ORIGINAL ARTICLE

Effects of Hepatitis B Virus Infection on Patients with COVID-19: A Meta-Analysis

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Abstract

Background The COVID-19 pandemic has brought new problems to patients infected with hepatitis B virus (HBV).

Aim We aim to know the effects of HBV infection on patients with COVID-19.

Methods We searched PubMed, Embase, and Web of Science for data and utilized Stata 14.0 software for this meta-analysis with a random-effects model. This paper was conducted in alignment with the preferred reporting items for systematic review and meta-analysis (PRISMA) guideline.

Results In total, 37,696 patients were divided into two groups: 2591 COVID-19 patients infected with HBV in the experimental group and 35,105 COVID-19 patients not infected with HBV in the control group. Our study showed that the in-hospital mortality of the experimental group was significant higher than that of the control group (OR = 2.04, 95% CI 1.49–2.79). We also found that COVID-19 patients infected with HBV were more likely to develop severe disease (OR = 1.90, 95% CI 1.32–2.73) than COVID-19 patients not infected with HBV. Upon measuring alanine aminotransferase (SMD = 0.62, 95% CI 0.25–0.98), aspartate aminotransferase (SMD = 0.60, 95% CI 0.30–0.91), total bilirubin (SMD = 0.45, 95% CI 0.23–0.67), direct bilirubin (SMD = 0.36, 95% CI 0.24–0.47), lactate dehydrogenase (SMD = 0.32, 95% CI 0.18–0.47), we found that HBV infection led to significantly higher laboratory results in COVID-19 patients.

Conclusion COVID-19 patients infected with HBV should receive more attention, and special attention should be given to various liver function indices during treatment.

Keywords COVID-19 · Meta-analysis · Hepatitis B virus · Liver function

Introduction

In December 2019, the first case of COVID-19 was detected in Wuhan, Hubei Province, China, followed by a rapid global outbreak of COVID-19 [1]. As of July 12, 2022, there were more than 556 million cases of COVID-19 and 6.35 million deaths worldwide [2]. COVID-19 is caused by SARS-CoV-2, which was isolated from a biological sample of the genus β-coronavirus [3]. The tracing of SARS-CoV-2 is still in progress, and the pathogenicity of COVID-19 is milder than that of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS); these are also caused by coronavirus, but the infectiousness is much higher [4]. The current transmission routes are divided into two main categories: human-to-human (direct contact, most often through droplets from coughing, sneezing, and talking) and indirect transmission (noncontact, through contaminated objects). Most cases have an incubation period of 1 to 14 days, usually 3 to 7 days, with a median of 5.5 days [5]. The typical clinical manifestations of COVID-19 are fever, dry cough, shortness of breath, malaise, muscle pain, no improvement with antibiotic treatment, loss of taste or smell, diarrhea, low white blood cell count, and pneumonia [6].

Although SARS-CoV-2 is considered to be a pneumophila virus, liver injury has emerged as a significant complication of COVID-19 [7]. Liver enzyme abnormalities are the most common clinical feature observed in these patients and are reported in approximately 50% of COVID-19 patients,

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raising significant clinical concerns [8]. Patients with liver disease are a high-risk group for COVID-19 infection [9]. Based on an analysis of the US national electronic health record database, it was found that patients who had recently sought medical care for chronic liver disease were at significantly increased risk of COVID-19 infection compared to patients without chronic liver disease [10]. Chronic viral hepatitis B, caused by infection with hepatitis B virus (HBV), is a blood-borne disease that causes a large burden of chronic liver disease worldwide, resulting in more than one million deaths from liver cancer and cirrhosis each year [11]. Despite the availability of effective vaccines, HBV remains a major public health threat, with approximately 300 million people infected worldwide [12]. Up to 60% of SARS patients suffer liver damage, and chronic HBV infection has been shown to be an independent risk factor for disease progression to acute respiratory distress syndrome (ARDS) [13]. Studies have confirmed that HBV infection can lead to an impaired innate immune response and an imbalanced acquired immune response [14]. Moreover, the uncontrolled innate response and impaired acquired immune response caused by SARS-CoV-2 may lead to local and systemic deleterious tissue damage [15]. Therefore, mixed infection with SARS-CoV-2 and fHBV may aggravate immune function and liver damage [16]. Some studies have shown that the prevalence of HBV infection in COVID-19 patients remains between 0 and 1.3%, and it is essential to understand the impact of HBV infection on COVID-19 patients [17]. The definitions of liver abnormalities and liver injury often differ between studies, which limits the feasibility of making comparisons between findings. Even within the same study, changes in the defined indices of liver abnormality and liver injury can have an impact on the prediction of clinical outcomes in COVID-19 patients [18]. A previous study enrolled 417 COVID-19 patients and classified the pattern of liver abnormalities in COVID-19 patients using two different definitions; the correlation between liver abnormalities and COVID-19 severity was significantly different across definitions [19]. Therefore, there was no specific definition of liver injury or liver abnormality in our meta-analysis. We compared the differences in various liver function indices between COVID-19 patients with HBV infection and COVID-19 patients without HBV infection and compared differences in COVID-19 severe illness and mortality.

Materials and Methods

Eligibility Criteria

The diagnostic criteria for COVID-19 included typical clinical symptoms, chest computed tomography, and a positive COVID-19 RNA result. The disease severity of COVID-19 were defined on the basis of the WHO guidelines [20] and/or the COVID-19 Diagnosis and Treatment Guidance (2020) of China [21].

Studies meeting the following criteria were included in the meta-analysis: (1) the study must be full-text; (2) all study subjects were COVID-19 patients; (3) patients in the experimental group were infected with HBV, and patients in the control group were not infected; and (4) the sample sizes of both the experimental group and the control group were more than five.

Information from abstracts, comments, reviews, posters, case reports, and patients with high risk of overlap was excluded.

Information Sources

We conducted a search of PubMed, Embase, and Web of Science for all literature on the association between hepatitis B and COVID-19 published before July 12, 2022, without restricting the language of the literature, to maximize the collection of valuable information globally.

Search Strategy

We used "subject terms" + "free terms" to search the database, and the search terms were limited to the title and abstract. The search strategy in PubMed is as follows: (("COVID-19"[Mesh]) OR (((((((((((((((((((((((((((((((((COVID 19[Title/Abstract]) OR (COVID-19 Virus Disease[Title/Abstract])) OR (COVID 19 Virus Disease[Title/Abstract])) OR (COVID-19 Virus Diseases[Title/Abstract])) OR (Disease, COVID-19 Virus[Title/Abstract])) OR (Virus Disease, COVID-19[Title/Abstract])) OR (COVID-19 Virus Infection[Title/Abstract])) OR (COVID 19 Virus Infection[Title/Abstract])) OR (COVID-19 Virus Infections[Title/Abstract])) OR (Infection, COVID-19 Virus[Title/Abstract])) OR (Virus Infection, COVID-19[Title/Abstract])) OR (2019-nCoV Infection[Title/Abstract])) OR (2019 nCoV Infection[Title/Abstract])) OR (2019-nCoV Infections[Title/Abstract])) OR (Infection, 2019-nCoV[Title/Abstract])) OR (Coronavirus Disease-19[Title/Abstract])) OR (Coronavirus Disease 19[Title/Abstract])) OR (2019 Novel Coronavirus Disease[Title/Abstract])) OR (2019 Novel Coronavirus Infection[Title/Abstract])) OR (2019-nCoV Disease[Title/Abstract])) OR (2019 nCoV Disease[Title/Abstract])) OR (2019-nCoV Diseases[Title/Abstract])) OR (Disease, 2019-nCoV[Title/Abstract])) OR (COVID19[Title/Abstract])) OR (Coronavirus Disease 2019[Title/Abstract])) OR (Disease 2019, Coronavirus[Title/Abstract])) OR (SARS Coronavirus 2 Infection[Title/Abstract])) OR (SARS-CoV-2 Infection[Title/Abstract])) OR (Infection, SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2 Infection[Title/

Abstract])) OR (SARS-CoV-2 Infections[Title/Abstract])) OR (COVID-19 Pandemic[Title/Abstract])) OR (COVID 19 Pandemic[Title/Abstract])) OR (COVID-19 Pandemics[Title/Abstract])) OR (Pandemic, COVID-19[Title/Abstract]))) AND (((hepatitis B[Title/Abstract]) OR (hepatitis B virus[Title/Abstract])) OR (HBV[Title/Abstract])).

Study Selection Process

Literature collected from the database was imported into NoteExpress software for filtration. After deleting duplicated literature, we first read the titles and abstracts before irrelevant pieces were eliminated. Articles that did not meet the requirements were then further screened based on the abstract or the full text. The related articles were used for subsequent data selection.

Data Selection Process and Items

Data extraction was completed independently by two authors. When those two authors disagreed on data selection, they would debate the problem before delivering it to a third author for the final conclusion.

The following data were recorded: number of seriously ill patients, number of patients who died, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, alkaline phosphatase (ALP) levels, gamma-glutamyl transferase (GGT) levels, total bilirubin (TB) levels, direct bilirubin (DB) levels, albumin (ALB) levels, globulin (GLO) levels, lactate dehydrogenase (LDH) levels, creatine kinase (CK) levels, prothrombin time (PT), and activated partial thromboplastin time (APTT).

Quality Assessment

The quality of the included studies was independently assessed using the Newcastle–Ottawa quality assessment scale. An overall score equal to or above seven was used to indicate high quality. The assessment was completed by one author and reviewed by another.

Publication Bias Assessment

Egger's test was used for quantitative analysis of publication bias. A p value < 0.05 indicates the presence of bias.

Statistical Analysis

In this paper, the odds ratio (OR) and standardized mean difference (SMD) were used for data analysis and evaluation, and the confidence interval (CI) was set at 95%. For the data with only sample size and quartile, we used the transformation formula to find their mean and standard deviation [22, 23]. The Cochrane's Q test and I^2 statistics were used to quantify the heterogeneity between studies, with $I^2 \leq 50\%$ indicating low heterogeneity, $50\% < I^2 \leq 75\%$ indicating moderate heterogeneity, and $I^2 > 75\%$ indicating high heterogeneity. This meta-analysis used a random-effects model for effect estimation, and all analyses were performed using Stata 14.0 software. A p value of z test < 0.05 was considered statistically significant.

Results

Study Selection

Overall, 2932 studies were searched in the database, of which 772 duplicated studies were deleted with NoteExpress software. According to the titles and abstracts, 1820 articles irrelevant to this study were eliminated. Of the remaining 340 papers, 327 were excluded after further screening, including comments, reviews, case reports, and papers with insufficient data or overlapping patients. Thirteen articles were finalized for inclusion in our meta-analysis. The flow diagram of the study selection is shown in Fig. 1.

Study Characteristics

Patients in our study came from four regions, including mainland China, Hong Kong, Korea, and Turkey. In total, 37,696 patients were included, of whom 2591 were COVID-19 patients infected with HBV, and 35,105 were COVID-19 patients not infected with HBV.

Quality of the Studies

All of the included studies had high quality based on the Newcastle–Ottawa quality assessment scale (Table 1).

Results of Individual Studies

The results of individual studies are presented in structured tables. Information on the characteristics of the experimental and control groups is listed in Tables 2 and 3.

Results of the Meta-Analysis

Our study showed that the in-hospital mortality of the experimental group was significant higher than that of the control group (OR = 2.04, 95% CI 1.49–2.79, $I^2 = 42.1\%$, $p < 0.001$, Fig. 2). We also found that COVID-19 patients infected with HBV were more likely to develop severe disease (OR = 1.90, 95% CI 1.32–2.73, $I^2 = 48.5\%$, $p < 0.001$, Fig. 3) than COVID-19 patients not infected with HBV. Upon
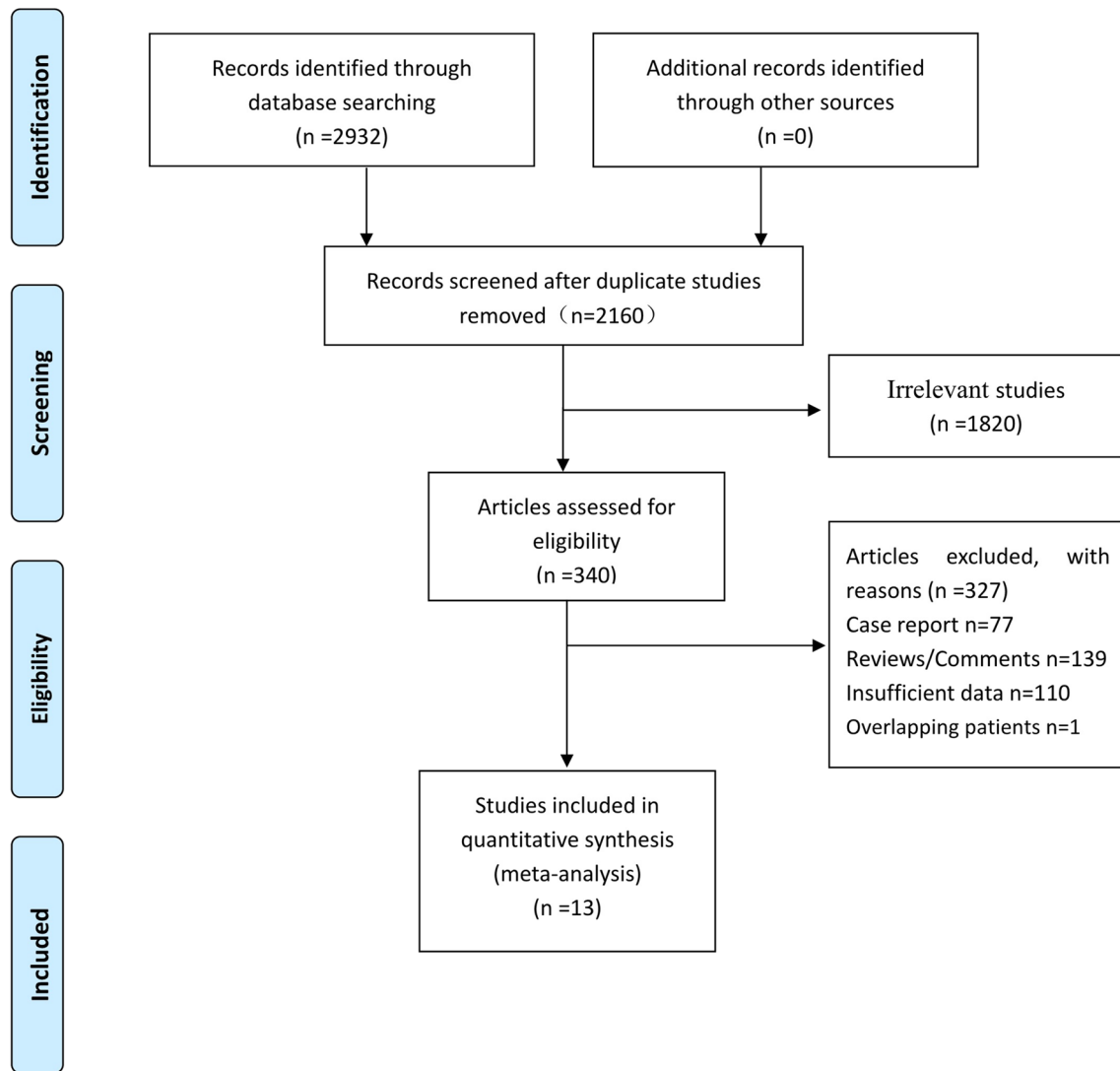
Fig. 1 Flow diagram of study selection

measuring ALT (SMD=0.62, 95% CI 0.25–0.98, I^2=96.6%, $p<0.001$, Fig. 4), AST (SMD=0.60, 95% CI 0.30–0.91, I^2=95.0%, $p<0.001$, Fig. 5), TB (SMD=0.45, 95% CI 0.23–0.67, I^2=87.4%, $p<0.001$, Fig. 6), DB (SMD=0.36, 95% CI 0.24–0.47, I^2=19.1%, $p<0.001$, Fig. 7), and LDH (SMD=0.32, 95% CI 0.18–0.47, I^2=48.3%, $p<0.001$, Fig. 8), we found that HBV infection led to significantly higher laboratory results in COVID-19 patients; in the case of ALP (SMD=0.11, 95% CI − 0.08 to 0.30, I^2=82.7.4%, $p=0.265$, Fig. 9), GGT (SMD=0.09, 95% CI − 0.30 to 0.49, $p=0.646$, Fig. 10), ALB (SMD=− 0.24, 95% CI − 0.49 to 0.01, I^2=91.5%, $p=0.061$, Fig. 11), GLO (SMD=− 0.16, 95% CI − 0.65 to 0.33, I^2=74.4%, $p=0.524$, Fig. 12), CK

(SMD=0.12, 95% CI − 0.58 to 0.81, I^2=85.4%, $p=0.744$, Fig. 13), PT (SMD=0.53, 95% CI − 0.14 to 1.20, I^2=92.5%, $p=0.122$, Fig. 14) and APTT (SMD=0.02, 95% CI − 0.14 to 0.18, I^2=0, $p=0.807$, Fig. 15), there were no significant differences between the two groups of patients.

Publication Bias

We used Egger's test for quantitative analysis of publication bias. The study of the effect of HBV infection on TB ($p=0.049$) and AST ($p=0.045$) of COVID-19 patients showed slight bias, while other results carried no significant bias (Supplementary File 1).

Table 1 Newcastle–Ottawa Quality Assessment Scale

Study	Publication year	Selection	Comparability	Outcome	Quality assessment score
Liu et al. [16]	2020	4	2	3	Good
Wang et al. [24]	2020	4	1	2	Good
Liu et al. [25]	2020	4	1	2	Good
Lin et al. [26]	2020	4	1	3	Good
Li et al. [27]	2020	4	1	2	Good
Chen et al. [28]	2020	4	1	2	Good
Chen et al. [29]	2020	4	1	3	Good
Wu et al. [30]	2020	4	1	2	Good
Yang et al. [31]	2022	4	2	3	Good
Yip et al. [32]	2021	4	2	2	Good
Bekcibasi et al. [33]	2021	4	2	3	Good
Kang et al. [34]	2020	4	1	2	Good
Choe et al. [35]	2022	4	1	3	Good

Discussion

There is growing evidence that many COVID-19 patients have abnormal liver function [36]. Currently, there are two main causes of liver function abnormalities in COVID-19 patients. On the one hand, SARS-CoV-2 may act directly on the liver, and liver biopsy specimens from some COVID-19 patients showed moderate microvascular steatosis with mild lobular and portal vein activity [37]. Chau et al. performed autopsies on 19 patients who died of SARS-CoV-2 infection. The reported results showed that the virus was detected in 41% of the liver tissues, with the highest viral load of 1.6×10^6 copies/g tissue [13]. Human hepatic duct-like organs allow SARS-CoV-2 infection and support substantial viral replication, which may lead to abnormal liver function indices [38]. On the other hand, drug-related liver injury is a key factor that cannot be ignored. Many COVID-19 patients have been treated with antibiotics and antivirals, which are toxic to the liver and may cause abnormal liver function [39].

Some studies have suggested that HBV coinfection does not increase the severity of COVID-19 or further enhance the inflammatory response caused by SARS-CoV-2, even reducing the probability of admission to the intensive care unit for COVID-19 patients, the liver tissue of patients with chronic HBV infection appeared to show a "muted" induction of the innate immune response [40–42]. However, after including a large amount of data in this meta-analysis, we found that HBV infection can worsen the condition of patients with COVID-19. Previous studies had shown that HBV in combination with other viruses, such as human immunodeficiency virus (HIV) and severe acute respiratory syndrome corona virus (SARS-CoV), was more likely to accelerate the progression of liver injury and lead to adverse clinical outcomes [43]; thus, it is not surprising that the same problem occurs with COVID-19. Glucocorticoids have potent anti-inflammatory effects and have been shown to alleviate clinical symptoms, shorten the course of treatment, and promote the absorption of pulmonary infiltrates in patients with severe acute respiratory syndrome [44]. Glucocorticoids as a common treatment strategy for patients with COVID-19 have been shown to increase the risk of hepatitis outbreaks in patients with hepatitis B and may affect liver enzyme markers in these patients [45]. In the case of methylprednisolone, one of the glucocorticoids, medium to high doses (≥ 10 mg) of methylprednisolone lead to a high risk of HBV reactivation [46]. In a study by Liu et al., six COVID-19 patients infected with HBV received methylprednisolone, and four developed hepatitis B reactivation, which was possibly caused by methylprednisolone [16].

Our study also found that some liver function indices were higher in COVID-19 patients infected with HBV than in COVID-19 patients not infected with HBV, including AST, ALT, TB, DB, and LDH, suggesting that more severe liver function abnormalities may be present. AST is present in high concentrations in the liver as well as the heart muscle, skeletal muscle, kidney, pancreas, and lung. Elevated AST levels suggest possible dysfunction in these tissues [47]. The aspartate aminotransferase-to-platelet ratio index score can be calculated by serum AST for the accurate prediction of cirrhosis and fibrosis in patients with chronic HBV infection, which is the most cost-effective noninvasive tool for the assessment of cirrhosis and active hepatitis [48]. The study of Xie et al. showed that patients with elevated AST had a 10.2 year shorter life expectancy, suggesting that, for all-cause and liver-related mortality, AST is an important predictor [49]. ALT is a biomarker that reflects the severity of many chronic liver diseases [50], wherein elevated serum

Table 2 The characteristics of COVID-19 patients infected with hepatitis B virus

Author	Rigion	Pub-lica-tion year	Num-ber	Age	Gender;male(%)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB	DB (umol/L)	ALB (g/L)	GLO (g/L)	LDH (U/L)	CK (U/L)	PT(s)	APTT(s)	Severe COVID-19	Death (%)
Liu et al. [16]	China	2020	21	52±14	12(57)	31.0±13.8	34.2±11.1	NA	31.0±21.2	13.4±4.5 (umol/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al. [24]	China	2020	109	54±15	71(65)	40.6±32.3	40.6±32.3	70.0±26.5	NA	11.2±6.0 (umol/L)	4.2±2.3	33.9±7.0	27.5±4.2	244.3±108.2	NA	14.8±2.2	38.1±5.0	30	13(12)
Liu et al. [25]	China	2020	50	61±13	29(58)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23	4(8)
Lin et al. [26]	China	2020	17	48±5	11(65)	37.4±27.6	34.3±21.9	74.2±17.8	46.8±51.7	16.8±11.6 (U/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li et al. [27]	China	2020	7	43±14	6(86)	32.9±8.3	32.9±8.3	NA	NA	13.6±5.1 (umol/L)	NA	40.8±8.6	NA	NA	NA	13.3±0.7	NA	0	0
Chen et al. [28]	China	2020	20	53±15	13(65)	28.9±20.7	30.8±16.2	60.6±17.8	24.9±15.8	11.1±7.1 (umol/L)	5.1±3.2	38.6±5.5	29.0±3.5	235.5±52.3	NA	NA	NA	2	0
Chen et al. [29]	China	2020	15	51±17	10(67)	28.6±22.9	35.6±31.9	76.7±40.9	20.7±11.5	13.6±6.1 (mmol/L)	NA	35.5±7.1	NA	NA	NA	12.8±2.0	30.4±3.9	7	2(13)
Wu et al. [30]	China	2020	70	50±16	42(60)	48.9±31.0	39.7±22.0	NA	NA	NA	NA	39.9±4.8	NA	244.0±111.3	97.4±72.7	12.3±1.7	33.3±8.7	23	0
Yang et al. [31]	China	2022	608	62±13	327(54)	32.8±39.0	26.7±27.2	80.9±46.6	NA	12.0±10.0 (umol/L)	4.9±6.9	37.2±4.9	NA	NA	NA	NA	NA	246	29(5)
Yip et al. [32]	Hong Kong	2021	712	59±14	356(50)	26.7±14.0	34.3±19.3	0.6±0.2 (ULN)	NA	0.5±0.4 (mg/dL)	NA	39.3±5.0	NA	242.2±114.7	NA	NA	NA	NA	29(4)
Bekcibasi et al. [33]	Turkey	2021	20	62±15	9(45)	38.4±29.5	49.7±29.4	53.0±23.9	32.6±34.3	0.5±0.3 (mg/dL)	NA	37.1±5.7	NA	315.3±87.4	116.1±95.6	NA	NA	1	0
Kang et al. [34]	Korea	2020	267	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12(5)
Choe et al. [35]	Korea	2022	675	59±16	333(49)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	91(14)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma–glutamyl transferase, *TB* total bilirubin, *DB* direct bilirubin, *ALB* albumin, *GLO* globulin, *LDH* lactate dehydrogenase, *CK* creatine kinase, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ULN* upper limit of normal

**Table 3** The characteristics of COVID-19 patients not infected with hepatitis B virus

Author	Region	Publication year	Number	Age	Gender.male(%)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB	DB (umol/L)	ALB (g/L)	GLO (g/L)	LDH (U/L)	CK (U/L)	PT(s)	APTT(s)	Severe COVID-19	Death(%)
Liu et al. [16]	China	2020	326	47±19	152(47)	21.4±10.5	27.0±10.6	NA	24.5±14.4	11.7±6.0 (umol/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al. [24]	China	2020	327	55±17	187(57)	18.70±9.0	22.1±8.2	64.52±28.9	NA	8.6±3.7 (umol/L)	3.4±1.3	39.4±4.1	29.1±4.3	214.2±52.9	0.7±0.5	13.5±0.8	37.9±3.2	42	8(2)
Liu et al. [25]	China	2020	56	62±10	31(55)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	27	4
Lin et al. [26]	China	2020	116	44±12	61(53)	22.4±14.7	23.6±10.2	68.2±20.3	27.3±21.2	8.9±5.6 (U/L)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li et al. [27]	China	2020	21	47±13	12(57)	36.7±31.2	29.1±10.3	NA	NA	11.9±7.7 (umol/L)	NA	39.8±2.4	NA	NA	NA	12.3±1.0	NA	2	NA
Chen et al. [28]	China	2020	306	50±21	155(51)	23.8±14.9	24.9±10.8	56.8±13.6	27.7±19.4	8.6±3.2 (umol/L)	4.2±1.7	40.1±4.0	28.4±4.1	231.7±64.1	NA	NA	NA	24	3(1)
Chen et al. [29]	China	2020	108	51±23	40(37)	23.2±13.4	27.1±13.5	66.3±19.4	24.9±16.2	9.8±3.5 (mmol/L)	NA	38.0±4.9	NA	NA	NA	13.0±1.1	30.7±3.0	26	3(3)
Wu et al. [30]	China	2020	550	48±19	273(50)	22.1±12.6	23.7±8.9	NA	NA	NA	NA	40.2±5.1	NA	204.8±66.9	75.7±45.3	12.3±1.7	33.3±8.6	84	14(3)
Yang et al. [31]	China	2022	2291	58±15	1151(50)	33.6±34.8	25.1±24.1	75.1±28.3	NA	10.3±4.8 (umol/L)	3.7±2.1	37.3±4.3	NA	NA	NA	NA	NA	541	37(2)
Yip et al. [32]	Hong Kong	2021	4,927	50±18	2387(48)	26.8±17.1	33.5±19.3	0.6±0.2 (ULN)	NA	0.5±0.3 (mg/dL)	NA	40.1±5.3	NA	220.1±89.1	NA	NA	NA	NA	109(2)
Bekcibasi et al. [33]	Turkey	2021	136	64±10	64(47)	27.2±12.7	39.5±19.5	59.1±19.6	42.4±33.7	0.5±0.2 (mg/dL)	NA	35.6±3.3	NA	292.8±104.2	150.0±129.9	NA	NA	33	13(10)
Kang et al. [34]	Korea	2020	7456	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	225(3)
Choe et al. [35]	Korea	2022	18,485	53±22	8732(47)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1524(8)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma−glutamyl transferase, *TB* total bilirubin, *DB* direct bilirubin, *ALB* albumin, *GLO* globulin, *LDH* lactate dehydrogenase, *CK* creatine kinase, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ULN* upper limit of normal, *MV* mechanical ventilation
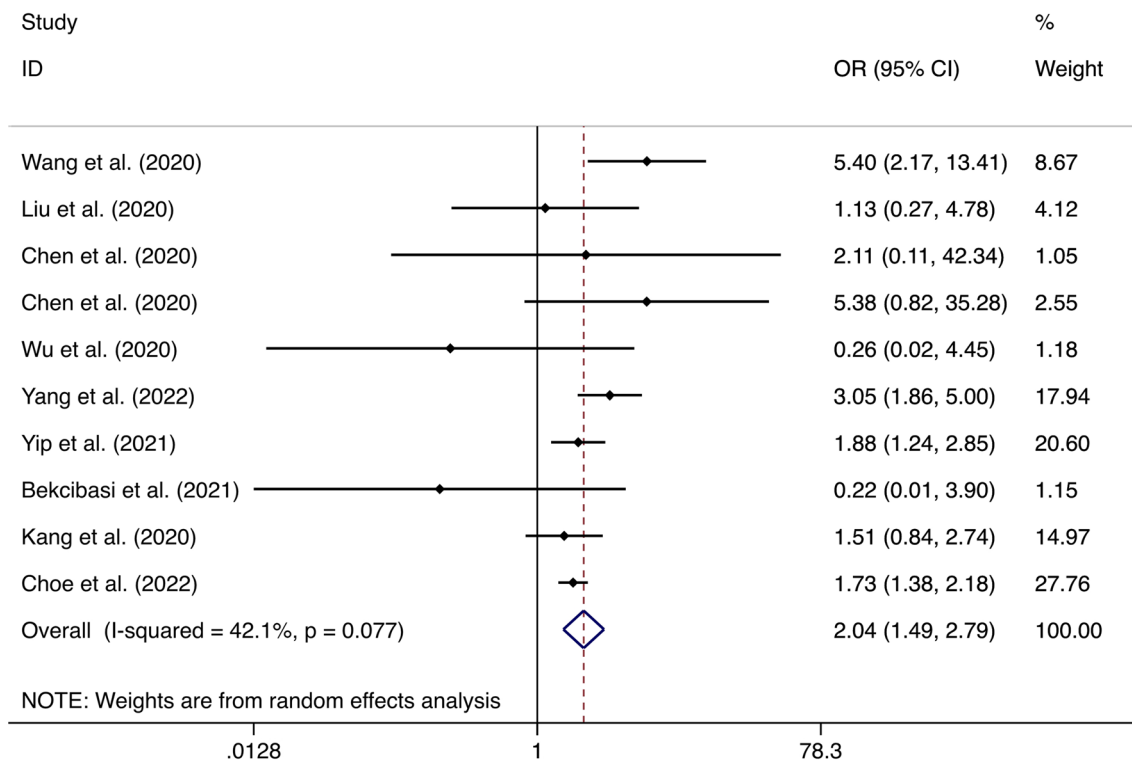
Fig. 2 Forest plot of the effect of hepatitis B virus infection on in-hospital mortality among COVID-19 patients
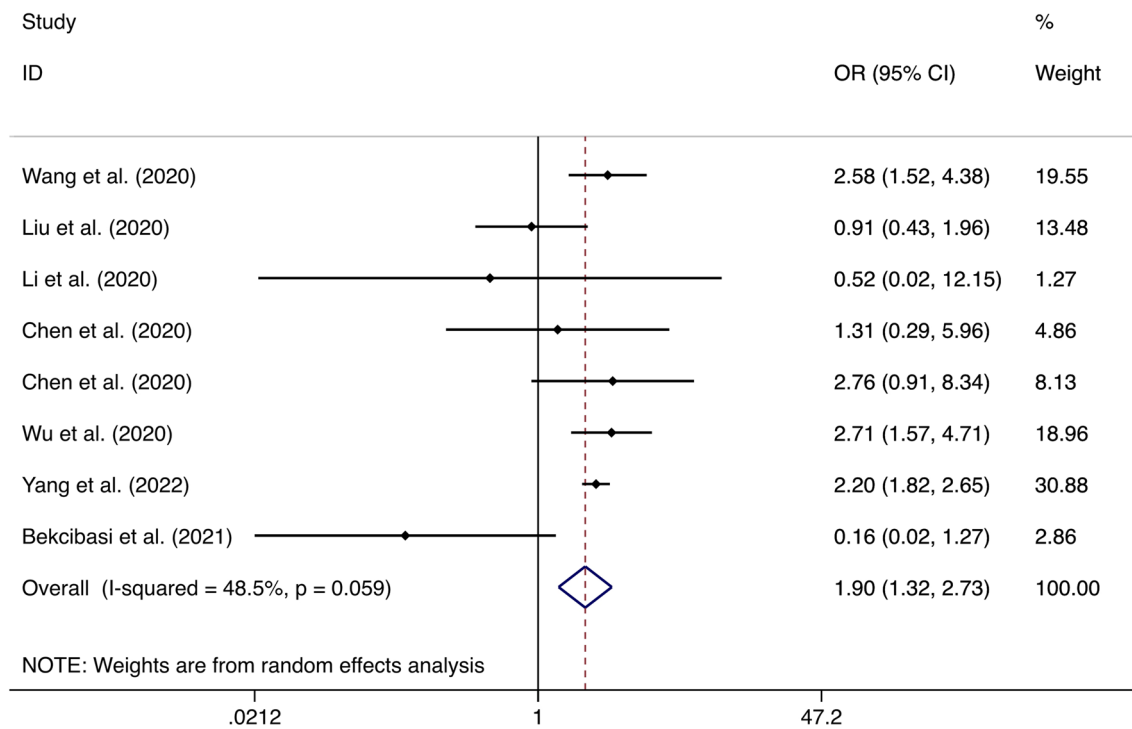
Fig. 3 Forest plot of the effect of hepatitis B virus infection on severity of COVID-19 patients
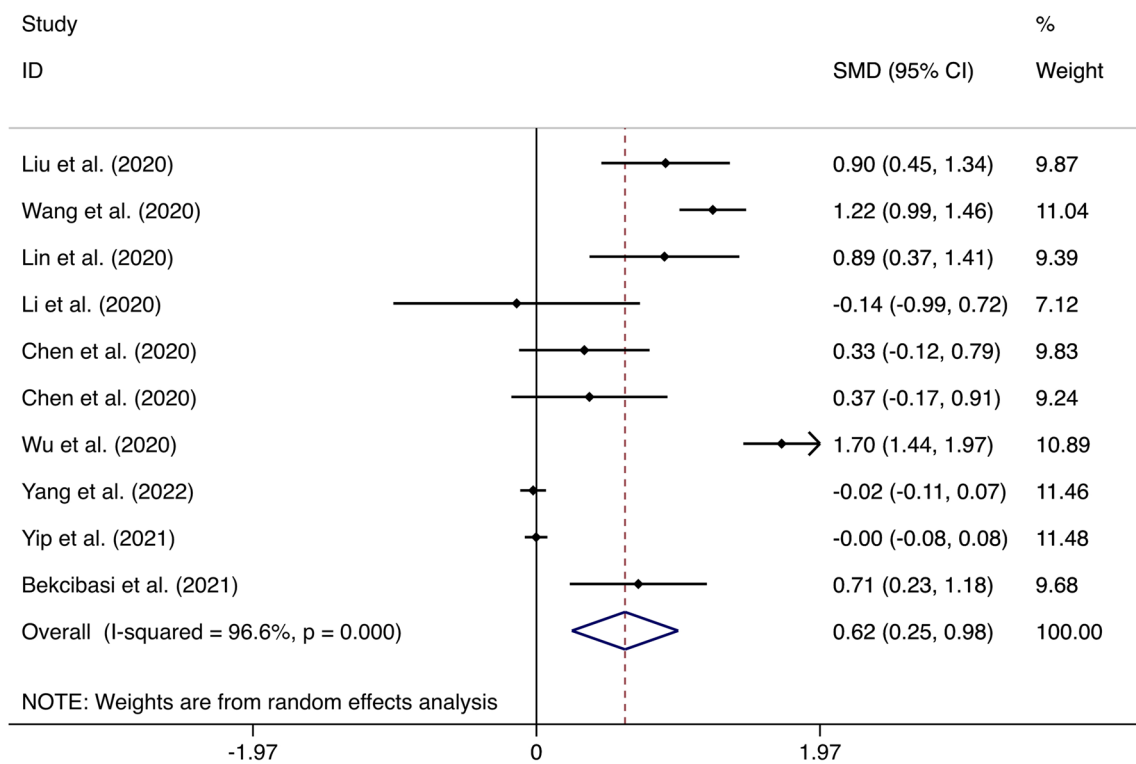
Fig. 4 Forest plot of the effect of hepatitis B virus infection on alanine aminotransferase of COVID-19 patients
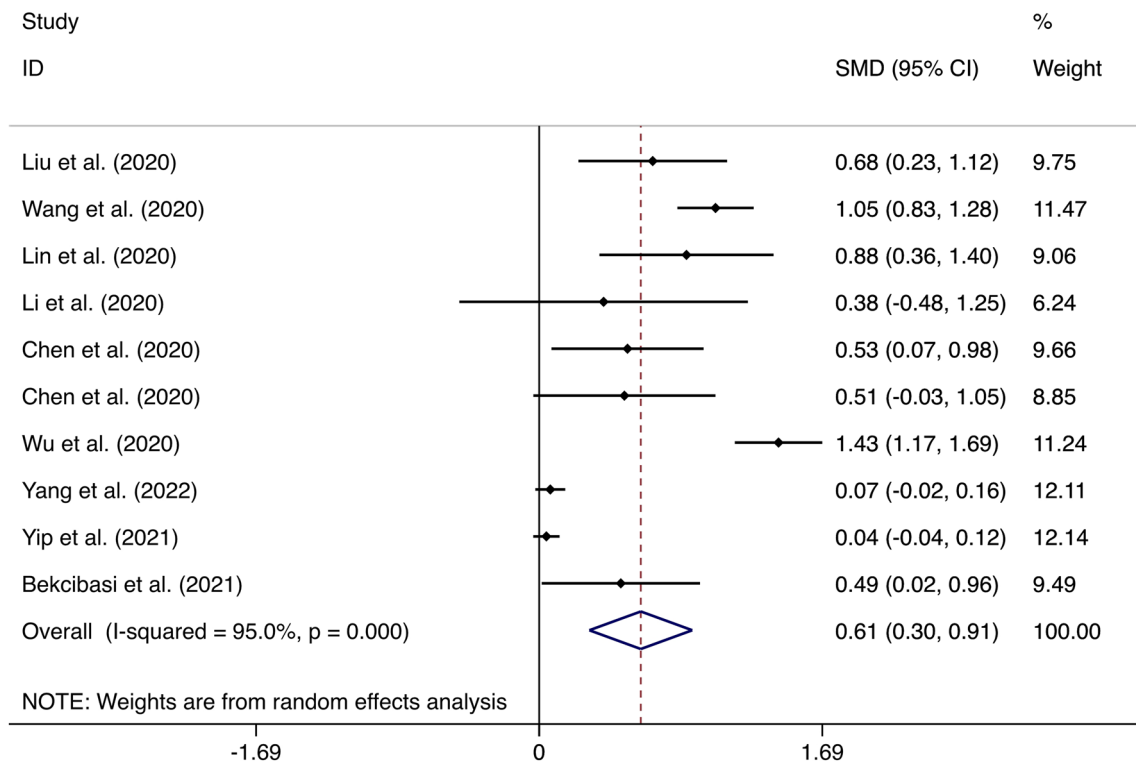
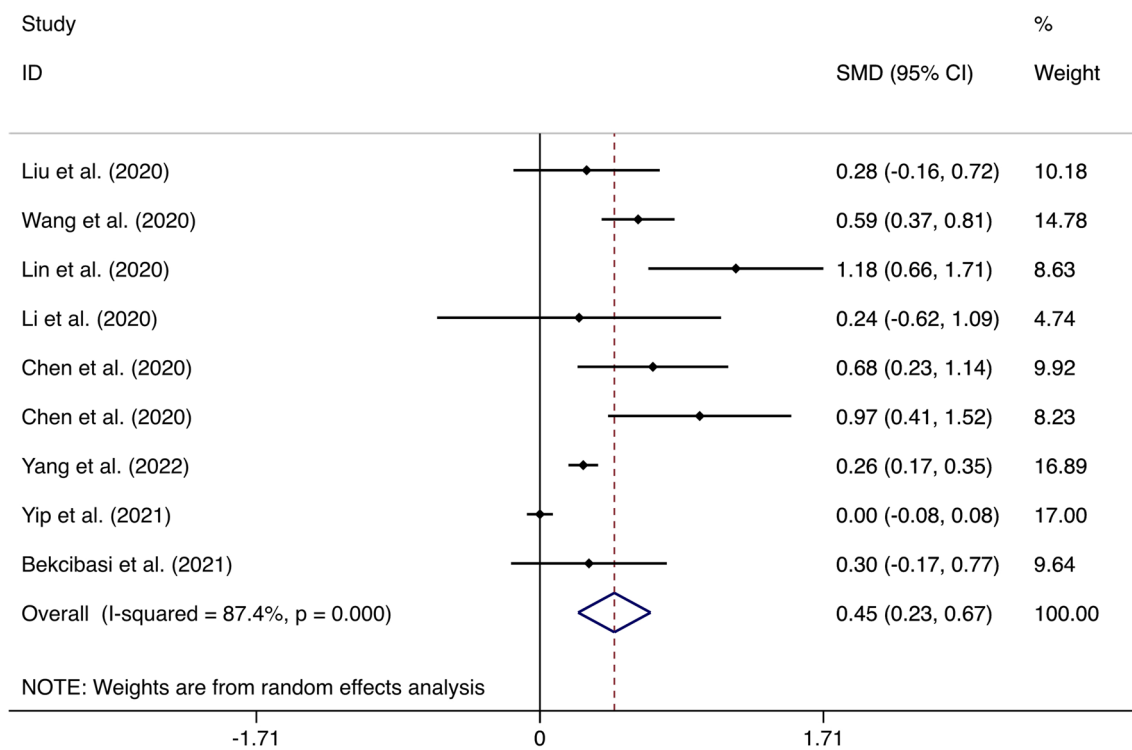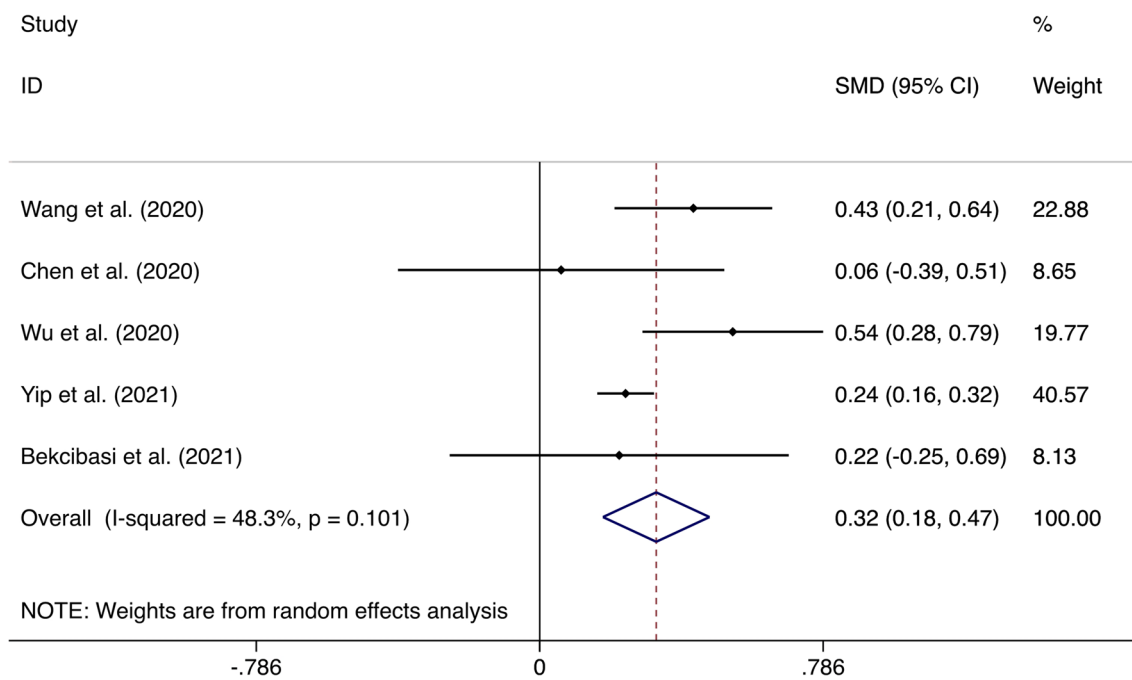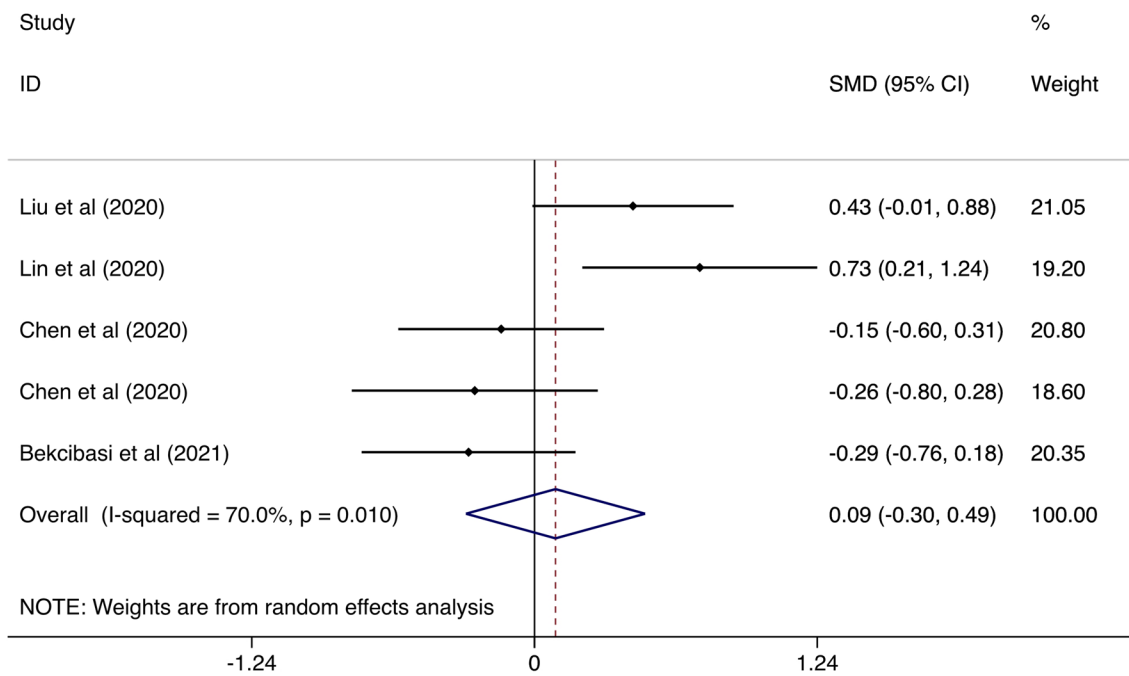**Fig. 5** Forest plot of the effect of hepatitis B virus infection on aspartate aminotransferase of COVID-19 patients
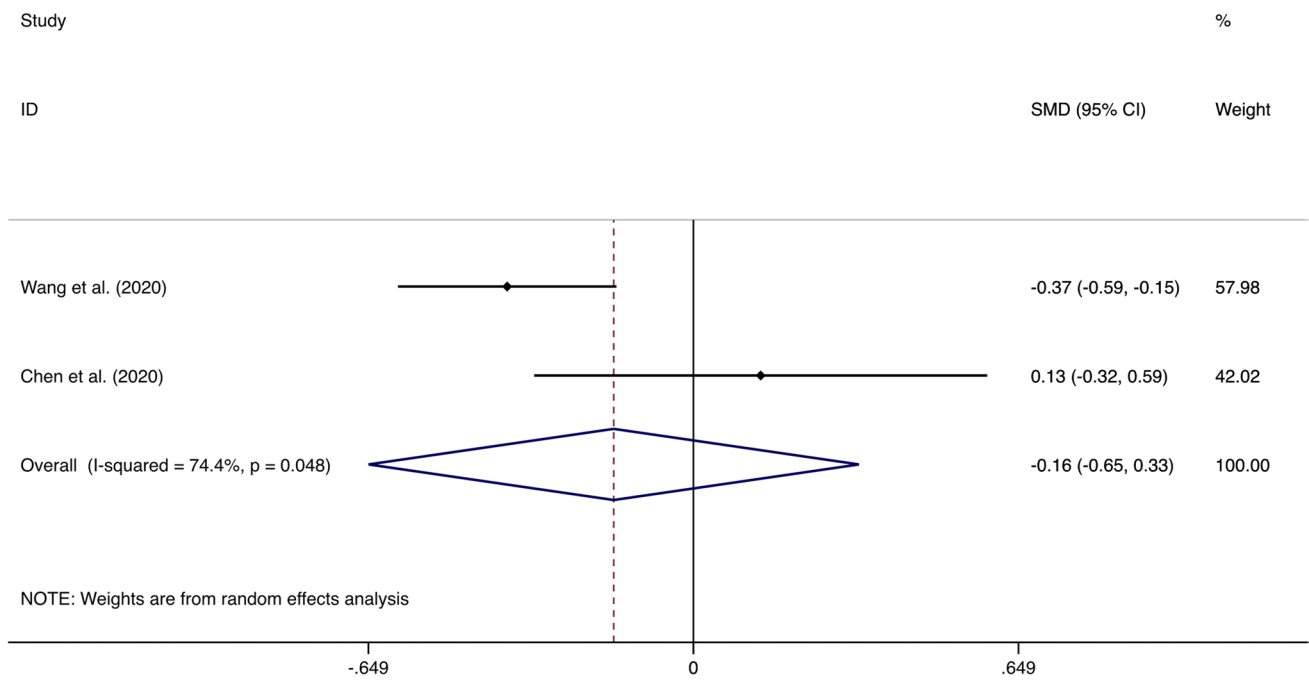
Fig. 6 Forest plot of the effect of hepatitis B virus infection on total bilirubin of COVID-19 patients
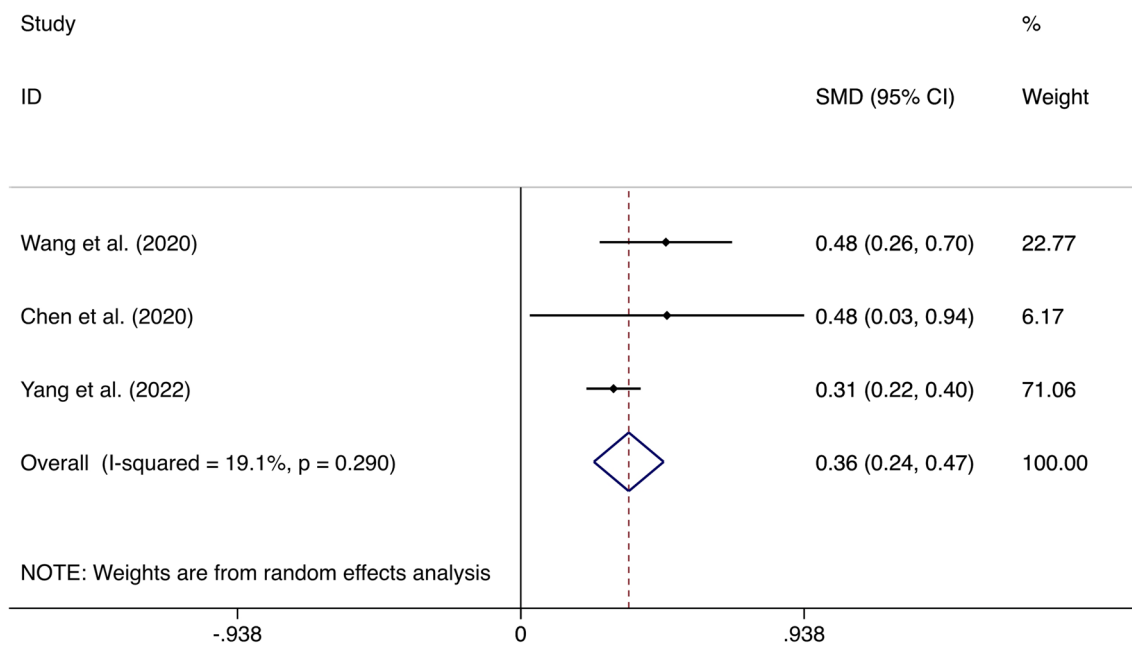
Fig. 7 Forest plot of the effect of hepatitis B virus infection on direct bilirubin of COVID-19 patients

ALT levels indicate a high specificity and a reasonable sensitivity liver injury and are associated with an increased risk of liver-specific mortality [51]. Serum bilirubin levels are good indicators of hepatic synthesis and excretion.

Most well-recognized prognostic models, including the Child–Pugh score and the Model for End-Stage Liver Disease score, take TB as a component, and TB indices are also early and independent predictors of chronic drug-induced

Study		
ID	SMD (95% CI)	% Weight
Wang et al. (2020)	0.43 (0.21, 0.64)	22.88
Chen et al. (2020)	0.06 (-0.39, 0.51)	8.65
Wu et al. (2020)	0.54 (0.28, 0.79)	19.77
Yip et al. (2021)	0.24 (0.16, 0.32)	40.57
Bekcibasi et al. (2021)	0.22 (-0.25, 0.69)	8.13
Overall (I-squared = 48.3%, p = 0.101)	0.32 (0.18, 0.47)	100.00

NOTE: Weights are from random effects analysis

-.786   0   .786

Fig. 8 Forest plot of the effect of hepatitis B virus infection on lactate dehydrogenase of COVID-19 patients

Study		
ID	SMD (95% CI)	% Weight
Wang et al. (2020)	0.19 (-0.02, 0.41)	18.13
Lin et al. (2020)	0.30 (-0.21, 0.81)	8.67
Chen et al. (2020)	0.28 (-0.18, 0.73)	10.02
Chen et al. (2020)	0.45 (-0.09, 1.00)	7.99
Yang et al. (2022)	0.18 (0.09, 0.27)	22.67
Yip et al. (2021)	-0.13 (-0.21, -0.05)	22.94
Bekcibasi et al. (2021)	-0.30 (-0.77, 0.17)	9.58
Overall (I-squared = 82.7%, p = 0.000)	0.11 (-0.08, 0.30)	100.00

NOTE: Weights are from random effects analysis

-.996   0   .996
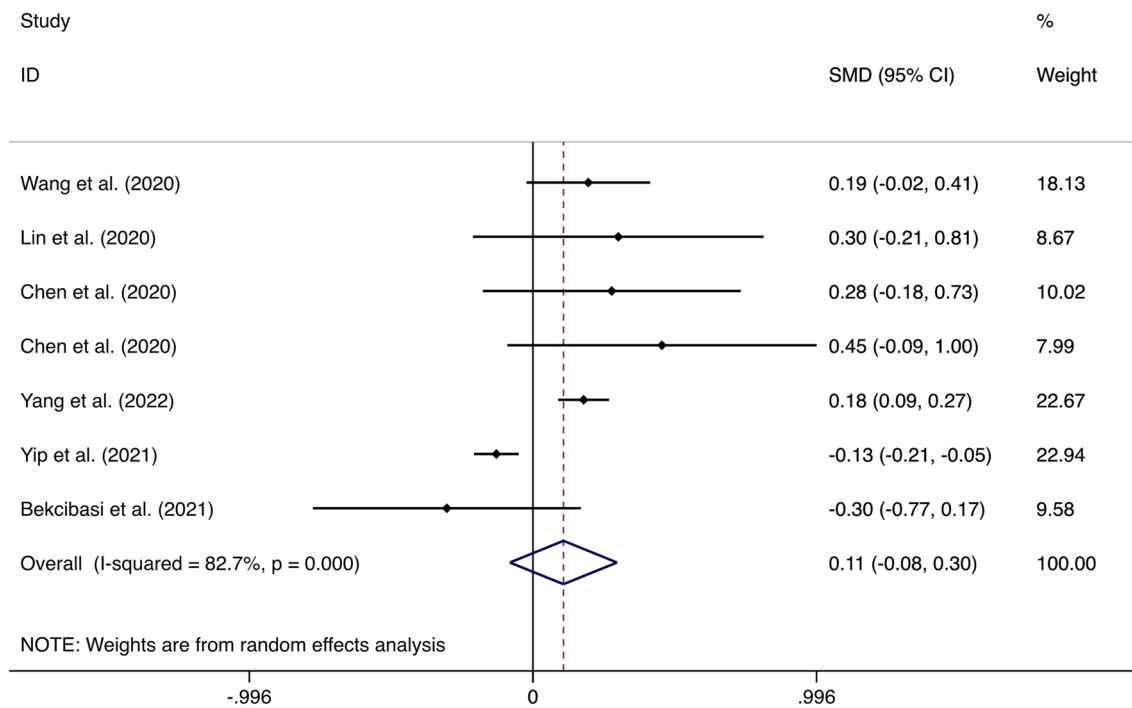
Fig. 9 Forest plot of the effect of hepatitis B virus infection on alkaline phosphatase of COVID-19 patients

liver injury. DB levels can be used to predict 6-month survival in patients with cirrhosis and are better than TB [52, 53]. LDH plays an important role in glucose metabolism by catalyzing the generation of lactate from pyruvate and also regulates the immune response by inducing T-cell activation and enhancing immunosuppressive cells by increasing lactate production. The degree of liver injury can be aggravated with increased LDH levels [54, 55]. Elevated LDH

Study   %

ID   SMD (95% CI)   Weight

Liu et al (2020)   0.43 (-0.01, 0.88)   21.05

Lin et al (2020)   0.73 (0.21, 1.24)   19.20

Chen et al (2020)   -0.15 (-0.60, 0.31)   20.80

Chen et al (2020)   -0.26 (-0.80, 0.28)   18.60

Bekcibasi et al (2021)   -0.29 (-0.76, 0.18)   20.35

Overall (I-squared = 70.0%, p = 0.010)   0.09 (-0.30, 0.49)   100.00

NOTE: Weights are from random effects analysis

-1.24   0   1.24

Fig. 10 Forest plot of the effect of hepatitis B virus infection on gamma-glutamyl transferase of COVID-19 patients

Study   %

ID   SMD (95% CI)   Weight

Wang et al. (2020)   -1.11 (-1.34, -0.88)   14.99

Li et al. (2020)   0.22 (-0.63, 1.08)   5.66

Chen et al. (2020)   -0.37 (-0.83, 0.08)   10.95

Chen et al. (2020)   -0.49 (-1.03, 0.06)   9.45

Wu et al. (2020)   -0.06 (-0.31, 0.18)   14.66

Yang et al. (2022)   -0.04 (-0.13, 0.05)   16.80

Yip et al. (2021)   -0.16 (-0.24, -0.08)   16.88

Bekcibasi et al. (2021)   0.42 (-0.05, 0.89)   10.62

Overall (I-squared = 91.5%, p = 0.000)   -0.24 (-0.49, 0.01)   100.00

NOTE: Weights are from random effects analysis

-1.34   0   1.34
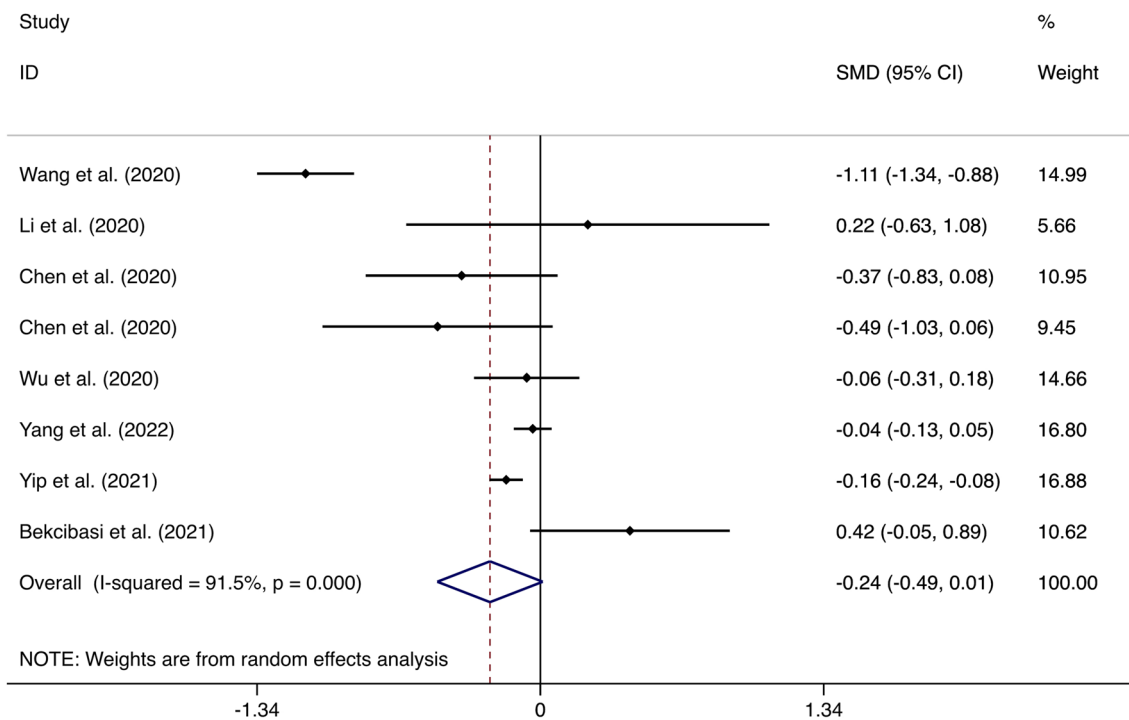
Fig. 11 Forest plot of the effect of hepatitis B virus infection on albumin of COVID-19 patients

has also been reported to be associated with adverse clinical outcomes in patients with SARS and MERS [56, 57].

The impact of the COVID-19 epidemic on hepatitis B is also not negligible. Although quarantine policies and travel restrictions implemented in many countries may reduce the transmission of COVID-19, these initiatives may also lead to an elevated risk of HBV transmission, including reduction in antiviral therapy and increased

Fig. 12 Forest plot of the effect of hepatitis B virus infection on globulin of COVID-19 patients
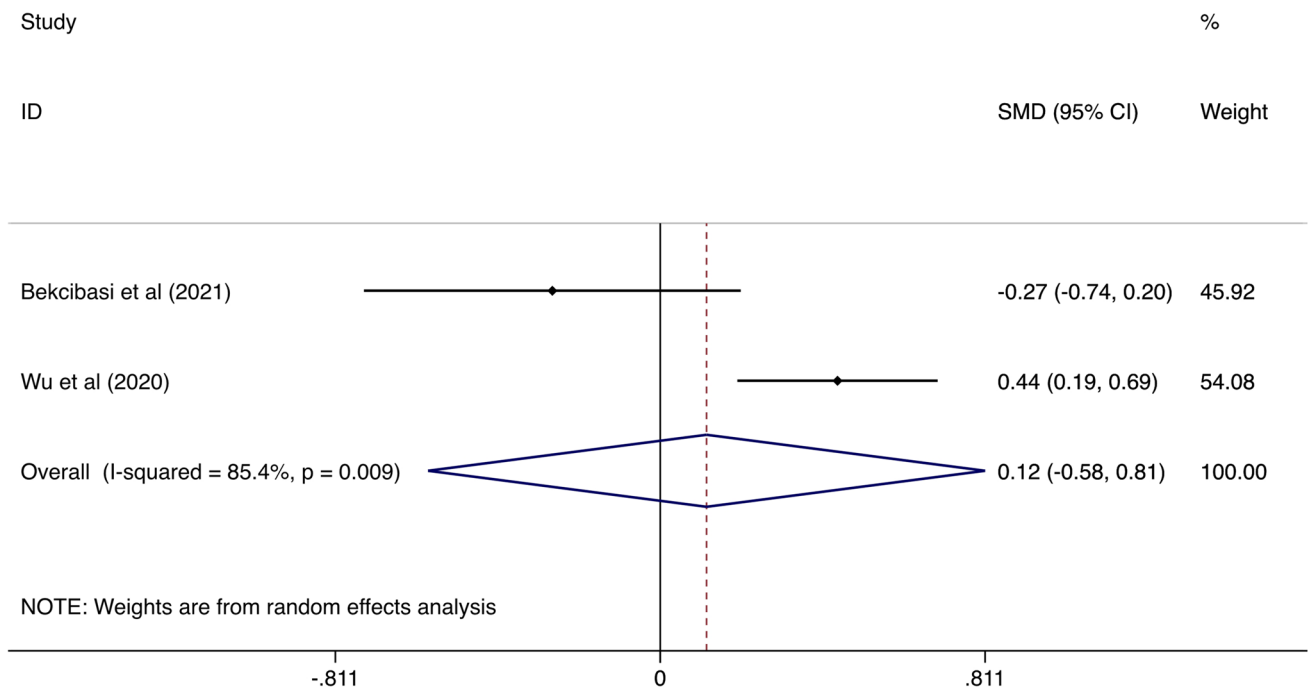
Fig. 13 Forest plot of the effect of hepatitis B virus infection on creatine kinase of COVID-19 patients

home births [58]. Vaccination against hepatitis B is an effective way to prevent transmission of the HBV, but vaccination efforts are highly vulnerable to epidemic outbreaks. During the 2013–2016 Ebola outbreak, vaccination rates in West Africa plummeted, leading to a rapid rebound in measles incidence [59]. In 2016, the World Health Organization (WHO) planned a hepatitis elimination project that aimed to reduce new infections by 90% and reduce hepatitis-related mortality by 65% by 2030. In the city of Dohuk in the Kurdistan Region of
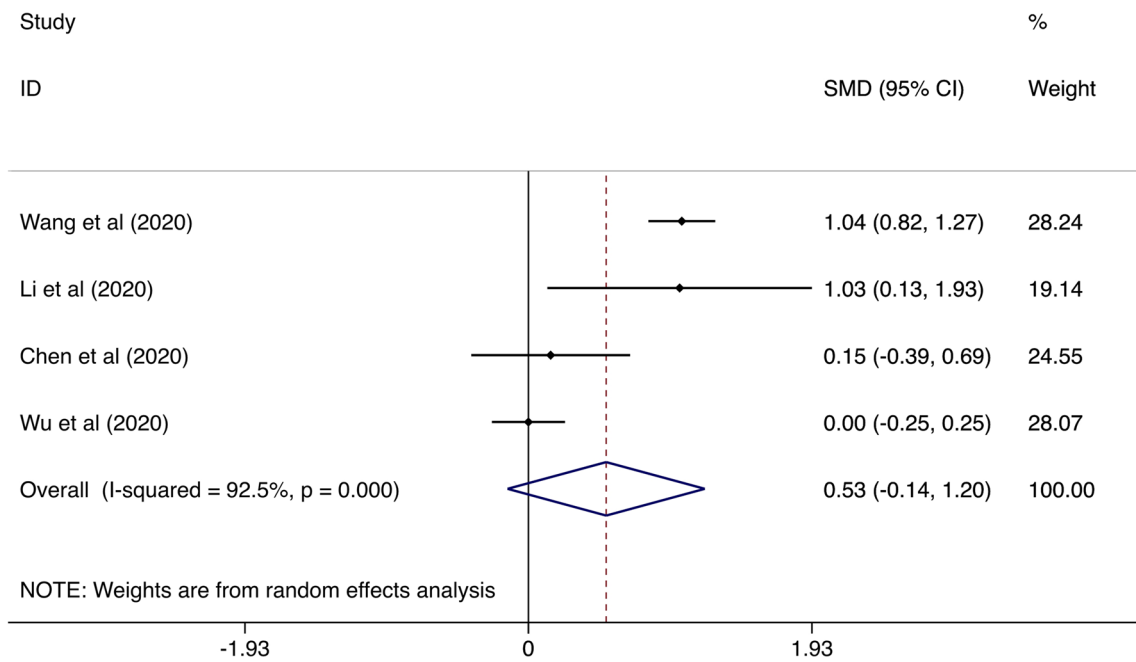
Fig. 14 Forest plot of the effect of hepatitis B virus infection on prothrombin time of COVID-19 patients
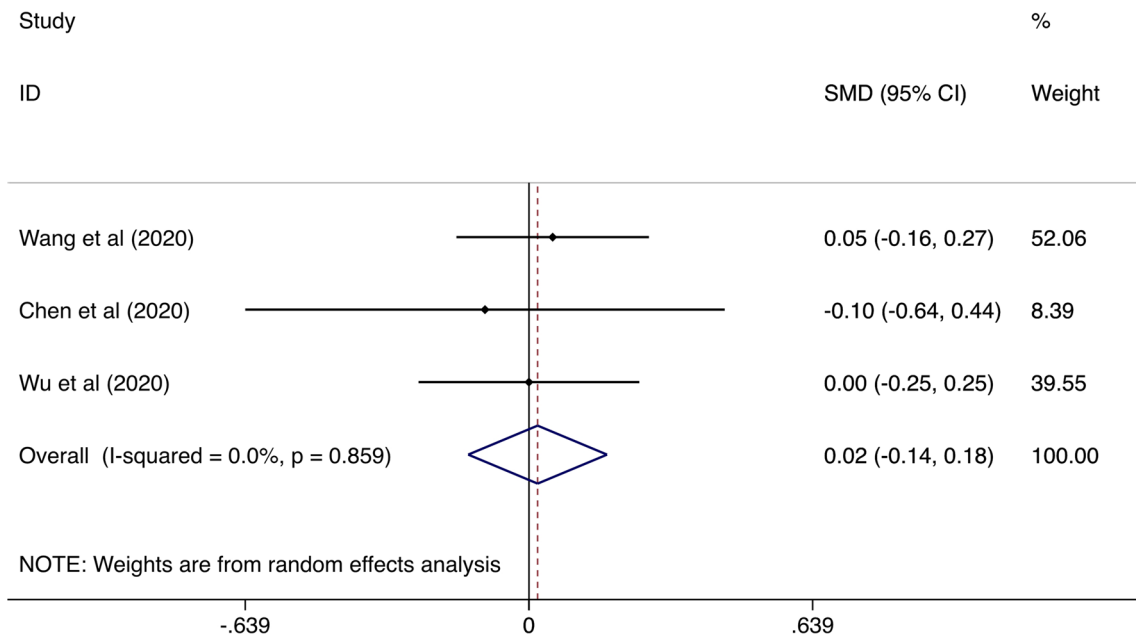
Fig. 15 Forest plot of the effect of hepatitis B virus infection on activated partial thromboplastin time of COVID-19 patients

Iraq, there was a local response to this call. However, the COVID-19 burden and strain on the health system, as well as the impact of social distance requirements and community isolation, forced the discontinuation of the hepatitis elimination program [60]. At the peak of the first wave of the epidemic in Italy, a quarter of the liver wards had been converted to COVID-19 wards, and services in a quarter of the hepatology clinics had been suspended [61]. Situations such as these should be brought to the attention of all countries.

Limitations

The worldwide epidemic of hepatitis B is distinctly regional, concentrated in sub-Saharan Africa and the Asia–Pacific region, and just 20 countries account for more than 75% of global HBV infections [62, 63]. Most studies assessing the effect of hepatitis B on COVID-19 are conducted in Chinese patients because of the high prevalence of HBV infection in China [34]. Therefore, the majority of the literature included in our study also originated from the Chinese region. HBV is divided into nine genotypes, A to I. The HBV genotype in China was mainly genotype B and C, but strongly varies in other parts of the world [64]. Whether the results of this meta-analysis can be applied to HBV patients all over the world needs more global data to verify.

We compared the difference in liver function indices of COVID-19 patients with and without HBV infection. Elevated indices can only suggest the possibility of abnormal liver function but cannot accurately define liver injury.

In this meta-analysis, there were two results with slight publication bias, which might be due to the inclusion of literature with small samples or the authors of the literature preferring positive results when data were included.

Conclusion

Our study showed that COVID-19 patients infected with HBV were more likely to develop severe disease and might have more severe liver function abnormalities than COVID-19 patients not infected with HBV. In-hospital mortality from COVID-19 was higher among patients with HBV infection than those without HBV infection. COVID-19 patients infected with HBV should receive more attention, and special attention should be paid to various liver function indices during treatment.

Declarations

Competing interest The authors report no conflicts of interest.

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