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RESEARCH ARTICLE

Protection of inactivated vaccine against SARS-CoV-2 infections in patients with comorbidities: a prospective cohort study

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Abstract **Protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of inactivated vaccines is not well characterized in people with comorbidities, who are at high risk of severe infection. We compared the risk of SARS-CoV-2 infection after complete vaccination with Sinopharm/BBIBP in people with comorbidities (e.g., autoimmune diseases, cardiovascular disease, chronic lung disease, and diabetes) with healthy individuals using a Cox-proportional hazard model. In July–September 2021, a total of 10 548 people (comorbidities, 2143; healthy, 8405) receiving the complete primary series of vaccination with Sinopharm/BBIBP in Bangkok, Thailand were prospectively followed for SARS-CoV-2 infection through text messaging and telephone interviewing for 6 months. A total of 295 infections from 284 participants were found. HRs (95% CI) of individuals with any comorbidities did not increase (unadjusted, 1.02 (0.77–1.36), *P* = 0.89; adjusted, 1.04 (0.78–1.38), *P* = 0.81). HRs significantly increased in the subgroup of autoimmune diseases (unadjusted, 2.64 (1.09–6.38), *P* = 0.032; adjusted, 4.45 (1.83–10.83), *P* = 0.001) but not in cardiovascular disease, chronic lung disease, or diabetes. The protection against SARS-CoV-2 infection of the Sinopharm vaccine was similar in participants with any comorbidities vs. healthy individuals. However, the protection appeared lower in the subgroup of autoimmune diseases, which may reflect suboptimal immune responses among these people.**

Keywords COVID-19; Sinopharm/BBIBP vaccine; immunocompromised patients; real-world

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been considered a pandemic public health crisis worldwide by the World Health Organization (WHO) since March 2020 [1]. It significantly affects all aspects of life. Several measures have been implemented to tackle the pandemic, and the emergency use of coronavirus disease 2019 (COVID-19) vaccines is a successful strategy for reducing severe SARS-CoV-2 infections and deaths. BBIBP-CorV (Sinopharm) vaccine is an inactivated vaccine approved by the WHO [2] as it shows efficacy in reducing severe SARS-CoV-2-infection and SARS-CoV-2-related mortality in phase I/II [3], phase III clinical trials [4], and in real-world settings [5,6]. Some believe that inactivated vaccines yield lower efficacy than vaccines developed from more novel technology [7]. However, inactivated vaccines confer a well-documented safety profile because this technology is commonly used in many vaccines against other pathogens. Even in people with multiple comorbidities, an inactivated vaccine showed no increased risk of adverse events [8]. Moreover, given that vaccine availability is limited during the early course of the pandemic, inactivated vaccines have become a major primary series of vaccines in low- and middle-income countries [9].

People with underlying medical conditions such as obesity, cardiovascular disease, cancer, and autoimmune disease are at increased risk of severe SARS-CoV-2 infection and SARS-CoV-2-related death [10–13]. Thus, COVID-19 vaccines are prioritized for people with comorbidities [14] as primary series and booster doses. However, real-world data on the robustness of COVID-19

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vaccines on these specific populations are scarce, especially among inactivated vaccines. Accordingly, we evaluated the risk of SARS-CoV-2 infection after receiving the Sinopharm vaccine in people with comorbidities compared with healthy individuals who were living in the same areas and received the same vaccine from the same vaccination centers simultaneously.

Methods

Study design and participants

Chulabhorn Royal Academy, in collaboration with three Bangkok public-health service centers organized by the health department of Bangkok Metropolitan Administration, has provided two doses three weeks apart of 0.5 mL of BBIP-CorV (Sinopharm) vaccine for people living in the Northwest area of Bangkok (Laksi, Don Mueang, and Saimai districts). Four mobile vaccination sites were organized consecutively, and the complete (second) dose of vaccine was provided between July 31, 2021, and September 18, 2021 (Table S1). Intended vaccine recipients must have registered themselves with the Bangkok public-health service centers (vaccine provider) and agreed to provide their information including national ID, age, gender, and place of residency to the vaccine provider. All vaccine providers in Thailand must send the vaccine recipients' data to the Ministry of Public Health Immunization Center to confirm that the intended vaccine recipients had not previously received a COVID-19 vaccine elsewhere and ensured the appropriate age of vaccination (⩾18 years). This process complied with the national policy regarding the early phase of COVID-19 vaccines being publicly available, and the vaccines had not yet been approved for use in children then. Furthermore, on the day before vaccinating each dose, intended vaccine recipients must have declared no SARS-CoV2 infections over the past two weeks.

A total of 12 063 people were considered eligible and turned up to receive the complete dose of the vaccine. On the vaccination day, the vaccine recipients who turned up were informed by registered nurses or health personnel in charge at the mobile vaccination centers that they would be interviewed about their comorbidity data and asked for their contact number to prospectively follow their SARS-CoV-2 infection status for up to 6 months. People with health issues or any concerns about the vaccine could also request to see physicians who volunteered to stand by at the mobile vaccination centers. Nevertheless, those who declined to participate in the study also received the same level of care.

A total of 11 290 people agreed to participate in the prospective cohort study (Fig. 1). Baseline data, including the date of birth, weight, height, personal medical illness, current medications, and contact number, were interviewed by the nurse or health personnel at the mobile vaccination centers using a prespecified questionnaire.

Comorbidities including diabetes mellitus, hypertension, cardiac disease, ischemic or hemorrhagic stroke, chronic kidney disease, chronic lung disease, cancer, and autoimmune diseases were listed in the questionnaire. A checklist was used to determine whether the participants were currently taking medications related to the listed comorbidities, including steroids and immunosuppressants. The list was based on the fact that these comorbidities are reportedly associated with increased morbidities and mortalities of SARS-CoV-2 infections [15–22]. Two open-ended questions about personal illness and current medications other than those listed were also available in the questionnaire. Autoimmune diseases were defined by a personal history of systemic autoimmune rheumatic diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus) or currently taking systemic glucocorticoids or immunosuppressants. Participants with cardiac disease or stroke were classified as having cardiovascular disease, and participants with asthma or chronic obstructive pulmonary disease were classified as having chronic lung disease. Participants with self-reported other comorbidities in the open-ended questions were included in the analysis as having any comorbidity.

The research question was whether the underlying comorbidities can affect the responsiveness to the Sinopharm vaccine, and the assumption was that healthy individuals would have ideal responsiveness to the vaccine. Therefore, the controls were participants without comorbidities (healthy individuals).

Data collection and follow-up

All participants were prospectively followed from the date of complete vaccination to 6 months. The status of SARS-CoV-2 infection, symptoms suggesting SARS-CoV-2 infection, and their relevant dates were collected by short message service or telephone interview using Research Electronic Data Capture [23], a secure, web-based data capture application hosted at the Chulabhorn Royal Academy. To reduce recall bias, we collected data intermittently at 30, 90, and 180 days after the date of complete vaccination. A total of 10 548 had a complete follow-up, and the dropout rate was 7% (Fig. 1).

Outcomes and covariables

The primary outcome was laboratory-confirmed SARS-CoV-2 infection using an RT-PCR or rapid antigen test, regardless of the presence of symptoms. During the study period, the Government fully supported the diagnostic and treatment cost of SARS-CoV-2 infection for all

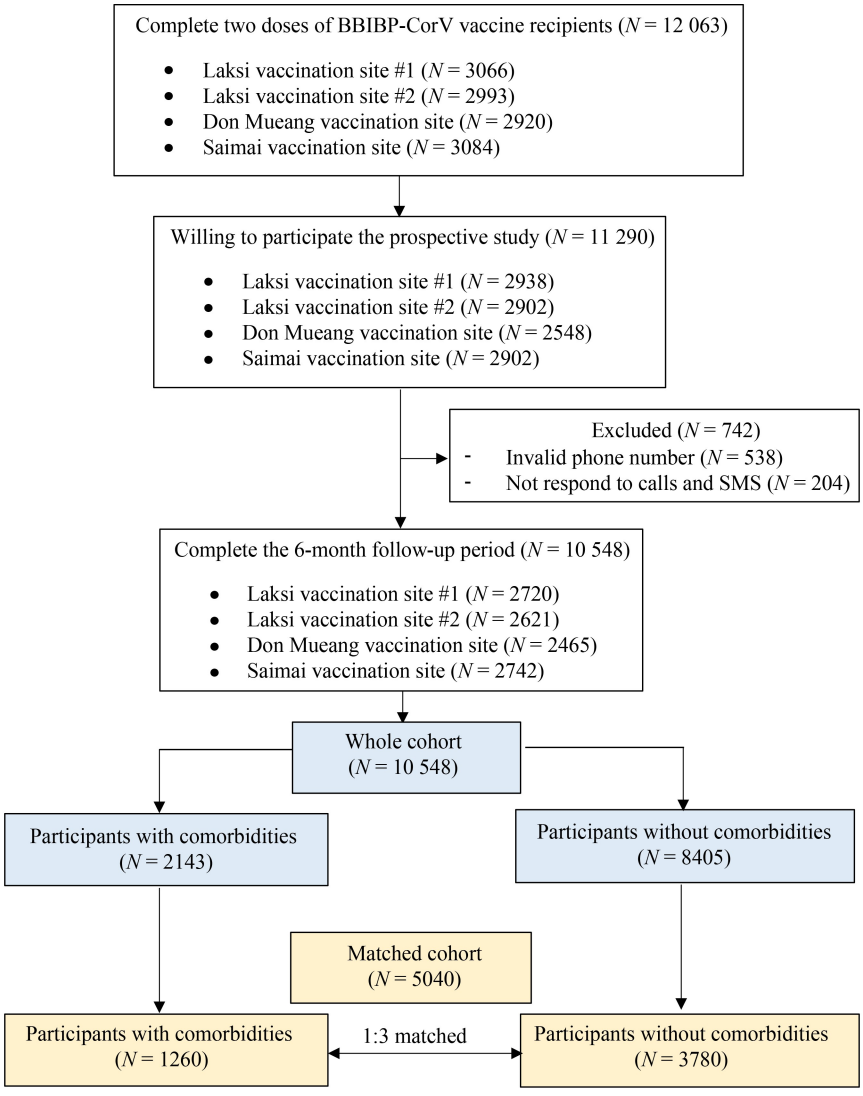

Fig. 1 Participant flow chart.

people in Thailand [24], so all positive cases were tested by laboratories accredited by the Department of Medical Sciences, Ministry of Public Health, Thailand [25]. Positive SARS-CoV-2 tests occurring within seven days of the complete vaccination were disregarded in the analyses. Other outcomes related to severe SARS-CoV-2 infection including death, pneumonia, ventilator-requiring pneumonia, and hospitalization were also collected.

We also considered a history of contact with a confirmed SARS-CoV-2 infection case and circulating SARS-CoV-2 variant corresponding with the study period in the risk estimation. A history of contact with a confirmed SARS-CoV-2 infection was checked either in the same household or in other settings for each time period of data collection. The difference in circulating SARS-CoV-2 variants in Thailand during the study period was explored using open data provided by the Government [26]. The circulating SARS-CoV-2 variants were periodically identified by the Department of Medical Sciences and 15 Regional Medical Sciences center laboratories using RT-PCR, targeted sequencing, and whole-genome sequencing from April 2021. We defined the study period into two periods according to the major circulating variant (> 70% of identified SARS-CoV-2 variants). Before December 2021 (corresponding with days 0–90 of the study period), the major variant was B.1617.2 (Delta). From early January 2022 (corresponding with days 90–120), the major variant was B.1.1.529 (Omicron).

Matched cohort

To improve the precision of the risk evaluation, we also used a matched cohort to re-estimate the risk of infection in participants with comorbidities compared with those without comorbidities. The matched cohort was derived

from 10 548 participants (the whole cohort). A total of 1260 participants with comorbidities (cases) were matched with those not having comorbidities (controls). Eligible controls within the same sex, 1-point body mass index, and 3-year age categories were approached until three controls were individually matched with each case, resulting in 3780 controls (Fig. 1).

Statistical analysis

We used descriptive statistics to describe the demographic and clinical characteristics at baseline of the participants of the whole cohort and the matched cohort classified by having or not having comorbidities. We compared the baseline characteristics of participants having comorbidities with those not having comorbidities using the chi-square test, student's *t*-test, or Mann–Whitney U test, whichever was appropriate.

Differences in risk of SARS-CoV-2 infections between participants with and without comorbidities were estimated using univariable and multivariable Cox regression models and displayed as unadjusted and adjusted hazard ratios (HR) with 95% CIs. Multiple failure survival analysis was used to allow all SARS-CoV-2 infections that recurred in the same participants during the follow-up period. Three levels of data according to the time of information collection from each participant (days 30, 90, and 180) were included in the models to precisely estimate the risk. A history of recent contact with people with SARS-CoV-2 infection concurring with each time level was included in the multivariable Cox regression models. We used conditional Cox regression models in the matched cohort to estimate unadjusted and adjusted HRs. We also calculated the rates of SARS-CoV-2 infection per 1 000 000 person-days in participants with and without comorbidities. The cumulative incidence curves of SARS-CoV2 infection in participants with and without comorbidities were estimated based on the first occurrence of infection (single-failure survival analysis).

The median time (in days) to the first occurrence of infection in participants with and without comorbidities was assessed. The protocol prespecified the separate analysis of the risk of SARS-CoV-2 infections in participants with four major comorbidities (diabetes mellitus, cardiovascular disease, chronic lung disease, and autoimmune disease). The risk of severe SARS-CoV-2 infections, defined by hospitalization and pneumonia, was also estimated.

In the matched cohort, the differences in risk of SARS-CoV-2 infection between participants with comorbidities and their individually matched controls were estimated. The risk was also estimated in the subgroups of participants with diabetes mellitus, cardiovascular disease, chronic lung disease, and autoimmune disease compared with their matched controls.

Sensitivity analysis

Our study was performed during the first widespread outbreak of SARS-CoV-2 infection, and home-use rapid antigen test kits were not yet widely available in Thailand. Accordingly, participants with symptoms suggesting SARS-CoV-2 infection but with no access to accredited laboratories were likely to be infected by SARS-CoV-2. We expanded the possibility of under-tested SARS-CoV-2 infection by using the inclusive outcome, which was defined by either laboratory-confirmed SARS-CoV-2 infection or having symptoms suggesting SARS-CoV-2 infection. Symptoms suggesting SARS-CoV-2 infection comprised unexplained fever, cough, running nose, body ache, headache, fatigue, anorexia, loss of taste or smell, and breathing difficulty. We evaluated the inclusive outcome by using the Cox Proportional Hazard model similar to when evaluating the primary outcome.

All analyses were performed using a standard software package (Stata SE, version 16.1; StataCorp). The study protocol was in compliance with the Helsinki declaration and approved by Human Research and Ethics Committee, Chulabhorn Research Institute (project code: 100/2564).

Results

Among the 10 548 participants with complete follow-up, 2143 (20.32%) had comorbidities. The most prevalent comorbidity was hypertension. The majority of participants were female (54.8%), and the median age (IQR) was 41 (29–52). The proportion of females, median age, and mean BMI was higher in those with comorbidities than in those without comorbidities. In the matched cohort, 1260 participants with comorbidities had a proportion of female, age, and BMI similar to 3780 participants who did not have comorbidities (Table 1). Among 164 participants with cardiovascular disease, 16 (9.8%) had both cardiac disease and stroke, 105 (64.0%) had only cardiac disease, and 43 (26.2%) had a stroke. Among 68 living with autoimmune diseases, 9 (13.2%) were taking steroids, 21 (30.9%) were taking other immunosuppressants, 20 (29.4%) were taking both steroids and immunosuppressants, and 18 (26.5%) did not use steroids or immunosuppressants. The majority of patients (N = 56 (82.4%)) had a rheumatic autoimmune disease (Table S2). Other self-reported comorbidities included dyslipidemia, Human immunodeficiency virus infection, thyroid disorders, and allergic rhinitis.

Among 742 participants who did not have complete follow-ups, the majority were male (52.3%). The median age (IQR) of those lost to follow-up was 40 (26–54), and

21.70% had comorbidities, which did not differ from the participants included in the study. The prevalence of diabetes mellitus, chronic lung disease, cardiac disease, and autoimmune disease was also similar, but the prevalence of stroke was slightly higher in those lost to follow-up (1.35% vs. 0.56%, $P = 0.008$; Table S3).

Laboratory-confirmed SARS-CoV-2 infection: the whole cohort

From a total period of follow-up time of 1 978 983 person-days, 295 infections from 284 participants were found, providing an incidence rate (95% CI) of 149.1 (133.0–167.1) per 1 000 000 person-days. The infection rates of individuals with and without comorbidities were similar (Table 2). The unadjusted HR (95% CI) in patients with any comorbidities was 1.02 (0.77–1.36) ($P = 0.89$). After adjusting for a history of contact with people who had SARS-CoV-2 infection, the HR (95% CI) was 1.04 (0.78–1.38) ($P = 0.81$), as shown in the cumulative incidence curve (Fig. 2). In participants with autoimmune diseases, the rate of infection was higher than those without autoimmune diseases (Table 2), providing the unadjusted and adjusted HRs of 2.64 (95% CI = 1.09–6.38, $P = 0.032$) and 4.45 (95% CI = 1.83–10.83, $P = 0.0010$), respectively. The cumulative incidence curve in participants with autoimmune diseases was clearly distinguishable from the curve of those without autoimmune diseases (Fig. 3A). In participants with cardiovascular disease, the unadjusted and adjusted

Table 1 Baseline characteristics

	Whole cohort				Matched cohort			
	Total ($N = 10\,548$)	Comorbidities ($N = 2143$)	No comorbidities ($N = 8405$)	*P*	Total ($N = 5040$)	Comorbidities ($N = 1260$)	No comorbidities ($N = 3780$)	*P*
Sex								
Male; *n* (%)	4767 (45.19)	844 (39.38)	3923 (46.67)	< 0.001	2096 (41.59)	524 (41.59)	1572 (41.59)	1.00
Female; *n* (%)	5781 (54.81)	1299 (60.62)	4482 (53.33)		2944 (58.41)	736 (58.41)	2208 (58.41)	
Median age (IQR); year	41 (29–52)	38 (27–48)	54 (45–61)	< 0.001	49 (40–55)	49 (40–55)	49 (40–55)	0.61
BMI; mean ± SD; kg/m^2	24.49 ± 4.92	26.20 ± 5.16	24.05 ± 4.77	< 0.001	24.89 ± 4.42	24.94 ± 4.39	24.87 ± 4.43	0.62
Diabetes mellitus; *n* (%)	645 (6.11)	645 (30.10)	–		293 (5.81)	293 (23.25)	–	
Hypertension; *n* (%)	1432 (13.58)	1432 (66.82)	–		723 (14.35)	723 (57.38)	–	
Chronic lung disease (%)	188 (1.78)	188 (8.77)	–		148 (2.94)	148 (11.75)	–	
Cardiac disease; *n* (%)	121 (1.15)	121 (5.65)	–		55 (1.09)	55 (4.37)	–	
Stroke; *n* (%)	59 (0.56)	59 (2.75)	–		27 (0.54)	27 (2.14)	–	
Chronic kidney disease; *n* (%)	36 (0.34)	36 (1.68)	–		19 (0.38)	19 (1.51)	–	
Cancer; *n* (%)	58 (0.55)	58 (2.71)	–		33 (0.65)	33 (2.62)	–	
Autoimmune disease; *n* (%)	68 (0.64)	68 (3.17)	–		64 (1.27)	64 (5.08)	–	

Note: $P < 0.05$, considered statistical significance.

Table 2 Incidence rates of laboratory-confirmed SARS-CoV-2 infection of participants following the primary series of Sinopharm vaccination in the whole cohort.

Participant cohort	No. of participants with events/ Total participants (%)		*P*	Number of events[a]		Incidence rate (95% CI)[b], No. event per 1 000 000 person-days		*P*
	Comorbidities	No comorbidities		Comorbidities	No comorbidities	Comorbidities	No comorbidities	
Any comorbidities	57/2143 (2.66%)	227/8405 (2.70%)	0.91	60	235	148.6 (115.4–191.4)	149.2 (131.3–169.5)	0.99
Autoimmune disease	5/68 (7.35%)	279/10480 (2.66%)	0.017	5	290	387.8 (161.4–931.6)	147.5 (131.5–165.5)	0.058
Cardiovascular disease	5/164 (3.05%)	279/10384 (2.69%)	0.77	7	288	226.7 (108.1–475.5)	147.8 (131.7–165.9)	0.27
Chronic lung disease	4/188 (2.13%)	280/10360 (2.70%)	0.62	4	291	113.4 (42.6–302.2)	149.7 (133.5–167.9)	0.62
Diabetes mellitus	11/645 (1.71%)	273/9903 (2.76%)	0.11	13	282	106.8 (62.0–184.0)	151.8 (135.1–170.6)	0.20

Note: Participants having comorbidities, including autoimmune disease, cardiovascular disease, chronic lung disease, diabetes mellitus, were compared with those not having comorbidities. [a]11 participants (3 with comorbidities and 8 without comorbidities) had two episodes of infection during the follow-up period; [b]Recurrent infections in the same participants during the follow-up period were included in the analysis; $P < 0.05$ indicated statistical significance.

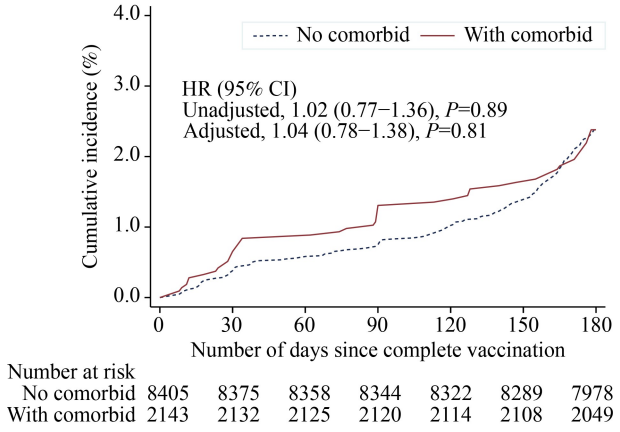

Fig. 2 Cumulative incidence of laboratory-confirmed SARS-CoV-2 infection following a primary series of Sinopharm vaccination in participants having any comorbidities compared with healthy individuals.

HRs also increased, but the difference had no statistical significance (Fig. 3B). In participants with chronic lung disease and diabetes mellitus, the HRs did not increase (Fig. 3C and 3D). No violation of the proportional hazard assumption was found in all analyzed models.

In the whole cohort, 219 of 295 infections (74.2%) were confirmed by RT-PCR tests. The proportion of RT-PCR-confirmed infections in individuals with comorbidities was higher than in those without comorbidities (85.0% vs. 71.5%, P = 0.033). In participants with comorbidities, 23 (38.3%) of 60 infections were reported concurrently with contact with a positive SARS-CoV-2 case, whereas 100 (42.6%) of 235 infections of individuals without comorbidities reported the same (P = 0.55).

During the spread of the Delta variant, the rate of laboratory-confirmed infection in participants with comorbidities did not differ from those without comorbidities (2.66% vs. 2.70%; P = 0.91). Similarly, during the Omicron spread, the infection rate in individuals with vs. without comorbidities did not differ (0.14% vs. 0.10%; P = 0.56).

Laboratory-confirmed SARS-CoV-2 infection: the matched cohort

In the matched cohort, 133 infections from 127 participants were recorded, and the incidence rate (95% CI) was 140.9 (118.9–167.0) per 1 000 000 person-days. The infection rate of cases with any comorbidities did not differ from the controls, and the HR did not statistically increase (Table 3). However, the adjusted HR

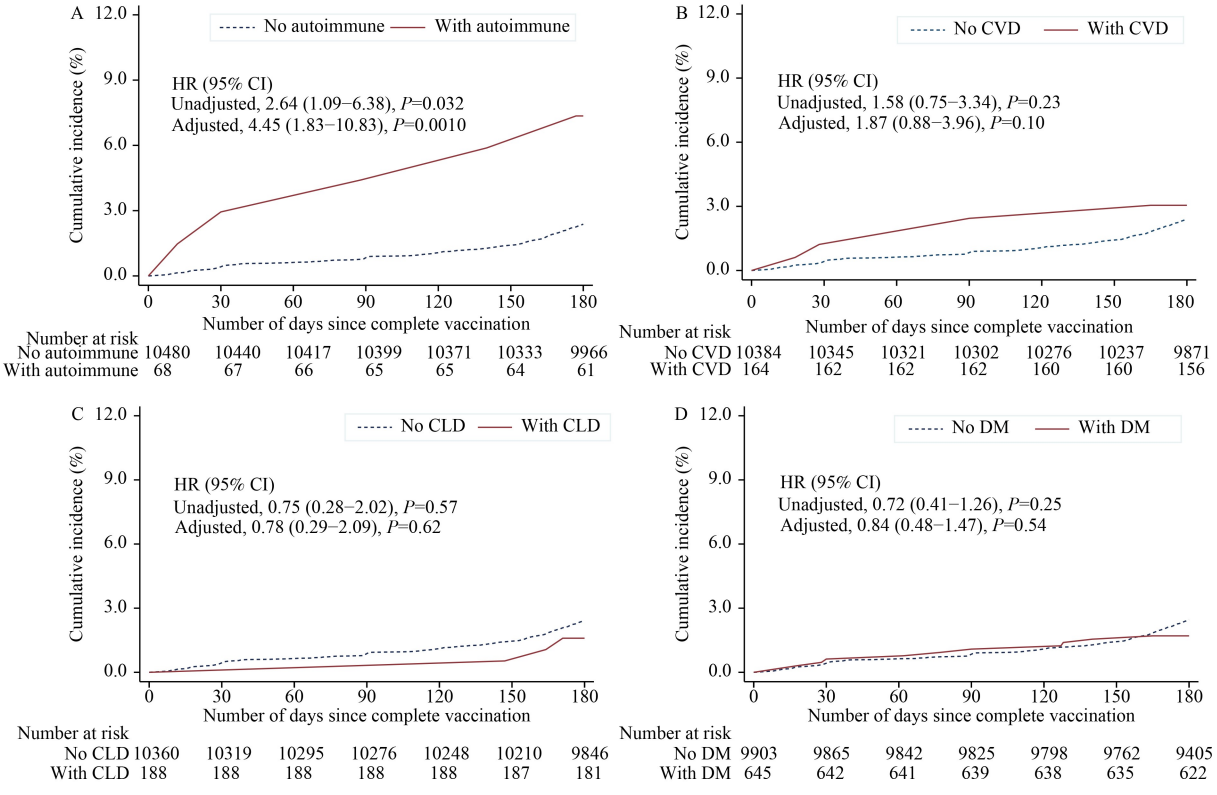

Fig. 3 Cumulative incidence of laboratory-confirmed SARS-CoV-2 infection following a primary series of Sinopharm vaccination in participants with (A) autoimmune disease, (B) cardiovascular disease (CVD), (C) chronic lung disease (CLD), and (D) diabetes mellitus (DM). Each was compared with participants without diseases.

Table 3 Hazard ratios of laboratory-confirmed SARS-CoV-2 infection following the primary series of Sinopharm vaccination in the matched cohort

Participant cohort	Total number of participants		Total number of events		Incidence rate (95% CI), No. of event per 1 000 000 person-days		*P*	Unadjusted HR (95% CI) [a, b]	*P*	Adjusted HR (95% CI) [a, b, c]	*P*
	Comorbid	No comorbid	Comorbid	No comorbid	Comorbid	No comorbid					
Any Comorbidities	1260	3780	38	95	160.5 (116.8–220.6)	134.3 (109.9–164.3)	0.35	1.21 (0.83–1.77)	0.31	1.17 (0.80–1.71)	0.40
Autoimmune disease	64	192	4	5	328.9 (123.4–876.2)	139.1 (57.9–334.2)	0.22	2.32 (0.62–8.69)	0.21	5.90 (1.08–32.33)	0.041
Cardiovascular disease	73	219	3	6	218.9 (70.6–678.7)	146.1 (65.6–325.2)	0.56	1.60 (0.40–6.43)	0.50	2.02 (0.48–8.45)	0.33
Chronic lung disease	148	444	3	11	108.3 (34.9–335.9)	132.7 (73.5–239.6)	0.79	0.80 (0.22–2.85)	0.72	0.82 (0.23–2.95)	0.76
Diabetes mellitus	293	879	7	23	127.2 (60.6–266.9)	139.4 (92.7–209.8)	0.86	0.92 (0.39–2.14)	0.84	0.99 (0.42–2.31)	0.97

Note: Participants with comorbidities, including autoimmune disease, cardiovascular disease, chronic lung disease, and diabetes mellitus, were compared with their individually matched controls who did not have any comorbidities. [a]Recurrent infections in the same participants during the follow-up period were included in the analysis; [b]Analyzed by Conditional Cox Regression models; [c]Adjusted for a history of contact with people having SARS-CoV-2 infection; $P < 0.05$ considered statistical significance.

of cases with autoimmune disease significantly increased (HR = 5.90 (95% CI = 1.08–32.33), $P = 0.041$, Table 3). Similar to the whole cohort, the HRs of cases with cardiovascular disease, chronic lung disease, or diabetes did not significantly increase (Table 3). No violation of the proportional hazard assumption was found in all analyzed models.

Severe SARS-CoV-2 infections

In participants with comorbidities, 21 (35.0%) of 60 infections needed hospitalization, whereas 76 (32.3%) of 235 infections in those without comorbidities needed hospitalization (RR = 1.08 (95% CI = 0.73–1.60), $P = 0.69$). Pneumonia was reported in 8.3% and 3.4% of infections in participants with and without comorbidities (RR = 2.45 (95% CI = 0.83–7.21), $P = 0.096$). No deaths or ventilator-requiring pneumonia occurred in any participants.

Time to the first SARS-CoV-2 infection

Median time (IQR) in days to the first SARS-CoV-2 infection in individuals with autoimmune disease was 88 (30–140) days, which was shorter than those with other comorbidities (117 (IQR, 31.5–172.5)) and those without comorbidities (147 (IQR, 77–170)), although no statistical significance existed ($P = 0.24$, Fig. 4).

Sensitivity analysis

A total of 401 participants (87 with and 314 without comorbidities) reported having symptoms suggesting SARS-CoV-2 infection or laboratory-confirmed infection. The inclusive outcome of participants with comorbidities did not differ from individuals without comorbidities (unadjusted HR = 1.06 (95% CI = 0.84–1.35), $P = 0.60$, Table 4). However, in participants with autoimmune diseases, the risk of having the inclusive outcome increased after adjustment (adjusted HR = 2.78 (95% CI = 1.15–6.73), $P = 0.024$, Table 4).

Discussion

This prospective cohort study provided real-world data on the protection against SARS-CoV-2 infections of the primary series of Sinopharm vaccine in a specific population (people with comorbidities) compared with the healthy population (without comorbidities). The occurrence of infections did not differ between people with and without comorbidities. The relative risk was separately evaluated into different types of comorbidities (autoimmune diseases, cardiovascular disease, chronic lung disease, and diabetes mellitus). The relative risk markedly increased in people with autoimmune diseases but not in other types of comorbidities.

We compared participants living in the same community during the same period. Important factors influencing infection (e.g., public-health measures, circulating variants, and environment) were similar between participants with and without comorbidities. This approach ensured a more scrutinized estimation of the relative risk of infection. Age, sex, and BMI were considered in the analysis by using the matched cohort, which also provided similar results. When symptoms suggesting SARS-CoV-2 infections were included in the analysis, the estimated relative risks were again similar. Additionally, data were periodically collected to minimize recall bias and allow the adjustment for a history of contact with a SARS-CoV-2-positive case in a

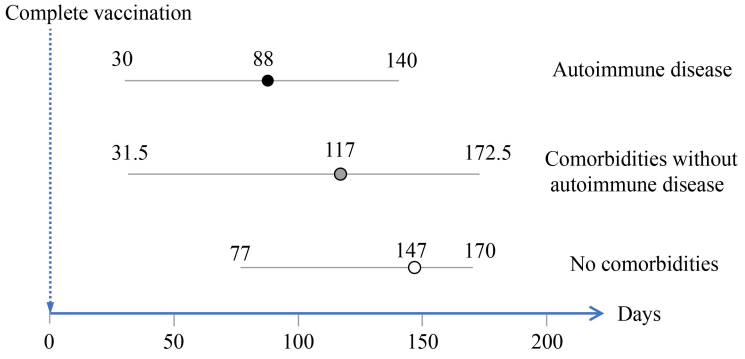

Fig. 4 Median (IQR) days of the first laboratory-confirmed SARS-CoV-2 infection after complete vaccination in participants with autoimmune disease, comorbidities without autoimmune disease, and no comorbidities.

Table 4 Hazard ratios of laboratory-confirmed SARS-CoV-2 infection or having symptoms suspected COVID-19 infection following the primary series of Sinopharm vaccination in the whole cohort

Participant cohort	No. of participants with events/Total participants (%)		Unadjusted HR [a]	*P*	Adjusted HR [a, b]	*P*
	Comorbidities	No comorbidities				
Any comorbidities	87/2143 (4.06%)	314/8405 (3.74%)	1.06 (0.84–1.35)	0.60	1.10 (0.87–1.39)	0.41
Autoimmune disease	6/68 (8.82%)	395/10480 (3.77%)	1.84 (0.76–4.46)	0.17	2.78 (1.15–6.73)	0.024
Cardiovascular disease	7/164 (4.27%)	394/10384 (3.79%)	1.40 (0.72–2.71)	0.31	1.63 (0.84–3.16)	0.14
Chronic lung disease	6/188 (3.19%)	395/10360 (3.81%)	0.81 (0.36–1.81)	0.60	0.82 (0.37–1.85)	0.63
Diabetes mellitus	17/645 (2.64%)	384/9903 (3.88%)	0.73 (0.46–1.16)	0.18	0.80 (0.51–1.27)	0.34

Note: Participants having comorbidities, including autoimmune disease, cardiovascular disease, chronic lung disease, diabetes mellitus, were compared with those not having comorbidities. [a]Recurrent infections in the same participants during the follow-up period were included in the analysis; [b]Adjusted for a history of contact with people having SARS-CoV-2 infection.

time-specific manner.

A large cohort study of Sinopharm has reported higher vaccine effectiveness in people with comorbidities than those without comorbid conditions; however, vaccine effectiveness has not been distinguished according to the types of comorbidities [5]. Different comorbidities confer different immune responses to the vaccines, so the risk should be evaluated separately. Herein, we found that the risk of breakthrough infection significantly increased in participants with autoimmune diseases. Conversely, it did not increase in those with cardiovascular disease, diabetes mellitus, and chronic lung disease. The significant increase in breakthrough infection among autoimmune diseases can be attributed to the state of a compromised immune response, especially when using immunomodulators or glucocorticoids. People with systemic rheumatic diseases show declined humoral immune responses to SARS-CoV-2 mRNA vaccines, but the antibody titers are restored after the booster (third) dose [27]. We also found that the breakthrough infection occurred earlier in people with autoimmune diseases than in people with other comorbidities. By extrapolation, commencing a booster dose in people with autoimmune diseases earlier than the general population may be sensible.

Poor glycemic control may worsen immunological response to SARS-CoV-2 infection [28]. However, studies on the immunological response to COVID-19 vaccines in patients with diabetes mellitus are inconsistent [29,30]. Notably, immunological studies cannot measure important factors influencing infection, such as the integrated function of the whole-body immune system. In our study, the risk of infection in people with diabetes did not differ from those without diabetes. However, we did not have information on other factors, such as personal protective measures and glycemic control, which may have contributed to the risk of infection. The risk of infection appeared higher in participants with cardiovascular disease but did not reach statistical significance. Conversely, in chronic lung disease, the risk did not increase. No a priori assumption was made about impaired immunologic responses under these conditions, and more studies are needed to confirm the risk estimated.

As expected, the rate of SARS-CoV-2-related pneumonia was higher in participants with comorbidities than in those without. However, the hospitalization rates did not differ, which may have resulted from the Government's policy to support hospitalization for people aged 60 years or over, regardless of underlying comorbidities.

Our study has potential limitations. First, the results of

this study should be carefully interpreted. This study was not designated to evaluate the Sinopharm vaccine effectiveness (i.e., both comorbid and no-comorbid groups received the vaccine). Therefore, the higher rate of breakthrough infection among people with autoimmune diseases observed in this study cannot disregard the effectiveness of the Sinopharm vaccine. However, our study confirmed that the Sinopharm vaccine effectively prevented severe SARS-CoV-2 infections because no death or ventilator-requiring pneumonia occurred in all participants, including those with autoimmune diseases. Underlying comorbidities were determined by interviewing, not documented by hospital or prescription records, although this was conducted by nurses or other health personnel, which can improve reliability. We evaluated the relative risk after commencing the primary series of vaccines where the immune responses may not be as robust as the booster vaccines. Given that the immune responses of people with autoimmune diseases performed better after the booster dose [27], the relative risk of breakthrough infection in people with autoimmune diseases was bound to decrease when evaluated after the booster doses. We did not have data for doses or types of immunosuppressants/glucocorticoids in participants with autoimmune disease and the degree of glycemic control in participants with diabetes, which may quantitatively affect the likelihood of infection. We also did not test SARS-CoV-2 antibodies before the vaccination, which may indicate a previous infection and can improve the robustness of the vaccination. However, people with documented SARS-CoV-2 infection within 2 weeks before enrolment were not included in this study. Given that more vaccines have been available in early 2022, some participants may have pursued a booster dose, which can also affect the risk estimation toward the end of the study period. Overall, the sample size was large. The subgroup of people with each kind of comorbidities was small, and most people with comorbidities had hypertension, but this reflected the distribution of diseases in the real-world population [31,32]. Even with a small sample size, the subgroup of autoimmune diseases yielded a significant increase in the risk of infections, raising concerns about a delay in receiving the booster doses in people with autoimmune diseases.

Our results showed that the risk of SARS-CoV-2 breakthrough infection after commencing a primary series of an inactivated COVID-19 vaccine in people with comorbidities was similar to that in healthy individuals. However, the risk increased in people with autoimmune diseases. These results were consistent with the WHO recommendation that COVID-19 vaccines should be prioritized for immunocompromised persons and adults with comorbidities in the highest and high-priority use, respectively. Our findings further suggested that receiving booster doses early should be considered in immunocompromised persons.

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Compliance with ethics guidelines

Kanchana Ngaosuwan, Kamonwan Soonklang, Chawin Warakul, Chirayu Auewarakul, and Nithi Mahanonda declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent for being included in the study was obtained from all participants.

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