ORIGINAL RESEARCH

Patients with COVID-19 and HBV Coinfection are at Risk of Poor Prognosis

Shanshan Yang [ID] · Shengshu Wang · Mingmei Du · Miao Liu · Yunxi Liu · Yao He

ABSTRACT

Introduction: This study aimed to determine whether there is a difference in the risk of death/critical illness between different stages of hepatitis B virus (HBV) (resolved hepatitis B, HBeAg (−) chronic hepatitis B [CHB]/infection, HBeAg (+) CHB/infection, and HBV reactivation) coinfected with coronavirus disease 2019 (COVID-19); and if there is a difference, whether it is due to abnormal liver function and to what extent.

Methods: This cohort study included all COVID-19 inpatients of a single-center tertiary care academic hospital in Wuhan, Hubei, China, between February 4, 2020, and follow-up to April 14, 2020. A total of 2899 patients with COVID-19 were included as participants in this study, and they were divided into five groups based on hepatitis B infection status. Follow-up was conducted for mortality and ICU admission during hospitalization.

Results: The median follow-up time was 39 days (IQR, 30–50), with 66 deaths and 126 ICU admissions. After adjustment, compared with patients without CHB, the hazard ratio (HR) for ICU admission was 1.86 (95% CI: 1.05–3.31) for patients with HBeAg (+) CHB/infection. The HR for death was 3.19 (95% CI: 1.62–6.25) for patients with HBeAg (+) CHB/infection. The results for the mediating effect

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indicated that the total effect of HBeAg (+) CHB/infection on death/ICU stay was partially mediated by abnormal liver function, which accounted for 79.60% and 73.53%, respectively. **Conclusion**: Patients with COVID-19 coinfected with HBV at the HBeAg (+) CHB/infection stage have an increased risk of poor prognosis, and abnormal liver function partially mediates this increased risk of poor prognosis caused by the coinfection.

Keywords: Coinfection; COVID-19; Hepatitis B virus; Prognosis

Key Summary Points

Unlike previous studies, this study found that COVID-19 patients coinfected with hepatitis B virus (HBV) at the HBeAg (+) CHB/infection stage are at increased risk of poor prognosis.

Abnormal liver function partially mediates the increased risk of poor prognosis caused by the coinfection.

This study suggested that we should pay more attention to patients with coinfection of HBV and COVID-19, especially those with HBeAg (+) CHB/infection, and be aware of the poor prognosis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], which is a positive-sense single-stranded RNA virus belonging to the genus *Betacoronavirus* [2]. As of August 20, 2021, the global COVID-19 pandemic, which started in December 2019, had resulted in more than 210 million confirmed cases worldwide, with more than 4.4 million deaths. Furthermore, researchers have reported that the virus is constantly evolving and spreading worldwide, further suggesting a

high global health threat, especially the severe type, which seriously affects and threatens people's health and may lead to the depletion of medical resources [3]. Therefore, it is essential to accurately identify the risk factors leading to severe illness and death and the patients at high risk.

Hepatitis B virus (HBV) infection is a major public health problem, with 248 million chronically infected individuals worldwide [4], especially in Africa and Asia [5]. In China, approximately 90 million individuals were reportedly infected with HBV [6]. Previous studies have shown that coinfection with HBV and other viruses can lead to rapid progression of liver disease and an increased risk of death [7]. In addition, COVID-19 also causes abnormal liver function and liver damage [8]. However, the results of previous studies are inconsistent on whether COVID-19 and HBV coinfection will increase the risk of death and critical illness [6, 9]. Furthermore, some questions on this topic remain unresolved: (1) whether there is a difference in the risk of death/critical illness between different stages of HBV (resolved hepatitis B, HBeAg (−) CHB/infection, HBeAg (+) CHB/infection, and HBV reactivation) coinfection with COVID-19, and (2) if there is a difference, whether it is due to abnormal liver function and to what degree. Therefore, based on Chinese COVID-19 cases, we compared the mortality and critical illness risk in different groups of patients with HBV coinfected with COVID-19 to further identify the groups at high risk of death and critical illness, and to explore the role of liver dysfunction in the association through mediation analysis.

METHODS

Participants

Between February 4, 2020, and April 14, 2020, all COVID-19 inpatients of a single-center tertiary care academic hospital in Wuhan, Hubei, China, were followed up [10]. Initially, 3059 patients with COVID-19 were enrolled in the trial; however, 12 patients were transferred to another referral hospital due to other difficulties

(such as dialysis), and 148 patients were excluded due to missing data on hepatitis B infection status. A total of 2899 patients with COVID-19 were included in this study. The participants were divided into five groups based on hepatitis B infection status: without CHB ($n = 2291$), resolved hepatitis B ($n = 503$), HBeAg (−) CHB/infection ($n = 44$), HBeAg (+) CHB/infection ($n = 55$) and HBV reactivation ($n = 6$). During the hospitalization, follow-up was also conducted for mortality and intensive care unit (ICU) admissions. The median follow-up period was 39 days (IQR, 30–50) (Fig. 1). According to the guidelines for clinical diagnosis and treatment of liver failure (2018) [11], no participants were diagnosed with acute liver failure in this study.

All patients with COVID-19 were diagnosed using the diagnostic criteria for COVID-19, which included typical clinical symptoms, chest computed tomography (CT), and a positive COVID-19 RNA and/or gene result (trial version 5–7) [12]. Participants with COVID-19 were divided into four types (light, common, severe, and critical) according to the new coronavirus pneumonia prevention and control program in China (trial version 5–7) [12].

Patient Involvement

Patients were not engaged in developing the research question or outcome measures, or in the design or administration of the study. Patients are not involved in the dissemination process.

Ethics

The Medical Ethics Committee of the Chinese PLA General Hospital approved this study (S2021-328-01), which was conducted in conformity with the Declaration of Helsinki. Before participating in the study, all individuals signed a written informed consent form.

Hepatitis B Infection Status and Liver Function

Hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B e antigen (anti-HBe), and antibody to hepatitis B core antigen (anti-HBc) are the five serological indicators. These markers were detected by patient serum and identified by standard
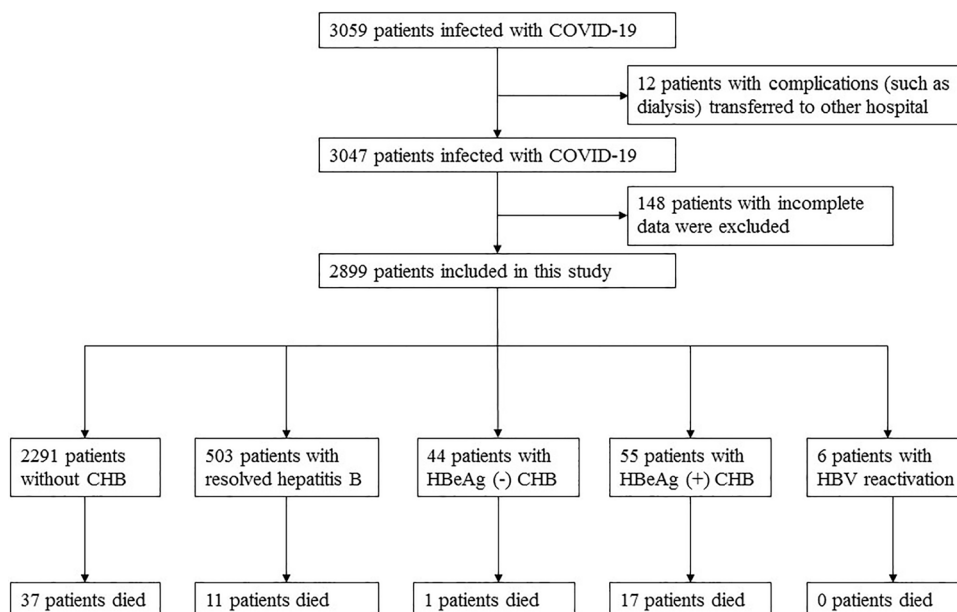

Fig. 1 Flow diagram of the study population

methods in the hospital's central laboratory. Patients with COVID-19 included in this study were divided into five groups based on infection status of hepatitis B: without chronic hepatitis (CHB), resolved hepatitis B, HBeAg (−) CHB/ infection, HBeAg (+) CHB/infection, and HBV reactivation. Patients without CHB were defined as those with normal liver function and negative/positive anti-HBs, negative HBsAg, negative anti-HBc, negative HBeAg, and negative anti-HBe; resolved hepatitis B was defined as negative HBsAg, negative/positive anti-HBs, positive anti-HBc or positive anti-HBe. HBeAg (−) CHB/ infection was defined as negative HBeAg and positive HBsAg. HBeAg (+) CHB/infection was defined as positive HBeAg and positive HBsAg. HBV reactivation was defined as a new appearance of positive HBsAg in a person with previously stable negative HBsAg CHB patients [13, 14].

Liver function was evaluated by serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT/AST, gamma-glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), total protein (TP), albumin (ALB), globulin (GLB), ALB/GLB, total bilirubin (TBIL), direct bilirubin (DBIL), and indirect bilirubin (IBIL) (Table S1) [15, 16]. The number of items with abnormal liver function (NIALF) was the number of abnormal liver function biomarker items mentioned above. The Model for End-Stage Liver Disease (MELD) score was used to evaluate the status of end-stage liver disease.

Study Outcome

The primary outcome of this cohort study is the death of the patients, and the secondary outcome is admission to the ICU.

Statistical Analysis

For continuous variables, data are expressed as mean ± standard deviation (SD) (normal distribution) or median (interquartile range, IQR) for non-normal distribution. For categorical variables, data are expressed as numbers (%). We compared the demographic characteristics among participants with different hepatitis B infection status using one-way analysis of variance (ANOVA) and chi-square tests. If the difference among the groups was significant ($P < 0.05$) in the ANOVA analysis, we subsequently applied Fisher's least significant difference (LSD) as a post hoc test to determine whether there were any differences between these groups. A multivariable Cox proportional risk model was used to assess the risks of the different hepatitis B infection status and to follow up regarding mortality/ICU admission with COVID-19 and further stratification of patients (male and female, different age groups). The hazard ratio (HR) and 95% confidence interval were computed after adjusting for demographic and clinically relevant factors. The study was conducted on a specified subset stratified by gender or age (60 years as the cutoff to distinguish the elderly from the non-elderly group). The potential mediating factors were investigated using Preacher and Hayes' analytical methodologies [17]. PROCESS, an SPSS macro by Hayes, was used to conduct all mediation analyses [18]. PROCESS model 4 was used to test the simple mediating effect [19, 20]. All estimated mediating effects in this study were unstandardized regression coefficients based on a 5000-sample bootstrapping set. SPSS version 26.0 and R programs (http://www.R-project.org, R Development Core Team) were used to conduct all analyses. Statistical significance was defined as a two-tailed $P < 0.05$.

RESULTS

Of the 2899 patients with COVID-19 (Fig. 1) recruited from February 4, 2020, and followed up to April 14, 2020, 49.0% ($n = 1421$) were female. The breakdown of coinfection was as follows: 79.0% ($n = 2291$) without CHB, 17.4% ($n = 503$) with resolved hepatitis B, 1.52% ($n = 44$) with HBeAg (−) CHB/infection, 1.90% ($n = 55$) with HBeAg (+) CHB/infection, and 0.21% ($n = 6$) with HBV reactivation. The mean age was 58.59 (SD 14.42) years. The median follow-up time was 39 days (IQR, 30–50) with 66 deaths and 126 ICU admissions.

Table 1 shows that, compared with patients with COVID-19 without CHB, patients with

Table 1 Demographics and clinical characteristics of 2899 patients with COVID-19 in different groups

	Without CHB	Resolved hepatitis B	HBeAg (−) CHB	HBeAg (+) CHB	HBV reactivation	Total	P-value
No.	2291	503	44	55	6	2899	
Age*	57.71 ± 14.53	61.65 ± 13.19	61.25 ± 13.44	63.78 ± 16.11	71.67 ± 10.07	58.59 ± 14.42	< 0.001
BMI*	24.25 ± 3.61	23.88 ± 3.47	25.39 ± 4.75	24.81 ± 3.99	21.53 ± 2.88	24.21 ± 3.62	0.008
DBP*	80.78 ± 11.04	81.72 ± 11.67	83.39 ± 11.29	80.24 ± 14.17	65.33 ± 10.19	80.94 ± 11.25	0.002
SBP	129.39 ± 16.03	130.71 ± 16.39	133.75 ± 15.35	132.25 ± 18.95	119.5 ± 21.59	129.72 ± 16.17	0.054
Age group							0.003
< 60 years	1123 (49.0)	216 (42.9)	18 (40.9)	19 (34.5)	0 (0.0)	1376 (47.5)	
≥ 60 years	1168 (51.0)	287 (57.1)	26 (59.1)	36 (65.5)	6 (100.0)	1523 (52.5)	
Gender							0.026
Male	1151 (50.2)	262 (52.1)	28 (63.6)	36 (65.5)	1 (16.7)	1478 (51.0)	
Female	1140 (49.8)	241 (47.9)	16 (36.4)	19 (34.5)	5 (83.3)	1421 (49.0)	
Nationality							0.570
Han	2280 (99.5)	503 (100)	44 (100)	55 (100)	6 (100)	2888 (99.6)	
Minority nationality	11 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.4)	
Marital status							0.583
Married	2062 (90.0)	445 (88.5)	38 (86.4)	47 (85.5)	5 (83.3)	2597 (89.6)	
Unmarried/widowed/divorced	229 (10.0)	58 (11.5)	6 (13.6)	8 (14.5)	1 (16.7)	302 (10.4)	
Type							< 0.001
Light	34 (1.5)	7 (1.4)	0 (0.0)	2 (3.6)	0 (0.0)	43 (1.5)	
Common	1716 (74.9)	307 (61.0)	27 (61.4)	18 (32.7)	1 (16.7)	2069 (71.4)	
Severe	523 (22.8)	181 (36.0)	15 (34.1)	28 (50.9)	3 (50.0)	750 (25.9)	
Critical	18 (0.8)	8 (1.6)	2 (4.5)	7 (12.7)	2 (33.3)	37 (1.3)	

Table 1 continued

	Without CHB	Resolved hepatitis B	HBeAg (−) CHB	HBeAg (+) CHB	HBV reactivation	Total	P-value
MELD score							< 0.001
< 10	2251 (98.3)	484 (96.2)	44 (100.0)	43 (78.2)	5 (83.3)	2827 (97.5)	
10–19	34 (1.5)	16 (3.2)	0 (0.0)	9 (16.4)	0 (0.0)	59 (2.0)	
≥ 20	6 (0.3)	3 (0.6)	0 (0.0)	3 (5.5)	1 (16.7)	13 (0.4)	
Hypertension							< 0.001
No	1541 (67.3)	282 (56.1)	27 (61.4)	32 (58.2)	2 (33.3)	1884 (65.0)	
Yes	750 (32.7)	221 (43.9)	17 (38.6)	23 (41.8)	4 (66.7)	1015 (35.0)	
Diabetes							0.005
No	1918 (83.7)	388 (77.1)	39 (88.6)	44 (80.0)	4 (66.7)	2393 (82.5)	
Yes	373 (16.3)	115 (22.9)	5 (11.4)	11 (20.0)	2 (33.3)	506 (17.5)	
CVD							< 0.001
No	2105 (91.9)	439 (87.3)	40 (90.9)	42 (76.4)	4 (66.7)	2630 (90.7)	
Yes	186 (8.1)	64 (12.7)	4 (9.1)	13 (23.6)	2 (33.3)	269 (9.3)	
Cancer							< 0.001
No	2161 (94.3)	466 (92.6)	38 (86.4)	45 (81.8)	4 (66.7)	2714 (93.6)	
Yes	130 (5.7)	37 (7.4)	6 (13.6)	10 (18.2)	2 (33.3)	185 (6.4)	
Steroid hormones							< 0.001
No	2035 (88.8)	436 (86.7)	39 (88.6)	35 (63.6)	2 (33.3)	2547 (87.9)	
Yes	256 (11.2)	67 (13.3)	5 (11.4)	20 (36.4)	4 (66.7)	352 (12.1)	
Antibiotics							0.013
No	1223 (53.4)	295 (58.6)	21 (47.7)	20 (36.4)	4 (66.7)	1563 (53.9)	
Yes	1068 (46.6)	208 (41.4)	23 (52.3)	35 (63.6)	2 (33.3)	1336 (46.1)	

Table 1 continued

	Without CHB	Resolved hepatitis B	HBeAg (−) CHB	HBeAg (+) CHB	HBV reactivation	Total	P-value
Antiviral medication							0.020
No	890 (38.8)	230 (45.7)	18 (40.9)	27 (49.1)	4 (66.7)	1169 (40.3)	
Yes	1401 (61.2)	273 (54.3)	26 (59.1)	28 (50.9)	2 (33.3)	1730 (59.7)	
Antineoplastic drugs							< 0.001
No	2239 (97.7)	457 (90.9)	40 (90.9)	49 (89.1)	4 (66.7)	2789 (96.2)	
Yes	52 (2.3)	46 (9.1)	4 (9.1)	6 (10.9)	2 (33.3)	110 (3.8)	
Death							< 0.001
No	2254 (98.4)	492 (97.8)	43 (97.7)	38 (69.1)	6 (100.0)	2833 (97.7)	
Yes	37 (1.6)	11 (2.2)	1 (2.3)	17 (30.9)	0 (0.0)	66 (2.3)	
ICU admission							< 0.001
No	2221 (96.9)	473 (94)	42 (95.5)	35 (63.6)	2 (33.3)	2773 (95.7)	
Yes	70 (3.1)	30 (6)	2 (4.5)	20 (36.4)	4 (66.7)	126 (4.3)	
AST (IU/L)	25.08 ± 24.05	24.78 ± 19.61	29.79 ± 35.23	41.01 ± 57.9	36.32 ± 40.89	25.42 ± 24.76	< 0.001
ALT (IU/L)	33.63 ± 34.83	31.66 ± 35.21	39.25 ± 69.87	39.71 ± 39.41	15.57 ± 9.30	33.45 ± 35.74	0.226
ALT/AST	1.28 ± 0.62	1.19 ± 0.54	1.16 ± 0.46	1.16 ± 0.75	0.69 ± 0.52	1.26 ± 0.61	0.001
γGT (IU/L)	44.75 ± 47.01	44 ± 42.8	35.41 ± 23.94	93.3 ± 106.14	19.37 ± 10.32	45.33 ± 48.22	< 0.001
ALP (IU/L)	75.07 ± 28.29	77.12 ± 27.96	74.95 ± 22.51	122.4 ± 121.61	66.35 ± 8.62	76.3 ± 33.06	< 0.001
TP (g/L)	64.7 ± 6.14	65.11 ± 6.56	64.49 ± 7.12	62.79 ± 7.40	57.88 ± 9.52	64.72 ± 6.28	0.006
ALB (g/L)	37.33 ± 4.28	37.46 ± 4.67	36.93 ± 5.34	34.7 ± 5.91	34.38 ± 6.16	37.29 ± 4.42	< 0.001
GLB (g/L)	27.41 ± 4.03	27.73 ± 4.41	27.71 ± 4.39	28.12 ± 4.26	23.05 ± 5.66	27.48 ± 4.13	0.033
ALB/GLB	1.39 ± 0.29	1.39 ± 0.38	1.36 ± 0.26	1.25 ± 0.27	1.52 ± 0.38	1.39 ± 0.31	0.019
TBIL (μmol/L)	10.34 ± 4.79	10.79 ± 4.98	12.86 ± 5.35	22.53 ± 27.27	8.20 ± 5.05	10.68 ± 6.30	< 0.001

Table 1 continued

	Without CHB	Resolved hepatitis B	HBeAg (−) CHB	HBeAg (+) CHB	HBV reactivation	Total	P-value
DBIL (μmol/L)	3.74 ± 2.10	3.98 ± 2.26	4.75 ± 2.53	12.88 ± 19.98	3.75 ± 2.73	3.97 ± 3.67	< 0.001
IBIL (μmol/L)	6.58 ± 3.07	6.81 ± 3.23	7.90 ± 3.47	9.92 ± 9.85	4.36 ± 2.32	6.71 ± 3.44	< 0.001
Number of items with abnormal liver function	3.22 ± 1.75	3.27 ± 1.75	3.38 ± 2.12	5.14 ± 2.71	4.33 ± 1.86	3.28 ± 1.80	< 0.001

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *MELD* Model For End-Stage Liver Disease, *CVD* cardiovascular disease, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γGT* gamma-glutamyl transpeptidase, *ALP* alkaline phosphatase, *TP* total protein, *ALB* albumin, *GLB* globulin, *TBIL* total bilirubin, *DBIL* direct bilirubin, IBIL indirect bilirubin
*Post hoc analysis results are shown in Tables S1–S3

HBeAg (+) CHB/infection and patients with HBV reactivation were older (63.78 ± 16.11, 71.67 ± 10.07 vs. 57.71 ± 14.53, $P < 0.05$), with a significantly higher proportion of women among patients with HBV reactivation, and a lower proportion of women among patients with HBeAg (+) CHB/infection (Table 1, $P < 0.05$). Further, compared with patients with COVID-19 without CHB, patients with HBeAg (+) CHB/infection and patients with HBV reactivation had a higher number of items with abnormal liver function, and they had a significantly higher proportion of severe and critical type, death, and ICU admissions (Table 1, $P < 0.05$).

Table 2 Model E shows that, after adjusting for age, sex, nationality, marital status, hypertension, diabetes, cardiovascular disease (CVD), cancer, body mass index (BMI), type, steroid hormones, antibiotics, antiviral medication, and antineoplastic drugs, compared with patients without CHB, the hazard ratio (HR) for ICU admissions was 1.86 (95% CI: 1.05–3.31) for patients with HBeAg (+) CHB/infection. The HR for death was 3.19 (95% CI: 1.62–6.25) for patients with HBeAg (+) CHB/infection (Table 2, Fig. 2). When excluding patients with MELD scores ≥ 20 ($n = 13$), the results were consistent (Table S4).

The adjusted model in Table S5 shows that, in male patients, after adjusting for age, sex, nationality, marital status, hypertension, diabetes, CVD, cancer, and BMI, compared with patients without CHB, the HR for ICU admission was 5.36 (95% CI: 2.73–10.51) for those with HBeAg (+) CHB/infection, and the HR for death was 6.50 (95% CI: 3.01–14.02) for patients with HBeAg (+) CHB/infection. In female patients, the HR for ICU admission was 14.79 (95% CI: 6.07–36.02) for those with HBeAg (+) CHB/infection, and 7.25 (95% CI: 1.96–26.82) for those with HBV reactivation. The HR for death was 42.50 (95% CI: 14.46–124.88) for female patients with HBeAg (+) CHB/infection (Table S1).

The adjusted model in Table S6 shows that, in patients aged < 60, after adjusting for age, sex, nationality, marital status, hypertension, diabetes, CVD, cancer, and BMI, compared with patients without CHB, the HR for ICU

Table 2 HRs and 95% CI of different HBV infection status for death and ICU admission in patients with COVID-19

	Cases	Model A	Model B	Model C	Model D	Model E
ICU admission						
Without CHB	70 (3.1)	1	1	1	1	1
Resolved hepatitis B	30 (6.0)	1.00 (0.64–1.55)	0.95 (0.61–1.47)	0.93 (0.60–1.44)	0.87 (0.56–1.34)	0.50 (0.31–0.80)
HBeAg (−) CHB	2 (4.5)	0.88 (0.22–3.61)	0.79 (0.19–3.23)	0.79 (0.19–3.24)	0.77 (0.19–3.16)	0.25 (0.06–1.07)
HBeAg (+) CHB	20 (36.4)	11.03 (6.70–18.18)	7.87 (4.73–13.07)	7.96 (4.80–13.21)	8.02 (4.77–13.49)	1.86 (1.05–3.31)
HBV reactivation	4 (66.7)	5.71 (2.00–16.31)	5.13 (1.76–15.02)	5.50 (1.88–16.11)	5.15 (1.66–16.02)	0.28 (0.08–1.02)
Death						
Without CHB	37 (1.6)	1	1	1	1	1
Resolved hepatitis B	11 (2.2)	0.95 (0.48–1.88)	0.87 (0.44–1.73)	0.86 (0.44–1.71)	0.82 (0.41–1.62)	0.54 (0.26–1.10)
HBeAg (−) CHB	1 (2.3)	1.02 (0.14–7.48)	0.88 (0.12–6.44)	0.88 (0.12–6.41)	0.94 (0.13–6.92)	0.40 (0.05–3.12)
HBeAg (+) CHB	17 (30.9)	18.61 (10.47–33.08)	13.13 (7.30–23.62)	13.08 (7.28–23.51)	11.57 (6.30–21.26)	3.19 (1.62–6.25)
HBV reactivation	0 (0.0)	(−)	(−)	(−)	(−)	(−)

Model A: Crude model
Model B: Adjusted for age and gender
Model C: Adjusted for age, gender, nationality, and marital status
Model D: Adjusted for age, gender, nationality, marital status, hypertension, diabetes, CVD, cancer, and BMI
Model E: Adjusted for age, gender, nationality, marital status, hypertension, diabetes, CVD, cancer, BMI, types, steroid hormones, antibiotics, antiviral medication, and antineoplastic drugs

admission was 15.94 (95% CI: 3.24–78.49) for patients with HBeAg (+) CHB/infection, and the HR for death was 19.65 (95% CI: 2.15–179.29) for those with HBeAg (+) CHB/infection. In patients aged ≥ 60, the HR for ICU admission was 7.74 (95% CI: 4.47–13.41) for those with HBeAg (+) CHB/infection, and 4.81 (95% CI: 1.53–15.17) for those with HBV reactivation. The HR for death was 11.65 (95% CI: 6.18–21.94) for female patients with HBeAg (+) CHB/infection (Table S2).

Further, among patients with COVID-19, we examined whether abnormal liver function mediated the relationship between HBeAg (+) CHB/infection and death/ICU admission, respectively, adjusting for age, sex, nationality, marital status, hypertension, diabetes, CVD, cancer, and BMI. The results of the mediating effect indicated that the total effect of HBeAg (+) CHB/infection on death/ICU admission was partially mediated by abnormal liver function, which accounted for 79.60% and 73.53%, respectively (Table 3 and Fig. 3).
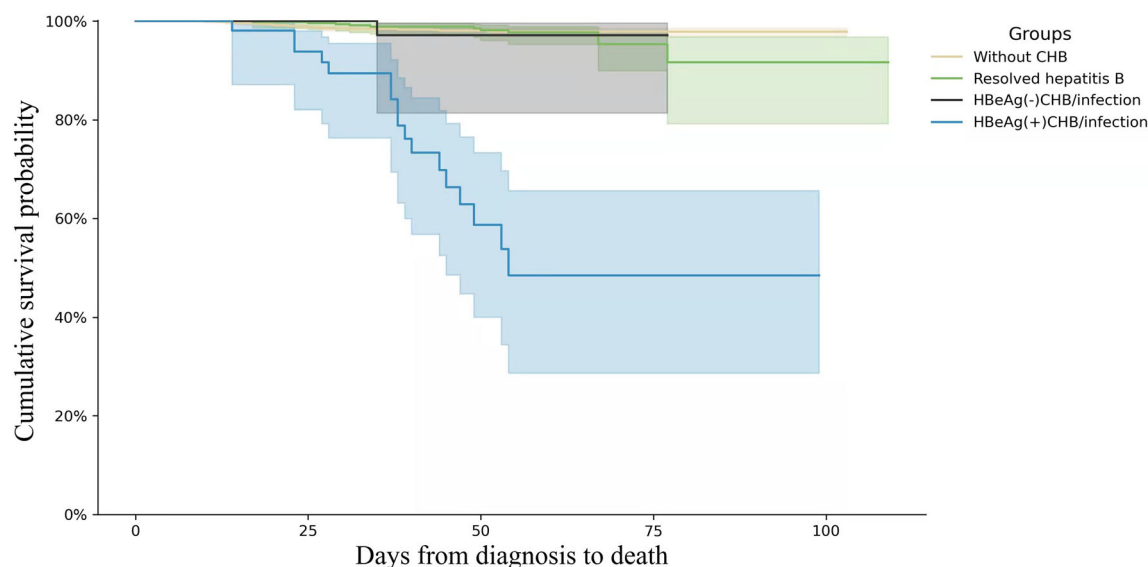
Fig. 2 Survival curve stratified by different HBV infection status groups among all COVID-19 patients: survival time against overall survival probability

DISCUSSION

The data on the 2899 patients with COVID-19 show that patients with COVID-19 coinfected with HBeAg (+) CHB/infection had a higher risk of death and ICU admission than those without CHB infection, and abnormal liver function partially mediated the increased risk of death and ICU admission caused by coinfection with COVID-19 and HBeAg (+) CHB/infection. The major strengths of our study were the large study sample, cohort study design, and comprehensive control and adjustment of a wide range of potential confounders using different statistical models. In addition, similar results in different sex and age groups demonstrated the robustness of the results.

Several previous studies showed that HBV coinfection did not negatively affect the prognosis of COVID-19. A cohort study [21] of 326 patients with COVID-19 (6.1% had HBV coinfection vs. 93.9% without HBV coinfection) reported no differences in the discharge rate and length of stay between the two groups, and only the level of prealbumin differed. Another retrospective study [22] based on 347 patients with COVID-19 infection (21 with chronic HBV vs. 51 matched without HBV infection patients)

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, a multicenter study [23] that included 15 patients with HBV infection out of 571 patients with COVID-19 reported that chronic HBV coinfection was not associated with disease severity or poor prognosis. However, the number of HBV coinfected patients in these studies was relatively small. A matched retrospective study [24] showed that HBV coinfection had no significant negative effect on the prognosis of COVID-19. However, the study did not include patients with HBeAg(+), and the main outcome was not death. A territory-wide retrospective cohort study [25] in Hong Kong with 5639 patients with COVID-19 (including 353 with current HBV coinfection and 359 past HBV infection) showed that current HBV coinfection was not significantly associated with death (HR = 1.29, 95% CI: 0.61–2.70). Mortality in the Hong Kong study (138/5639, 2.4%) was similar to that of the present study (66/2899, 2.2%), although the follow-up (14, 9–20 days) was shorter than in this study (39, 30–50 days), and the Hong Kong study did not classify patients at different stages of HBV infection.

Table 3 The mediating effect of abnormal liver function between HBeAg (+) CHB/infection and poor prognosis

	Coefficient	Standard deviation	t value	P	Total effect	Mediating effect
Death					3.2081	0.7960
HBeAg (+) → NIALF	1.6131	0.2427	6.6474	< 0.0001		
NIALF → ICU	0.4935	0.0684	7.2194	< 0.0001		
HBeAg (+) → ICU	2.4121	0.4069	5.9279	< 0.0001		
ICU					2.6174	0.7353
HBeAg (+) → NIALF	1.6131	0.2427	6.6474	< 0.0001		
NIALF → death	0.4558	0.0502	9.0760	< 0.0001		
HBeAg (+) → death	1.8821	0.3741	5.0316	< 0.0001		

Adjusted for age, gender, nationality, marital status, hypertension, diabetes, CVD, cancer, and BMI

NIALF number of items with abnormal liver function
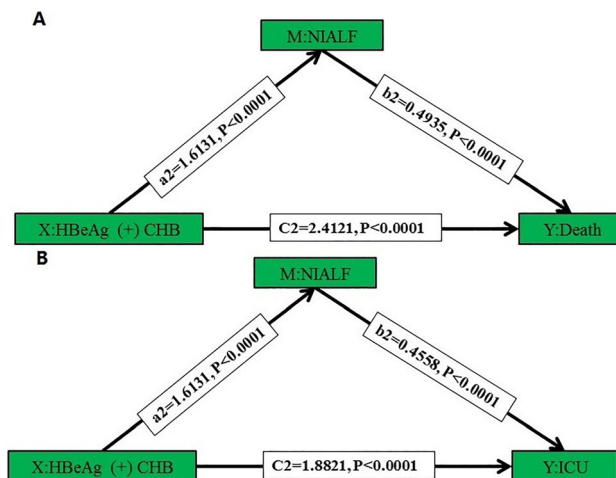
Fig. 3 The simple mediating effects of abnormal liver function between HBeAg (+) CHB/infection (*x*-axis) and poor prognosis (*y*-axis). Graph **A** represents death, and graph **B** represents ICU admission, respectively. Effect values refer to unstandardized regression coefficients

A few studies, however, have reported conflicting results. A multicenter descriptive study [6] showed that the proportion of severely/critically ill patients in the HBV coinfection group was higher than that in the non-HBV infection group (32.86% vs. 15.27%), and patients in the coinfection group had higher ALT, AST, and activated partial thromboplastin time. Another study [26] of 15 patients with HBV and COVID-19 coinfection found a more severe disease course and a higher mortality rate (13.3% vs.

2.8%) compared with those without HBV coinfection. However, these studies did not classify patients at different stages of HBV infection.

Previous studies [27] have shown that a certain percentage of patients with COVID-19 have liver injury (2.5%–50.0%). Compared with patients with COVID-19 infection alone, patients with COVID-19 and HBV coinfection had higher AST, ALT, and TBIL [6, 26]. A retrospective study [28] that included 105 patients with COVID-19 and HBV coinfection showed

that liver injury was associated with disease severity and poor prognosis. A large retrospective cohort study conducted at three centers in Wuhan, China [29] showed that abnormal AST (HR = 1.39; 95% CI: 1.04–1.86) and DBIL (HR = 1.66; 95% CI: 1.22–2.26) levels were independent risk factors for COVID-19 mortality, although the high mortality rate (9.7%) in the study may be due to the inclusion of patients during the early outbreak in Wuhan (insufficient medical resources). The present study found that abnormal liver function partially mediated the increased risk of death and ICU admission caused by COVID-19 and HBeAg (+) CHB/infection coinfection. However, this mediating effect could only explain 24.8% (0.7960/3.2081, Table 3). This suggests that there are mechanisms of adverse prognostic effects of coinfection besides aggravating liver injury, such as immune dysfunction caused by chronic HBV infection. However, further research is needed to verify this.

This was a cohort study with a full sample from one center, and diseases from onset to mortality (hard endpoint) were used to calculate time variables to avoid the time lag in transfer treatment. However, the study had several limitations. Firstly, although we collected all data during hospitalization, we did not conduct a long-term follow-up after discharge. Secondly, although a full sample from one center was included, the sample of patients with HBV reactivation was still small (only 6). Thirdly, this study did not collect data on hepatitis B treatment and liver fibrosis status. However, we used the MELD score to judge the severity of liver disease and conducted sensitivity analysis excluding patients with MELD scores ≥ 20, and the results were consistent (Table S4).

CONCLUSIONS

This study based on a full sample of patients with COVID-19 from one center showed that patients with COVID-19 coinfected with HBV at the HBeAg (+) CHB/infection stage are at increased risk of poor prognosis, and that abnormal liver function partially mediates the

increased risk of poor prognosis caused by the coinfection. Therefore, in treating COVID-19, we should pay attention to coinfected patients (HBV and COVID-19), especially those at the HBeAg (+) CHB/infection stage, and be aware of the adverse prognosis. The mechanism underlying the greater risk beyond the mediating effect of liver function injury also warrants further research.

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