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ORIGINAL RESEARCH

Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccine (BBIBP-CorV) in Hypertensive and/or Diabetic People Aged over 60 Years: A Prospective Open-Label Study

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ABSTRACT

Aims: Severe acute respiratory syndrome coronavirus type 2 (SARS-COV-2) infection may increase the risk of developing dangerous symptoms among the elderly with underlying medical conditions. The aim of this study was to evaluate the safety and immunogenicity of the SARS-CoV-2 inactivated vaccine (Vero) in patients over 60 years of age with hypertension and/or diabetes.

Methods: An open-label, multi-center, prospective clinical trial was conducted at three medical sites in Fujian, China. Participants aged 60 years and above with hypertension, diabetes, and healthy controls were included in four groups: hypertension, diabetes, combined disease, and healthy controls. Volunteers received two doses of the inactivated SARS-COV-2 vaccine (BBIBP-CorV) on days 0 and 21. Adverse events were recorded for 21 days after each dose. Blood samples were taken before the first vaccination and 28 days after the second vaccination to detect the serum conversion rate and geometric mean titer (GMT) of neutralizing antibodies.

Results: A total of 480 participants (110 hypertension, 110 diabetes, 100 combined hypertension and diabetes, and 160 healthy controls) were recruited. The incidences of adverse events in the four groups were 10 (9.1%) in the hypertension group, 19 (17.3%) in the diabetes group, 11 (11.0%) in the combined disease group, and 11 (6.9%) in healthy controls, with no statistical significance ($P > 0.05$). At 28 days after the second vaccination, the positive conversion rates of serum neutralizing antibody in the four groups were 97.3%(107/110), 97.3% (107/110), 100.0% (99/99),and 98.7%(155/157), respectively, and the GMTs were 75.28 (95% CI 64.03–88.50), 69.4 (95% CI 59–81.63), 77.21 (95% CI 66.68–89.41), and 78.64 (95% CI 69.87–88.50), respectively. There was no significant difference in neutralizing antibody responses among the four groups ($P > 0.05$). Additionally, the GMT after immunization was higher in females than in males (OR = 2.59, 95% CI 1.31–5.12).

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Conclusions: The BBIBP-CorV vaccine is safe and elicits an adequate antibody response in patients over 60 years of age with hypertension and/or diabetes.
Trial Registration: ClinicalTrials.gov identifier, NCT05065879.

Keywords: SARS-CoV-2 vaccine; Hypertension; Diabetes; Safety; Neutralizing antibody

Key Summary Points

Why carry out this study?

Owing to the possible weaker immune response in patients over 60 years old and higher risk for SARS-COV-2 infection among patients with chronic diseases, it is essential to evaluate the immunogenicity and safety of the SARS-COV-2 vaccines specifically in patients with hypertension and/or diabetes over 60 years old. There are insufficient data on the immunogenicity and safety of the vaccine.

This study aims to evaluate the post-vaccination immunogenicity and safety of an inactivated SARS-CoV-2 vaccine in this specific group of people.

What was learned from the study?

The results of our study showed no significant differences in the positive conversion rate of neutralizing antibodies, post-vaccination GMT, or incidence of adverse reactions among the four groups (hypertension, diabetes, combined disease, and healthy control).

The inactivated SARS-CoV-2 vaccine is safe in patients over 60 years of age with hypertension and/or diabetes, and elicits an adequate antibody response.

INTRODUCTION

In early 2020, coronavirus disease 2019 (COVID-19) rapidly spread across the world. Up to 7 April 2022, COVID-19 has infected more than 492 million people worldwide, resulting in 6.15 million deaths [1]. The World Health Organization (WHO) has declared COVID-19 a global pandemic [2]. Vaccination, as a means of disease prevention, can effectively interrupt the epidemic of SARS-COV-2 [3]. A number of COVID-19 vaccines produced by different technologies have been reported in various clinical studies [4–7] and approved for use worldwide.

WHO has added China's two inactivated SARS-CoV-2 vaccines (Beijing Institute of Biological Products Co. Ltd. and Sinovac Life Sciences Co. Ltd.) with good safety and immunogenicity [8–12] to its emergency use list. However, there is insufficient evidence on the safety and efficacy of COVID-19 vaccines in elderly people with chronic diseases. To further expand vaccination coverage and build the herd immunity of the population, it is necessary to vaccinate the elderly and patients with preexisting chronic disease. WHO reported that an estimated 1.28 billion people worldwide have been diagnosed with hypertension [13], and the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014 [14]. The prevalence of diabetes among Chinese adults reached 12.4% in 2018 [15]. An analysis of hospitalized SARS-COV-2 infections in China showed that 16.9% of the total patients were associated with hypertension and 8.2% with diabetes. Among patients with critical illness, the proportion of patients with hypertension and diabetes increased to 40.5% and 23.7%, respectively [16]. Recently, the fifth wave of COVID-19 in Hong Kong gave us a lesson about protecting the vulnerable population aged over 60 years against SARS-COV-2 with effective vaccines [17]. People with underlying diseases such as hypertension, diabetes, or cardiovascular disease are more likely to develop severe disease or even death when infected with SARS-COV-2 [18–20].

This study aimed to further guide patients over 60 years old with hypertension and diabetes to get vaccinated by exploring the safety and immunogenicity of the inactivated SARS-CoV-2 vaccine (Beijing Institute of Biological Products Co. Ltd.) in these specific groups.

METHODS

Study Design

An open-label, multi-center, nonrandomized prospective clinical trial was conducted at three medical sites in Quanzhou and Sanming cities, Fujian Province, China. The safety and immunogenicity of two doses of inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Beijing Institute of Biological Products Co. Ltd.) were evaluated in people aged over 60 years of age with hypertension or diabetes or both, and healthy controls (in this study, healthy controls are defined as participants who were not diagnosed with hypertension and/or diabetes by medical institutions). This study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2013. The study protocol and informed consent were approved by the Ethics Committee of Fujian Provincial Center for Disease Control and Prevention (FJCDCIRB2021-005). Recruitment for the study began on 15 October 2021, and follow-up was completed on 30 January 2022. Written informed consent were obtained from all participants prior to enrollment. The trial was registered at ClinicalTrials.gov, NCT05065879.

Based on the results of a previous study, the seroconversion rate for people aged $\geq$ 60 years was 92% [11]. The sample size was calculated with the seroconversion rate of serum antibody of 92%, a two-sided test level α of 0.05 and a statistical power 1-β of 0.80. The sample size estimation was a minimum of 89 in each group. The total number of participants in this study was 480.

Inclusion Criteria

Individuals aged 60 years and older, with hypertension (blood pressure on the day of vaccination should be $<$ 160 mmHg systolic and $<$ 100 mmHg diastolic) and/or diabetes (fasting blood glucose value on the day or within the previous 3 days of vaccination should be $\leq$ 13.9 mmol/L). We recruited 110 patients with hypertension (hypertension group), 110 patients with diabetes (diabetes group), 100 patients with hypertension and diabetes (combined disease group), and 160 elderly people without diabetes or hypertension (healthy controls). Patients with hypertension/diabetes needed to be diagnosed by primary healthcare facilities or medical institutions. Only patients with type 2 diabetes were included in the study. We measured blood pressure and did a 2-h oral glucose tolerance test (OGTT) daily 3 days before vaccination to exclude hypertension and/or diabetes in healthy controls.

Exclusion criteria

The exclusion criteria were as follows: have been diagnosed or asymptomatically infected with COVID-19; had a history of SARS-CoV-2 vaccination; were known to be allergic to any component (including excipients) contained in the vaccine; had received injection of non-specific immunoglobulin within 1 month prior to enrollment; received other vaccines within 14 days prior to vaccination; had severe allergic reaction to vaccine (e.g., acute allergic reaction, urticaria, angioneurotic edema, respiratory distress, etc.); and had uncontrolled epilepsy or other progressive neurological disorders, or had a history of Guillain–Barre syndrome, etc.

Procedures

Participants received two doses of the inactivated SARS-CoV-2 vaccine (Vero) in the deltoid muscle of the upper arm (0.5 ml, containing SARS-CoV-2 antigen 6.5 U) on days 0 and 21. All vaccines were in the same batch (batch number 2021050799). Blood samples were collected

before the first vaccination (baseline) and 28 days after the second vaccination to evaluate the SARS-CoV-2 neutralizing antibody titers. Study data including baseline characteristics (gender, age, ethnicity, study site, etc.) and adverse events were recorded in the case report form (CRF).

Safety Assessment

Participants actively recorded the occurrence of any adverse event within 0–21 days after each dose of the vaccination. Solicited adverse events included local adverse events (soreness, hardness, swelling, rash, redness, pruritus, erythema) and systemic adverse events [fever, dizziness, headache, cough, fatigue, nausea, vomiting, chest tightness, diarrhea, constipation, dysphagia, anorexia, muscle pain (non-injection site), arthralgia, dyspnoea, non-injection site pruritus (no skin lesions), skin mucosal abnormalities, acute allergic reactions, facial nerve symptoms]. Adverse events were classified as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or death (grade 5), according to the Guidelines for Adverse Event Classification Standards for Clinical Trials of Preventive Vaccines [21]. To correctly collect information about adverse events, participants were given instructions about filing information truthfully and adequately during observation periods following vaccination.

Antibody Test

Blood samples were collected before the first dose and 28 days after the second dose. About 5 ml of venous blood was collected each time, and the serum was separated for detection of SARS-COV-2 neutralizing antibodies. The serum antibody levels were tested using a plaque reduction neutralization test at the National Institute for Viral Disease Control and Prevention, China CDC. Detailed methods for the SARS-CoV-2 neutralizing assay are as follows: serum samples were measured by neutralization capacity testing using infectious SARS-CoV-2 virus [strain 19nCoVCDC-Tan-Strain04 (QD01)] by the 50% cell culture infectious dose. Serum was successively diluted 1:4 to the required concentration by a twofold series, and an equal volume of challenge virus solution was added. After neutralization in a 37 °C incubator for 2 h, a 1.0–2.5 $\times$ 10^5/ml cell suspension was added to the wells (0.1 m per well) and cultured in a CO_2 incubator at 37 °C for 4 days. Titers were expressed as the reciprocal of the highest dilution protecting 50% of cells from virus challenge. Convalescent sera were included as an internal positive control in every assay. A positive antibody response (seroconversion) was defined as: if the neutralizing antibody titer was less than 1:4 at baseline, the neutralizing antibody titer was at least 1:16 at 28 days after vaccination; or if the neutralizing antibody titer was at least 1:4 at baseline, the titer increased at least fourfold at 28 days after vaccination compared with baseline [22].

Outcomes

The primary immunogenicity indicators were seroconversion rates and GMT of SARS-COV-2 neutralizing antibodies at day 28 after the second dose of vaccine in per protocol (PP) population (n = 476), who had a negative seroresponse at day 0 and completed the full course of vaccination. The primary safety outcome was the incidence of adverse events within 21 days after each dose of vaccination among all participants [safety population; intention to treat (ITT) population, n = 480], who received at least one dose of the study vaccine (Fig. 1).

Statistical Analysis

Categorical variables are displayed as the number and percentages. Numerical variables are displayed as mean and standard deviation (normal distribution) or median interquartile ranges (non-normal distribution). SARS-COV-2 neutralizing antibody levels are displayed in GMT and 95% confidence intervals (CI). After logarithmic transformation of GMT, analysis of variance (ANOVA) or Kruskal–Wallis test were used to explore the differences of neutralizing antibody levels among different groups.

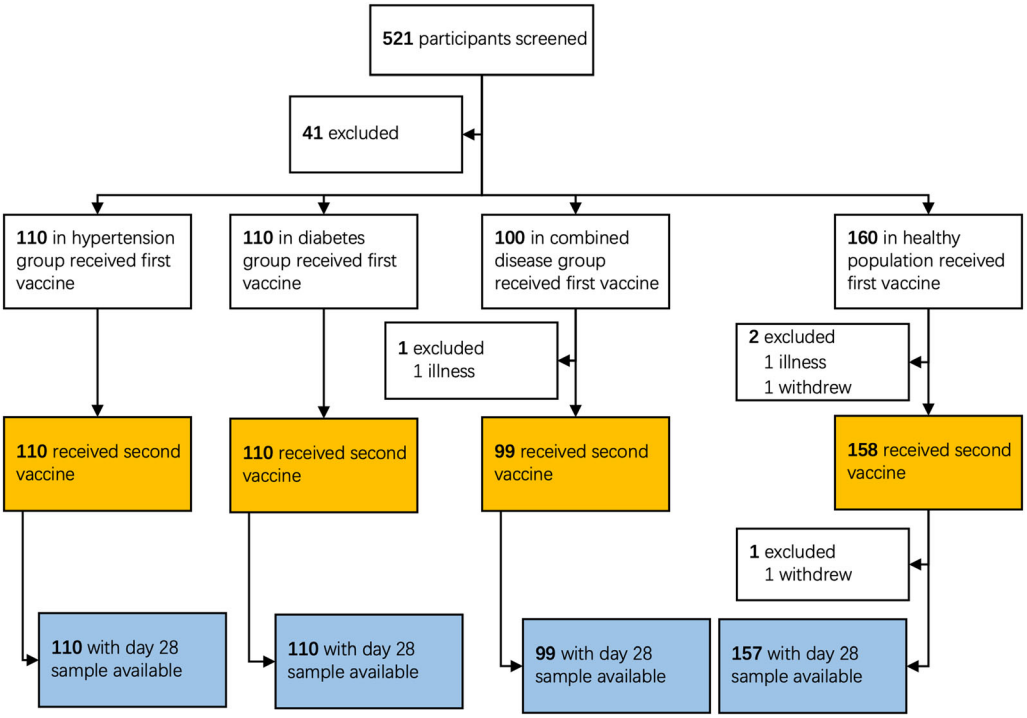

Fig. 1 Flowchart of the study. The chart depicts the groups of study subjects screened prior to the study and the specific groups being enrolled and studied. The orange square represents the ITT population (safety population) and blue represents the per protocol (PP) population

Pearson's chi-squared test or Fisher's exact test were used to assess the differences among groups for categorical variables. The level of neutralizing antibodies was transformed into categorical variables (GMT $\geq$ 32) before regression analysis was performed. The influence factors of neutralizing antibody level of SARS-COV-2 vaccine were analyzed by binary logistic regression. The hypothesis test was a two-sided test, and *P*-values less than 0.05 were considered as significant. The statistical analyses were performed in IBM SPSS Statistics 19.0 and Graphpad Prism 9.2.

RESULTS

A total of 480 participants (110 hypertension, 110 diabetes, 100 combined hypertension and diabetes, and 160 healthy controls) were recruited between 15 October and 22 October 2021. The number of subjects screened and included is shown in Fig. 1. The main reasons for screening failure were refusal to participate, uncontrolled blood pressure or fasting blood glucose, or having received SARS-COV-2 vaccines before enrollment of the study. A total of 480 participants received the first dose of vaccine and were included in the safety population; 99.2% of study subjects received a second dose of the vaccine and were included in the per protocol (PP) population. The demographic characteristics of all groups are presented in Table 1. The average age of participants was 67.66 $\pm$ 5.21 years, ranging from 60 to 86 years. Participants aged 60–69 years and over 70 years accounted for 30% and 70%, respectively. There were no significant differences in gender, ethnicity, or study site among the four groups ($P > 0.05$). The proportion of comorbidities was higher in the hypertension group (32/110, 29.1%) than in other groups, and lowest in the healthy controls (17/160, 10.6%). Coronary heart disease (CHD) was the most common comorbidities among all participants. The proportions of CHD were higher in the

Table 1 Baseline characteristics of participants

Characteristics	Hypertension (n = 110)	Diabetes (n = 110)	Combined disease (n = 100)	Healthy controls (n = 160)	P-value
Age groups					
60–69 years	77 (70.0)	77 (70.0)	70 (70.0)	112 (70.0)	1.000
≥ 70 years	33 (30.0)	33 (30.0)	30 (30.0)	48 (30.0)	
Sex					
Male	52 (47.3)	42 (38.2)	31 (31.0)	78 (48.8)	0.200
Female	58 (52.7)	68 (61.8)	69 (69.0)	82 (51.2)	
Ethnicity					
Han ethnicity	110 (100.0)	110 (100.0)	99 (99.0)	160 (100.0)	0.208
Other	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	
Study sites					
Foreland	46 (41.8)	46 (41.8)	42 (42.0)	66 (41.3)	0.999
Inland	64 (58.2)	64 (58.2)	58 (58.0)	94 (58.8)	
Comorbidities					
Any	32 (29.1)[a]	20 (18.2)[ab]	21 (21.0)[ab]	17 (10.6)[b]	0.002
Coronary artery disease	11 (10.0)[a]	5 (4.5)[ab]	10 (10.0)[a]	2 (1.3)[b]	0.004
Sequela of apoplexy	3 (2.7)	7 (6.4)	4 (4.0)	2 (1.3)	0.129[c]
Hepatobiliary disease	4 (3.6)	1 (0.9)	2 (2.0)	4 (2.5)	0.606[c]
Chronic gastritis	2 (1.8)	2 (1.8)	2 (2.0)	3 (1.9)	1.000[c]

Data are displayed as number (%)
[a, b]Significant difference with the different letters
[c]Fisher's Exact Test

hypertension group (11/110, 10%) and the comorbidities group (10/100, 10%) than in the other two groups.

Vaccine Safety

A total of 51 (10.62%) participants reported at least one adverse event within 21 days of vaccination (see Table 2 for details). The incidences of adverse events were 10 (9.1%), 19 (17.3%), 11 (11.0%), and 11 (6.9%) in the hypertension, diabetes, combined disease, and healthy controls group, respectively. There was no significant difference ($P < 0.05$) among different study groups according to the total number of adverse events, or the number of local and systemic adverse events. Most adverse events were mild (grade 1) and moderate (grade 2). The most common solicited local adverse event was pain at the injection site, which occurred in 18 out of 480 participants (3.8%). The most common solicited systemic adverse event was fatigue,

Table 2 Adverse events after either dose of SARS-CoV-2 vaccines

	Hypertension (*n* = 110)	**Diabetes (*n* = 110)**	**Combined disease (*n* = 100)**	**Healthy controls (*n* = 160)**
Solicited adverse events within 0–21 days				
Any	10 (9.1)	19 (17.3)	11 (11.0)	11 (6.9)
Grade 1	9 (8.2)	13 (11.8)	7 (7.0)	10 (6.3)
Grade 2	1 (0.9)	6 (5.5)	4 (4.0)	1 (0.6)
Injection site adverse events				
Pain	3 (2.7)	5 (4.5)	5 (5.0)	5 (3.1)
Grade 1	3 (2.7)	5 (4.5)	5 (5.0)	5 (3.1)
Swelling	0 (0.0)	2 (1.8)	1 (1.0)	0 (0.0)
Grade 1	0 (0.0)	1 (0.9)	1 (1.0)	0 (0.0)
Grade 2	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Grade 1	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Systematic adverse events				
Dizziness	1 (0.9)	8 (7.3)	3 (3.0)	1 (0.6)
Grade 1	1 (0.9)	6 (5.5)	3 (3.0)	1 (0.6)
Grade 2	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Fatigue	3 (2.7)	4 (3.6)	3 (3.0)	4 (2.5)
Grade 1	3 (2.7)	4 (3.6)	2 (2.0)	4 (2.5)
Headache	1 (0.9)	4 (3.6)	3 (3.0)	1 (0.6)
Grade 1	1 (0.9)	2 (1.8)	3 (3.0)	1 (0.6)
Grade 2	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Grade 1	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Grade 2	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Chest tightness	0 (0.0)	1 (0.9)	1 (1.0)	1 (0.6)
Grade 1	0 (0.0)	1 (0.9)	1 (1.0)	1 (0.6)
Nausea	0 (0.0)	1 (0.9)	2 (2.0)	1 (0.6)
Grade 1	0 (0.0)	1 (0.9)	2 (2.0)	1 (0.6)
Non-injection site pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Arthralgia	1 (0.9)	0 (0.0)	1 (1.0)	0 (0.0)

Table 2 continued

	Hypertension (n = 110)	Diabetes (n = 110)	Combined disease (n = 100)	Healthy controls (n = 160)
Grade 2	1 (0.9)	0 (0.0)	1 (1.0)	0 (0.0)
Muscle pain	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.3)
Grade 1	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.3)
Skin mucosal abnormalities	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Grade 1	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Grade 2	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Constipation	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.6)
Grade 1	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Vomiting	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)
Grade 1	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)
Unsolicited adverse events within 0–21 days				
Any	7 (6.4)	6 (5.5)	6 (6.0)	6 (3.8)
Grade 1	6 (5.5)	3 (2.7)	2 (2.0)	2 (1.3)
Grade 2	1 (0.9)	3 (2.7)	4 (4.0)	4 (2.5)

Data are displayed as number (%), representing the total number of participants who had adverse events related to vaccination

which presented in 14 out of 480 participants (2.9%). Grade 3 or severe adverse events (SAE) were not observed in the hypertension and diabetes groups, but occurred in 1.0% (1/100) in the combined disease group and 1.3% (2/160) in healthy controls. None of these serious adverse events were related to the vaccines. There were no vaccine-related deaths. In addition, 25 of the 480 (5.2%) participants reported unsolicited adverse events (see Table 2 for details).

SARS-CoV-2 Vaccination Immunogenicity

All participants had neutralizing antibody titers of less than 1:4 at baseline. At day 28 after the second dose, the conversion rates of serum neutralizing antibody (GMT $\geq$ 16) were 97.3% (107/110), 97.3% (107/110), 100.0% (99/99), 98.7% (155/157) in the hypertension, diabetes, combined disease, and healthy control groups, respectively. There was no significant difference in the seroconversion rates of neutralizing antibody among the four groups (P = 0.343) (Fig. 2A). After adjusting for age, sex, study site, and comorbidities, the difference was still not statistically significant (P = 0.845). The

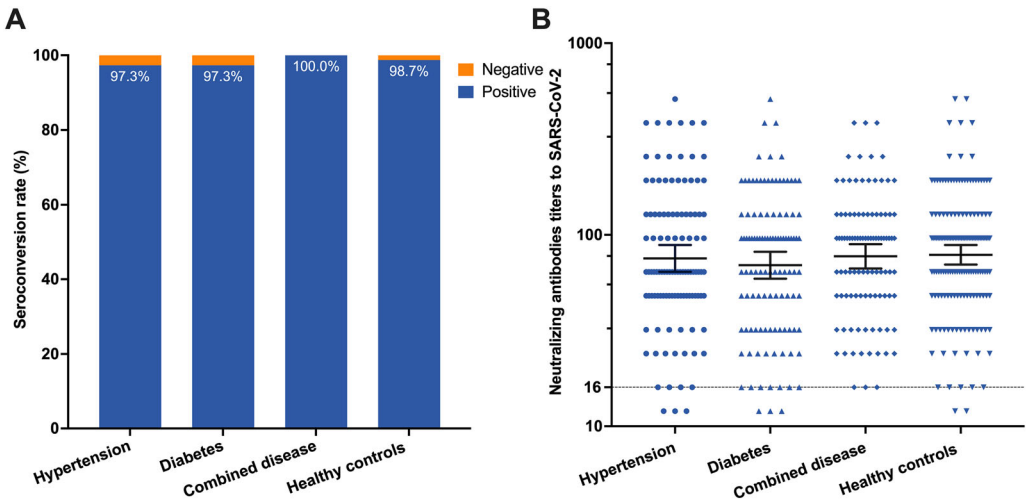

Fig. 2 Neutralizing antibody response of SARS-CoV-2 vaccines. Positive rates (**A**) and neutralizing antibodies GMT (**B**) to SARS-CoV-2 induced after the whole schedule of SARS-CoV-2 vaccination in hypertension, diabetes, combined disease, and healthy controls. The dotted black line indicates the cutoff level of positive neutralizing antibodies. Each colored dot represents one serum sample. The solid black lines indicate the geometric mean and 95% CI of neutralizing antibodies

neutralizing antibody GMT post-vaccination in the hypertension, diabetes, combined disease, and healthy controls group were 75.28 (95% CI 64.03–88.50), 69.4 (95% CI 59–81.63), 77.21 (95% CI 66.68–89.41), and 78.64 (95% CI 69.87–88.50), respectively, and there was no significant difference in GMT among the four groups ($P = 0.298$) (Fig. 2B). After adjusting for age, sex, study site, and comorbidities, the result was similar ($P = 0.559$).

In addition, the correlation factors of SARS-COV-2 neutralizing antibody titers were analyzed according to different serological conversion standard values (GMT $\geq$ 32) among participant with diseases, including hypertension and diabetes. The results showed that the level of neutralizing antibodies after immunization was higher in females than in males (OR = 2.59, 95% CI 1.31–5.12, $P = 0.006$). Age, study site, comorbidities, and disease groups had no effect on serological transformation ($P < 0.05$) (Table 3).

DISCUSSION

Although good safety and immunogenicity of theiInactivated SARS-CoV-2 vaccines has been demonstrated in previous studies [11, 22, 23], further data on post-vaccination among patients with chronic diseases such as hypertension and/or diabetes are essential. In this open-label, multi-center, prospective clinical trial, we evaluated the safety and immunogenicity of two doses of inactivated SARS-CoV-2 vaccine among 480 elderly people aged over 60 years with or without hypertension and diabetes. No serious vaccine-related adverse events occurred, and the majority of participants produced an adequate neutralizing antibody response.

For vaccine safety, preliminary results suggested that the incidence of adverse events was not higher in people with hypertension or diabetes. Results of a previous phase III trial [22] with only 1.6% of the study participants aged older than 60 years, indicated that the overall incidence of solicited adverse events within 21 days of vaccination was 39.1%, higher than the 10.6% in this study. Safety data from phase I and phase II inactivated vaccine trials showed that 21% participants aged over 60 years reported at least one adverse event within 28 days after vaccination [10], and the incidence of adverse events among volunteers aged $\geq$ 60 years was lower than among

Table 3 Multivariate analysis of factors influencing the SARS-COV-2 neutralizing antibody in patient population

Characteristics	GMT < 32 (n = 43)	GMT ≥ 32 (n = 277)	OR (95% CI)	P-value
Age groups				
60–69 years	25 (58.1)	199 (71.8)	0.62 (0.31–1.27)	0.197
≥ 70 years	18 (41.9)	78 (28.2)		
Sex				
Male	26 (60.5)	99 (35.7)	2.59 (1.31–5.12)	0.006
Female	17 (39.5)	178 (64.3)		
Study sites				
Foreland	17 (39.5)	117 (42.2)	1.10 (0.56–2.15)	0.788
Inland	26 (60.5)	160 (57.8)		
Comorbidities				
Yes	35 (81.4)	212 (76.5)	1.46 (0.63–3.42)	0.378
No	8 (18.6)	65 (23.5)		
Disease groups[a]				
Hypertension	14 (32.6)	96 (34.7)	–	–
Diabetes	18 (41.9)	92 (33.2)	0.99 (0.42–2.36)	0.983
Combined disease	11 (25.6)	89 (32.1)	0.69 (0.30–1.57)	0.376

Data are displayed as number (%)

GMT geometric mean titer, *OR* odds ratio, *CI* confidence interval

[a]OR of diabetes and combined disease were compared with hypertension

volunteers aged 18–59 years [24]. Furthermore, most adverse events in the studies above were mild (grade 1) or moderate (grade 2), transient, and self-limited. Another study showed an increase in glycated hemoglobin (HbA1c) levels among healthy volunteers who received inactivated SARS-COV-2 vaccine, even reaching the range of pre-diabetes [25]. In addition, there have been reports of diabetic ketoacidosis (DKA) in diabetes mellitus type 1 (T1DM) patients after receiving SARS-COV-2 vaccine [26]. In this trial, no adverse events such as DKA were observed through close monitoring of subjects, especially among patients with diabetes.

This study showed no statistically significant difference in neutralizing antibody GMT among the chronic disease groups and the healthy control group. Neutralizing antibody GMT [range from 69.40 (95% CI 59.00–81.63) to 78.64 (95% CI 69.87–88.50)] in all four groups appeared to be lower than that in a previous study [109.7 (95% CI 97.4–123.4)][27]. A prospective study of the BNT162b2 COVID-19 vaccine conducted among healthcare workers indicated lower immunoglobulin (Ig)G concentrations and lower neutralizing antibody concentrations (did not reach significance) in patients with diabetes, and the trial also found a significant association with lower antibody responses in patients with hypertension [28]. A similar conclusion was also found in another study conducted with an inactivated vaccine [29]. It is important to note that patients with comorbidities, such as diabetes, need be considered with priority of vaccination given the increased risk of severe COVID-19 and death

associated with SARS-COV-2 infection [30, 31]. No difference in the immune response to inactivated SARS-CoV-2 vaccines was observed in patients aged over 60 years with diabetes and hypertension compared with healthy subjects. These results could help reduce vaccine hesitancy and increase vaccine confidence in elderly patients with chronic disease.

In our study, females appeared to have stronger immune responses after vaccination than males, which was consistent with the results of the inactivated influenza vaccine [32]. In addition, other inactivated and live-attenuated vaccines have similar descriptions of gender differences in immunity among elderly, possibly due to genetic, hormonal, and environmental factors [33, 34].

Our study still has several limitations. First, although neutralizing antibody responses were estimated with the inactivated SARS-CoV-2 vaccine in the vast majority of participants with hypertension and diabetes, the efficacy of the vaccine against SARS-COV-2 infection requires further study. Second, this study did not detect related clinical laboratory indicators, such as cholesterol, triglyceride, or HbA1c, which may provide more safety data. Third, the results may only apply to inactivated vaccines and should be generalized with caution to vaccines produced by different technologies and platforms. Finally, further studies on the safety and efficacy of SARS-COV-2 vaccines in elderly patients with hypertension and diabetes need to expand the cohort and extend the follow-up time. Since our research focused on hypertension and/or diabetes, we have not enrolled sufficient subjects with other chronic diseases such as renal disease. Relevant research is not included in our study and will be considered in follow-up studies.

CONCLUSIONS

Sufficient neutralizing antibodies against SARS-COV-2 were observed in patients over 60 years old with hypertension and/or diabetes after two doses of inactivated SARS-COV-2 vaccine. In addition, we observed that females had a stronger immune response after vaccination than males. There was no significant difference in vaccine safety compared with healthy controls. Further studies on persistence of immunogenicity and actual protection are needed.

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Compliance with Ethics Guidelines. This study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. World Health Organization. Coronavirus disease(COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 7 Apr 2022.

2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a pandemic. Acta Biomed. 2020;91:157–60. https://doi.org/10.23750/abm.v91i1.9397.

3. Kwok KO, McNeil EB, Tsoi MTF, Wei VWI, Wong SYS, Tang JWT. Will achieving herd immunity be a road to success to end the COVID-19 pandemic? J Infect. 2021;83:381–412. https://doi.org/10.1016/j.jinf.2021.06.007.

4. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384:2187–201. https://doi.org/10.1056/NEJMoa2101544.

5. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384:1412–23. https://doi.org/10.1056/NEJMoa2101765.

6. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373: n1088. https://doi.org/10.1136/bmj.n1088.

7. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021;397:671–81. https://doi.org/10.1016/s0140-6736(21)00234-8.

8. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020;369:77–81. https://doi.org/10.1126/science.abc1932.

9. Wang H, Zhang Y, Huang B, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell. 2020;182:713-721.e719. https://doi.org/10.1016/j.cell.2020.06.008.

10. Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:803–12. https://doi.org/10.1016/s1473-3099(20)30987-7.

11. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21:39–51. https://doi.org/10.1016/s1473-3099(20)30831-8.

12. Xia S, Duan K, Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. JAMA. 2020;324:951–60. https://doi.org/10.1001/jama.2020.15543.

13. World Health Organization. Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed 7 Apr 2022.

14. World Health Organization. Diabetes. https://www.who.int/news-room/fact-sheets/detail/Diabetes. Accessed 7 Apr 2022.

15. Wang L, Peng W, Zhao Z, et al. Prevalence and treatment of diabetes in China, 2013–2018. JAMA. 2021;326:2498–506. https://doi.org/10.1001/jama.2021.22208.

16. Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med. 2020;180:1081–9. https://doi.org/10.1001/jamainternmed.2020.2033.

17. Cheung PH, Chan CP, Jin DY. Lessons learned from the fifth wave of COVID-19 in Hong Kong in early 2022. Emerg Microbes Infect. 2022;11:1072–8. https://doi.org/10.1080/22221751.2022.2060137.

18. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. Rev Med Virol. 2021;31:1–10. https://doi.org/10.1002/rmv.2146.

19. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20:425–34. https://doi.org/10.1016/s1473-3099(20)30086-4.

20. Tian S, Hu N, Lou J, et al. Characteristics of COVID-19 infection in Beijing. J Infect. 2020;80:401–6. https://doi.org/10.1016/j.jinf.2020.02.018.

21. National Medical Products Administration. NMPA Issued the Guidelines for Adverse Event Classification Standards for Clinical Trials of Preventive Vaccines. https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20191231111901460.html. Accessed 7Apr 2022.

22. Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021;326:35–45. https://doi.org/10.1001/jama.2021.8565.

23. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:181–92. https://doi.org/10.1016/s1473-3099(20)30843-4.

24. Abarca K, Iturriaga C, Urzúa M, et al. Safety and efficacy of two immunization schedules with an inactivated SARS-CoV-2 vaccine in adults. A randomized non-inferiority clinical trial. medRxiv. 2022. https://doi.org/10.1101/2022.02.07.22270215.

25. Liu J, Wang J, Xu J, et al. Comprehensive investigations revealed consistent pathophysiological alterations after vaccination with COVID-19 vaccines. Cell Discov. 2021;7:99. https://doi.org/10.1038/s41421-021-00329-3.

26. Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022;16: 102371. https://doi.org/10.1016/j.dsx.2021.102371.

27. World Health Organization. Prequalification of Medical Products. https://extranet.who.int/pqweb/file/bibppegtageulreportfinal04june21pdf. Accessed 8 Apr 2022.

28. Lustig Y, Sapir E, Regev-Yochay G, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in healthcare workers. Lancet Respir Med. 2021;9:999–1009. https://doi.org/10.1016/s2213-2600(21)00220-4.

29. Dinc HO, Saltoglu N, Can G, et al. Inactive SARS-CoV-2 vaccine generates high antibody responses in healthcare workers with and without prior infection. Vaccine. 2022;40:52–8. https://doi.org/10.1016/j.vaccine.2021.11.051.

30. Mantovani A, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies. Nutr Metab Cardiovasc Dis. 2020;30:1236–48. https://doi.org/10.1016/j.numecd.2020.05.014.

31. Team CC-R. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19)—United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:343–6. https://doi.org/10.15585/mmwr.mm6912e2.

32. Engler RJ, Nelson MR, Klote MM, et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004–2005): age, dose, and sex effects on immune responses. Arch Intern Med. 2008;168:2405–14. https://doi.org/10.1001/archinternmed.2008.513.

33. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38. https://doi.org/10.1038/nri.2016.90.

34. Fink AL, Engle K, Ursin RL, Tang WY, Klein SL. Biological sex affects vaccine efficacy and protection against influenza in mice. Proc Natl Acad Sci U S A. 2018;115:12477–82. https://doi.org/10.1073/pnas.1805268115.