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Original Article

Patients with chronic hepatitis B under nucleos(t)ide analog therapy with Omicron BA.5 infection: A retrospective study in South China

Peipei Wang [a, b, c], Junjian Chen [c, d], Dabiao Chen [a, b, c], Ziying Lei [a, b, c], Zhishuo Mo [a, b, c], Ying Zhang [a, b, c, *]

[a] Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[b] Guangdong Provincial Key Laboratory of Liver Disease Research, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[c] Key Laboratory of Tropical Disease Control (Sun Yat-sen University), Ministry of Education, Guangzhou, Guangdong, China
[d] Institute of Human Virology, Zhongshan School of Medicine (Sun Yat-sen University), Guangzhou, Guangdong, China

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ABSTRACT

Background and aims: Clinical data regarding patients with chronic hepatitis B (CHB) after Omicron BA.5 infection are currently limited. This study aimed to assess the clinical characteristics of patients with CHB and Omicron BA.5 infection in South China.

Methods: This retrospective study was conducted from January to March 2023 in a cohort of 485 healthy individuals and 553 patients with CHB. Clinical features, encompassing COVID-19-related symptoms, levels of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies, vaccination status, liver functions, and virological markers of hepatitis B virus (HBV) infection were measured.

Results: COVID-19-related symptom patterns were similar in both groups, except for fever, which was notably less prevalent (85.4% *vs.* 90.4%, $P = 0.047$) among patients with CHB who experienced a significantly shorter duration of fever (median 2.2 (25th–75th percentile, 1.0–3.0) days *vs.* 2.3 (1.0–3.0) days, $P = 0.048$) and a shorter time for symptom relief (9.2 (5.0–14.0) *vs.* 11.1 (5.0–14.0) days, $P = 0.015$). The levels of SARS-CoV-2 antibodies were comparable between the two groups but increased after booster vaccinations. In patients with CHB, globulin (GLB) and hepatitis B envelope antibody levels were significantly increased after Omicron BA.5 infection, regardless of nucleos(t)ide analog regimens comparing entecavir (ETV) with tenofovir (TFV). Patients with CHB treated with TFV had significantly higher levels of SARS-CoV-2 antibodies than those treated with ETV (1065.1 (346.9–1188.5) COI *vs.* 765.5 (24.5–1119.1) COI, $P = 0.025$).

Conclusions: No significant exacerbation of COVID-19 symptoms was observed in conjunction with the efficacy of COVID-19 booster vaccinations. There were no notable alterations in liver functions except for GLB. HBV reactivation, as evidenced by increased HBV DNA, was observed among patients with CHB after Omicron BA.5 infection. These changes were not affected by ETV versus TFV administration; however, TFV resulted in a significant increase in SARS-CoV-2 antibody levels. Further studies are required to improve care and therapeutics for patients with CHB who contracted COVID-19.

1. Introduction

Hepatitis B virus (HBV) is the primary causative agent of liver infection worldwide, affecting more than 300 million individuals. China contributes to approximately 80 million cases of chronic HBV infections, emphasizing the urgent need for timely curative interventions.[1,2] Nucleos(t)ide analogs (NAs), such as entecavir (ETV), tenofovir alafenamide (TAF), and tenofovir disoproxil (TDF), have shown notable efficacy in inhibiting HBV replication, and are important therapeutic alternatives for attenuating chronic hepatitis B (CHB) progression.[3,4]

The coronavirus disease 2019 (COVID-19) pandemic has emerged as a significant global public health emergency,[5] resulting in numerous fatalities and affecting healthcare services for patients

* Corresponding author. Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China.
E-mail address: zhangyg5@mail.sysu.edu.cn (Ying Zhang).
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with CHB. The limitations on clinical visits, treatments, and hospitalizations during the pandemic have hindered the control efforts against HBV. Furthermore, HBV and SARS-CoV-2 coinfection has raised additional concerns because of the potential for both viruses to cause liver dysfunction.[6,7]

Since October 2022, Omicron BA.5 has been the dominant strain of the COVID-19 pandemic in Southern China. Investigations on the clinical features of patients with CHB infected with Omicron BA.5 can provide valuable insights for this specific population, aiding in the development of therapeutic strategies for future coronavirus disease outbreaks. Currently, information regarding the baseline characteristics of patients with CHB and COVID-19, as well as the outcomes of HBV and SARS-CoV-2 coinfection is limited. Further investigation is necessary to evaluate the effectiveness of various NA regimens in treating CHB patients, who are coinfected with different SARS-CoV-2 variants. This is crucial due to the ongoing controversy regarding HBV reactivation and the severity of COVID-19 in these patients.[8–11] This study aimed to determine the prevalence of COVID-19-related illnesses in patients with CHB and assess whether their HBV-associated clinical characteristics are altered or linked to NA regimens after Omicron BA.5 infection.

2. Materials and methods

2.1. Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocols and consent forms were approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (approval number: II2023-048-01). All participants provided written informed consent.

2.2. Participants

This study was conducted at the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, which is one of the largest liver disease centers in South China. From January to March 2023, patients with CHB were recruited after the COVID-19 pandemic (Omicron BA.5) in South China. The study followed the STROBE criteria for reporting cohort studies (https://strobe-statement.org). Individuals with the following conditions were included: (i) chronic HBV infection, ascertained by the presence of detectable hepatitis B surface antigen (HBsAg) for a minimum duration of 6 months; (ii) age 18–65 years; (iii) daily intake of NAs; (iv) negative hepatitis B envelope antigen (HBeAg) status; and (v) HBV DNA <100 IU/mL. Conversely, individuals who met any of the following criteria were excluded: (i) hospitalization with decompensated cirrhosis, (ii) diagnosis of hepatocellular carcinoma (HCC) or other malignancies, or (iii) liver diseases by other factors or mixed factors, such as excessive alcohol consumption, hepatitis C, hepatitis D, autoimmune liver disease, Wilson's disease, and hemochromatosis. All participants were instructed to complete and submit a written or online questionnaire. No compensation was offered, and participants were free to exit the study at any time. Individuals who consented for SARS-CoV-2-specific antibody testing were offered the opportunity to receive voluntary counseling to obtain their test results concurrently. The healthy control was composed of healthy HBsAg-seronegative volunteers, randomly selected from the health examination center at the same hospital during the identical time frame through the computer-generated random method. All participants contracted their first SARS-CoV-2 infection at the commencement of the COVID-19 pandemic. However, neither individuals with CHB nor the healthy control participants were subjected to any form of antiviral treatment for COVID-19.

2.3. SARS-CoV-2 antibody detection

Between March 3 and March 17, 2023, the Third Affiliated Hospital of Sun Yat-sen University conducted examinations on total antibodies against SARS-CoV-2 in all individuals who provided their consent. Considering that most infections were documented in December 2022, the antibody testing results in this study were obtained three months after SARS-CoV-2 infection. For SARS-CoV-2 antibody detection, the participants were classified into three distinct groups according to the number of vaccines administered: (i) unvaccinated, did not accept vaccines; (ii) two doses, accepted two doses of inactivated vaccines; and (iii) three doses, accepted three doses of inactivated vaccines. From the participants who provided written informed consent for antibody testing, a total of 2 mL of peripheral blood was collected and transferred to EDTA anticoagulation tubes. Subsequently, 500 μL of plasma was obtained from the blood after centrifugation for 10 min at 500 *g*. Antibody detection kits were purchased from Wantai BioPharm (BT0483-12, Wantai, Beijing, China). SARS-CoV-2-specific antibodies were measured using commercial kits from Wantai BioPharm using a magnetic particle chemiluminescence immunoassay on a Wan200 Plus automated system (Wantai, Beijing, China), following the manufacturer's protocols.

2.4. Serological parameters

Most patients were infected with Omicron BA.5 for their first-time in December 2022 in South China but underwent serological testing including SARS-CoV-2 antibody detection through in-person visits approximately three months later because of the countrywide relaxation in the preventive and control measures for COVID-19 announced by National Health Planning Commission on January 18, 2023. Biochemical indexes of liver function were detected using an automatic biochemical analyzer (HITACHI 7600, Hitachi, Tokyo, Japan). Tests for HBsAg, HBeAg, and hepatitis B envelope antibody (HBeAb) levels were performed using Roche COBAS E601 automatic electrochemiluminescence assay (Roche Diagnostics, Manheim, Germany). HBsAg was measured using Elecsys HBsAg II Quant Reagent Kits (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA was assayed with a Roche COBAS AmpliPrep/COBAS TaqMan HBV Test v2.0 (Roche Diagnostics, Mannheim, Germany). These analyses were performed at the laboratory department of the Third Affiliated Hospital of Sun Yat-sen University, and all procedures were performed following the manufacturer's instructions.

2.5. Data sources and definitions

For all participants, COVID-19 diagnosis was performed by real-time reverse-transcription polymerase chain reaction (RT-PCR) or antigen test against SARS-CoV-2. Accordingly, a laboratory-confirmed COVID-19 case was defined as an enrolled patient who tested positive for SARS-CoV-2 by real-time RT-PCR or antigen test using samples obtained from nasopharyngeal or oropharyngeal swabs. Testing was performed either in hospital settings or self-measured at home. The dominant period of a SARS-CoV-2 variant was defined as the period when the corresponding variants accounted for more than 80% of sequenced isolates according to the national monitoring data from the Chinese Center for Disease Control and Prevention (CDC). The Omicron BA.5 period was defined as the period from October 1, 2022, to March 31, 2023, in Guangzhou (China CDC, https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_13141/202301/t20230125_263519.html; Guangdong provincial CDC, http://cdcp.gd.gov.cn/ywdt/tfggwssj/content/post_4143738.html). Clinical data regarding age, sex, COVID-19

vaccination status, and COVID-19 infection-related symptoms were collected through questionnaires. Additional data were obtained by reviewing patients' medical records. Baseline liver function (before the infection of Omicron BA.5) was defined as the last liver function parameters in 3 months prior to COVID-19 diagnosis.

2.6. Statistical analysis

Continuous variables do not have a normal distribution, so they were compared using the Mann–Whitney *U* test. The Chi-squared test and Fisher's exact probability test were used to evaluate differences between qualitative variables. Comparisons among three or more groups were performed using one-way analysis of variance (ANOVA). A paired *t*-test for normally distributed data was used to compare the parameters before and after COVID-19 diagnosis in patients with CHB. LSD post hoc test was used to compare the mean differences between the two cohorts. Propensity score matching (PSM) at a ratio of 1:1 was used to balance the confounding factors including age and sex to ensure the comparability between the two cohorts. The "Matching" package in R software (version 4.2.0; R Core Team, Vienna, Austria) was used to conduct the propensity matching. Continuous variables were expressed as *n* (%), median (25th and 75th percentiles) or median (1st and 100th percentiles). Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses, except PSM, were performed using SPSS for Windows (version 26.0; IBM, Chicago, IL, USA).

3. Results

3.1. Study cohorts

This study included 485 healthy individuals (healthy control) and 553 CHB patients who completed questionnaires. From October 2022 to March 2023, 407 healthy individuals and 479 patients with CHB were confirmed to have SARS-CoV-2 infection through laboratory testing (RT-PCR and/or Ag positive). The percentage of individuals with a confirmed diagnosis was 83.9% in the healthy control compared with 86.6% in the CHB patients ($P = 0.220$). Specifically, 226 patients with confirmed infection in the healthy control and 172 in the CHB patients voluntarily consented to undergo the SARS-CoV-2 antibody testing. A flowchart of the enrolled participants is shown in Fig. 1.

3.2. COVID-19-related symptoms were similar in both cohorts, but CHB patients experienced less frequent fevers and relief time

Before PSM, significant disparities were observed in the mean age (31.0 (23.0–41.0) years *vs.* 37.0 (31.0–46.0) years, $P < 0.001$) and sex distribution (male, 40.8% *vs.* 60.8%; female, 59.2% *vs.* 39.2%, $P < 0.001$) between the healthy control and CHB patients; the mean age of the CHB patients was older than that of the healthy control, and most patients diagnosed with HBV were male. However, after 1:1 PSM, a total of 684 participants were included in analysis, 342 in each group were matched, adjustments were made to achieve a more balanced distribution of baseline covariates between the two cohorts (Supplemental Table 1). Subsequently, a statistical analysis was conducted on the matched cohorts. The administration rates of COVID-19 vaccination (≥1 dose) exceeded 90% in both cohorts, with no significant difference observed (health control *vs.* CHB patients: 95.6% *vs.* 93.6%, $P = 0.318$). However, the rate of booster vaccination in the healthy control group was significantly higher than that in the CHB patients group (80.4% *vs.* 65.5%, $P < 0.001$). The prevalence of COVID-19-related symptoms, such as pharyngodynia, myalgia, headache, cough, expectoration, nasal congestion, runny nose, and diarrhea, did not significantly differ between the two cohorts ($P > 0.05$). The incidence of COVID-19-associated

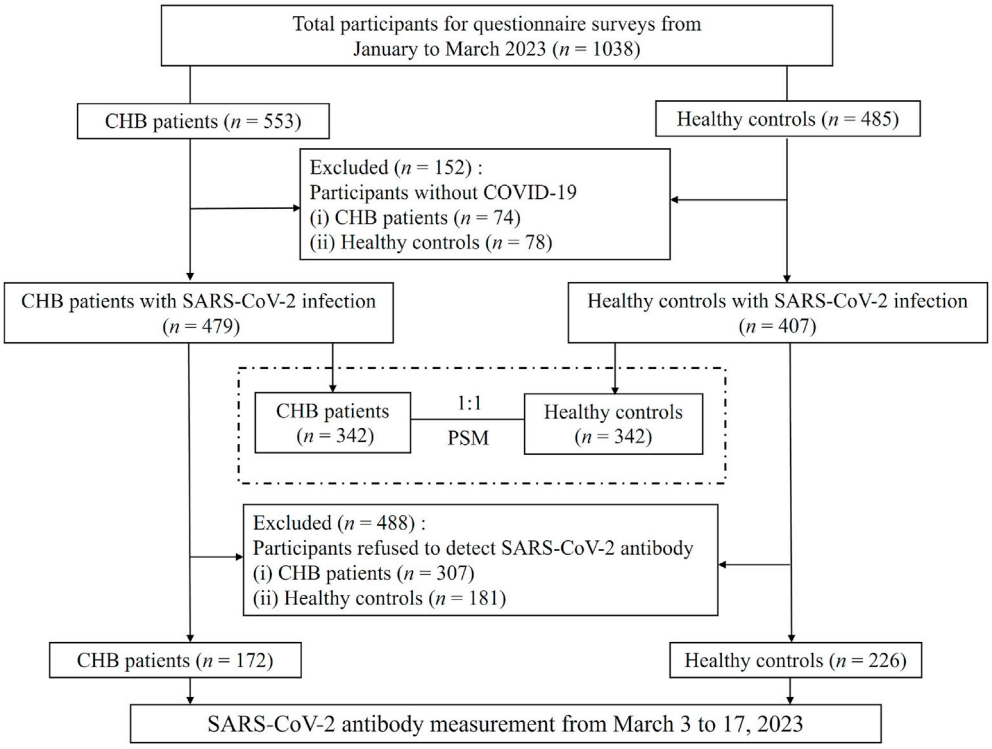

Fig. 1. Study flowchart of patient enrollment. All healthy controls were negative for HBV antigens. Abbreviations: CHB, chronic hepatitis B; COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; PSM, propensity score matching; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

pneumonia was not significantly different between the healthy control group and the CHB patients group (11.1% *vs.* 13.7%, $P = 0.297$). Among the participants, one individual from the healthy control group and two from the CHB patients group required hospitalization for pneumonia (0.3% *vs.* 0.6%, $P = 0.563$), whereas the remaining participants received medical care at home. A markedly higher prevalence of fever (90.4% *vs.* 85.4%, $P = 0.047$) along with significant increases in the mean fever duration (2.3 (1.0–3.0) days *vs.* 2.2 (1.0–3.0) days, $P = 0.048$) were observed in the healthy control group compared to the CHB patients group. The mean days post-symptom onset (DPSO) was longer in the healthy control group compared to the CHB patients (11.1 (5.0–14.0) days *vs.* 9.2 (5.0–14.0) days, $P = 0.015$) (Table 1).

3.3. Comparable SARS-CoV-2 antibody responses between two cohorts following Omicron BA.5 infection

The male and female cohorts were segregated to analyze the levels of SARS-CoV-2 antibodies. In the male population, the CHB patients exhibited higher levels of SARS-CoV-2 antibodies than the healthy control group. In the female population, the CHB patients displayed slightly lower antibody levels than the control group. However, the analysis of antibody levels, with or without consideration of sex, demonstrated no significant differences between the two cohorts (Fig. 2A and Table 2).

3.4. Increased SARS-CoV-2 antibody responses in CHB patients following vaccinations

After comparing the three groups (unvaccinated group, two-dose group, and three-dose group), the CHB patients and healthy control group demonstrated similar SARS-CoV-2 antibody levels (Fig. 2B and Table 2). There were no significant differences in SARS-CoV-2 antibody levels among the three vaccination subgroups in the healthy control group ($P = 0.211$). Furthermore, pairwise comparisons did not show significant differences (unvaccinated *vs.* two-dose group, $P = 0.239$; unvaccinated *vs.* three-dose group, $P = 0.082$; two-dose *vs.* three-dose group, $P = 0.650$). Similarly, in the CHB patients, no significant difference was found (unvaccinated *vs.* two-dose *vs.* three-dose groups, $P = 0.212$; unvaccinated *vs.* two-dose group, $P = 0.420$; unvaccinated *vs.* three-dose group, $P = 0.112$; two-dose *vs.* three-dose groups, $P = 0.318$) (Fig. 2C and Supplemental Table 2). However, in both cohorts, the SARS-CoV-2 antibody levels increased by approximately 1.5-fold after the administration of booster vaccinations (three-dose group) when compared with the unvaccinated group.

3.5. Changes of liver functions in HBV patients following Omicron BA.5 infection

To assess the effect of Omicron BA.5 infection on liver functions in the CHB patients, ten biochemical indexes of liver functions were analyzed using blood samples. No significant differences in the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), gamma-glutamyl transferase (GGT), creatine kinase (CK), lactate dehydrogenase (LDH), albumin (ALB), total bile acid (TBA), and alpha-fetoprotein (AFP) were found before and after Omicron BA.5 infection, except for globulin (GLB, 29.72 (20.54–44.20) g/L *vs.* 31.62 (22.19–52.80) g/L, $P < 0.0001$), which increased significantly after Omicron BA.5 infection (Fig. 3A–J and Table 3). Overall, these data indicate that Omicron BA.5 infection is not likely to affect liver functions in patients with CHB.

3.6. Changes of HBV virological markers following Omicron BA.5 infection

Blood samples were obtained from patients with CHB for testing HBV virological markers. Specifically, the serum levels of HBV DNA, HBsAg, HBeAg, and HBeAb were measured to assess any alterations after Omicron BA.5 infection. Consequently, HBV DNA, HBsAg, and HBeAg were all comparable. However, HBeAb levels increased significantly, indicating a notable change in patients with CHB and Omicron BA.5 infection (Supplemental Fig. 1 and Table 3).

Table 1
Characteristics of confirmed COVID-19 cases in two cohorts after PSM ($N = 684$).

Characteristics	Healthy control ($n = 342$)	CHB patients ($n = 342$)	*P*-value
Age (years)	35.6 (26.0–43.0)	35.9 (26.0–41.0)	0.740
Male, *n* (%)	164 (48.0)	190 (55.6)	0.056
Vaccination status for COVID-19[a], *n* (%)	327 (95.6)	320 (93.6)	0.318
Unvaccinated	15 (4.4)	22 (6.4)	
One dose	7 (2.0)	6 (1.8)	
Two doses	45 (13.2)	90 (26.3)	
Three doses	275 (80.4)	224 (65.5)	<0.001
COVID-19-related symptoms, *n* (%)			
Fever	309 (90.4)	292 (85.4)	0.047
Pharyngodynia	209 (61.1)	205 (59.9)	0.775
Myalgia	220 (64.3)	202 (59.1)	0.157
Headache	187 (54.7)	186 (54.4)	0.939
Cough	220 (64.3)	235 (68.7)	0.225
Expectoration	138 (40.4)	121 (35.4)	0.181
Nasal congestion	136 (39.8)	135 (39.5)	0.983
Runny nose	115 (33.6)	106 (31.0)	0.462
Diarrhea	35 (10.2)	21 (6.1)	0.051
Pneumonia[b]	38 (11.1)	47 (13.7)	0.297
Mean fever duration[c] (day)	2.3 (1.0–3.0)	2.2 (1.0–3.0)	0.048
Hospitalization, *n* (%)	1 (0.3)	2 (0.6)	0.563
DPSO[d]	11.1 (5.0–14.0)	9.2 (5.0–14.0)	0.015

Data are shown as *n* (%) or median (25th and 75th percentiles).
Abbreviations: CHB, chronic hepatitis B; COVID-19, coronavirus disease 2019; DPSO, days post-symptom onset; PSM, propensity score matching.
[a] All vaccines mentioned here are inactivated types and vaccination status was defined as receiving two doses of vaccines and a third dose was treated as booster.
[b] Detection of viral pneumonia by chest imaging.
[c] The mean fever duration for all participants was calculated as the time-weighted average in the same group from fever onset to the time the body temperature normalized.
[d] DPSO was defined as the period from the onset of symptoms to their disappearance.

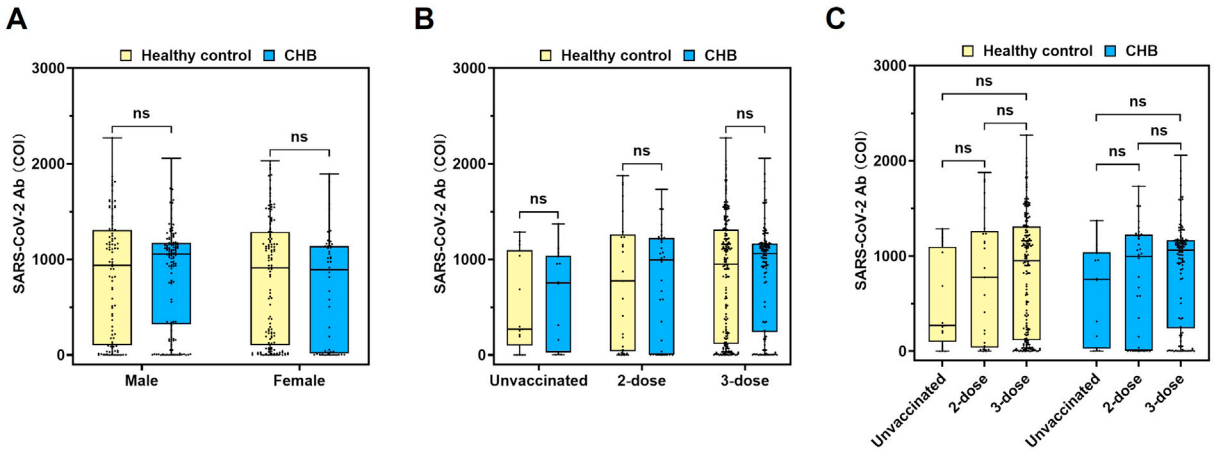

Fig. 2. SARS-CoV-2 antibody levels in both cohorts after Omicron BA.5 infection or vaccinations. (A) Comparison of SARS-CoV-2 antibody levels between the healthy control and CHB patients by sex. **(B)** Comparison of SARS-CoV-2 antibodies between the healthy control and CHB patients without vaccinations or vaccinated with two or three doses. **(C)** Comparison of SARS-CoV-2 antibodies within the same cohort without vaccinations or vaccinated with two or three doses respectively. In both cohorts, the levels of SARS-CoV-2 antibodies increased in those who received two or three doses of vaccines. Abbreviations: Ab, antibody; CHB, chronic hepatitis B; COI, cut-off index; ns, not significant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2
SARS-CoV-2 antibody levels in two cohorts with different number of vaccinations.

Variable	Healthy control[a]		CHB patients[b]		*P*-value
	n	SARS-CoV-2 Ab (COI)	*n*	SARS-CoV-2 Ab (COI)	
Total	226	921.80 (112.21–1286.83)	172	1024.93 (162.57–1162.25)	0.562
Male	96	938.74 (111.21–1300.04)	124	1056.61 (334.08–1170.41)	0.919
Female	130	909.62 (113.35–1279.55)	48	890.57 (22.71–1138.48)	0.160
Unvaccinated	13	269.68 (194.09–1038.66)	14	754.27 (63.56–1010.85)	0.650
Two doses of vaccines	25	775.46 (54.21–1233.18)	34	995.02 (13.01–1221.36)	0.701
Three doses of vaccines	183	949.63 (118.09–1309.40)	118	1061.86 (276.18–1164.52)	0.937

Data are shown as median (25th and 75th percentiles).
Abbreviations: Ab, antibody; CHB, chronic hepatitis B; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Five patients received one dose of vaccine in the healthy control group.
[b] Six patients received one dose of vaccine in the CHB patients.

3.7. CHB patients treated with TFV exhibited higher SARS-CoV-2 antibodies than those treated with ETV

In this study, CHB patients were divided into ETV group and tenofovir (TFV) group (including the use of TDF and TAF) according to various NA regimens, and the effects of ETV and TFV on liver functions, HBV virological markers, and SARS-CoV-2 antibody levels were examined in the CHB patients. The comparison between the ETV and TFV groups revealed no significant differences at the baseline levels of biochemical indexes of liver functions (Supplemental Table 3). However, significant increases in HBeAb (ETV, 0.340 (0.003–0.972) COI *vs.* 0.490 (0.003–1.170) COI, $P < 0.001$ and TFV, 0.310 (0.002–0.686) COI *vs.* 0.380 (0.003–0.876) COI, $P < 0.001$) and GLB (ETV, 29.9 (27.4–31.7) g/L *vs.* 31.2 (27.3–33.7) g/L, $P < 0.001$ and TFV, 29.7 (26.2–31.6) g/L *vs.* 31.9 (29.0–34.1) g/L, $P < 0.0001$) were observed in the CHB patients treated with either regimens after Omicron BA.5 infection (Fig. 4A–D, Supplemental Fig. 2 and Supplemental Table 4). Moreover, the TFV group of patients with CHB exhibited significantly higher SARS-CoV-2 antibody levels than those of the ETV group (1065.1 (346.9–1188.5) COI *vs.* 765.5 (24.5–1119.1) COI, $P = 0.025$) (Fig. 4E), implying that TFV can serve as an optimal treatment for patients with CHB and Omicron BA.5 infection.

4. Discussion

Omicron BA.5 exhibits higher transmissibility but lower pathogenicity than previous SARS-CoV-2 variants.[12,13] This study involved a total of 1038 participants, with three hospitalized patients. This finding supports the idea that Omicron BA.5 has reduced pathogenicity. Accordingly, most COVID-19 symptoms were similar between the CHB patients and the control group, except for fever, which was less prevalent among patients with CHB. In addition, the CHB patients exhibited a notable reduction in the mean duration of fever and the mean time required for symptom relief. A portion of the pathological effects attributed to COVID-19 infection can be ascribed to the host immune response. In individuals with chronic hepatitis B virus infection, the immune system is characteristically suppressed, potentially leading to attenuated COVID-19 symptomatology in these patients.[5,7] These observations imply that coinfection with HBV does not influence the progression of severe COVID-19. Furthermore, this claim is reinforced by the comparable quantities of SARS-CoV-2 antibodies detected in both cohorts, indicating a similar degree of immunity against COVID-19.

The SARS-CoV-2 antibody response was evaluated to assess disease progression and efficacy of vaccination.[14] In our investigation of SARS-CoV-2 antibody responses, levels of IgG and IgM antibodies were assessed in both cohorts. Recognizing the value of sex-disaggregated data in informing optimal public health interventions,[15,16] we ensured the inclusion of both sexes in this study. Subsequent analysis revealed comparable levels of SARS-CoV-2 antibodies in both cohorts after sex disaggregation. In this study, most participants were administered inactivated booster vaccinations to protect against COVID-19.[17] Subsequently, both cohorts had similar levels of SARS-CoV-2 antibodies after

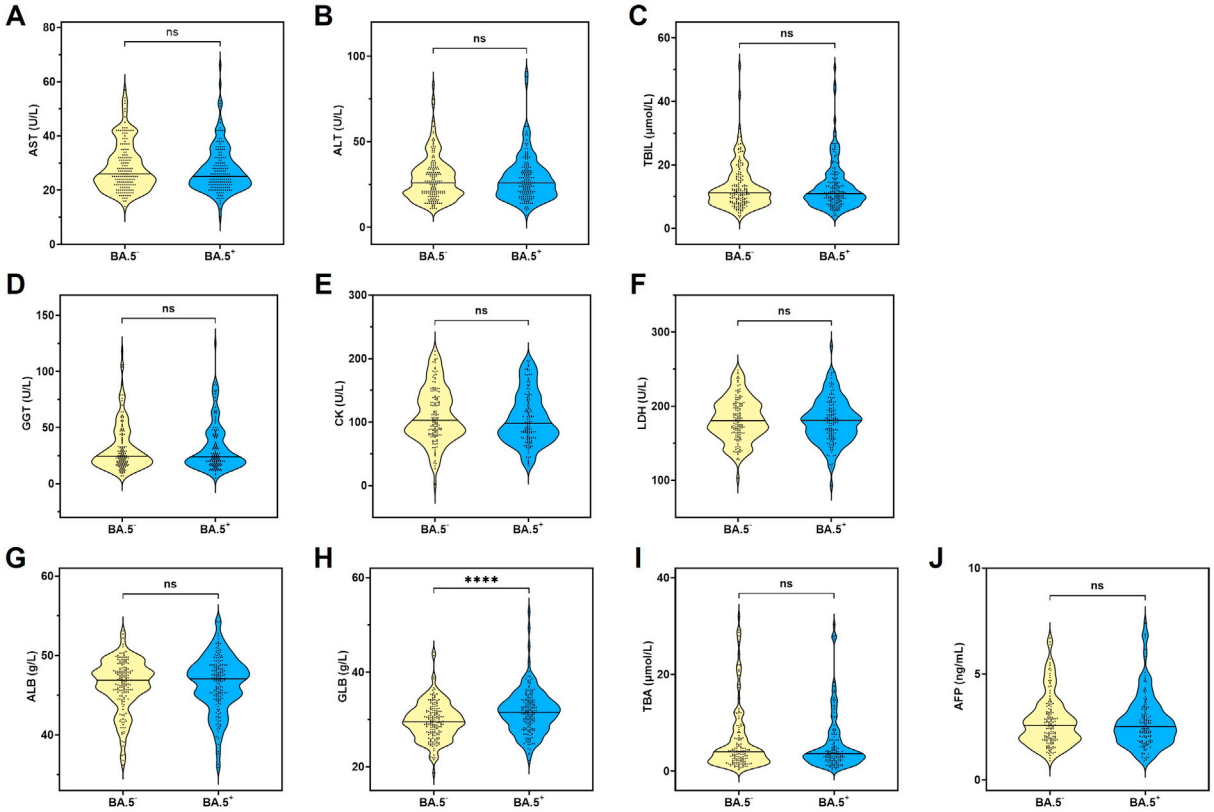

Fig. 3. Liver function indexes in patients with CHB before and after Omicron BA.5 infection. Ten biochemical indexes detected in patients with CHB were monitored to determine changes in liver functions before and after Omicron BA.5 infection. BA.5^{-} represents pre-Omicron BA.5 infection, and BA.5^{+} represents post-Omicron BA.5 infection. ****$P < 0.0001$. Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CK, creatine kinase; GGT, gamma-glutamyl transferase; GLB, globulin; LDH, lactate dehydrogenase; ns, not significant; TBA, total bile acids; TBIL, total bilirubin.

Table 3
Liver function indexes and markers of HBV infection in patients with CHB before and after Omicron BA.5 infection ($n = 172$).

Variable	Before infection	After infection	*P*-value
AST (U/L)	28.54 (15.18–57.00)	27.48 (11.77–66.00)	0.075
ALT (U/L)	28.37 (11.00–83.00)	28.38 (9.01–91.00)	0.594
TBIL (μmol/L)	12.94 (3.85–51.20)	12.98 (3.90–50.70)	0.570
GGT (U/L)	31.94 (7.00–118.00)	31.99 (6.26–125.00)	0.989
CK (U/L)	110.90 (10.38–212.00)	105.39 (32.02–197.00)	0.157
LDH (U/L)	181.95 (111.25–249.00)	180.48 (100.92–281.00)	0.539
ALB (g/L)	46.29 (36.58–53.10)	46.49 (36.15–54.30)	0.233
GLB (g/L)	29.72 (20.54–44.20)	31.62 (22.19–52.80)	<0.0001
TBA (μmol/L)	6.16 (0.41–32.00)	5.57 (0.43–30.30)	0.618
AFP (ng/mL)	2.78 (0.96–6.69)	2.77 (0.92–7.40)	0.746
HBV DNA (IU/mL)	2.00 (0–46.00)	3.04 (0–134.00)	0.338
HBsAg (IU/mL)	1124.29 (0–17046.00)	1061.67 (0–15257.00)	0.228
HBeAg (COI)	0.18 (0.06–0.96)	0.17 (0.07–0.81)	0.336
HBeAb (COI)	0.340 (0.002–1.440)	0.450 (0.002–2.140)	<0.0001

Data are shown as median (1st and 100th percentiles).
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; COI, cut-off index; GGT, gamma-glutamyl transferase; GLB, globulin; HBeAb, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; LDH, lactate dehydrogenase; TBA, total bile acids; TBIL, total bilirubin.

receiving booster vaccinations. However, these levels increased by approximately 1.5-fold in both cohorts compared with the unvaccinated cohort, indicating the protective efficacy of booster vaccinations.

HBV and SARS-CoV-2 coinfection was documented to exacerbate liver burden and increase the risk for patients with CHB.[18–20] But in our study, we did not find a single serious case due to these two viruses' superinfection. This can be attributed to the diminished pathogenicity of Omicron BA.5 as mentioned earlier, which reduces the likelihood of triggering an inflammatory storm, and the administration of NAs to manage HBV, resulting in the absence of significant injury in patients with CHB. However, a notable rise in globulin levels was observed in patients with CHB and Omicron BA.5 infection, possibly due to heightened humoral responses defending against either SARS-CoV-2 or HBV. These findings align with those of previous studies indicating that HBV and SARS-CoV-2 coinfection does not exacerbate liver damage or lead to liver-related complications in patients with CHB.[21,22]

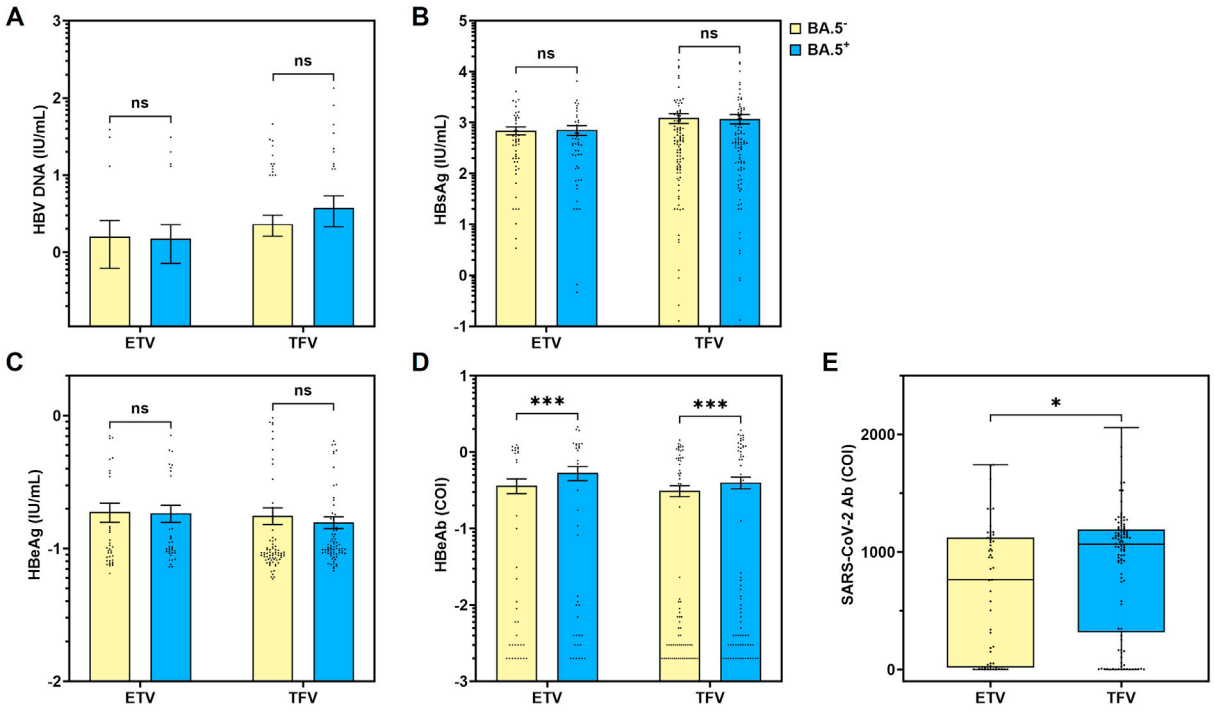

Fig. 4. HBV markers and SARS-CoV-2 antibody levels in patients with CHB treated using ETV versus TFV before and after Omicron BA.5 infection. (A–D) Four HBV virological markers detected in patients with CHB were evaluated for their changes before and after Omicron BA.5 infection comparing the ETV and TFV groups. BA.5^{-} represents pre-Omicron BA.5 infection, and BA.5^{+} represents post-Omicron BA.5 infection. Data are presented as the mean ± standard error of the mean. **(E)** Comparison of SARS-CoV-2 antibodies in patients with CHB between the ETV and TFV groups after Omicron BA.5 infection. Data are presented as the median (25th and 75th percentiles). *P < 0.05 and ***P < 0.001. Abbreviations: CHB, chronic hepatitis B; COI, cut-off index; ETV, entecavir; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBeAb, hepatitis B envelope antibody; ns, not significant; TFV, tenofovir.

In accordance with the Guidelines for The Prevention and Treatment of Chronic Hepatitis B (2022 Edition) published by the Chinese Medical Association,[23] HBV reactivation was characterized as an increase in at least 2 log10 IU/mL from the initial level of HBV DNA or the conversion of HBV DNA or HBsAg from negative to positive. COVID-19 or COVID-19 treatment can potentially trigger HBV reactivation.[8,24,25] In this study, the HBV DNA levels in patients with CHB were examined before and after Omicron BA.5 infection. The results showed that HBV DNA levels remained relatively stable and undetectable in >90% of patients with CHB. Furthermore, no reversion of HBsAg from negative to positive was observed. Among the 172 patients with CHB, only 13 (7.6%) exhibited a slight increase in HBV DNA levels, which remained below 2 log10 IU/mL. However, 11 out of 13 participants experienced reversion from negative to positive HBV DNA, indicating a reactivation of the virus in patients with CHB after Omicron BA.5 infection. The long-term presence of positive HBeAb was associated with the integration of the HBV DNA into the host hepatocyte chromosome DNA, leading to the establishment of HBV latency.[26] In this study, we observed a significant increase in HBeAb levels in patients with CHB and Omicron BA.5 infection, which may serve as a predictive marker for HBV latency. Collectively, our findings indicate that Omicron BA.5 infection does not significantly alter liver function but enhances humoral responses against HBV, which appears to be more pronounced in patients with CHB and Omicron BA.5 infection.

To examine the effects of NA regimens on the clinical outcomes of patients with CHB after Omicron BA.5 infection, a comparative analysis was conducted between ETV and TFV as treatments for patients with CHB. Both regimens exhibited a notable rise in globulin levels after Omicron BA.5 infection, indicating an augmented humoral response against viral agents. Furthermore, neither regimen had a significant effect on the outcome of HBeAb, which exhibited a significant increase after Omicron BA.5 infection. These findings indicate no discernible differences in the effects of ETV and TFV on liver functions and HBV virological markers. Notably, the SARS-CoV-2 antibody levels significantly increased in patients with CHB treated with TFV compared with those treated with ETV after Omicron BA.5 infection. TFV was approved for the treatment of HIV and subsequently developed to treat CHB.[27] TFV can bind to RNA-dependent RNA polymerase (RdRp) and terminate RNA synthesis of SARS-CoV-2,[28–30] and the combination of TFV with interferon was supposed to improve the therapeutics for patients with CHB.[31,32] Furthermore, compared with ETV, TFV was associated with a significantly lower risk of HCC for treating patients with naive CHB.[33] In this regard, the enhanced therapeutic efficacy of TFV compared with ETV reflected by the significantly high levels of SARS-CoV-2 antibodies in patients with CHB in this study indicates that TFV may be the preferred treatment option for patients with CHB in terms of COVID-19 prevention. Nevertheless, further investigation is warranted to ascertain the therapeutic benefits of TFV against other strains of coronavirus in patients with CHB.[34,35]

This study has several limitations. First, most participants received booster vaccinations approximately 6 months before being diagnosed with Omicron BA.5 infection, which introduces the possibility that SARS-CoV-2 infection could have influenced the analysis of SARS-CoV-2 antibody levels despite vaccination. We also hypothesized that the vaccinated groups would exhibit a significantly higher increase in SARS-CoV-2 antibody levels than the unvaccinated groups. However, the limited number of unvaccinated individuals in both cohorts further restricts the statistical power of our findings. Furthermore, comorbidities, such as diabetes, hypertension, and obesity, were not investigated in either cohort, potentially leading to unidentified confounding factors within our study.

5. Conclusions

In this study, the severity of COVID-19 symptoms did not increase in patients with CHB. We also showed the efficacy of COVID-19 booster vaccinations against Omicron BA.5, with no notable alterations in liver functions despite significant HBV reactivation indicated by the increased HBeAb levels in patients with CHB after Omicron BA.5 infection. These observed changes occurred irrespective of the NA regimens. However, SARS-CoV-2 antibody levels in the TFV-treated CHB patients increased significantly compared with that in the ETV-treated CHB patients after Omicron BA.5 infection. These findings hold potential significance in guiding the development of care and therapeutics for patients with CHB and COVID-19 in the future.

Data availability statement

The datasets used and/or analyzed during the study are available from the corresponding author, Ying Zhang, upon reasonable request.

Authors' contributions

Peipei Wang: Writing – original draft, Methodology. **Junjian Chen:** Writing – original draft. **Dabiao Chen:** Validation, Writing – review & editing. **Ziying Lei:** Data curation, Writing – review & editing. **Zhishuo Mo:** Supervision, Data curation. **Ying Zhang:** Supervision, Conceptualization. All authors approved the final version of this manuscript.

Declaration of competing interest

The authors declare that there are no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.livres.2024.11.003.

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