326 confirmed COVID-19 patients, of which 20 (6.1%) had HBV coinfection, Chen *et al*[22] reported that there were no differences in discharge rate and length of stay between the two groups. HBV coinfection did not affect the course and prognosis of COVID-19. In another study by Liu *et al*[23], 21 (6.4%) patients with COVID-19 and HBV coinfection were included, and 51 matched COVID-19 patients without HBV were used for comparison. They explored the independent impact of chronic HBV infection on the progression to severe COVID-19 and found that HBV did not delay SARS-CoV-2 shedding and did not increase the risk of progression and poor outcomes related to SARS-CoV-2. Similarly, Li *et al*[24] and He *et al*[25] enrolled seven (2%) and fifteen (2.6%) patients with HBV infection out of 342 and 571 COVID-19 patients, respectively. They found that chronic HBV coinfection was not associated with disease severity or poor prognosis.

However, a few studies have reported conflicting results. A study of 15 (12.2%) patients with chronic hepatitis B and COVID-19 found that they had a more severe disease course and higher mortality rate (13.3% *vs* 2.8%) compared with those without HBV infection, suggesting that HBV coinfection may facilitate the development of liver injury, which is associated with adverse outcomes[39]. Another recent study involving 70 cases of coinfection by Wu *et al*[40] indicated that ALT, AST, and activated partial thromboplastin time were significantly higher in patients with COVID-19 and HBV coinfection. The proportion of severe/critically ill patients was also higher than that in the non-HBV infection group (32.86% *vs* 15.27%). Despite this, all patients with HBV coinfection in the study of Wu *et al*[40] were discharged, and the length of hospital stay and negative nucleic acid tests were both consistent with those without HBV coinfection, indicating no differences in clinical outcomes between the two groups. Comparison of disease severity and clinical outcome (discharge rate and mortality rate) in the above studies are shown in Figure 1. These studies appeared to suggest that in most cases, chronic HBV infection did not increase the risk of disease severity or lead to a worse prognosis in COVID-19.

Cirrhosis and HCC

Clinicians may be concerned about whether HBV-related cirrhosis and carcinoma are associated with poor outcomes in COVID-19. Data on this issue are currently scarce. Zhang *et al*[26] compared the impact of different hepatitis B status (HBV carrier group, hepatitis B/cirrhosis group) on COVID-19. Most HBV carriers do not develop severe or critical illness, and no significant differences were found in the length of hospital stay, disease severity, and prognosis between the two groups. It is worth mentioning that only one patient was cirrhotic in this study, although there may have been biasing in the results.

A large cohort[41] enrolled 745 CLD patients from 29 countries, of whom 386 had cirrhosis and 359 did not, and mortality was significantly higher in the cirrhotic patients (32% *vs* 8%). Mortality increased with Child-Turcotte-Pugh class, which showed for the first time that the stage of liver disease is strongly associated with COVID-19 mortality. The data from some other multicenter retrospective studies also supported the conclusion that patients with liver cirrhosis in COVID-19 had higher mortality and worse prognosis compared with patients without cirrhosis[42-45].

HBV-related cirrhosis only accounted for a small proportion of patients, and most cases of cirrhosis were attributed to nonalcoholic fatty liver disease (24%-32.5%), alcohol-related liver disease (4.6%-24%), and chronic hepatitis C virus infection (24%)[44,46]. More importantly, HBV accounted for the lowest proportion of severe cases and deaths compared with other etiologies. Alcohol-related liver disease rather than HBV was an independent risk factor associated with the outcome of COVID-19. Although the severity of cirrhosis is closely related to mortality and prognosis in COVID-19, the limited data about HBV-related cirrhosis are insufficient to confirm that HBV worsens the clinical outcome.

As for patients with HCC, they usually have a higher risk of infection and poor outcome due to their immunocompromised condition. Much of the research has revealed that individuals with cancer are more vulnerable to SARS-CoV-2 and have an increased risk of mortality[47,48]. However, there is no available data about HBV-related HCC in patients with COVID-19. Therefore, reducing exposure and preventing SARS-CoV-2 infection is important for these patients.

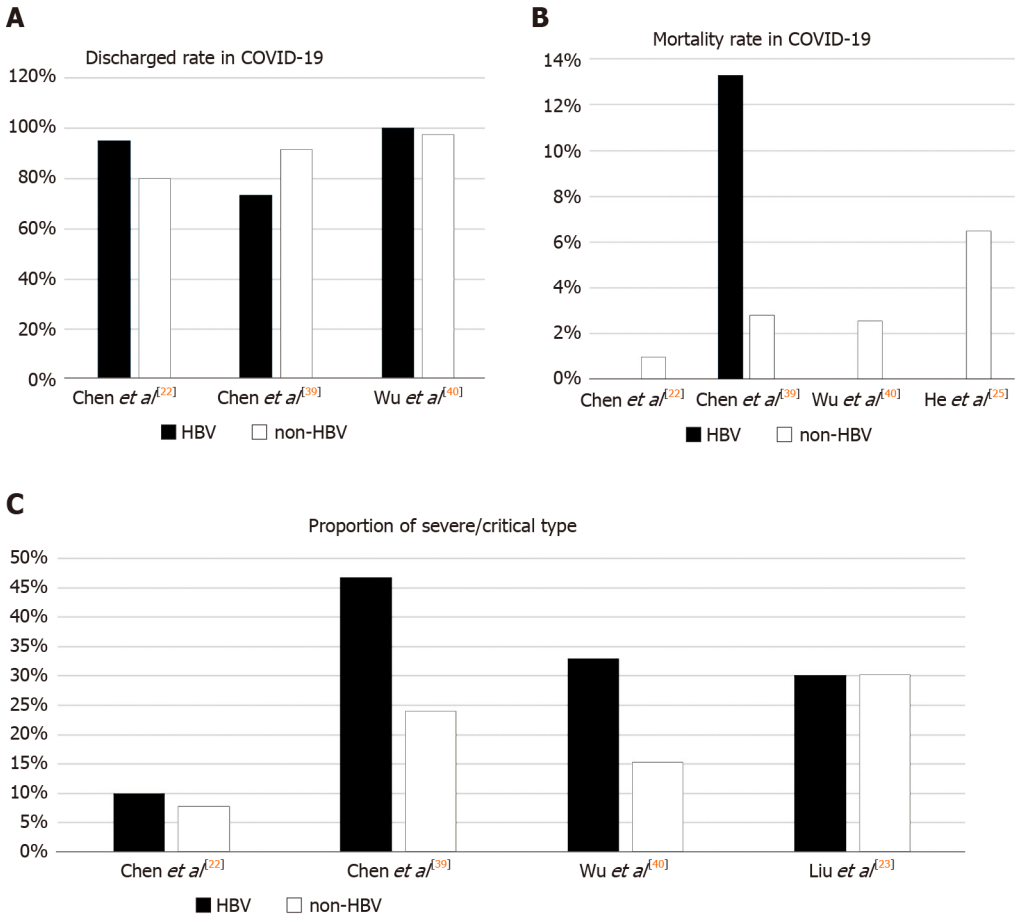

Figure 1 Comparison of clinical outcomes of coronavirus disease 2019 in hepatitis B virus and non-hepatitis B virus groups. A: Discharge rate; B: Mortality rate; C: Proportion of severe/critically ill patients. The data were collected from different clinical studies. COVID-19: Coronavirus disease 2019; HBV: Hepatitis B virus.

Interpretation of results

According to the limited research, HBV infection is not associated with the clinical outcome of COVID-19, although some patients may have a higher level of liver enzymes. We analyzed the underlying reasons behind this phenomenon.

(1) Some of the hepatitis B patients included in the study received nucleoside analogs as anti-HBV therapy (entecavir, tenofovir, *etc.*) in the long term, which may play a role in combating SARS-CoV-2 to some extent. Tenofovir tightly binds to SARS-CoV RNA-dependent RNA polymerase (RdRp) and terminates RNA synthesis catalyzed by SARS-CoV-2 RNA-dependent RNA polymerase[49,50]. These results provide a molecular basis for these nucleotide analogs to be viewed as a potential therapy for COVID-19. Additionally, a large cohort study in Spain found that the incidence of SARS-CoV-2 infection was low (0.4%, 8/1764) in patients with chronic hepatitis B who took tenofovir as anti-HBV therapy, which indirectly reflected that nucleoside analogs have a positive effect on resisting the novel coronavirus[51].

(2) Immune dysfunction caused by chronic HBV infection may play a crucial role in disease progression in COVID-19. Studies have proved that chronic HBV infection is associated with exhaustion of virus specific $CD4^+$ and $CD8^+$ T cells due to persisting viral antigens[52,53]. HBV-specific exhausted T cells lead to impaired secretion of cytokines, especially interleukin (IL) 2 and tumor necrosis factor-alpha, which is accompanied by progressive reduced antiviral function[54]. To our knowledge, the excessive immune response to SARS-CoV-2 infection (cytokine storm) results in overproduction of proinflammatory cytokines (such as IL-2, IL-6, and tumor necrosis factor-alpha), which is a critical factor associated with disease severity and mortality[55]. Under this circumstance, it is plausible that the exhaustion of HBV-specific T lymphocytes and the status of immunosuppression may avoid an overactive immune response to the novel coronavirus and reduce the cytokine storm, resulting in milder disease.

(3) Viral interference, which is defined as one virus in the host competitively

suppressing the replication of a second coinfecting virus, probably participates in the disease outcome in SARS-CoV-2 and HBV coinfection. Several studies have found that impaired type I interferon activity is a major feature in severe COVID-19 patients, which is associated with autoantibodies and genetic defects[56-58]. Viral interference can suppress coinfected viruses by enhancing type I interferon signaling[59]. Prior studies have proved that viral interference can occur in influenza virus, hepatitis virus, and human immunodeficiency virus[59-61]. For example, hepatitis C virus infection can limit the replication of HBV, and GB virus C and human immunodeficiency virus coinfection can reduce viral loads and prolong survival compared with patients with human immunodeficiency virus-1 infection. These observations support the hypothesis that HBV coinfection can affect replication and proliferation of SARS-CoV-2 by interferon-mediated viral interference.

(4) The number of patients with HBV coinfection in the published retrospective studies was small, which may have influenced the results. Almost all available studies about SARS-CoV-2 and HBV coinfection did not describe the baseline characteristics of HBV infection well, so the clinical stage of the patients could not be determined clearly. Hence, these results should be interpreted with caution and further conclusive research is needed.

IMPACT OF SARS-COV-2 ON HBV

For severe COVID-19 patients with HBV coinfection, there is a risk of HBV reactivation. There has been little consensus about the standardized definition of HBV reactivation. Primarily reactivation is defined as a sudden and rapid increase in HBV DNA levels in individuals with previously detectable HBV DNA or reappearance of HBV DNA viremia in individuals without detectable viral DNA[62]. HBV reactivation is usually associated with immunosuppressive therapy such as IL-6 receptor antagonists (tocilizumab and siltuximab), IL-1 receptor antagonists (anakinra), and high-dose corticosteroids[63-65]. In severe COVID-19 patients, these therapies may be used to control the cytokine storm, thus reducing the immune-mediated multiorgan injury.

In a retrospective study[23] of 21 patients with SARS-CoV-2 and HBV coinfection, 19 patients were tested for HBV DNA viral load at least twice during hospitalization. Of the 19 patients, three patients developed HBV reactivation and manifested as a rapid increase in HBV DNA viral load from undetectable to a high level. These three patients were negative for hepatitis B e antigen and did not receive any anti-HBV treatment before admission. During the hospitalization, two of the three patients received methylprednisolone, which may account for the reactivation, and one did not receive any corticosteroids. Another case report[66] showed that one patient with COVID-19 had acute HBV infection, and laboratory results showed AST (4933 U/L), ALT (4758 U/L), total bilirubin (183.9 mmol/L), HBsAg (+), hepatitis B core antibody immunoglobulin M (+), hepatitis B e antigen (–), hepatitis B e antibody (+), and HBV DNA viral load was 2490 IU/mL. The patient did not receive any immunosuppressive therapy. Regardless whether corticosteroids were used, the patient could have a risk of HBV reactivation.

The mechanisms of HBV reactivation following infection with SARS-CoV-2 are primarily due to a broken balance between the host's immune state and viral replication. In addition to the host baseline virological indicators, the intensity of glucocorticoids or immunosuppression therapies is a primary risk factor for reactivation of HBV during treatment of COVID-19[11,62].

Although infection with SARS-CoV-2 has a risk of HBV reactivation, the overall risk is low. One prospective study[67] evaluated the risk of HBV reactivation in 61 patients with severe COVID-19 and resolved HBV infection (HBsAg-negative, anti-hepatitis B core antibody-positive) undergoing immunosuppressive therapy. After at least 1 mo of follow-up, they found no cases develop HBsAg seroconversion and only two (3%) patients had detectable serum HBV DNA (< 15 IU/mL). Therefore, for patients with severe COVID-19 and coexistent HBV infection, corticosteroids and immunosuppressants can be selected clinically.

Given the risk of reactivation, the American Association for the Study of Liver Diseases guidelines strongly recommend that anti-HBV treatment should be initiated or continued once COVID-19 was diagnosed[68]. At the same time, routine HBV virologic indicators and liver-injury related indicators should be closely monitored during the disease.

CONCLUSION

In this review, we summarized reports about SARS-CoV-2 and HBV coinfection and explored the interaction between chronic hepatitis B and COVID-19. The limited clinical evidence reflects that chronic HBV infection does not increase the severity and outcome of COVID-19 in most cases (Figure 2). Given that the stages in patients with chronic hepatitis B are ambiguous (immune tolerance or low viral replication), these findings need to be confirmed in further studies. HBV reactivation is possible in the course of the disease. Therefore, liver function and hepatitis-B-related indicators should be monitored regularly.

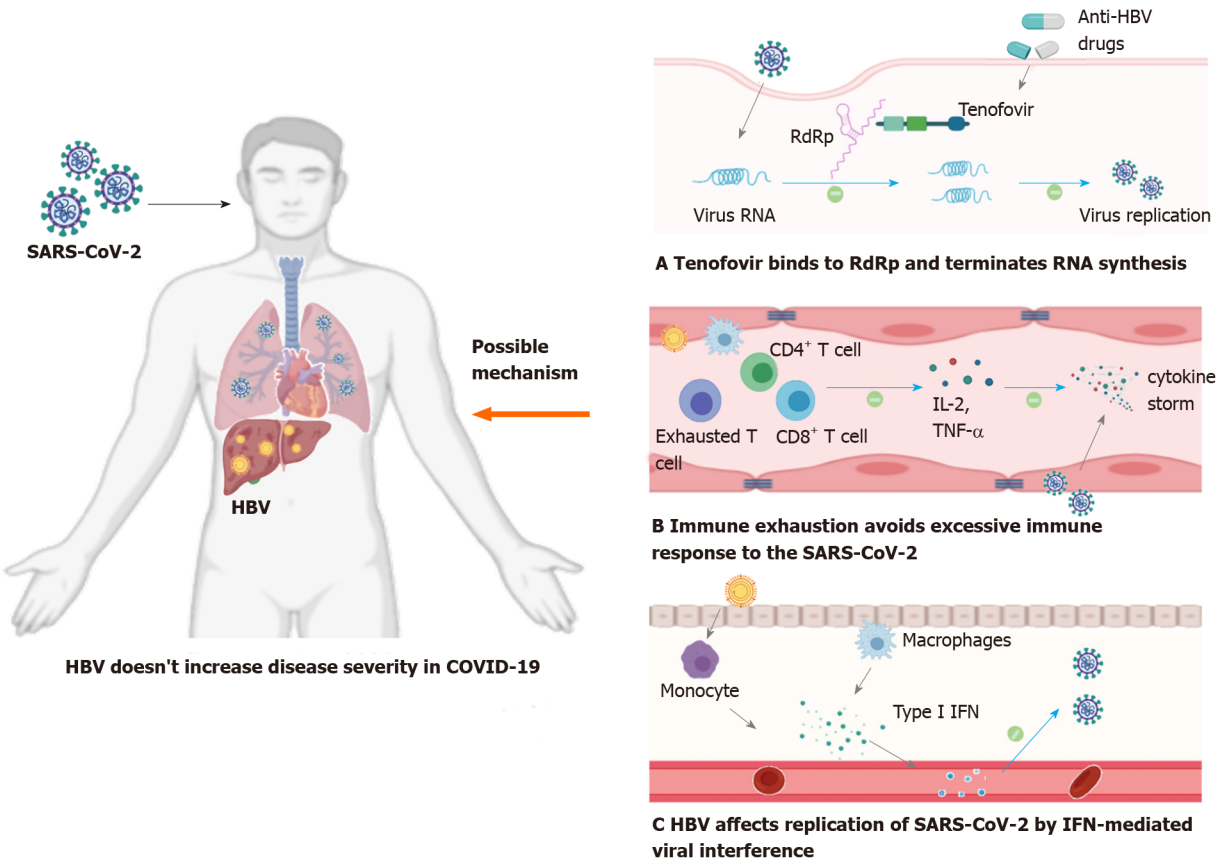

Figure 2 Graphical abstract. COVID-19: Coronavirus disease 2019; HBV: Hepatitis B virus; IFN: Interferon; IL: Interleukin; RdRp: RNA-dependent RNA polymerase; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TNF-α: Tumor necrosis factor-alpha.

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