Reviewer #1: The manuscript is a very thorough analysis of the currently existing records of COVID-19 and HBV co-existance. The manuscript presents a magnificent highlighting of the mechanisms involved in the dual-sense interaction of COVID-19 and HBV. Also, the likely causes of bias in the selected studies are clearly stated in the last part of the article. However, a few issues should be corrected in order to improve the reading flow of the article. The changes mentioned further below are mostly not related to the scientific content, but to the structuring and conciseness of the text.

Thank you very much for your hard work on our manuscript. Your suggestions were objective, pertinent, detailed, and professional, such as the comments on reference 54 and the replacement of "liver cell" with "hepatocyte", which is very professional. Here are our responses to your suggestions, with corrections made in the manuscript in the appropriate places, as well as corrections for similar errors that were not pointed out by the reviewers.

* Page 1, line#10 and #33: "And vice versa, does COVID-19 accelerate the progressive course of hepatitis B ..." I advise the authors to keep only one term, either "progression" or "course", as they both hold similar significance in this sentence.

All " the progressive course" have been changed to "the progression".

* Page 2, line#49: A verb is missing in the sentence starting with "The literature search in...". I suggest this to be replaced with "An experienced information specialist searched literature in the following online databases: PubMed, ...".

Corrected to "An experienced information specialist searched literature in the following online databases: PubMed,...".

* Page 2, line#58: I suggest "Some articles included after..." to be replaced with

"Several articles were included after ...".

Corrected to "Several articles were included after ...".

* Page 2, line #66: I suggest replacing "inclusion and exclusion" with "inclusion workflow".

It has been corrected as "inclusion workflow".

* Page 5: I believe that the article - reference number 54 - is not quite relevant for the current review. The sample size is only 19 patients, and despite the fact that there are several selected articles with way less patients, this one - 54 - shows very little significance. There is only one report with HBV among the 19 cases, there are no information regarding biochemistry or outcome; conclusions would therefore rely mostly on observations at admission, and co-infection HBV-COVID-19 biochemical characteristics would not be supported by any quantitative data. A liver-damage-frequency comparison of 19 COVID-19-positive patients against non-COVID-19 patients consists an inadequate sample number, I believe. Furthermore, in the original article by Zhao et al. there is no statistical comparison of COVID-19 and non-COVID-19 patient biochemical profile to support the observed liver profile marker elevations. The conclusions stated in the original article, also, do not bring too much significance to the current review.

This study (Ref. 54) has been excluded. All "58 studies" have been changed to "57 studies", Table 1 and Table 2 were recreated, and the reference sequence numbers between 54 and 61 were shifted forward by one accordingly, and the corresponding reference sequences and the percentage for China in the manuscript were revised. The pie-charts and the relevant proportions of each component have been revised.

* Page 7: Article - reference number 50 - does not bring enough contribution to

the current review, I believe. The original sample of positive COVID-19 patients is not the smallest, yet there is only one case of HBV co-infection among them. Thus, this article can be regarded as a single patient case-report for the current review. I certainly do not suggest it to be removed, but care to be taken when interpreting the results.

We strongly agree with you that this study (Ref. 50) is primarily a study of the relationship between liver injury and severity of COVD-19 and does not focus on the relationship between hepatitis B and COVID-19, which is exactly what we have mentioned in the limitations. In this study, there was only one case of co-infection with hepatitis B and there is no clear description about the regression of this one patient, so extra caution should be taken in the interpretation of this study. Fortunately, this study was not supported as an independent argument in our review.

* Page 12: Several spacings are missing.

Spaces have been added where needed. (Some of the missing spaces may be due to file downloads)

* Page 13, line#81: Please delete the unnecessary rows and bring the numbering "1." in the same row as "Results and interpretations".

Unnecessary rows have been removed. (This may be caused by inserting Tables)

* Page 13, line#85: The term "blood picture" is not clear. Please replace with "blood parameters" or "serum liver enzyme profile" or similar.

Corrected to "blood parameters".

* Page 13, line#90: I suggest adding a dash between the words "liver transplant", since they are immediately followed by "patients".

Corrected to "liver-transplant".

* Page 13, Figure 2 title. Please rephrase the figure title, as it is now misleading. I suggest using "Pie-chart distribution by country of the 58 included studies" or similar.

The title of Figure 2 has been changed to "Pie-chart distribution by country of the 57 included studies".

* Page 14, line #120: Please add a short phrase regarding the use frequency and benefit of corticosteroid therapy in COVID-19.

Sentence "Corticosteroids have been widely used to treat and benefit COVID-19[70]." has been added.

* Page 14, line#129: Please define the acronym "ALB". Please also remove the definition from page 18, line#284. *

All "ALB" in the manuscript have been replaced with "albumin".

Page 14, line#131: Please replace "liver cell" with "hepatocyte".

We have replaced "liver cell" with "hepatocyte".

* Page 14, line#134: I suggest replacing "recovery" with "resolution".

We have replaced "recovery" with "resolution".

* Page 15, line#140: I strongly advise adding a short piece of text regarding a more thorough explanation regarding the mechanism of thrombocytopenia in COVID-19 patients, using the same reference.

We have added a short piece of text regarding a more thorough explanation regarding the mechanism of thrombocytopenia in COVID-19 patients.

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.

* Page 15, line#161: Please rephrase "Older men with severe comorbidities are also considered as risk factors for HBV reactivation" with "Age, male sex and severe comorbidities are considered risk factors for HBV reactivation" or similar. Also, please describe and denote which severe comorbidities are regarded as risk factors.

Corrected to "Age, male sex and severe complications (such as hypertension, diabetes, hypercholesterolemia and chronic kidney disease) are considered risk factors for HBV reactivation."

"Severe comorbidities" in the original text refers to "hypertension, diabetes mellitus, hypercholesterolemia and chronic kidney disease".

* Page 16, line#182: Please disclose "higher percentages" compared to what? Previous marker elevations are way above bilirubin total level.

The ambiguity here was caused by the difference in expression between Chinese and English. Corrected to "..., and several studies have reported elevated total bilirubin (5.1% to 11.5%)..."

* Page 16, line#189: I advise adding some information regarding clinical correlation of NT-proBNP with patients' prognosis.

We have added the following information regarding clinical correlation of NT-proBNP with patients' prognosis and added 3 references (Ref.93-95).

Among these, several studies have confirmed that NT-proBNP is strongly and independently associated with mortality in COVID-19 patients.

* Page 17, line#240: I suspect "junction" should be replaced with "function", otherwise the sentence is misleading.

We wanted to express that "D-dimer has also been found in COVID-19 patients to be associated with poor outcome and abnormally dysregulated in CHB patients". The word "junction" has been changed to "outcome".

* Page 18, line#263: I recommend replacing "been reported to the contrary that the incidence" with "been reported the contrary - that is, the incidence ...".

We have replaced "been reported to the contrary that the incidence" with "been reported the contrary - that is, the incidence ...".

* Page 20, line #363: Please state which gender has been associated with higher risk.

The word "gender" has been changed to "male".

* Page 20, line#375: Please use a synonym of inhibit, instead of "improving", such as "interfere with.

Here, we are trying to express the ability of nucleoside analogues to improve hepatic histological lesions.

* Page 21, line#390: I recommend replacing "lack of continuous" with "discontinuation of".

We have replaced "lack of continuous" with "discontinuation of".

A Word Document of the original manuscript will be attached, for the authors to easily follow the mentioned changes.

Thanks again for all your hard work!

References (Follow the sequence in the manuscript)

[80] **Lefrançais E**, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, Thornton EE, Headley MB, David T, Coughlin SR, Krummel MF, Leavitt AD, Passegué E, Looney MR. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature. 2017-04-06;544(7648):105-109. PMID: 28329764. DOI: 10.1038/nature21706.

[81] **Amgalan A**, Othman M. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. J Thromb Haemost. 2020-06-01;18(6):1514-1516. PMID: 32278338. DOI: 10.1111/jth.14832.

[82] **Hottz ED**, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pão CRR, Righy C, Franco S, Souza TML, Kurtz P, Bozza FA, Bozza PT. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood. 2020-09-10;136(11):1330-1341. PMID: 32678428. DOI: 10.1182/blood.2020007252.

[70] **World Health Organization.** Corticosteroids for COVID-19. In: WorldHealth Organization [Internet]. Available from: https://apps.who.int/Home/News/Listings of WHO's response to COVID-19.

[93] **Caro-Codón J**, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S, Rodriguez-Sotelo L, Martinez LA, Marco I, Merino C, Martin-Polo L, Garcia-Veas JM, Martinez-Cossiani M, Gonzalez-Valle L, Herrero A, López-de-Sa E, Merino JL, CARD-COVID Investigators.

Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail. 2021-03-01;23(3):456-464. PMID: 33421281. DOI: 10.1002/ejhf.2095.

[94] **Belarte-Tornero LC**, Valdivielso-Moré S, Vicente Elcano M, Solé-González E, Ruíz-Bustillo S, Calvo-Fernández A, Subinara I, Cabero P, Soler C, Cubero-Gallego H, Vaquerizo B, Farré N. Prognostic Implications of Chronic Heart Failure and Utility of NT-proBNP Levels in Heart Failure Patients with SARS-CoV-2 Infection. J Clin Med. 2021-01-17;10(323)1-14. PMID: 33477268. DOI: 10.3390/jcm10020323.

[95] **Weng H**, Yang F, Zhang L, Jin H, Liu S, Fan F, Liu Z, Zheng X, Yang H, Li Y, Yi T, Li H, Zhang Y, Li J. Joint Predictive Value of cTnI and NT-proBNP on Mortality in Patients with Coronavirus Disease 2019: A Retrospective Research in Wuhan, China. J Transl Intern Med. 2021-09-28;9(3):177-184. PMID: 34900628. DOI: 10.2478/jtim-2021-0034.

Reviewer #2:

Thank you very much for your hard work on our manuscript. Your suggestions are very professional, and here are our point-by-point answers against your suggestions.

1) Change the title to Systematic review.

We have changed the title of the review to "CORRELATION BETWEEN COVID-19 AND HBV: A SYSTEMATIC REVIEW".

2) Provide PRISMA checklist and register this systematic review in PROSPERO systematic review database.

We have registered this review in PROSPERO systematic review database (https://www.crd.york.ac.uk/prospero/#recordDetails), and have submitted PRISMA checklist.

3) Usually incidence rate of mortality or event is calculated every year but the authors have collected the data of more than 2 years. Please justify this.

Thank you for your very professional comments. It is true that human mortality is usually expressed in terms of per thousand people per year. Here I would like to answer you in two parts. First, regarding the 'Outcomes: Death(n,%)' in Table 1 or Table 2, it is only the number of deaths and the percentage of the target number (co-infected), which we want to use as a simple visualization of the interaction between COVID-19 and hepatitis B. In a general sense, the greater the percentage of deaths, the greater the interaction between COVID-19 and hepatitis B. Of course, here it is also influenced by many factors, such as the small number of sample cases (there are many case reports) the focus of the study is not on hepatitis B patients, etc., which we have mentioned in the limitations. Therefore the percentages here are not limited by time span, and the time span of our included literature is December 2019 to September 2022. Second, regarding the mortality rates in the manuscript, whether it is the effect of hepatitis B on COVID-19 or COVID-19 on hepatitis B, the mortality rates therein are direct quotes from the original literature.

4) I would suggest to place the table 1 in supplementary data section and prepare a table on Total number of studies, Total number of patients, co-infection, Outcome (mortality, survivability), complications, Various drugs used for COVID-19 or HBV infections.

We have created a new, more generalized table (Table 1) based on your suggestions, placed the details of some entries in Table 2 as supplementary data, and added the two entries you provided for "Complications" and "Drug treatment" (see red content in Table 2). Because many studies did not give complications, we have included complications or comorbidities in the table.

5) Double check if studies are entered as duplicates in Table 1.

We have checked again the literature included in Table 1 one by one and there were no duplicates, two studies (Ref.[2] & Ref.[7]) had the same first author, but not the same study.

Table 1 Characteristics of included studies

First author [reference number]	Site	Sample size (n)	No. of Patients With HBV (n,%)	Major serum biochemical characteristics of co-infected patients	Outcomes Death (n,%)	Survival (n,%)
Guan WJ [53]	China	1590	28 (1.8)	NR	1 (3.6)	27 (96.4)
Zou X [2]	China	93	93 (100.0)	Abnormal liver function	7 (7.5)	86 (92.5)
Song SH [47]	China	4	2 (50.0)	Abnormal blood parameters	0 (0.0)	2 (100.0)
Qi X [10]	China	3	1 (33.3)	Abnormal liver enzyme	1 (100)	0 (0.0)
Hambali NL [11]	Malaysia	1	1 (100.0)	Abnormal liver enzyme	0 (0.0)	1 (100.0)
Ali E [12]	Qatar	1	1 (100.0)	Elevated liver enzymes	1 (100)	0 (0.0)
Zha L [13]	China	31	2 (6.5)	Elevated liver enzymes	0 (0.0)	2 (100.0)
Cai Q [14]	China	298	5 (1.7)	Elevated liver enzymes	NR	NR
Naderi M [15]	Iran	93[a]	13[b] (13.8)	Elevated liver enzymes	0 (0.0)	13 (100.0)
Yip TC [16]	Hong Kong SAR, China	5639	353[c] (6.3)	ALT abnormality	8 (2.3)	345 (97.7)
Richardson S [17]	USA	5700	8 (0.1)	Elevated liver enzymes	NA	NA
Kang SH [54]	Korea	7723	267 (3.5)	NR	12（5.1）	255 (94.9)
Li Y [18]	China	7	7 (100.0)	Elevated liver enzymes	0 (0.0)	7 (100.0)
Chen X [9]	China	123	15 (12.2)	Abnormal	2（13.3）	13 (86.7)

				liver enzyme		
Bongiovanni M [19]	Italy	1	1 (100.0)	Liver enzymes increased	0 (0.0)	1 (100.0)
He Q [20]	China	571	15 (2.6)	Liver enzymes increased	0 (0.0)	15 (100.0)
Wen M [21]	China	110	5 (4.5)	Abnormal liver enzyme	NA	NA
Zou X [7]	China	105	105 (100.0)	Liver enzymes increased	98 (93.3)	7 (6.7)
Wang J [8]	China	436	109 (25.0)	Abnormal liver enzyme system	13 (11.93)	96 (88.1)
Chen L [5]	China	326	20 (6.1)	Lower level of prealbumin	0 (0.0)	20 (100.0)
Zhang B [22]	China	23	23 (100.0)	Liver enzymes increased	0 (0.0)	23 (100.0)
Liu R [48]	China	220	50 (22.7)	Abnormal blood parameters	4 (8)	46 (92.0)
Yu R [6]	China	67	7 (10.4)	No significant change	0 (0.0)	7 (100.0)
Liu J [23]	China	71[d]	20[d] (28.2)	Abnormal liver enzyme system	0 (0.0)	20 (100.0)
Lin Y [24]	China	133	17 (12.8)	Liver enzymes increased	NR	NR
Bekçibaşı M	Turkey	156	20 (12.8)	Liver	0 (0.0)	20 (100.0)

[25]				enzymes increased		
Colaneri M [26]	Italy	1	1 (100.0)	Liver enzymes increased	0 (0.0)	1 (100.0)
Ma GG [50]	China	109	1 (0.9)	Normal liver enzymes	NA	NA
Chen T [27]	China	274	11 (4.0)	Abnormal liver function	5 (45.5)	6 (54.5)
Ding ZY [28]	China	2073	134 (6.5)	Liver enzymes increased	8 (6.0)	126 (94.0)
Rodríguez-Tajes S [29]	Spain	484	72 (14.9)	Liver enzymes increased	8 (11.1)	64 (88.9)
Parlar Y [51]	Turkey	479[e]	43[b] (9.0)	No significant change	0 (0.0)	43 (100.0)
Yang S [30]	China	2899	105 (3.6)	Liver enzymes increased	18 (17.1)	87 (82.9)
Yigit Y [31]	Qatar	1	1 (100.0)	Liver enzymes increased	1 (100)	0 (0.0)
Aldhaleei WA [32]	United Arab Emirates	1	1 (100.0)	Liver enzymes increased	0 (0.0)	1 (100.0)
Ji D [33]	China	140	7 (5.0)	Liver enzymes increased	0 (0.0)	7 (100.0)
Kim D [34]	USA	867	62 (7.2)	Liver enzymes increased	5 (8.1)	57 (91.9)

Wang H [35]	China	1	1 (100.0)	Abnormal liver enzyme system.	0 (0.0)	1 (100.0)
Zhong Z [36]	China	2	1 (50.0)	Liver enzymes increased	0 (0.0)	1 (100.0)
Fernández-Ruiz M [49]	Spain	18	2 (11.1)	Decreased white blood cells	1 (50.0)	1 (50.0)
Huang JF [37]	China	1	1 (100.0)	Elevated total bilirubin	1 (100)	0 (0.0)
Patrono D [55]	Italy	10	2 (20.0)	NR	0 (0.0)	2 (100.0)
Qin J [38]	China	1	1 (100.0)	Abnormal liver enzyme system	0 (0.0)	1 (100.0)
Liu B [56]	China	1	1 (100.0)	NR	0 (0.0)	1 (100.0)
Loinaz C [39]	Spain	19	4 (21.1)	Abnormal liver enzyme system	1 (25.0)	3 (75.0)
Adali G [40]	Turkey	231	77 (33.3)	Abnormal liver enzyme system	6 (7.8)	71 (92.2)
Oruç Z [57]	Turkey	92	4 (4.3)	NR	0 (0.0)	4 (100.0)
Guardigni V [58]	Italy	606	12 (2.0)	NR	NA	NA
Sagnelli C [41]	Italy	1	1 (100.0)	Liver enzymes increased	1 (100)	0 (0.0)
Lens S [59]	Spain	1764[e]	9[b] (0.5)	NR	0 (0.0)	9 (100.0)
Phipps MM [42]	USA	2273	15 (0.7)	Abnormal liver enzyme system	NA	NA

Li L [52]	China	85	2 (2.4)	Normal liver enzymes	0 (0.0)	2 (100.0)
Wu YF [43]	China	1	1 (100.0)	Elevated liver enzyme	0 (0.0)	1 (100.0)
Wu J [44]	China	620	70 (11.3)	Elevated liver enzymes	0 (0.0)	70 (100.0)
Iavarone M [45]	Italy	50	5 (10.0)	Elevated liver enzymes	NA	NA
Marjot T [60]	United Kingdom	745	96 (12.9)	NR	23 (24.0)	73 (76.0)
Huang SP [46]	China	1	1 (100.0)	Elevated liver enzymes	0 (0.0)	1 (100.0)
Total	57	37375	1932			

Notes: [a]93 cases were the sample size of the experimental group and the other healthy control group was 62 cases. 93 cases were all CHB patients. [b]Patients with HBV co-infection with SARS-CoV-2. [c]The 353 cases were patients with current co-infection with HBV, and another 359 patients with past infection with HBV were not included. [d]Sample size after PSM. [e]All were CHB patients. No.: Number; NA: Data not available; NR: Data not reported; COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HBV: Hepatitis B virus; CHB: Chronic hepatitis B; PSM: Propensity score matching; ALT: Alanine aminotransferase.

Table 2 Details of the included studies and related parameters

First author [reference number]	Accessed Date	Site	Study design	Sample size (n)	No. of Patients With HBV (n,%)	Major serum biochemical characteristics of co-infected patients	Outcomes Death (n,%)	Survival (n,%)	Complications/ Comorbidities	Representative drugs used for treatment	Study notes
Guan WJ [53]	May, 2020	China	Multicenter retrospective study	1590	28 (1.8)	NR	1 (3.6)	27 (96.4)	COPD, diabetes, hypertension, cardiovascular disease, cerebrovascular disease	NR	Patients with comorbidities comorbidity yielded poorer clinical outcomes than those without.

Zou X [2]	August, 2020	China	Retrospective study	93	93 (100.0)	Most of the patients had different degrees of abnormal liver function.	7 (7.5)	86 (92.5)	Acute respiratory distress syndrome, acute-on-chronic liver failure, acute myocardial injury, acute renal insufficiency, septic shock	Nucleoside drugs	Abnormal liver function is common in patients with CHB and COVID-19.
Song SH [47]	July, 2020	China	Case series	4	2 (50.0)	Decrease in lymphocytes including total $CD3^+$ T cells, B cells, and natural killer cells.	0 (0.0)	2 (100.0)	COPD, hypertension, cardiovascular disease	Oseltamivir, caspofungin, and moxifloxacin	The treatment of SARS-CoV-2 infection in cancer patients is challenged by the immunosup

											pressive state of these patients under chemotherapy or surgery.
Qi X [10]	July, 2020	China	Case series	3	1 (33.3)	Liver enzyme system was mildly elevated.	1 (100)	0 (0.0)	Bacterial pneumonia, fungal pneumonia, pleural effusion, ascites, melaena, acute on chronic liver failure, acute kidney injury, shock, ARDS	Antiviral and antibiotic treatment	Decompensated cirrhosis may be a risk factor for poor prognosis in COVID-19 patients.
Hambali NL [11]	November, 2020	Malaysia	Case report	1	1 (100.	The liver enzyme	0 (0.0)	1 (100.	Ascites due to cirrhosis	Spironolactone and tenofovir	The elevated IL-6 level in

					0)	system was elevated and the level of interleukin 6 was very high.	0)				a COVID-19 patient is not necessarily associated with severe COVID-19.
Ali E [12]	October, 2020	Qatar	Case report	1	1 (100.0)	The liver enzyme system was elevated.	1 (100)	0 (0.0)	Multiorgan failure, acute liver failure, acute renal failure, and disseminated intravascular coagulation	NR	It is uncommon for SARS-CoV-2 infection with mild respiratory symptoms to result in severe systemic disease and organ failure.

Zha L [13]	May, 2021	China	Multicenter retrospective study	31	2 (6.5)	The liver enzyme system was elevated.	0 (0.0)	2 (100.0)	Hypertension, diabetes, coronary heart disease	Corticosteroid, lopinavir/ritonavir	The virus clearance was slower in two patients with chronic hepatitis B infections.
Cai Q [14]	July, 2020	China	Retrospective study	298	5 (1.7)	The serum biochemical indexes of the liver were significantly increased.	NR	NR	Hypertension, diabetes, coronary heart disease, cancer.	Lopinavir/ritonavir and favipiravir	Those having higher IL-6 levels were more likely to progress to severe COVID-19.
Naderi M [15]	July, 2021	Iran	Retrospective study	93[a]	13[b] (13.8)	The liver enzyme system was significantly elevated.	0 (0.0)	13 (100.0)	NR	Hydroxychloroquine, hydroxychloroquine, antibiotic, tenofovir, and entecavir	CHB infection did not predispose COVID-19

											patients to more severe outcomes and antiviral agents decreased susceptibility to COVID-19 infection.
Yip TC [16]	October, 2021	Hong Kong SAR, China	Retrospective cohort study	5639	353[c] (6.3)	ALT abnormality	8 (2.3)	345 (97.7)	Circulatory system disease, diabetes, malignant tumor, nervous system disease, respiratory disease,	Antibiotics, antifungal agents, corticosteroid, and entecavir	Current or past HBV infections were not associated with more liver injury and mortality in COVID-19.

									kidney disease		
Richardson S [17]	May, 2020	USA	Multicenter retrospective study	5700	8 (0.1)	Elevated liver enzymes	NA	NA	Hypertension, obesity, diabetes, coronary artery disease, kidney disease	Angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker	Abnormal liver function is common in patients with COVID-19 and hepatitis B.
Kang SH [54]	October, 2021	Korea	Cohort study	7723	267 (3.5)	NR	12（5.1）	255 (94.9)	Hypertension, diabetes, liver cirrhosis	Adefovir, entecavir, tenofovir	HBV co-infection did not increase the risk of disease severity in COVID-19. Antiviral agents

											decreased susceptibility to SARS-CoV-2 infection.
Li Y [18]	November, 2020	China	Case series	7	7 (100.0)	Elevated liver enzyme system and decreased albumin	0 (0.0)	7 (100.0)	None	Lopinavir/ritonavir, atomized inhalation of interferon α-2b, arbidol	No patient developed severe liver-related complications during hospitalization.
Chen X [9]	December, 2020	China	Retrospective study	123	15 (12.2)	Elevated total bilirubin and decreased lymphocytes	2 （13.3）	13 (86.7)	Hypertension, cardiovascular disease, diabetes, malignancy, COPD, liver cirrhosis	Arbidol and/or lopinavir, antibiotic, corticosteroid	HBV patients would suffer from more severe situation during the disease

											progress when they were encountered with SARS-CoV-2 infection.
Bongiovanni M [19]	January, 2021	Italy	Case report	1	1 (100.0)	Liver enzymes increased	0 (0.0)	1 (100.0)	None	NR	The prognosis of COVID-19 appears to be worse in patients with preexisting liver disease.
He Q [20]	February, 2021	China	Multicenter retrospective study	571	15 (2.6)	Liver enzymes increased	0 (0.0)	15 (100.0)	NR	Entecavir	Patients with preexisting HBV infection may have a lower

										incidence of admission to the intensive care unit or death.
Wen M [21]	March, 2020	China	Retrospective study	110	5 (4.5)	Liver enzymes increased and albumin decreased	NA	NA	Hypertension, cardiovascular disease, diabetes, coronary heart disease	NR	No synergistic effect of HBV and SARS-CoV-2 on hepatocyte injury.
Zou X [7]	March, 2021	China	Retrospective study	105	105 (100.0)	Significantly elevated liver enzyme levels	98 (93.3)	7 (6.7)	Diabetes, hypertension, coronary heart disease	Arbidol, lopinavir/ritonavir, interferon, ribavirin, antibiotic, methylprednisolone	Liver injury in patients with SARS-CoV-2 and chronic HBV co-infection was

										associated with severity and poor prognosis of disease.
Wang J [8]	February, 2022	China	Multicenter retrospective study	436	109 (25.0)	The serum levels of inflammatory cytokines and liver enzyme system were significantly elevated.	13 (11.93)	96 (88.1)	Disseminated intravascular coagulation	Immunoglobulin, antibiotic, antiviral agents	COVID-19 patients with CHB were more likely to develop into severe illness and die.
Chen L [5]	December, 2020	China	Retrospective study	326	20 (6.1)	Lower level of prealbumin	0 (0.0)	20 (100.0)	NR	NR	No evidence was found that SARS-CoV-2/HBV

											co-infection could aggravate liver injury or extend duration of hospitalization.
Zhang B [22]	October, 2020	China	Multicenter retrospective study	23	23 (100.0)	Liver enzymes increased	0 (0.0)	23 (100.0)	Obesity, COPD, hypertension, ARDS, deep venous thrombosis	Antibiotics, herbal medicine, glucocorticoid	Dynamic monitoring of liver function should be performed in patients with COVID-19 who have abnormal liver tests on admission.

Liu R [48]	April, 2021	China	Retrospective study	220	50 (22.7)	More severe monocytopenia and thrombocytopenia.	4 (8)	46 (92.0)	Diabetes, cardiovascular diseases, hypertension cerebral infarction, malignancy	Chloroquine, arbidol, traditional Chinese medicine, oseltamivir, ribavirin	Chronic HBV infection did not predispose COVID-19 patients to more severe outcomes.However, co-infection with SARS-CoV-2 and HBV leads to a higher degree of host dysfunction.
Yu R [6]	January, 2021	China	Retrospective	67	7 (10.4)	Changes in liver	0 (0.0)	7 (100.	Pulmonary disease,	lopinavir/ritonavir	Effects of SARS-CoV-2

			study			function were not significant.		0)	diabetes, hypertension	on the dynamics of chronic HBV infection seemed not apparent. Those COVID-19 patients co-infected with chronic HBV could have a risk of hepatitis B reactivation. SARS-CoV-2 and HBV co-infection exacerbates liver function of
Liu J [23]	November, 2020	China	Retrospective study	71[d]	20[d] (28.2)	Abnormal liver enzyme system	0 (0.0)	20 (100.0)	Diabetes, hypertension, cardiovascular disease, cancer	Methylprednisolone and antiviral agents
Lin Y [24]	July,2021	China	Retrospective study	133	17 (12.8)	Liver enzymes increased	NR	NR	None	Arbidol, lopinavir/ritonavir, interferon, antibiotic, methylprednisolone

											the patients with COVID-19.
Bekçibaşı [25]	M	September, 2021	Turkey	Retrospective study	156	20 (12.8)	The liver enzyme system was elevated, and creatine kinase levels were significantly elevated.	0 (0.0)	20 (100.0)	NR	Antiviral agents	SARS-CoV-2/HBV co-infection did not change the severity and outcome of COVID-19.
Colaneri [26]	M	November, 2020	Italy	Case report	1	1 (100.0)	Liver enzymes increased	0 (0.0)	1 (100.0)	None	Hemoperfusion [f]	Hemoperfusion may be an alternative treatment for SARS-COV-2 co-infection

										with HBV.
Ma GG [50]	January, 2021	China	Retrospective study	109	1 (0.9)	Normal liver enzymes	NA	NA	Hypertension, diabetes, coronary heart disease, COPD, chronic renal disease	Antibiotic, immunoglobulin, glucocorticoid	Liver injury had no negative effect on the prognosis and treatment of COVID-19.
Chen T [27]	March, 2020	China	Retrospective study	274	11 (4.0)	Concentrations of liver enzymes, N-terminal pro-brain natriuretic peptide, and D-dimer were markedly	5 (45.5)	6 (54.5)	ARDS, type I respiratory failure, sepsis, acute cardiac injury, heart failure, shock, alkalosis, hyperkalaemia, acute kidney injury, hypoxic encephalopat	Oseltamivir, arbidol, lopinavir/ritonavir, glucocorticoid, immunoglobulin, interferon α inhalation, antibiotic	SARS-CoV-2 infection can cause both pulmonary and systemic inflammation, leading to multi-organ dysfunction in patients at high risk.

						higher.			hy		
Ding ZY [28]	June, 2021	China	Retrospective study	2073	134 (6.5)	Liver enzymes increased	8 (6.0)	126 (94.0)	ARDS, septic shock, cirrhosis	NR	HBV infection in patients did not increase the risk of poor COVID-19-associated outcomes.
Rodríguez-Tajes S [29]	January, 2021	Spain	Retrospective study	484	72 (14.9)	Liver enzymes increased	8 (11.1)	64 (88.9)	Hypertension, diabetes, hypercholesterolaemia, cardiovascular disease, chronic renal disease	Tocilizumab, siltuximab, baricitinib, anakinra	The risk of HBV reactivation in patients with severe COVID-19 and resolved

Parlar Y [51]	July, 2022	Turkey	Multicenter retrospective study	479[e]	43[b] (9.0)	CHB patients with and without COVID-19 infection did not differ in laboratory parameters.	0 (0.0)	43 (100.0)	NR	Nucleos(t)ide analogs	HBV infection undergoing immune modulator treatment was low. The course of COVID-19 infection was not severe in patients with CHB, probably due to the effective antiviral therapy received by CHB

										patients.
Yang S [30]	April, 2022	China	Cohort study	2899	105 (3.6)	Liver enzymes Significantly increased	18 (17.1)	87 (82.9)	Hypertension, diabetes, cardiovascular disease, cancer	Steroid hormones, antibiotics, antiviral medication, antineoplastic drugs	Patients with COVID-19 co-infected with HBV at the HBeAg (+) CHB infection stage have an increased risk of poor prognosis.
Yigit Y [31]	February, 2021	Qatar	Case report	1	1 (100.0)	Liver enzymes increased	1 (100)	0 (0.0)	None	Azithromycin, chloroquine, and oseltamivir	The liver damage occurring in COVID-19 is caused by an impaired innate

											immune system rather than by direct cell damage caused by SARS-CoV-2.
Aldhaleei WA [32]	June, 2020	United Arab Emirates	Case report	1	1 (100.0)	Liver enzymes Significantly increased	0 (0.0)	1 (100.0)	Mental disturbances	Lactulose, entecavir, vitamin K, thiamin	Patients with abnormal liver functions tend to have an increased risk of COVID-19.
Ji D [33]	September, 2020	China	Multicenter retrospective study	140	7 (5.0)	Liver enzymes increased	0 (0.0)	7 (100.0)	Hypertension, diabetes, cardiovascular disease, chronic lung	Methylprednisolone, human γ-Immune goblins, moxifloxacin	Disease progression was significantly faster in

								disease		those COVID-19 patients combined with CHB.
Kim D [34]	July, 2021	USA	Multicenter, observational cohort study	867	62 (7.2)	Liver enzymes increased	5 (8.1)	57 (91.9)	Diabetes, COPD, hypertension, hyperlipidemia, cardiovascular disease, HIV, asthma, cancer	Remdesivir, steroids, hydroxychloroquine, azithromycin	Chronic liver disease are associated with severe COVID-19.
Wang H [35]	July, 2020	China	Case report	1	1 (100.0)	Abnormal liver enzyme system	0 (0.0)	1 (100.0)	None	Lopinavir, ritonavir, abidor, ribavirin, methylprednisolone	For COVID-19 patients with HBV co-infection, liver function

											should be closely monitored. Reduced immunosuppression combined with low doses of methylprednisolone can benefit solid organ transplant recipients with COVID-19 combined with hepatitis B.
Zhong Z [36]	July, 2020	China	Case series	2	1 (50.0)	Liver enzymes increased	0 (0.0)	1 (100.0)	Hepatocellular carcinoma, renal failure	Oseltamivir, abidol, moxifloxacin, recombinant human interferon alpha, methylprednisolone, human immunoglobulin	

Fernández-Ruiz M [49]	July, 2020	Spain	Case series	18	2 (11.1)	Decreased white blood cells	1 (50.0)	1 (50.0)	Hypertension, diabetes, coronary artery disease, hypertensive nephropathy, lung cancer	Lopinavir/ritonavir, mycophenolate mofetil, mycophenolic	SARS-CoV-2 and HBV co-infection has a severe course in solid organ transplant recipients.
Huang JF [37]	July, 2020	China	Case report	1	1 (100.0)	Elevated total bilirubin	1 (100)	0 (0.0)	Decompensated cirrhosis	Lopinavir/ritonavir, piperacillin tazobactam, tacrolimus, mycophenolate	When treating COVID-19, consideration should be given to using as low a dose of immunosuppressants as possible.
Patrono D	October,	Italy	Case	10	2	NR	0	2	Obesity	Hydroxychloroquine	Mortality

[55]	2020		series		(20.0)		(0.0)	(100.0)		, mycophenolate mofetil, tacrolimus	appears to be higher in liver transplant recipients affected by COVID-19. Long term follow-up and close monitoring of liver function should be carried out in transplant patients with COVID-19
Qin J [38]	October, 2020	China	Case report	1	1 (100.0)	Abnormal liver enzyme system	0 (0.0)	1 (100.0)	Liver cancer	Tacrolimus, glucocorticoids, antimicrobial agents, caspofungin	
Liu B [56]	July, 2020	China	Case report	1	1 (100.0)	NR	0 (0.0)	1 (100.0)	Cirrhosis	Umifenovir, lopinavir/ritonavir	Temporary cessation of immunosup

											pression and low-dose corticosteroid use may be beneficial for COVID-19 transplant recipients.
Loinaz C [39]	October, 2020	Spain	Case series	19	4 (21.1)	One patient with severe disease had elevated enzyme system, the rest had no significant abnormalities.	1 (25.0)	3 (75.0)	Diabetes, lung disease, hypertension	Everolimus, mycophenolate mofetil, tacrolimus	A broad spectrum of disease severity in liver transplant patients with COVID-19, with a favorable outcome in most of them.

Adali G [40]	September, 2021	Turkey	Retrospective study	231	77 (33.3)	Abnormal liver enzyme system	6 (7.8)	71 (92.2)	Obesity, COPD, cardiovascular disease, diabetes, hypertension	Hydroxychloroquine, azithromycin	HBV infection was not associated with mortality in patients with COVID-19 and nucleotide analogue treatment for HBV infection might have an antiviral effect on SARS-CoV-2 infection.
Oruç Z [57]	April, 2022	Turkey	Retrospective	92	4 (4.3)	NR	0 (0.0)	4 (100.	Breast cancer, gastrointestin	NA	Hepatitis B immune

			study				0)	al system cancers, genitourinary system cancers, lung cancer			status was not associated with the risk of COVID-19 transmission and death.
Guardigni V [58]	April, 2022	Italy	Retrospective study	606	12 (2.0)	NR	NA	NA	NR	NR	The preexisting viral liver infection did not have any impact on the clinical and virological evolution of COVID-19.
Sagnelli C [41]	July, 2022	Italy	Case report	1	1 (100.0)	Liver enzymes increased	1 (100)	0 (0.0)	NA	Dexamethasone, low-molecular-weight heparin	The primary cause of HBV

											reactivation may be the corticosteroids and other immunosuppressive drugs given to COVID-19 patients rather than the actual SARS-CoV-2 infection itself.
Lens S [59]	November, 2021	Spain	Multicenter retrospective study	1764[e]	9[b] (0.5)	NR	0 (0.0)	9 (100.0)	NR	Sofosbuvir/velpatasvir, tenofovir	The efficacy of direct-acting antivirals or tenofovir against SARS-CoV-2

										is unfavorable.
Phipps MM [42]	September, 2020	USA	Retrospective cohort study	2273	15 (0.7)	The serum levels of liver enzyme system and inflammatory cytokines were elevated.	NA	NA	Diabetes, chronic kidney disease, asthma, COPD, pulmonary fibrosis	NR	Severe liver injury is associated with the most severe clinical outcome.
Li L [52]	March, 2020	China	Retrospective study	85	2 (2.4)	Normal liver enzymes	0 (0.0)	2 (100.0)	Chronic hepatic diseases	NR	Liver injury may be a complication of COVID-19 infection.
Wu YF [43]	July, 2021	China	Case report	1	1 (100.0)	Elevated liver enzymes and	0 (0.0)	1 (100.0)	None	Recombinant interferon-alpha-2b, lopinavir/ritonavir, methylprednisolone,	COVID-19 or treatment associated immunosup

						increased HBV DNA				tenofovir fumarate	pression may trigger hepatitis B virus reactivation.
Wu J [44]	January, 2021	China	Multicenter retrospective study	620	70 (11.3)	Elevated liver enzymes	0 (0.0)	70 (100.0)	NR	NR	The original characteristics of COVID-19 cases combined with HBV infection were higher rate of severe tendency and increased susceptibility.

Iavarone M [45]	November, 2020	Italy	Multicenter retrospective study	50	5 (10.0)	Elevated liver enzymes	NA	NA	Diabetes, COPD, hypertension, obesity, chronic kidney disease	Hydroxychloroquine, lopinavir/ritonavir	COVID-19 is associated with liver function deterioration and elevated mortality in patients with cirrhosis.
Marjot T [60]	March, 2021	United Kingdom	Multicenter retrospective study	745	96 (12.9)	NR	23 (24.0)	73 (76.0)	Obesity, diabetes, hypertension, COPD	Chloroquine/hydroxychloroquine, lopinovir/ritonavir, interferon-alpha	The stage of liver disease is strongly associated with COVID-19 mortality.
Huang SP [46]	May, 2020	China	Case report	1	1 (100.0)	Elevated liver enzymes	0 (0.0)	1 (100.0)	Hypertension	Entecavir, silibinin meglumine	COVID-19 patients with HBV co-infection can lead to

HBV reactivation, and treatment with nucleoside analogs is recommended.

Notes: [a]93 cases were the sample size of the experimental group and the other healthy control group was 62 cases. 93 cases were all CHB patients. [b]Patients with HBV co-infection with SARS-CoV-2. [c]The 353 cases were patients with current co-infection with HBV, and another 359 patients with past infection with HBV were not included. [d]Sample size after PSM. [e]All were CHB patients. [f]The authors did not report pharmacological treatment, but instead reported hemoperfusion treatment. No.: Number; NA: Data not available; NR: Data not reported; COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HBV: Hepatitis B virus; CHB: Chronic hepatitis B; PSM: Propensity score matching; ALT: Alanine aminotransferase; COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome.