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Vaccination against coronavirus disease 2019 in patients with pulmonary hypertension: a national prospective cohort study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has potential risks for both clinically worsening pulmonary hypertension (PH) and increasing mortality. However, the data regarding the protective role of vaccination in this population are still lacking. This study aimed to assess the safety of approved vaccination for patients with PH.

Methods: In this national prospective cohort study, patients diagnosed with PH (World Health Organization [WHO] groups 1 and 4) were enrolled from October 2021 to April 2022. The primary outcome was the composite of PH-related major adverse events. We used an inverse probability weighting (IPW) approach to control for possible confounding factors in the baseline characteristics of patients.

Results: In total, 706 patients with PH participated in this study (mean age, 40.3 years; mean duration after diagnosis of PH, 8.2 years). All patients received standardized treatment for PH in accordance with guidelines for the diagnosis and treatment of PH in China. Among them, 278 patients did not receive vaccination, whereas 428 patients completed the vaccination series. None of the participants were infected with COVID-19 during our study period. Overall, 398 patients received inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, whereas 30 received recombinant protein subunit vaccine. After adjusting for baseline covariates using the IPW approach, the odds of any adverse events due to PH in the vaccinated group did not statistically significantly increase (27/428 [6.3%] *vs.* 24/278 [8.6%], odds ratio = 0.72, $P = 0.302$). Approximately half of the vaccinated patients reported at least one post-vaccination side effects, most of which were mild, including pain at the injection site (159/428, 37.1%), fever (11/428, 2.6%), and fatigue (26/428, 6.1%).

Conclusions: COVID-19 vaccination did not significantly augment the PH-related major adverse events for patients with WHO groups 1 and 4 PH, although there were some tolerable side effects. A large-scale randomized controlled trial is warranted to confirm this finding. The final approval of the COVID-19 vaccination for patients with PH as a public health strategy is promising.

Keywords: Coronavirus disease; COVID-19; Pulmonary hypertension; Vaccination

Introduction

More than three years have passed since the outbreak of coronavirus disease 2019 (COVID-19), and the global COVID-19 pandemic has caused more than 0.76 billion cases and more than 6.9 million deaths worldwide until June 4, 2022.[1] Great progress has been achieved in fighting against COVID-19, among which vaccination plays one of the most essential roles.[2,3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are highly efficient in reducing infection, as well as deterioration and death of COVID-19, especially among patients with pre-existing medical conditions.[4]

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Patients with chronic pulmonary or cardiovascular disease are at a higher risk of progressing to catastrophic outcomes. Therefore, vaccination is recommended in these populations.[5]

Pulmonary hypertension (PH) is a syndrome characterized by remodeling of the pulmonary vasculature and a progressive increase in the pulmonary vascular load that leads to right-sided heart failure and even death.[6,7] Pulmonary arterial hypertension (PAH) is a group of precapillary PH, also the WHO group 1 PH, mainly including idiopathic, heritable, drug/toxin-induced, and other disease-induced (connective tissue disease [CTD], congenital heart disease [CHD], human immunodeficiency virus [HIV], portal hypertension, and schistosomiasis) PH. In China, the prevalence of PAH is about 15–60 per million.[8] Group 4 PH results mainly from chronic thromboembolic pulmonary disease (CTEPH) but can also be from rare causes such as tumors or arteritis.[9] The exact incidence of CTEPH is unknown but appears to approximately 0.8% within one year among survivors of acute pulmonary embolism.[10] Such patients have higher risks than the general population during the COVID-19 pandemic, with a similar cumulative incidence of infection but worse outcomes,[11,12] which is why vaccination is essential. Despite inactivated whole-virion SARS-CoV-2 vaccines and recombinant protein subunit vaccines having been approved by World Health Organization (WHO) for emergency use in numerous countries and widely inoculated in China,[13] hesitancy due to safety concerns have hampered the acceptance of vaccinations among the population with PH. Most studies evaluated vaccination effectiveness without considering patients with pre-existing cardiopulmonary problems such as PH. Moreover, accumulating evidence suggests that COVID-19 aggravates clinical conditions and increases mortality in patients with PH.[14–16] Unfortunately, few published data are available on the role of vaccination in this population, which makes it difficult for physicians or patients to decide whether they should recommend or receive the vaccination. To address this issue, we conducted a prospective cohort study using the data from National Rare Diseases Registry System of China to assess PH-related major adverse events of the approved vaccines.

Methods

Ethics statements

This study was reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital (No. S-K1829), and all patients provided informed consent. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Study design and participants

This was a national prospective cohort study initially hosted on a digital platform, Questionnaire Star (https://www.wjx.cn/), with the link made available on the social network WeChat. We enrolled patients diagnosed according to the World Health Organization (WHO) diagnostic criteria as groups 1 and 4 PH by right heart catheterization or other necessary tests according to the current guidelines[6], among whom patients with idiopathic pulmonary arterial hypertension (IPAH) were registered in the National Rare Diseases Registry System of China. Inclusion criteria were age ≥18 years, patients who agreed to participate in the questionnaire survey, and patients to be followed up for 4–6 months. Patients who received the adenovirus vaccine were excluded, because its vaccination rate was too low.

We initiated our survey by asking, "Have you ever received vaccines against COVID-19?" (Response options: yes or no). Participants who responded with "no" were then asked the following question: "Why did you not get vaccinated?" The response options included "rejected by the local due to PH," "afraid of the side effects or allergy," "afraid of pulmonary hypertension progression," "unstable condition," and "waiting to be scheduled." Participants who were not vaccinated were followed up for 4 months, while those who received vaccines were followed up for 3 months after vaccination. The follow-up of all patients was mainly completed online through telephone, WeChat, and videos.

COVID-19 vaccination

Complete vaccination was defined as receiving two doses of inactivated vaccine (CoronaVac® Sinovac Biotech, Beijing, China) or three doses of protein subunit vaccine (ZF2001® Zhifei Longcom, Hefei, Anhui, China), while incomplete vaccination was defined as refusing further vaccination for any reason.

Data collection

Data on patients' characteristics at first admission for PH were collected, including demographic information, disease duration, profiles on the diagnosis of PH, comorbidities (hypertension, diabetes mellitus, coronary arterial disease, and chronic kidney disease), WHO functional classes, and medical therapies (PH-targeted therapy, calcium channel blockers, anticoagulant drugs, diuretics, digoxin, steroids, immunosuppressant drugs, and antiplatelet therapy). We also collected clinical signs and nucleic acid test results to determine if a patient was infected with SARS-CoV-2.

Outcomes

The primary outcome was the composite of PH-related major adverse events, including all-cause mortality, hospitalization for heart failure/worsening PH, unplanned targeted medication adjustment, and worsening WHO functional class. The secondary outcomes were vaccination adverse reactions (ADRs), including injection site pain, fever, fatigue, swelling, dyspnea, palpitation, diarrhea, dizziness, and skin lesions.

Statistical analysis

Baseline variables are summarized as frequency (%), mean ± standard deviation, or median (interquartile range) as appropriate. Comparisons were made between groups using the chi-squared test for categorical variables, two independent-sample Student's *t*-tests for normally distributed variables, and the Mann–Whitney *U* test for non-normally distributed variables.

Logistic regression models were used to evaluate the association between vaccination status and adverse events. To control for possible confounding factors in the patients' baseline characteristics, we used an inverse probability weighting (IPW) approach with the estimated propensity score.[18] The propensity score was calculated as the probability that patients would be vaccinated, using logistic regression analysis based on patient characteristics at baseline. Baseline homogeneity in patient characteristics between the vaccinated and unvaccinated groups after IPW adjustment was assessed using a generalized linear model. Furthermore, the unadjusted and IPW-adjusted odds ratios of adverse events between the vaccinated and unvaccinated groups were calculated. Given that the amount of missing data was very small, complete case analyses were performed. In all analyses, a two-tailed *P*-value <0.05 was considered statistically significant. All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Study population and patient characteristics at baseline

Between October 2021 and April 2022, 806 patients diagnosed with PH were screened [Figure 1]. Among them, 78 patients aged <18 years, 5 patients with group 2 PH, 10 patients with group 3 PH, and 5 patients with group 5 PH were excluded. Two patients received the adenovirus vaccine. All patients were followed up for 4–6 months, two of whom were lost after one month of follow-up, and three were lost after 4 months of follow-up, representing a loss rate of 0.7%.

Finally, 706 patients with PH were included in the study, with 428 vaccinated (VAC group) and 278 unvaccinated (unVAC group). The reasons why patients did not receive vaccinations are presented in Figure 2. The main reason for refusal was fear of PH deterioration (197 [70.9%]), and 7 (2.5%) of patients in the unVAC group were waiting in line for vaccination. The baseline characteristics are summarized in Table 1. Overall, 543 (76.9%) patients were female, and the mean age was 40.3 ± 12.5 years with a mean duration of 8.2 ± 7.4 years after PH diagnosis. A total of 220 (31.2%) patients diagnosed as IPAH or heritable pulmonary arterial hypertension (HPAH); 313 (44.3%) had the PAH associated with CHD; 72 (10.2%) had PAH associated with CTD; 71 (10.1%) had CTEPH; and 26 (3.7%) had PH associated with Takayasu arteritis (TA).

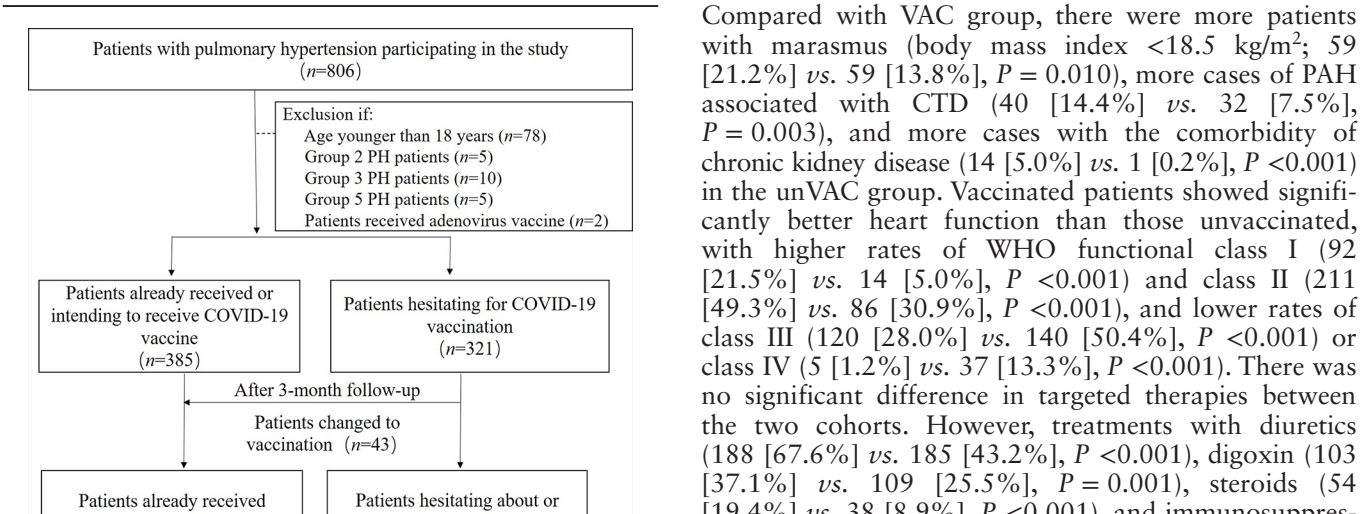

Figure 1: Flowchart of the inclusion of patients. A total of 706 patients with PH were finally included in the study, with 428 vaccinated and 278 unvaccinated. COVID-19: Coronavirus disease 2019; PH: Pulmonary hypertension.

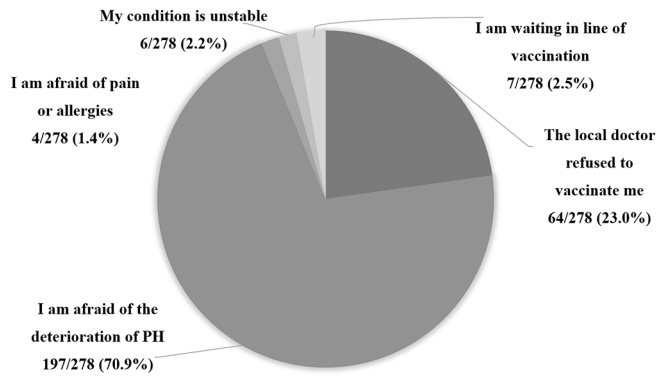

Figure 2: Reasons why patients with PH are unvaccinated against COVID-19 (total population: 278). COVID-19: Coronavirus disease; PH: Pulmonary hypertension.

Compared with VAC group, there were more patients with marasmus (body mass index <18.5 kg/m^2; 59 [21.2%] *vs.* 59 [13.8%], $P = 0.010$), more cases of PAH associated with CTD (40 [14.4%] *vs.* 32 [7.5%], $P = 0.003$), and more cases with the comorbidity of chronic kidney disease (14 [5.0%] *vs.* 1 [0.2%], $P < 0.001$) in the unVAC group. Vaccinated patients showed significantly better heart function than those unvaccinated, with higher rates of WHO functional class I (92 [21.5%] *vs.* 14 [5.0%], $P < 0.001$) and class II (211 [49.3%] *vs.* 86 [30.9%], $P < 0.001$), and lower rates of class III (120 [28.0%] *vs.* 140 [50.4%], $P < 0.001$) or class IV (5 [1.2%] *vs.* 37 [13.3%], $P < 0.001$). There was no significant difference in targeted therapies between the two cohorts. However, treatments with diuretics (188 [67.6%] *vs.* 185 [43.2%], $P < 0.001$), digoxin (103 [37.1%] *vs.* 109 [25.5%], $P = 0.001$), steroids (54 [19.4%] *vs.* 38 [8.9%], $P < 0.001$), and immunosuppressant drugs (42 [15.1%] *vs.* 31 [7.2%], $P = 0.001$) were more common in the unVAC group than in the VAC group. After adjustment for IPW, all clinical covariates were well balanced between the groups, except for obesity [Table 1].

Table 1: Baseline characteristics of the study population with PH stratified by COVID-19 vaccination status.

		Unadjusted data				Data adjusted with the use of IPW[†]			
Characteristics	Total (*n* = 706)	Vaccinated (*n* = 428)	Unvaccinated (*n* = 278)	OR (95% CI)	*P*-value	Vaccinated (*n* = 428)	Unvaccinated (*n* = 278)	OR (95% CI)	*P*-value
Age (years)	40.3±12.5	40.0±12.4	41.0±12.7	0.34 (0.05–2.32)	0.275	40.2±0.6	40.4±0.9	1.20 (0.14–10.18)	0.866
Female	543 (76.9)	325 (75.9)	218 (78.4)	1.15 (0.80–1.65)	0.444	320 (74.8)	210 (75.5)	0.96 (0.64–1.46)	0.860
Obesity/BMI >248.0 kg/m^2	19 (2.7)	10 (2.3)	9 (3.2)	0.72 (0.29–1.78)	0.472	9 (2.0)	17 (6.2)	0.31 (0.11–0.85)	0.023
Marasmus/BMI <18.5 kg/m^2	118 (16.7)	59 (13.8)	59 (21.2)	0.59 (0.40–0.88)	0.010	68 (15.9)	44 (15.9)	1.00 (0.65–1.55)	1.000
Duration of the disease (years)	8.2±7.4	8.0±7.0	8.6±8.0	0.80 (0.29–2.72)	0.829	8.2±0.4	7.9±0.5	0.77 (0.24–2.51)	0.665
PAH (group 1 PH)[*]									
Idiopathic PAH/heritable PAH	220 (31.2)	144 (33.6)	76 (27.3)	1.35 (0.97–1.88)	0.078	129 (30.2)	85 (30.4)	0.99 (0.68–1.45)	0.969
PAH associated with CHD	313 (44.3)	193 (45.1)	120 (43.2)	1.08 (0.80–1.47)	0.614	193 (45.0)	122 (43.9)	1.05 (0.74–1.48)	0.806
PAH associated with CTD	72 (10.2)	32 (7.5)	40 (14.4)	0.48 (0.29–0.79)	0.003	45 (10.4)	29 (10.4)	1.00 (0.57–1.74)	0.991
Group 4 PH									
CTEPH	71 (10.1)	47 (11.0)	24 (8.6)	1.22 (0.73–2.03)	0.449	42 (9.9)	31 (11.0)	0.88 (0.49–1.60)	0.683
TA-PH	26 (3.7)	11 (2.6)	15 (5.4)	0.46 (0.21–1.02)	0.057	17 (4.0)	11 (3.8)	1.07 (0.45–2.56)	0.880
Concomitant disease									
Hypertension	55 (7.8)	29 (6.8)	26 (9.4)	0.70 (0.41–1.22)	0.214	31 (7.2)	24 (8.7)	0.82 (0.42–1.57)	0.538
Diabetes mellitus	12 (1.7)	6 (1.4)	6 (2.2)	1.55 (0.50–4.86)	0.451	6 (1.5)	3 (1.1)	0.79 (0.23–2.67)	0.702
Coronary arterial disease	27 (3.8)	15 (3.5)	12 (4.3)	1.24 (0.57–2.70)	0.583	22 (5.2)	15 (5.5)	1.05 (0.41–2.71)	0.917
Chronic kidney disease	15 (2.1)	1 (0.2)	14 (5.0)	22.64 (2.96–173.20)	<0.001	4 (1.0)	6 (2.1)	2.22 (0.29–17.08)	0.444
WHO functional class					<0.001			1.01 (0.72–1.42)	0.958
Class I	106 (15.0)	92 (21.5)	14 (5.0)	5.16 (2.88–9.27)					
Class II	297 (42.1)	211 (49.3)	86 (30.9)	2.17 (1.58–2.98)					
Class III	261 (37.0)	120 (28.0)	141 (50.7)	0.38 (0.28–0.52)					
Class IV	42 (5.9)	5 (1.2)	37 (13.3)	0.08 (0.03–0.20)					
Single-targeted therapy	193 (27.3)	123 (28.7)	70 (25.2)		0.300	116 (27.2)	80 (28.7)	0.93 (0.62–1.38)	0.710
Double-targeted therapy	367 (52.0)	214 (50.0)	153 (55.0)	0.82 (0.60–1.11)	0.191	218 (50.9)	143 (51.6)	0.97 (0.69–1.38)	0.865
Triple-targeted therapy	74 (10.5)	38 (8.9)	36 (12.9)	0.66 (0.40–1.06)	0.084	43 (10.0)	28 (9.9)	1.01 (0.59–1.72)	0.975
Anticoagulation	124 (17.6)	67 (15.7)	57 (20.5)	0.74 (0.50–1.09)	0.102	65 (15.3)	54 (19.4)	0.75 (0.48–1.19)	0.228
Diuretic use	373 (52.8)	185 (43.2)	188 (67.6)	0.36 (0.27–0.50)	<0.001	223 (52.1)	145 (52.1)	1.00 (0.71–1.42)	0.992
Calcium-channel blocker use	14 (2.0)	10 (2.3)	4 (1.4)	0.61 (0.19–1.97)	0.584	9 (2.0)	8 (3.0)	1.52 (0.44–5.30)	0.508
Digoxin use	212 (30.0)	109 (25.5)	103 (37.1)	0.59 (0.43–0.82)	0.001	126 (29.5)	84 (30.1)	0.97 (0.67–1.40)	0.871
Steroid use	92 (13.0)	38 (8.9)	54 (19.4)	0.40 (0.26–0.63)	<0.001	54 (12.5)	43 (15.4)	0.79 (0.47–1.32)	0.362
Immunosuppressant drug use	73 (10.3)	31 (7.2)	42 (15.1)	0.45 (0.28–0.74)	0.001	40 (9.3)	32 (11.5)	0.79 (0.45–1.39)	0.414
Antiplatelet therapy	43 (6.1)	25 (5.8)	18 (6.5)	1.12 (0.60–2.09)	0.731	32 (7.5)	16 (5.8)	0.76 (0.38–1.54)	0.450

Data are expressed as mean ± standard deviation or *n* (%). [*]Except for idiopathic PAH/heritable PAH, PAH associated with CHD, and PAH associated with CTD, there were also three patients with PAH associated with portal hypertension and one patient with pulmonary veno-occlusive disease included in this study. [†]The adjusted numbers were rounded to integer values and therefore they may not exactly match the percentages. BMI: Body mass index; CHD: Congenital heart disease; CI: Confidence interval; COVID-19: Coronavirus disease 2019; CTD: Connective tissue disease; CTEPH: Chronic thromboembolic pulmonary hypertension; IPW: Inverse probability weighting; OR: Odds ratio; PAH: Pulmonary arterial hypertension; PH: Pulmonary hypertension; SD: Standard deviation; TA: Takayasu arteritis; WHO: World Health Organization.

Adverse events after vaccination

PH-related deterioration events occurred in a total of 57 (8.1%) patients during the follow up. We observed numerically more patients with PH-related major adverse events in the unVAC group than in the VAC group (35 [12.6%] *vs.* 22 [5.1%]), but the difference was not significant after IPW adjustment ($P = 0.302$). Regarding the subcomponent of primary outcomes, similar results were observed in the worsened WHO functional class (32 [11.5%] *vs.* 19 [4.4%], IPW-adjusted $P = 0.227$), unplanned medication adjustments (27 [9.7%] *vs.* 10 [2.3%], adjusted $P = 0.010$), and hospitalization due to heart failure (19 [6.8%] *vs.* 8 [1.9%], adjusted $P = 0.072$). The only case of death due to severe mycoplasma pneumonia occurred in the VAC group, resulting in an overall all-cause mortality of 0.1%. All the reported PH-related major adverse events are listed in Table 2.

Comparison of side effects between patients with different vaccines

Among the 428 patients with PH in the VAC group, 30 received the protein subunit vaccine, and the remaining 398 patients received inactivated vaccine. Among them, 216 (50.5%) reported at least one post-vaccination side effects or adverse events. The most frequent side effect was injection site pain (159 [37.1%]), followed by fatigue (26 [6.1%]), total deterioration (22 [5.1%]), palpitations (20 [4.7%]), and dyspnea (15 [3.5%]). A list of side effects is presented in Table 3.

Discussion

This real-world population-based prospective cohort study recruited more than 700 patients with WHO groups 1 and 4 PH diagnoses across 30 provinces, municipalities, and autonomous regions in China, and investigated the adverse outcomes of COVID-19 vaccination. To our knowledge, this is one of the largest studies to evaluate the COVID-19 vaccination rate and safety in a specific population with a devastating cardiopulmonary disease. Our results indicate that inactivated whole-virion and protein subunit vaccines are well tolerated. However, uncertainty and hesitancy exist in unvaccinated patients about whether to receive the vaccination, which is mainly driven by concerns about disease deterioration after vaccination. Our study revealed no

Table 2: Adverse events of PH patients during the follow-up period: unadjusted and adjusted analyses.

		Unadjusted data				Data adjusted using IPW[†]			
Adverse event	Total (n = 706)	Vaccinated (n = 428)	Unvaccinated (n = 278)	OR (95% CI)	P-value	Vaccinated (n = 428)	Unvaccinated (n = 278)	OR (95% CI)	P-value
Total deterioration[*]	57 (8.1)	22 (5.1)	35 (12.6)	0.38 (0.22–0.66)	<0.001	27 (6.3)	24 (8.6)	0.72 (0.39–1.34)	0.302
Worsened WHO functional class	51 (7.2)	19 (4.4)	32 (11.5)	0.36 (0.20–0.64)	0.001	23 (5.3)	22 (7.8)	0.67 (0.34–1.29)	0.227
Unplanned medication adjustments	37 (5.2)	10 (2.3)	27 (9.7)	0.22 (0.11–0.47)	<0.001	10 (2.4)	17 (6.2)	0.37 (0.17–0.79)	0.010
Hospitalization due to heart failure	27 (3.8)	8 (1.9)	19 (6.8)	0.26 (0.11–0.60)	0.002	9 (2.1)	13 (4.7)	0.44 (0.18–1.08)	0.072
All-cause mortality	1 (0.1)	1 (0.2)	0 (0)	NE		1 (0.2)	0 (0)	NE	

Data are expressed as n (%). [*]Total deterioration represents the total number of PH patients with adverse events occurred during the follow-up period. [†]The adjusted numbers were rounded to integer values and therefore they may not exactly match the percentages. CI: Confidence interval; COVID-19: Coronavirus disease 2019; IPW: Inverse probability weighting; NE: Not Evaluated; OR: Odds ratio; PH: Pulmonary hypertension; WHO: World Health Organization.

Table 3: Adverse events of PH patients after vaccination against COVID-19.

Adverse event	Total (n = 428)	Inactivated vaccine (n = 398)	Protein subunit vaccine (n = 30)
Injection site pain	159 (37.1)	144 (36.2)	15 (50.0)
Fever	11 (2.6)	9 (2.3)	2 (6.7)
Fatigue	26 (6.1)	21 (5.3)	5 (16.7)
Swelling	3 (0.7)	3 (0.8)	0 (0)
Dyspnea	15 (3.5)	15 (3.8)	0 (0)
Palpitation	20 (4.7)	18 (4.5)	2 (6.7)
Diarrhea	4 (0.9)	4 (1.0)	0 (0)
Dizziness	6 (1.4)	4 (1.0)	2 (6.7)
Skin lesion	2 (0.5)	2 (0.5)	0 (0)
Total deterioration[*]	22 (5.1)	22 (5.5)	0 (0)

Data are expressed as n (%). [*]Total deterioration represents the total number of PH patients with adverse events occurred during the follow-up period. COVID-19: Coronavirus disease; PH: Pulmonary hypertension.

significant association between vaccination and disease deterioration.

Vaccine hesitancy was listed as one of the ten major threats to global health in 2019 by WHO, which was further exacerbated by the COVID-19 pandemic.[19] CoronaVac is an inactivated vaccine against COVID-19 developed by Sinovac. It has been evaluated in phase III clinical trials in Brazil, Chile, Indonesia, the Philippines, and Turkey,[20] and has been used in vaccination campaigns worldwide in Asia, South America, North America, and Europe.[21] ZF2001 is a recombinant protein subunit vaccine against COVID-19 in phase III trials with 29,000 participants in China, Ecuador, Malaysia, Pakistan, and Uzbekistan. In a large cohort of 28,873 participants, the ZF2001 vaccine was shown to be safe and effective against symptomatic and severe-to-critical COVID-19 for at least 6 months after full vaccination.[22]

There are few studies regarding the hesitancy of receiving COVID-19 vaccines among patients with PH. In a Polish study, the rates of vaccine willingness of patients with PAH and CTEPH were higher than those of the general population.[23] Moreover, the authors did not find significant differences in the WHO functional class deterioration and presence of concomitant disease between vaccinated and unvaccinated patients. Unlike previous studies,[23–25] in which patients with chronic diseases had higher vaccine acceptance than the general population, our study revealed the opposite: patients with PH exhibited a higher hesitancy rate (271/706, 38.4%) than the general Chinese population (422/2377, 17.8%).[26]

In our study, patients with worse disease status were more reluctant to receive vaccination than their counterparts. Furthermore, significant refusals to COVID-19 vaccines have appeared in patients with PAH associated with CTDs. It is fundamental to recognize the real reason for vaccine hesitancy in this specific population. We found that the most common reason for unwillingness to receive COVID-19 vaccination was worries about PH deterioration, as declared by 70.9% (197/278) of patients who refused vaccination. Under China's zero-COVID strategy,[27,28] the infection rate is probably the lowest worldwide. In China, only 3 months after the first case of COVID-19 was observed, the government showed strong policy capabilities by effectively containing the spread of the pandemic and restoring economic and social order to normal.[29] Owing to the zero-COVID policy, only a small proportion of the people in China have been exposed to SARS-CoV-2.[29,30] Hence, the anxiety and uncertainty of fluctuations in health conditions after vaccination among patients might surpass the fear of COVID-19 infection partially due to their belief in government. Thus, the safety-related evidence of COVID-19 vaccines in patients with PH is key to affecting vaccine acceptance. Most people in China have received inactivated virus vaccine made either by Sinovac or state-owned Sinopharm.

Our data suggest that the adverse reactions of inactivated whole-virion COVID-19 vaccine and protein

subunit vaccine are mild, tolerable, and self-limited in patients with PH. No unexpected safety issues were reported, and the rates of side effects were consistent with those in previous reports.[31–33] As a result, by using IPW analysis, we found that vaccination was not significantly associated with disease progression.

Measures was taken to avoid potential bias: patients were recruited continually irrespective of their status to minimize potential selection bias, and follow-up assessment was performed according to formulated steps by trained physicians unaware of patients' clinical data.

Nevertheless, our study has some limitations. First, owing to the small sample size, we were unable to compare the adverse events among different vaccines. Second, the single-center online survey may have resulted in sampling bias. For instance, most participants had good adherence, so the results might not be generalizable to a random population sample. Third, the administration of other health vaccines such as the influenza vaccine may also have an impact on whether patients experience adverse events, thus creating some bias.[34] Fourth, limited by the natural characteristics of an observational study, some baseline characteristics were unbalanced between the vaccinated and unvaccinated groups, and there might be some other confounders that we did not consider. Furthermore, the data on adverse events after vaccination were collected from the patients' reports, which may have introduced possible reporting bias.

In summary, this study indicated that COVID-19 vaccination did not augment the PH-related major adverse events for patients with groups 1 and 4 PH, although there were some tolerable side effects. A large-scale randomized controlled trial is warranted to confirm this finding. The final approval of the COVID-19 vaccination for patients with PH as a public health strategy is promising.

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Conflicts of interest

None.

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