Heliyon 10 (2024) e28405

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Acceptance, safety, and immunogenicity of a booster dose of inactivated SARS-CoV-2 vaccine in patients with primary biliary cholangitis

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ARTICLE INFO

Keywords:
Primary biliary cholangitis
COVID-19
Antibody
Vaccine
Immune response

ABSTRACT

Inactivated coronavirus disease 2019 (COVID-19) vaccines showed impaired immunogenicity in some autoimmune diseases, but it remains unclear in primary biliary cholangitis (PBC). This study aimed to explore the antibody response to the inactivated COVID-19 vaccine in individuals with PBC, as well as to evaluate coverage, safety, and attitudes toward the COVID-19 vaccine among them. Two cohorts of patients with PBC were enrolled in this study. One cohort was arranged to evaluate the immunogenicity of the inactivated COVID-19 vaccine, another cohort participated in an online survey. The titers of the anti-receptor-binding domain (RBD)-specific immunoglobulin G (IgG), neutralizing antibody (NAb) toward severe acute respiratory syndrome coronavirus 2 wild-type, and NAb toward Omicron BA.4/5 subvariants were detected to assess antibody response from the vaccine. After booster vaccination for more than six months, patients with PBC had significantly lowered levels of anti-RBD-specific IgG compared to HCs, and the inhibition rates of NAb toward wild-type also declined in individuals with PBC. The detected levels of NAb toward Omicron BA.4/5 were below the positive threshold in patients with PBC and HCs. Laboratory parameters did not significantly correlate with any of the three antibodies. The online survey revealed that 24% of patients with PBC received three COVID-19 vaccines, while 63% were unimmunized. Adverse effect rates after the first, second, and third vaccine doses were 6.1%, 10.3%, and 9.5%, respectively. Unvaccinated patients with PBC were more worried about the safety of the vaccine than those who were vaccinated ($P = 0.004$). As a result, this study fills the immunological assessment gap in patients with PBC who received inactivated COVID-19 vaccines.

1. Introduction

The coronavirus disease 2019 (COVID-19) has placed a heavy burden on medical treatment, public health, and the economy [1].

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https://doi.org/10.1016/j.heliyon.2024.e28405
Received 15 October 2023; Received in revised form 18 March 2024; Accepted 18 March 2024
Available online 19 March 2024

Primary biliary cholangitis (PBC) is an autoimmune disease leading to non-suppurative destruction of intrahepatic bile ducts and specific anti-mitochondrial antibodies [2]. Patients with PBC might not be more prone to contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [3,4]. However, individuals with PBC were reported to have poor prognosis for COVID-19 because their hospitalization rates and mortality differ significantly from that of the general population [4].

While specific medications have been utilized in the clinical management of COVID-19, the COVID-19 vaccine remains essential in decreasing virus transmission, severity, and mortality of COVID-19 [5]. Humoral response detection is critical for assessing the efficiency of the COVID-19 vaccine in immunocompromised individuals, such as solid tumors, hematological malignancies, and autoimmune diseases [6]. A dysregulated immune system is associated with PBC pathogenesis through the abnormal activation of various immune cell subsets [7], which may affect the COVID-19 vaccine's effectiveness. Furthermore, critical or severe COVID-19 patients may experience cytokine storms which are observed in the presence of elevated levels of proinflammatory cytokines, such as interferon-gamma, interleukin, chemokine, etc [8,9]. Patients with PBC also showed increased circulating levels of cytokines-related proinflammatory cytokines [10–12], which may exacerbate the severity of COVID-19 when they become infected, making the prognosis poor. Therefore, patients with PBC should receive a COVID-19 vaccine to prevent infections and severe COVID-19. However, the immunogenicity of the COVID-19 vaccine in individuals with PBC is still unknown, resulting in unreported vaccination effects in patients with PBC. There has been only one study investigating the antibody response of the second dose of mRNA vaccine in individuals with PBC and primary sclerosing cholangitis (PSC), and no significant alternation was found in humoral immunity within PBC/PSC and healthy controls (HCs) [13].

In China, the inactivated vaccine is the main type of COVID-19 vaccine used widely. In this study, the levels of the anti-receptor-binding domain (RBD)-specific immunoglobulin G (IgG), neutralizing antibody (NAb) toward SARS-CoV-2 wild-type (WT), and NAb toward Omicron BA.4/5 subvariants were detected, in order to explore the humoral response to the inactivated COVID-19 vaccine in individuals with PBC who completed booster vaccinations. To further guide vaccination, we also investigated coverage, safety, and attitudes toward the COVID-19 vaccine among individuals with PBC.

2. Materials and methods

2.1. Study cohort

Two cohorts were enrolled at Peking Union Medical College Hospital (PUMCH). In order to explore the immunogenicity of the vaccine, 73 patients with PBC and 73 HCs were included in cohort 1 (Fig. 1). Another cohort comprising 86 patients with PBC participated in an online survey constructed using www.wjx.cn to investigate their attitude, coverage, and safety regarding the COVID-19 vaccine among patients with PBC (Fig. 1) (The questionnaire was uploaded as Supplementary file 1). Additionally, an online survey was conducted to assess SARS-CoV-2 infection (The questionnaire was uploaded as Supplementary file 2). The European Association for the Study of Liver Diseases' practice guidelines for PBC diagnosis were applied to all patients with PBC. The criteria for patients with PBC in cohort 1 were as follows: (1) After a definite PBC diagnosis, a two-dose strategy of inactivated vaccine (BBIBP-CorV or CoronaVac) were shotted; (2) Patients with PBC had detailed medical records and laboratory parameters. Among all individuals in cohort 1, the exclusion criteria were as follows: (1) Fever, cough, or fatigue while sampling; (2) individuals with a history of SARS-CoV-2 infection before sampling; (3) < 18 years. The Medical Ethics Committee of PUMCH approved this study. Written Informed consents were obtained from all participants. The EC approval number of this study is I-23PJ174.

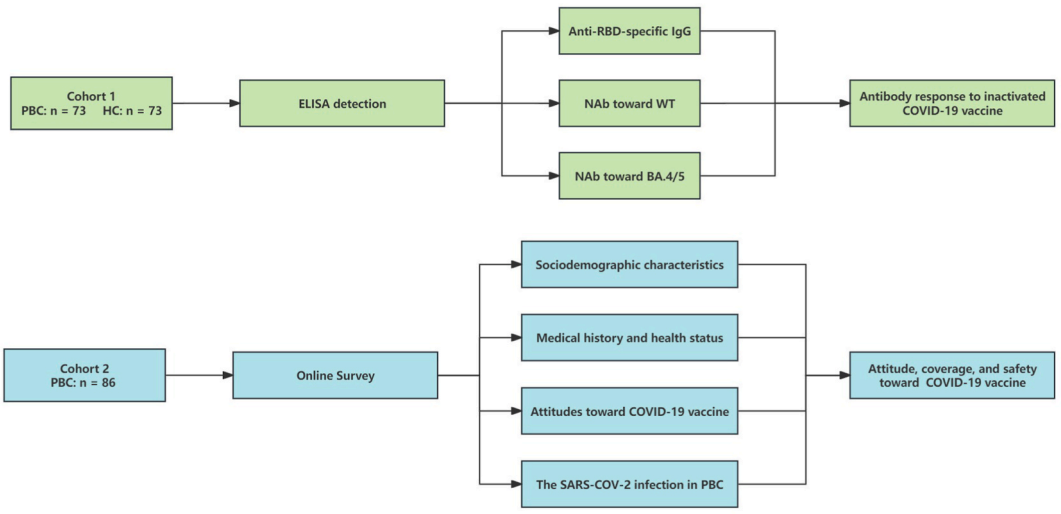

Fig. 1. Flow chart of the study.

Table 1
Demographics and clinical characterization of patients with PBC and HCs.

	2nddoseafter14–89days			2nddoseafter180days			3rddoseafter14–89days			3rddoseafter90–180days			3rddoseafter180days		
Variables	HCs (n = 7)	PBC (n = 7)	*P*	HCss (n = 13)	PBC (n = 13)	*P*	HCs (n = 12)	PBC (n = 12)	*P*	HCs (n = 13)	PBC (n = 13)	*P*	HCs (n = 28)	PBC (n = 28)	*P*
Age-year	34 ± 6.34	65 ± 10.17	< 0.001	33.92 ± 6.22	67.58 ± 6.72	< 0.001	60 (52–65)	62.92 ± 11.16	0.198	64 (47–67)	57.46 ± 13.33	0.724	63 (53–69)	63 (50–68)	0.818
Female-sex	5 (71.4%)	5 (71.4%)	1	9 (69.2%)	13 (100.0%)	0.096	10 (83.3%)	10 (83.3%)	1	11 (84.6%)	11 (84.6%)	1	24 (85.7%)	23 (82.1%)	1
Period of last vaccination at the time of sampling (day)	55.71 ± 27.32	53.85 ± 26.74	0.9	317.85 ± 93.26	309.77 ± 90.98	0.825	61.75 ± 23.72	51.92 ± 22.39	0.219	144.15 ± 23.72	138.31 ± 28.11	0.572	235.79 ± 32.77	248.5 (215.25–302.75)	0.114
Serological examinations															
ALP-U/L	63.00 ± 15.64	130.28 ± 30.15	< 0.001	64.69 ± 20.67	92 (80–133)	< 0.001	76.55 ± 23.67	157 (97–187)	0.002	71.23 ± 20.41	154.08 ± 61.15	< 0.001	76.04 ± 18.22	109 (92–107)	< 0.001
GGT-U/L	24.29 ± 18.07	70.29 ± 52.44	0.038	20.46 ± 16.80	62 (41–89)	< 0.001	21.64 ± 11.85	61 (32–147)	< 0.001	15 (14–23)	76.23 ± 57.35	< 0.001	18 (14–25)	58 (37–176)	< 0.001
ALT-U/L	18.43 ± 11.54	20 (17–59)	0.097	14 (9–19)	24 (15–33)	< 0.001	14 (12–22)	32.83 ± 21.30	0.151	15 (14–22)	34.38 ± 17.72	0.019	17.61 ± 6.62	23 (16–44)	0.013
AST-U/L	20.00 ± 5.57	31.71 ± 12.51	0.128	19.17 ± 6.84	36 (18–43)	0.006	21 (17–30)	41.67 ± 21.13	0.009	20 (19–22)	37.00 ± 9.24	< 0.001	23.32 ± 5.55	35 (22–44)	< 0.001
TP-g/Ll	74.00 ± 2.71	72.29 ± 5.06	0.444	72 (70–75)	76.00 ± 5.56	0.871	72.36 ± 3.98	75.43 ± 3.58	0.066	71.46 ± 3.38	78.00 ± 6.08	0.002	71.96 ± 3.21	76.75 ± 5.89	< 0.001
ALB-g/L	46.14 ± 1.68	44.57 ± 2.30	0.170	46.31 ± 2.21	43.08 ± 2.64	0.003	44.91 ± 2.30	43.50 ± 2.61	0.186	44.85 ± 6.34	43 (42–46)	0.336	44.46 ± 1.37	43 (42–46)	0.191
TBIL—μmol/L	13.19 ± 3.95	12.10 (11.60–16.50)	0.710	12.88 ± 2.76	14.92 ± 9.30	0.311	11.2 (8.7–11.4)	12.21 ± 2.86	0.608	14.58 ± 2.56	12.24 ± 3.44	0.06	12.1 (9.6–15.1)	12.1 (10.6–16.8)	0.793
DBIL—μmol/L	4.06 ± 1.02	3.7 (3.5–4.1)	0.902	3.78 ± 0.73	3.6 (3.4–4.9)	1	2.7 (2.5–5.1)	4.06 ± 1.72	0.379	4.23 ± 0.96	3.98 ± 1.58	0.545	3.78 ± 1.27	3.9 (3.4–5.3)	0.171
TBA—μmol/L[a]	NA	6.5 (5.1–6.6)	NA	NA	6.3 (4.4–12.2)	NA	NA	9.10 (7.78–15.83)	NA	NA	11.54 ± 8.38	NA	NA	9.6 (6.5–13.3)	NA
IgG—g/L[b]	NA	11.35 ± 1.89	NA	NA	15.39 ± 4.18	NA	NA	14.51 (11.23–17.89)	NA	NA	15.98 ± 4.32	NA	NA	14.69 (12.24–15.80)	NA
IgA—g/L[b]	NA	2.81 ± 0.45	NA	NA	3.30 ± 1.23	NA	NA	2.28 ± 1.18	NA	NA	3.15 ± 1.52	NA	NA	2.89 ± 1.56	NA
IgM—g/L[b]	NA	1.19 ± 0.46	NA	NA	3.19 ± 1.67	NA	NA	2.85 (1.02–6.55)	NA	NA	2.98 ± 1.91	NA	NA	1.94 (1.15–3.43)	NA

Abbreviations: HCs, healthy controls; PBC, primary biliary cholangitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; DBIL, direct bilirubin; GGT, gamma glutamyl transferase; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LDL, low-density lipoprotein; TBA, total bile acid; TBIL, total bilirubin; TC, total cholesterol; TG, total triglycerides; TP, total protein; UA, uric acid.

[a] available in 69 patients with PBC.

[b] available in 61 patients with PBC.

2.2. Data and sample collection

The age, sex, and laboratory parameters of participants in cohort 1 were collected from the hospital information system of PUMCH. All participants' vaccination information was collected from the State Council client applet or responded to the online survey questionnaire. According to the vaccination status, participants in cohort 1 were divided into four subgroups: participants (PBC: n = 7; HCs: n = 7) who were fully vaccinated after 14–89 days; participants (PBC: n = 13; HCs: n = 13) who received their second dose after 180 days; participants (PBC: n = 12; HCs: n = 12) who got booster immunization after 14–89 days, participants (PBC: n = 13; HCs: n = 13) who were given their third dose after 90–180 days, and participants (PBC: n = 28; HCs: n = 28) who were shot with their third dose after 180 days. Each participant's EDTA plasma was collected after fasting for 10 h and then stored at −80 °C until use.

There were four major components to the online survey: (1) sociodemographic characteristics; (2) current health status and past history; (3) attitudes toward the COVID-19 vaccine; and (4) Infection condition of SARS-CoV-2 in patients with PBC. Detailed information on each component is shown in Supplementary file 1 and Supplementary file 2.

2.3. Three types of SARS-CoV-2 antibody detection

The participants in cohort 1 were detected with the anti-RBD-specific IgG (PROPRIUM, Hangzhou, China), and Nabs toward SARS-CoV-2 WT and Omicron BA.4/5 subvariant (Genscript, Nanjing, China). For this assay, anti-RBD antibody concentrations were calibrated to the first World Health Organization (WHO) international standard (NIBSC code: 20/136), and levels were transformed to binding antibody units per milliliter (BAU/ml) [14], with a conversion factor of 10. The assay provides nanograms as measurement values, and the measurement range for analysis was 1–100 ng/ml. A nanogram equals 10 BAU according to the first WHO international standard. Based on the performance of the assay, it shows 100% specificity, 97.8% sensitivity, and 10% coefficient of variation. The details are described in our previous study [15,16].

2.4. Statistical analysis

The IBM SPSS version 23.0 software was used to analyze the data. To assess the normality of the data distribution, the Shapiro-Wilk test was used. The mean and standard deviation were presented for normally distributed data, while the median [interquartile range] was presented for non-normally distributed data; continuous variables were compared with Student's t-test or the Mann–Whitney *U*

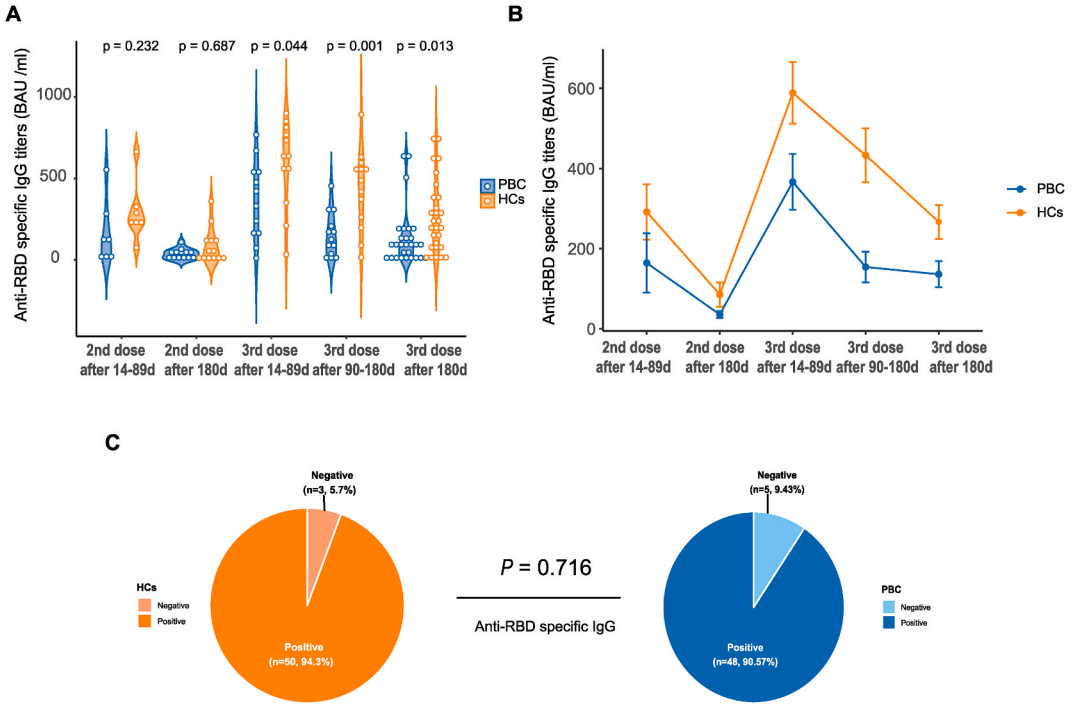

Fig. 2. Anti-RBD specific IgG is increased after third dose of inactivated COVID-19 vaccines among patients with PBC. (A) Levels (BAU/ml) of anti-RBD specific IgG in patients with PBC and HCs at pre- and post-booster (third) dose of inactivated vaccine. (B) Kinetics of anti-RBD specific IgG before and after triple dose injection. (C) Seropositivity of anti-RBD specific IgG in patients with PBC (blue) comparing with HCs (orange). For anti-RBD-specific IgG, 11.6 BAU/ml was a threshold to divide sero-positive and -negative samples. HCs, healthy controls; PBC, primary biliary cholangitis; RBD, receptor-binding domain. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

test, while the Kruskal-Wallis test was used to detect statistical differences between multiple groups. The chi-squared test or Fisher's exact test was applied for categorical variables. An analysis of Spearman's correlation between three types of detected antibodies and laboratory biomarkers was conducted. A two-tailed $P < 0.05$ was regarded as statistical significance. An online plot website was performed to make visualization [17].

3. Results

3.1. Individual characteristics in cohort 1 with regard to demographics and clinical features

There were five subgroups of patients with PBC and controls based on the vaccination dose, the interval between the sampling and vaccination, and humoral response. In the second injection of the vaccine for 90 days, there was a decline in humoral response [18–20], and NAb seropositivity decreased after the third dose for 90 days [21]. The five subgroups included individuals who received their second dose after 14–89 and after 180 days, and those who received their third inactivated vaccine dose after 14–89, after 90–180, and >180 days. The data on the clinical features of enrolled participants in cohort 1 are shown in Table 1. In all subgroups, HCs were matched in age and duration of vaccination.

3.2. Booster vaccination induced increased levels of anti-RBD-specific IgG and NAb toward WT among patients with PBC

After the second shot of the vaccine, there was no significant alternation between HCs and patients with PBC in anti-RBD-specific IgG (Fig. 2A; Table S1). However, anti-RBD-specific IgG titers were lower among individuals with PBC after the third sampling dose compared to HCs (Fig. 2A, data are shown in Table S1). Dynamic changes following each vaccine dose in patients with PBC (Fig. 2B), a significant decrease in anti-RBD-specific IgG was observed after two-dose vaccines of 180 days (35.69 ± 31.93 vs. 164.09 ± 196.34, $P = 0.001$; Table S1), while obvious increment was indicated at "post-third dose" (35.69 ± 31.93 vs. 366.66 ± 241.82, $P < 0.001$; Table S1). After booster vaccination, patients with PBC and HCs had comparable anti-RBD-specific IgG responses (90.6% vs. 94.3%, $P = 0.716$) (Fig. 2C).

After the third dose of 14–89 days, there was no significant alternation between HCs and patients with PBC in NAb inhibition rates toward WT (Fig. 3A, Table S1), whereas patients with PBC had significantly lower inhibition rates than those with HCs 90–180 and >180 days after booster vaccination (Fig. 3A; Table S1). In patients with PBC, plasma samples with post-third doses showed an increase

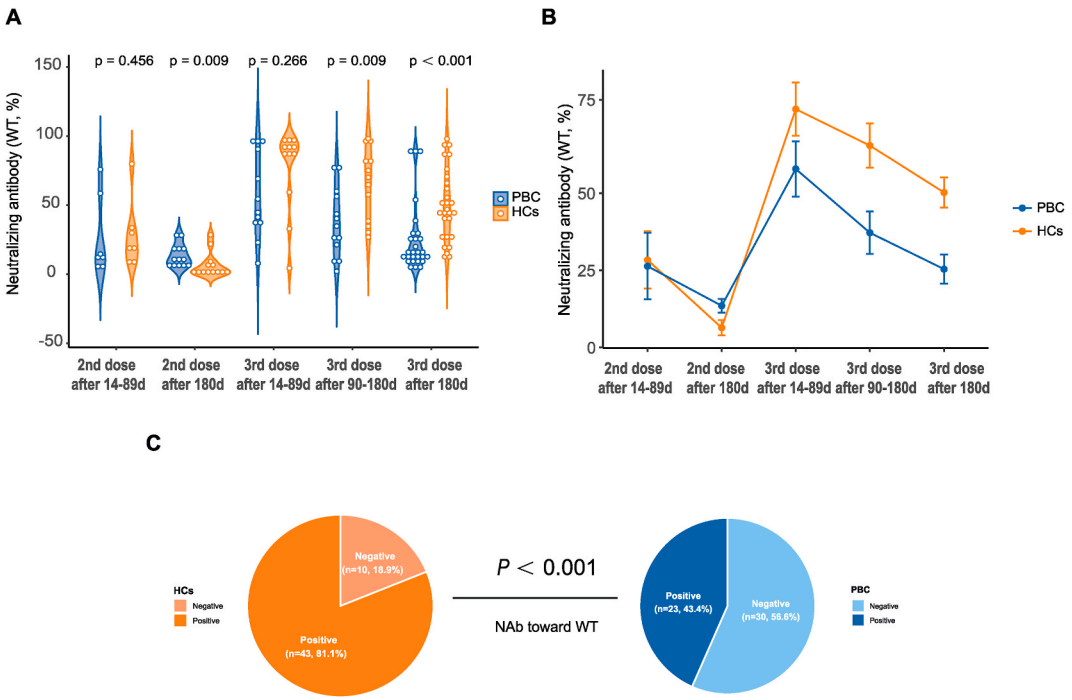

Fig. 3. Neutralizing effect to SARS-CoV-2 wild-type (WT) are elevated after triple dose of inactivated COVID-19 vaccines among patients with PBC. (A) Inhibition rates (%) of NAb toward WT detected in patients with PBC and HCs at pre- and post-booster (third) dose of inactivated vaccine. (B) Kinetics of NAb toward WT before and after triple dose injection. (C) Seropositivity of NAb toward WT in patients wiht PBC (blue) comparing with HCs (orange). The inhibition rate ≥30% was regarded as positive in neutralizing antibodies. HCs, healthy controls; PBC, primary biliary cholangitis; NAb, neutralizing antibody. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in NAb levels toward WT (13.56 ± 8.04 vs. 57.92 ± 31.19, $P < 0.001$; Table S1; Fig. 3B). Moreover, the positivity of NAb toward WT in patients with PBC was significantly different from that in HCs (43.4% vs. 81.1%, $P < 0.001$; Fig. 3C), especially in those who were given the third shot after 90–180 days (71.4% vs. 21.4%, $P < 0.001$; Table S2). Additionally, apparent discrepancies in the period between the last vaccination and sampling after receiving the third dose were observed between patients with PBC with the positivity of NAb toward WT and those without NAbs ($P < 0.001$, Table S3).

3.3. Patients with PBC showed waning humoral response to variants of concern after booster vaccination

The increase of NAb toward BA.4/5 before and after booster vaccination (0.32 [0–3.83] vs. 8.53 [5.65–19.43], $P < 0.001$; Table S1; Fig. 4B) was observed in patients with PBC. However, patients with PBC gradually reduced their levels of NAb toward BA.4/5 after booster vaccination (8.53 [5.65–19.43]vs. 1.85 [0–9.21], $P < 0.023$; 8.53 [5.65–19.43] vs. 2.85 [0.24–5.82], $P = 0.004$; Table S1; Fig. 4B). Moreover, levels of NAb toward BA.4/5 were still below the positive threshold that the kits provided after a third shot of the vaccine in all participants (Fig. 4A). In terms of seropositivity, all participants showed no significant alternation after booster vaccination in NAb toward BA.4/5 (5.7% vs. 15.1%, $P = 0.201$; Fig. 4C)

3.4. The relationship between vaccination duration of three types of antibodies after booster vaccination

In this study, no laboratory indicators were associated with the three types of detected antibodies (Fig. 5A). However, the time following the third dose was negatively associated with the titers of anti-RBD-specific IgG, NAb toward WT and BA.4/5 in all individuals (Fig. 5B). Furthermore, NAb toward WT and BA.4/5 indicated a significant correlation with anti-RBD-specific IgG, and NAb toward WT was also associated with NAb toward BA.4/5 (Fig. 5C).

3.5. Online survey of participants in cohort 2

The sociodemographic characteristics of the participants in Cohort 2 were used to perform an online survey (Table 2). Results from the online survey of patients with PBC revealed that only 24.4% (n = 21) got booster vaccination (Fig. 6A). However, 61.6% (n = 53) of patients with PBC remained unimmunized (Fig. 6A). The desire of unimmunized participants to get COVID-19 vaccination was investigated, and 11.3% (n = 6) refused the COVID-19 vaccine shot (Fig. 6B). "Doctors do not recommend vaccination" (n = 32, 60.4%) was the main reason for not getting COVID-19 vaccination (Fig. 6C). The inactivated COVID-19 vaccine showed good safety among patients with PBC because no self-reported adverse effects were observed in this cohort. Fatigue, sleeplessness, local pain,

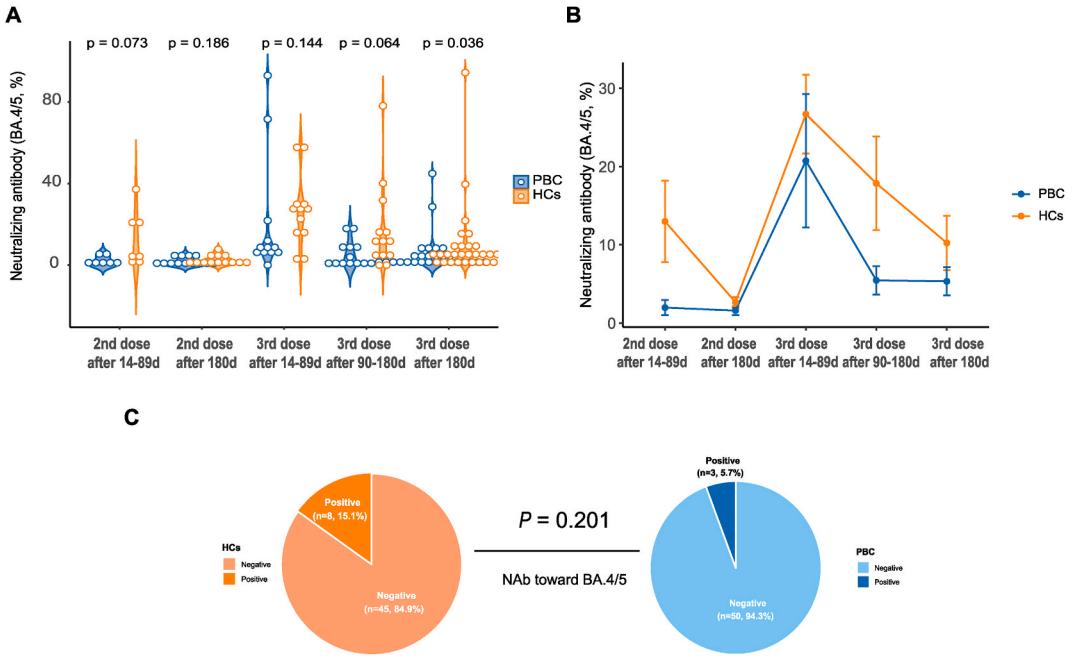

Fig. 4. Neutralizing effect to SARS-CoV-2 Omicron sublineage BA.4/5 are elevated after triple dose of inactivated COVID-19 vaccines among patients with PBC. (A) Inhibition rates (%) of NAb toward BA.4/5 detected in patients with PBC and HCs at pre- and post-booster (third) dose of inactivated vaccine. (B) Kinetics of NAb toward BA.4/5 before and after triple dose injection. (C) Seropositivity of NAb toward BA.4/5 in patients wiht PBC (blue) comparing with HCs (orange). The inhibition rate ≥30% was regarded as positive in neutralizing antibodies. HCs, healthy controls; PBC, primary biliary cholangitis; NAb, neutralizing antibody. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

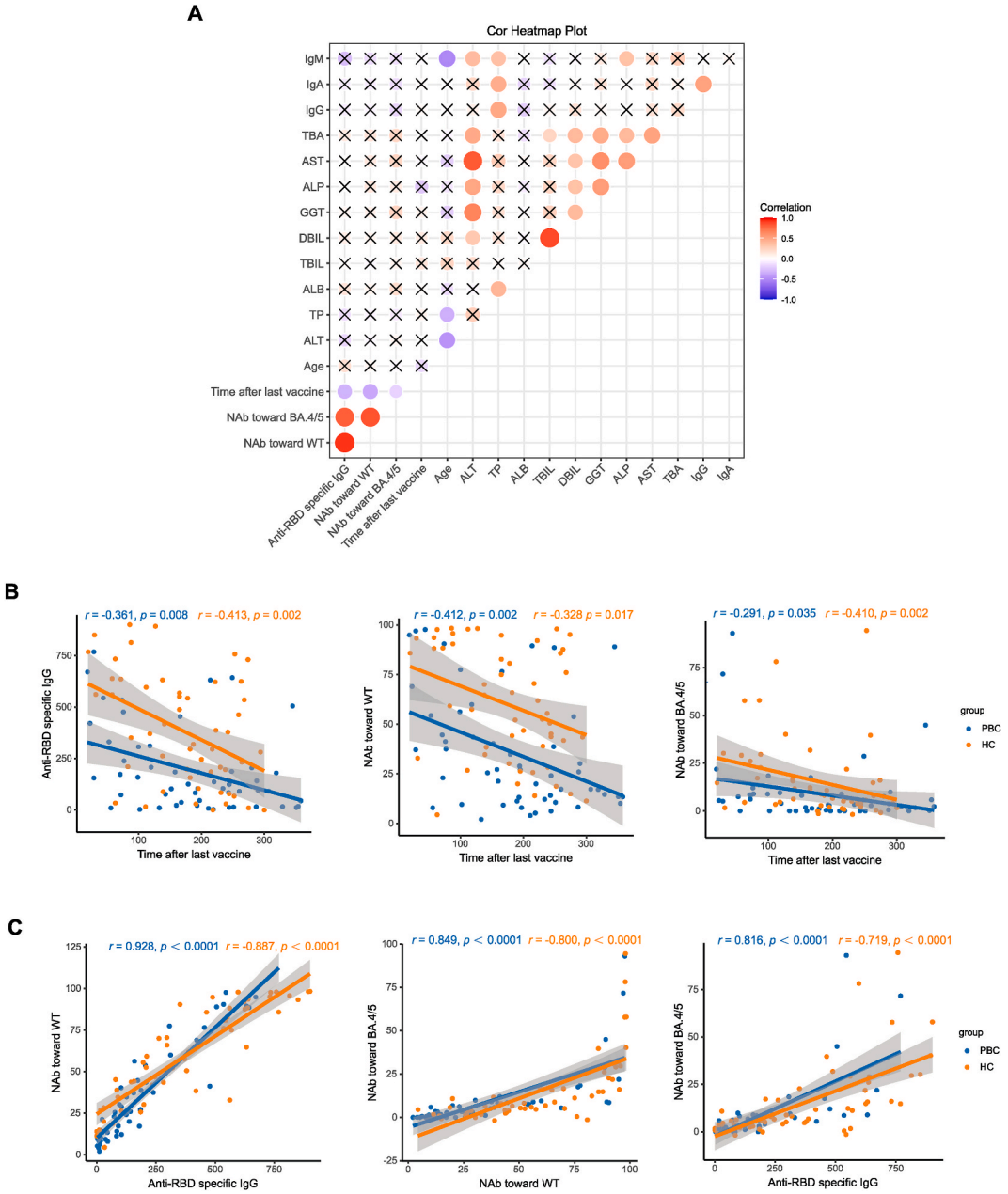

Fig. 5. Correlation of vaccination period and the magnitude of SARS-CoV-2 antibodies after the third dose. (A) Correlation heatmap visualized the association between SARS-CoV-2 antibodies and clinical characteristics among patients with PBC. (B) Associations of immunoglobulin G (IgG anti-RBD antibodies titers (BAU/ml), NAb toward WT (%), NAb toward BA.4/5 (%), and time after last vaccine. (C) Associations of IgG anti-RBD antibodies (BAU/ml), NAb against WT (%) and NAb against BA.4/5 (%). COVID-19, coronavirus disease 2019; HCs, healthy controls; PBC, primary biliary cholangitis; RBD, receptorbinding domain; NAb, neutralizing antibody; WT, wild-type.

headache, and pruritus were reported in patients with PBC who experienced adverse effects after receiving the inactivated vaccine (Table S4). No differences were observed in chronic disease, allergy, smoking, or drinking history between vaccinated and unvaccinated patients with PBC (Table S5). Compared with vaccinated patients, unvaccinated patients with PBC worried more about COVID-19 vaccine safety (Table S6). Additionally, they tended to acquire detailed information about COVID-19 vaccines from health workers (Table S6). Due to the Chinese government's optimal epidemic prevention policies, SARS-CoV-2 spread widely throughout China in early December 2022. There were 72 patients with PBC (83.7%) getting SARS-CoV-2 infection (Table S7). Moreover, a higher proportion of cohabitants (93.1%, n = 67, $P < 0.001$) had infection conditions of SARS-CoV-2 found in infected individuals with PBC compared to those uninfected (Table S7).

Table 2
Sociodemographic characteristics of the participants in Cohort 2.

Characteristic	All Participants (n = 86)	Unvaccinated participants (n = 53)	Vaccinated participants (n = 33)	X^2	*P*
Sex					
Male	10 (11.6%)	5 (9.4%)	5 (15.2%)	0.647	0.497
Female	76 (88.4%)	48 (90.6%)	28 (84.8%)		
Age group, years					
< 60	60 (69.8%)	17 (32.1%)	24 (72.7%)	13.473	< 0.001
≥60	26 (30.2%)	36 (67.9%)	9 (27.3%)		
Education level					
Below high school	15 (17.4%)	11 (20.8%)	4 (12.1%)	3.71	0.295
High school	16 (18.6%)	12 (22.6%)	4 (12.1%)		
College	46 (53.5%)	26 (49.1%)	20 (60.6%)		
Postgraduate	9 (10.5%)	4 (7.5%)	5 (15.2%)		
Marital status					
Single	1 (1.2%)	0	1 (3.0%)	2.066	0.559
Married or cohabitating	74 (86.0%)	47 (88.7%)	27 (81.8%)		
Divorced or separated	6 (7.0%)	3 (5.7%)	3 (9.1%)		
Widowed	5 (5.8%)	3 (5.7%)	2 (6.1%)		
Work status					
Unemployed	10 (11.6%)	7 (13.2%)	3 (9.1%)	10.41	0.015
Employed	33 (38.4%)	17 (32.1%)	16 (48.5%)		
Retired	42 (48.8%)	28 (52.8%)	4 (12.1%)		
Student	1 (1.2%)	1 (1.9%)	0		
Residence					
Rural	7 (8.1%)	5 (9.4%)	2 (6.1%)	0.31	0.703
Urban	79 (91.9%)	48 (90.6%)	31 (93.9%)		
Monthly personal income (Chinese yuan †)					
< 2000	6 (7.0%)	4 (7.5%)	2 (6.1%)	1.878	0.598
2000-4999	29 (33.7%)	20 (37.7%)	9 (27.3%)		
5000-10000	34 (39.5%)	18 (34.0%)	16 (48.5%)		
> 10000	17 (19.8%)	11 (20.8%)	6 (18.2%)		

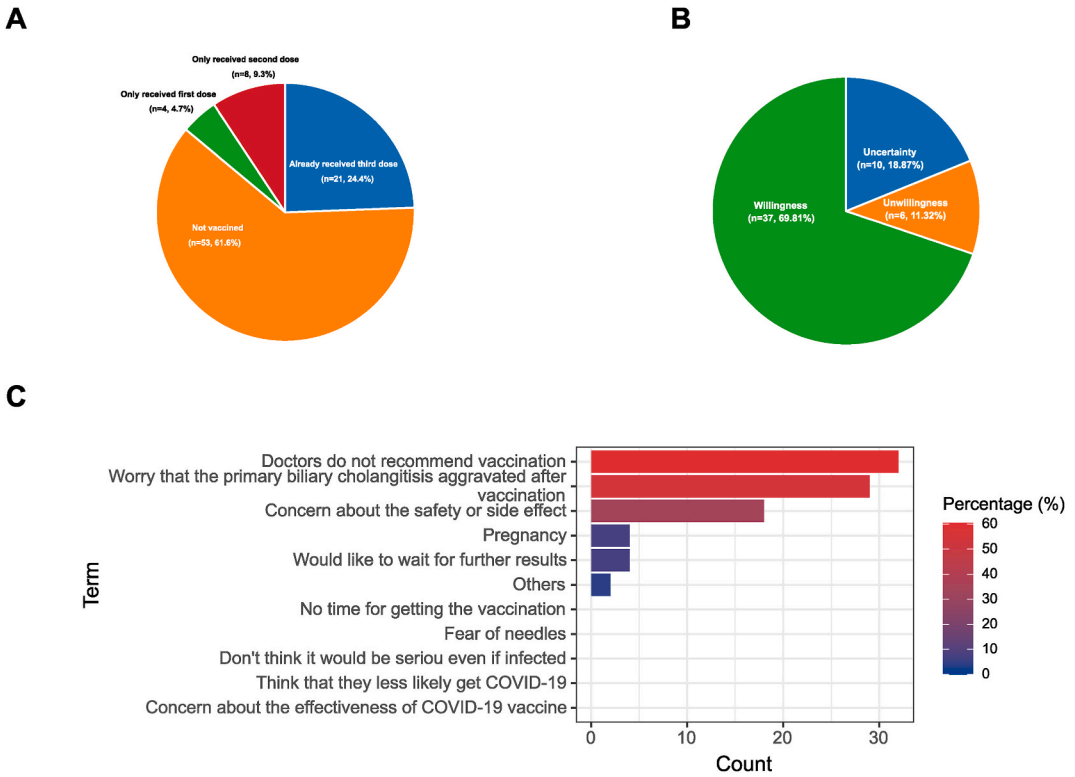

Fig. 6. Online survey to investigate the coverage, willingness, and attitude of COVID-19 vaccine among patients with PBC. (A) The COVID-19 vaccination status among patients with PBC (n = 86). (B) The willingness toward COVID-19 vaccine among unvaccinated participants (n = 53). (C) The reasons for not receiving COVID-19 vaccines (n = 53). PBC, primary biliary cholangitis.

4. Discussion

As part of this study, three types of antibodies were detected to evaluate the immunogenicity of inactivated COVID-19 among individuals with PBC, indicating an impaired humoral response after booster vaccination, especially those who had been vaccinated for > six months because the levels of all three detected antibodies were significantly lower than HCs (Table S1). Furthermore, patients with PBC and HCs were more likely to contract BA.4/5 since the NAb inhibition rates for subvariants remained below the cut-off values for positivity, regardless of when booster vaccinations were given (Table S1).

The morbidity of PBC in China is 21.05/100,000 [22], indicating that nearly 310,000 patients with PBC, according to the total population of China, were observed, and a large number of patients with PBC have been reported in China. Due to the poor prognosis of COVID-19 in PBC, more attention should be given to prevention of SARS-CoV-2. In China, inactivated vaccines are the main types of COVID-19 vaccines primarily used. However, individuals with some autoimmune diseases have poorer immunogenicity to fully inactivated vaccines than HCs [23–25], indicating that booster vaccination may be needed in these populations. PBC is an autoimmune disease characterized by dysfunction of immune cells and anti-mitochondrial antibody. Therefore, the efficiency of inactivated COVID-19 among individuals with PBC needs to be understood. The results of our research provide new insights into the booster vaccination among individuals with PBC.

The levels of all three detected antibodies significantly increased after the boost shot with inactivated COVID-19 vaccine in all participants (Table S1), indicating that booster vaccination contributes to enhancing protection by immunization. The results indicated that the NAb levels toward WT were positively associated with anti-RBD-specific IgG levels (Fig. 5C), indicating that anti-RBD-specific IgG could reflect neutralization potency [26,27]. The levels of anti-RBD-specific IgG and NAb toward the WT showed a significant decrease among individuals with PBC after receiving the boost shot for >3 months (Table S1). Furthermore, the levels of two antibodies decrease with time after booster vaccination (Fig. 5B). Therefore, patients with PBC may need to consider receiving an extra vaccine dose due to the decreasing effectiveness of the vaccine [28,29]. Our study also showed that 18.9% of the HCs did not produce NAb toward WT after booster vaccination (Fig. 3C), which is consistent with previous studies [16,30,31]. Antigen-specific memory T cells contribute to stimulating antigen-specific B cell clone activation and promoting Nab production [32]. Therefore, the dysfunction of SARS-CoV-2 specific memory T cells may fail HCs to develop neutralizing antibodies. The roles of the T cell function in individuals without NAb production need further study.

In addition, the resistance toward Omicron BA.4/5 subvariants was insufficient in patients with PBC and HCs, whether they have received booster vaccination. Omicron variants and their sublineages with high transmissibility and easy-to-escape immune responses are the predominant circulating variants worldwide [33,34]. This study used an inactivated COVID-19 vaccine designed to target WT spike protein [35]. However, the Omicron variant and its subvariants contain >30 amino acid alternations in their spike protein and have an antigenic shift [36], resulting in the inactivation of established neutralizing antibody epitopes, and the Omicron variant is capable of partially escaping the formerly generated WT strain-based immunity to SARS-CoV-2 [37]. Furthermore, omicron BA.4/5 enhanced its transmissibility and immune evasion and showed more significant antibody escape than other Omicron subvariants [35,38]. Tuekprakhon et al. [39] also observed that Omicron BA.4/5 showed a stronger antibody escape to the humoral response from booster-vaccinated individuals, which is associated with the F486V and L452R mutated in the RBD, contributing to escape from the antibody response to vaccination [39,40]. There is strong evidence that amino acid changes in the RBD of Omicron BA.4/5 lead to immune escape from the humoral response established against the WT spike protein [37,41]. Owing to the enhanced transmissibility and immune escape of Omicron BA.4/5 compared with other subvariants, leading to failure to produce enough NAb toward Omicron BA.4/5 after booster vaccination [39]. Therefore, promoting vaccination tailored for the Omicron variant in susceptible populations is necessary [42].

The online survey showed that 61.6% of the participants had never received the COVID-19 vaccine, indicating a lower vaccination rate in individuals with PBC than in the general population in China (Available at: https://epaper.chinadaily.com.cn/a/202207/25/WS62ddc06ba3109375516eddb7.html). The main reason for non-vaccination in patients with PBC in this study was that “Doctors do not recommend vaccination”. Doctors’ recommendations seem to affect vaccination behaviors in patients with PBC. The potential reasons may be associated with the lack of evidence and studies on vaccine safety among individuals with PBC, leading to difficulties for doctors when patients consult them. Additionally, the immune system and function are dysregulated in patients with PBC towing to alternations in the status and distribution of immune cells. Therefore, some unvaccinated patients with PBC worry more about the COVID-19 vaccine safety and whether PBC is aggravated after vaccination. All vaccinated patients with PBC were vaccinated with inactive COVID-19 vaccine which was considered safe because no severe adverse effects were observed in this study. However, the number of patients vaccinated with PBC was limited in this study, and more patients need to be included to investigate the safety of PBC. Approximately 83.7% of participants with PBC were contracted with SARS-CoV-2 when the Chinese government optimized the control measures in November 2022. SARS-CoV-2 susceptibility could be reduced as UDCA downregulates angiotensin-converting enzyme 2 [43]. In addition, John et al. observed that patients with cirrhosis who received UDCA were not prone to be infected with SARS-CoV-2 [44]. However, we found no association between the difference in UDCA treatment dose and infection in participants with PBC (Table S7). Additionally, the infection rates of close contacts and co-residents were higher among infected individuals than uninfected individuals (Table S7). Therefore, UDCA may be one of the factors that contribute to preventing SARS-CoV-2 invasion, and more protective measures need to be adopted to decrease the probability of infection among individuals with PBC.

There are limitations to this study. A cross-sectional study design prevented us from observing dynamic changes in SARS-CoV-2 antibody levels after each shot of vaccine in individuals with PBC, and the sample size in cohort 1 was small. Cellular immunity also contributes to preventing virus invasion. Further studies are needed to discover the cellular immunity elicited by inactivated COVID-19 vaccine. In addition, the online survey conducted in cohort 2, relying on self-reported data, could have impacted the

accuracy of information.

In conclusion, this study fills the gap in the immunological assessment of individuals with PBC who were immunized with inactivated COVID-19 vaccines. Booster shots of vaccines evoked SARS-CoV-2 specific antibody levels in patients with PBC, but they still have poorer humoral response compared to HCs. A decreased inhibition rate of Nab toward BA.4/5 was shown among all participants, indicating a higher possibility of contracting infections, and further booster vaccination is needed.

Ethical statement

The Ethics Committee of the PUMCH reviewed and approved this study (I-23PJ174).

Data availability statement

Data will be made available on request.

Funding

This work was supported by Beijing Natural Science Foundation (M23008), National Key Research and Development Program of China (2018YFE0207300), and the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-124).

Conflict of interest disclosure

There are no conflicts of interest.

CRediT authorship contribution statement

Haolong Li: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Xu Wang:** Methodology, Investigation, Funding acquisition, Formal analysis. **Siyu Wang:** Investigation. **Xinxin Feng:** Methodology, Investigation. **Li Wang:** Supervision, Investigation, Conceptualization. **Yongzhe Li:** Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28405.

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