

## 問題 1

高等学校の数学範囲の記述問題を 1 題作成し、その模範解答を記載してください。

## 問題 2

添付資料 1 は、2024 年 2 月に国際論文誌 Nature Communications で出版された論文[1]である。本論文を生成 AI の一つである GPTs アプリケーション「Paper Interpreter」[2]によって、日本語の解説を与えたものが添付資料 2 である。生成 AI の記述は必ずしも正確でないことに注意しながら、以下の問いに答えなさい。

**問 1.** 論文中の Table 1 では、全研究参加者のうち SARS-CoV-2 感染患者のグループを「Unvaccinated（ワクチン未接種）」、「Incomplete vaccination（不完全なワクチン接種）」、「Fully vaccinated（完全なワクチン接種）」、「Received booster dose（ブースター接種\*1）」の 4 グループに分けて、各種統計を示しています。これについて、以下の 2 つの問い（ア）と（イ）に答えなさい。

（ア）ここで、各グループはどのように定義されていますか。その定義とそれが正しいと言える根拠を述べなさい。

（イ）本研究でこのように 4 グループに分けた理由は何ですか。それに対する、あなたの考えを述べなさい。

**問 2.** 添付資料 2 の「結論」の段落では、「ワクチン接種を完了した患者やブースター接種を受けた患者は、ワクチン未接種者や不完全接種者に比べて、健康影響のリスクが低かったことが観察されました。」と述べられています。その根拠は論文中のどの図表のどんなデータを見れば読み取ることができるかを、図表のキャプションにも注意しながら、論理的に解説しなさい。

**問 3.** 添付資料 2 の「限界」の段落では、「研究は後ろ向きコホート研究\*2 であり、因果関係を確立することはできません」と述べられています。これについて、以下の 2 つの問い（ア）と（イ）に答えなさい。

（ア）「因果関係」とは何と何の間の因果関係を指していますか。

（イ）「因果関係」と「相関」の違いに注意して、なぜ本研究では「因果関係を確立することはできない」のかを論理的に説明しなさい。

\*1 ブースター接種：ワクチンの効果を高め、持続させるための追加接種のこと

\*2 後ろ向きコホート研究：特定の条件を満たした集団（コホート）を対象にして診療記録などから過去の出来事に関する調査を行う研究手法のこと

## 参考文献など


- [1] Lam, I. C. H., Zhang, R., Man, K. K. C., Wong, C. K. H., Chui, C. S. L., Lai, F. T. T., Li, X., Chan, E. W. Y., Lau, C. S., Wong, I. C. K., & Wan, E. Y. F. (2024). Persistence in risk and effect of COVID-19 vaccination on long-term health consequences after SARS-CoV-2 infection. *Nature Communications*, 15(1). <https://doi.org/10.1038/s41467-024-45953-1>
- [2] <https://chat.openai.com/g/g-hxDOCBQrs-paper-interpreter-japanese>

# Persistence in risk and effect of COVID-19 vaccination on long-term health consequences after SARS-CoV-2 infection

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The persisting risk of long-term health consequences of SARS-CoV-2 infection and the protection against such risk conferred by COVID-19 vaccination remains unclear. Here we conducted a retrospective territory-wide cohort study on 1,175,277 patients with SARS-CoV-2 infection stratified by their vaccination status and non-infected controls to evaluate the risk of clinical sequelae, cardiovascular and all-cause mortality using a territory-wide public healthcare database with population-based vaccination records in Hong Kong. A progressive reduction in risk of all-cause mortality was observed over one year between patients with SARS-CoV-2 infection and controls. Patients with complete vaccination or have received booster dose incurred a lower risk of health consequences including major cardiovascular diseases, and all-cause mortality than unvaccinated or patients with incomplete vaccination 30–90 days after infection. Completely vaccinated and patients with booster dose of vaccines did not incur significant higher risk of health consequences from 271 and 91 days of infection onwards, respectively, whilst un-vaccinated and incompletely vaccinated patients continued to incur a greater risk of clinical sequelae for up to a year following SARS-CoV-2 infection. This study provided real-world evidence supporting the effectiveness of COVID-19 vaccines in reducing the risk of long-term health consequences of SARS-CoV-2 infection and its persistence following infection.

Since the outbreak of the Coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus in late 2019, substantial research has been undertaken to uncover the health consequences associated with SARS-CoV-2 infection. The current body of evidence has reported that patients with SARS-CoV-2 infection may incur a greater risk of acute and post-acute health consequences involving multiple organ systems and associated mortality following SARS-CoV-2 infection<sup>1–3</sup>.

A universal definition of post-COVID-19 condition remains to be determined owing to the discrepancy in definition published by

different healthcare regulatory bodies<sup>4</sup>. Nevertheless, the current literature referred to clinical presentations develop within 30 days of initial infection as acute clinical sequelae, while complications that developed or persisted beyond the acute phase of SARS-CoV-2 infection were referred to as post-acute clinical sequelae<sup>5</sup>. Despite the current evidence suggesting that most patients may recover from SARS-CoV-2 infection within two to four weeks of symptoms appearance, the increased risk of incident cardiovascular, neurological, psychiatric diseases, diabetes and all-cause mortality was shown to persist for up to two years<sup>6–10</sup>. Patients with a severe SARS-CoV-2 infection or

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critically ill patients are at particular risk of developing long-term adverse outcome beyond their acute infection. Nevertheless, evidence emerged from the earlier stage of the pandemic were limited by the selection of under-represented samples as the study population<sup>11</sup>. Moreover, findings reported from the current body of literature were based largely on the assumption of a constant risk increase of clinical sequelae over a prolonged duration which may not be able to account for the change in risk over time, thus hindering the representativeness on the burden of the long-term health consequences of SARS-CoV-2 infection. Such speculation was evident from the gradual improvement in pulmonary function in most patients who recovered from severe SARS-CoV-2 infection over a three-monthly observation period for 12 months<sup>12</sup>. Meanwhile, a recent study in Israel have reported a considerably reduced risk of PASC towards the later period of SARS-CoV-2 infection over a course of one year amongst patients with mild infection<sup>13</sup>.

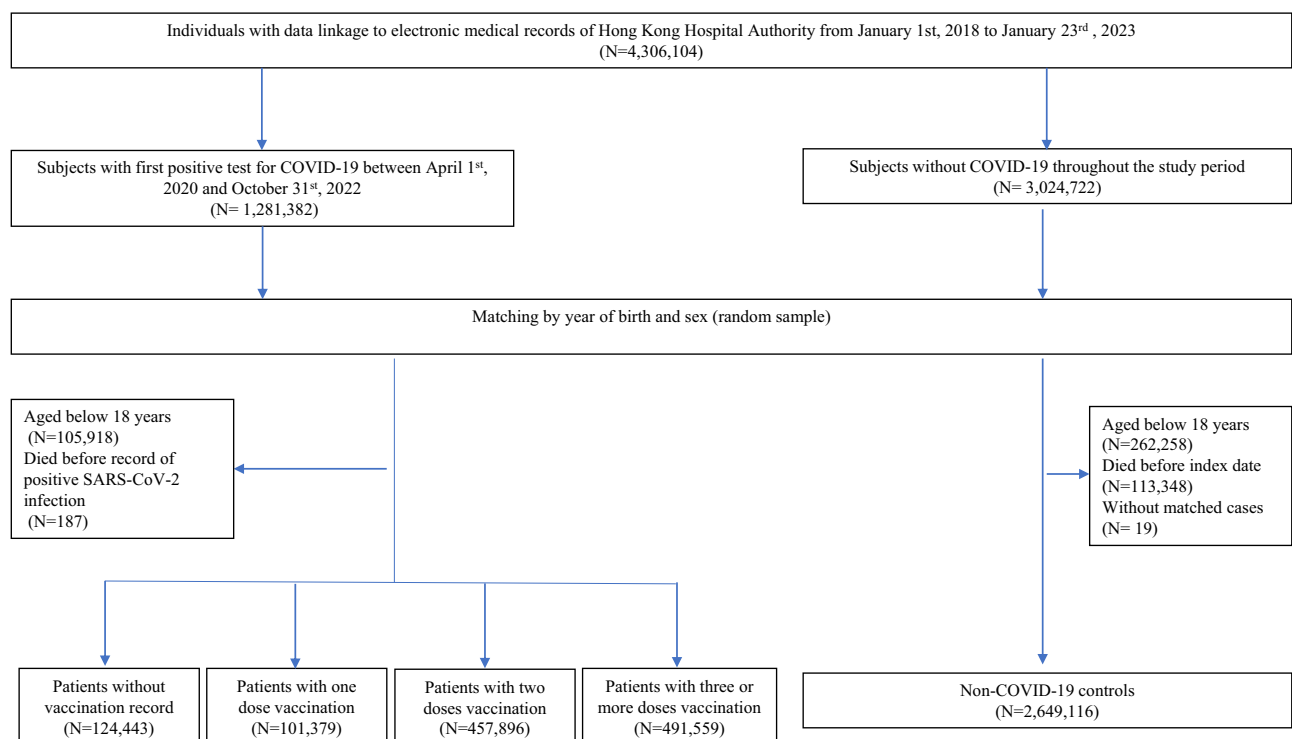
Shortly after the outbreak of the pandemic, the global initiative to develop vaccines against SARS-CoV-2 infection followed by the international vaccination campaign has been shown to successfully reduce the risk of primary infection, disease severity and hospitalization associated with SARS-CoV-2 infection<sup>14</sup>. A two dose vaccination regimen was initially recommended for the vast majority of brand of COVID-19 vaccines including the BioNtech and CoronaVac offered in Hong Kong based on the efficacy profile in preventing primary infection established from earlier clinical trials<sup>15,16</sup>. Nevertheless, a third and even fourth booster dose of the vaccine was later introduced in certain countries to restore immunity within the population in the face of the Omicron variant of SARS-CoV-2<sup>17,18</sup>. Despite the cumulative evidence of the covid-19 vaccines' ability to reduce disease burden during acute infection, its effect in preventing the adverse outcome in the post-acute phase of SARS-CoV-2 infection remained largely unknown owing to the inconsistent findings from the existing studies<sup>19,20</sup>. While a protective effect of COVID-19 vaccination on incident health outcomes has been reported in several population and community-based studies, the extent of risk reduction, especially from the booster dose of vaccines remains to be evaluated<sup>21,22</sup>.

This population-based study aims to evaluate the progressive risk of health consequences associated with SARS-CoV-2 infection over 1 year and compare the risk and persistence of such risk differences between patients of different COVID-19 vaccination statuses.

## Results

A total of 1,175,277 patients with SARS-CoV-2 infection were identified in this study, of those, 124,443, 101,379, 457,896, and 491,559 patients were unvaccinated, had one, two and three or more doses of COVID-19 vaccination record prior to infection, respectively (Fig. 1). The median time between the latest dose of vaccination and SARS-CoV-2 infection for patients who have received one, two and three or more doses of COVID-19 vaccination was 18 (interquartile range 12–42), 175 (119–208) and 101 (37–170) days, respectively. The median follow-up period for controls, patients with SARS-CoV-2 who were unvaccinated, have received one, two and three or more doses of COVID-19 vaccination were 318 (173–329), 320 (253–331), 324 (312–329), 325 (312–330), and 171 (135–316) days, respectively. The baseline characteristics before and after weighting were summarized in Tables 1 and 2, respectively. The SMDs of all baseline characteristics after weighting were less than 0.1, indicating a good balance between groups of patients with different vaccination statuses. The number of patients at risk at each observation period between days 0–30, 31–90, 91–180, 181–270, 271–365 were 2,815,023, 2,801,396, 2,764,243, 2,119,507, and 1,876,858, respectively.

Overall, a graded reduction in the risk of clinical sequelae among infected patients was observed over time and with the increased number of doses of COVID-19 vaccines received prior to infection. Compared to non-infected controls, patients with SARS-CoV-2 infection were observed to incur a greater risk of clinical sequelae including major cardiovascular diseases [HR dose=0: 4.64 (4.00, 5.38); dose=1: 3.13 (2.60, 3.76); dose=2: 2.53 (2.21, 2.89); dose ≥3: 1.99 (1.72, 2.29)], and all-cause mortality [HR dose=0: 18.89 (18.07, 19.74); dose=1: 8.96 (8.46, 9.48); dose=2: 3.95 (3.71, 4.20); dose ≥3: 1.74 (1.50, 2.02)] across patients with different COVID-19 vaccination status during the acute phase of infection. A graded decrease in risk was



**Fig. 1** | Flowchart for identifying study population.

**Table 1 | Baseline characteristics of patients with COVID-19 stratified by vaccine status and controls from the Hong Kong Hospital Authority before propensity-score weighting**

Baseline characteristics	Hong Kong Hospital Authority (April 1, 2020 to October 31, 2022)					
	Controls (N = 2,649,116)	COVID-19				SMD
		Unvaccinated (N = 124,443)	Incomplete vaccina- tion (N = 101,379)	Fully vaccinated (N = 457,896)	Received booster dose (N = 491,559)	
	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	
Age (years)	54.6 (18.17)	60.2 (21.93)	59.6 (19.88)	50.2 (17.70)	52.1 (16.07)	0.293
Sex, male	1,158,800 (43.7)	55,091 (44.3)	44,557 (44.0)	201,942 (44.1)	227,573 (46.3)	0.022
Charlson Comorbidity Index	1.67 (1.80)	2.61 (2.53)	2.38 (2.20)	1.33 (1.69)	1.35 (1.57)	0.354
Pre-existing morbidities						
Respiratory disease	48,373 (1.8)	5942 (4.8)	3759 (3.7)	8285 (1.8)	7877 (1.6)	0.096
Diabetes	305,099 (11.5)	21,585 (17.3)	18,407 (18.2)	49,344 (10.8)	48,954 (10.0)	0.133
Cardiovascular disease	198,820 (7.5)	24,098 (19.4)	14,776 (14.6)	27,798 (6.1)	27,318 (5.6)	0.229
Myocardial infarction	17,961 (0.7)	3019 (2.4)	1443 (1.4)	2592 (0.6)	2256 (0.5)	0.085
Chronic heart failure	24,386 (0.9)	5846 (4.7)	2,613 (2.6)	3518 (0.8)	2455 (0.5)	0.139
Peripheral vascular disease	6899 (0.3)	1185 (1.0)	574 (0.6)	859 (0.2)	749 (0.2)	0.057
Cerebrovascular disease	91,852 (3.5)	12,920 (10.4)	7461 (7.4)	12,618 (2.8)	10,975 (2.2)	0.181
COPD	48,202 (1.8)	5900 (4.7)	3742 (3.7)	8265 (1.8)	7868 (1.6)	0.096
Dementia	7068 (0.3)	2795 (2.2)	1359 (1.3)	1308 (0.3)	581 (0.1)	0.108
Paralysis	5364 (0.2)	1105 (0.9)	485 (0.5)	720 (0.2)	499 (0.1)	0.058
Diabetes without chronic complication	291,744 (11.0)	19,919 (16.0)	17,417 (17.2)	47,374 (10.3)	47,199 (9.6)	0.123
Diabetes with chronic complication	19,421 (0.7)	2523 (2.0)	1477 (1.5)	2974 (0.6)	2562 (0.5)	0.071
Chronic kidney disease	29,575 (1.1)	4957 (4.0)	2740 (2.7)	4305 (0.9)	3862 (0.8)	0.113
Mild liver disease	3657 (0.1)	523 (0.4)	255 (0.3)	608 (0.1)	493 (0.1)	0.031
Moderate-severe liver disease	2420 (0.1)	396 (0.3)	168 (0.2)	436 (0.1)	315 (0.1)	0.028
Ulcers	25,808 (1.0)	2754 (2.2)	1722 (1.7)	4182 (0.9)	3949 (0.8)	0.061
Rheumatoid arthritis and other inflam- matory polyarthropathies	10,659 (0.4)	912 (0.7)	626 (0.6)	1816 (0.4)	1858 (0.4)	0.025
Acquired immune deficiency syn- drome (AIDS)	6 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.001
Malignancy	75,108 (2.8)	7166 (5.8)	4,994 (4.9)	11,615 (2.5)	11,003 (2.2)	0.098
Metastatic solid tumor	11,699 (0.4)	1698 (1.4)	937 (0.9)	1771 (0.4)	1324 (0.3)	0.063
Medication history						
Renin-angiotensin system agents	370,280 (14.0)	27,128 (21.8)	22,749 (22.4)	59,417 (13.0)	61,874 (12.6)	0.151
Beta-blockers	233,781 (8.8)	20,025 (16.1)	15,684 (15.5)	37,189 (8.1)	35,296 (7.2)	0.158
Calcium channel blockers	523,591 (19.8)	35,937 (28.9)	31,214 (30.8)	84,331 (18.4)	86,862 (17.7)	0.173
Diuretics	76,619 (2.9)	11,741 (9.4)	6564 (6.5)	11,775 (2.6)	10,650 (2.2)	0.166
Nitrates	56,049 (2.1)	7452 (6.0)	4482 (4.4)	8262 (1.8)	8424 (1.7)	0.121
Lipid-lowering agents	538,003 (20.3)	35,491 (28.5)	30,986 (30.6)	82,681 (18.1)	92,072 (18.7)	0.164
Insulins	43,083 (1.6)	5867 (4.7)	3435 (3.4)	7039 (1.5)	5991 (1.2)	0.108
Antidiabetic drugs	281,408 (10.6)	19,480 (15.7)	17,638 (17.4)	47,601 (10.4)	47,592 (9.7)	0.122
Oral anticoagulants	30,393 (1.1)	4928 (4.0)	2797 (2.8)	4220 (0.9)	3855 (0.8)	0.113
Antiplatelets	205,166 (7.7)	22,446 (18.0)	15,121 (14.9)	30,357 (6.6)	30,444 (6.2)	0.202
Immunosuppressants	11,624 (0.4)	1241 (1.0)	819 (0.8)	2032 (0.4)	2295 (0.5)	0.036
Number of past healthcare visits						
Hospital admission	0.3 (2.0)	1.2 (5.3)	0.8 (4.6)	0.3 (2.5)	0.3 (2.3)	0.125
Doctor consultation	2.6 (3.7)	3.8 (4.8)	4.0 (4.6)	2.9 (4.0)	2.7 (3.6)	0.184
Doses of COVID-19 vaccines received						
0	441,450 (16.7)	124,443 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	198,158 (7.5)	0 (0.0)	101,379 (100.0)	0 (0.0)	0 (0.0)	
2	914,720 (34.5)	0 (0.0)	0 (0.0)	457,896 (100.0)	0 (0.0)	
3 or above	1,094,788 (41.3)	0 (0.0)	0 (0.0)	0 (0.0)	491,559 (100.0)	

SMD standard mean difference, COPD chronic obstructive pulmonary disease.

Age, Charlson Comorbidity Index, Inpatient hospital and Specialist and general outpatient visits are presented in mean  $\pm$  SD; SMD  $\leq$  0.1 is considered a good balance between cohorts.

observed in patients with a greater number of doses of COVID-19 vaccination with unvaccinated and incompletely vaccinated patients incurring a greater risk of most clinical sequelae than those completely vaccinated and those who received booster doses of vaccines. Most notably, there was an approximately five-fold reduction in risk

of all-cause mortality between unvaccinated patients (18.89; 18.07, 19.74) and patients with complete vaccination (3.95; 3.71, 4.20) during the acute phase of infection. Such risk was further reduced amongst patients who received booster dose of vaccines (1.74; 1.50, 2.02).

**Table 2 | Baseline characteristics of patients with COVID-19 stratified by vaccine status and controls from the Hong Kong Hospital Authority after propensity-score weighting**

Baseline characteristics	Hong Kong Hospital Authority (April 1, 2020 to October 31, 2022)					SMD
	Controls (N = 3,828,075)	COVID-19			Received booster dose (N = 3,854,149)	
		Unvaccinated (N = 3,809,700)	Incomplete vaccination (N = 3,801,677)	Fully vaccinated (N = 3,818,571)		
	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	N/mean (%/SD)	
Age (years)	54.1 (18.19)	52.4 (20.79)	53.4 (19.75)	54.0 (18.02)	54.1 (16.90)	0.040
Sex, male	1,690,639 (44.2)	1,681,641 (44.1)	1,692,265 (44.5)	1,689,322 (44.2)	1,716,080 (44.5)	0.005
Charlson Comorbidity Index	1.65 (1.82)	1.59 (1.95)	1.64 (1.86)	1.65 (1.86)	1.74 (2.06)	0.032
Pre-existing morbidities						
Respiratory disease	69,540 (1.8)	97,239 (2.6)	91,668 (2.4)	81,724 (2.1)	84,607 (2.2)	0.024
Diabetes	444,079 (11.6)	428,379 (11.2)	438,048 (11.5)	446,612 (11.7)	472,078 (12.2)	0.014
Cardiovascular disease	291,084 (7.6)	331,874 (8.7)	307,673 (8.1)	292,762 (7.7)	304,869 (7.9)	0.019
Myocardial infarction	27,309 (0.7)	30,844 (0.8)	27,559 (0.7)	28,154 (0.7)	31,849 (0.8)	0.007
Chronic heart failure	37,531 (1.0)	53,104 (1.4)	43,631 (1.1)	43,140 (1.1)	42,721 (1.1)	0.016
Peripheral vascular disease	10,610 (0.3)	13,600 (0.4)	10,275 (0.3)	9430 (0.2)	11,916 (0.3)	0.009
Cerebrovascular disease	132,775 (3.5)	179,833 (4.7)	153,715 (4.0)	136,713 (3.6)	136,145 (3.5)	0.031
COPD	69,276 (1.8)	96,613 (2.5)	91,266 (2.4)	81,544 (2.1)	84,507 (2.2)	0.024
Dementia	9916 (0.3)	38,782 (1.0)	28,411 (0.7)	17,978 (0.5)	8948 (0.2)	0.055
Paralysis	7705 (0.2)	11,966 (0.3)	9190 (0.2)	8585 (0.2)	9048 (0.2)	0.010
Diabetes without chronic complication	423,588 (11.1)	405,241 (10.6)	418,941 (11.0)	427,648 (11.2)	447,257 (11.6)	0.013
Diabetes with chronic complication	30,253 (0.8)	29,564 (0.8)	25,827 (0.7)	28,255 (0.7)	39,233 (1.0)	0.016
Chronic kidney disease	45,952 (1.2)	48,784 (1.3)	45,533 (1.2)	48,248 (1.3)	70,173 (1.8)	0.022
Mild liver disease	5453 (0.1)	5909 (0.2)	5303 (0.1)	6099 (0.2)	7418 (0.2)	0.006
Moderate-severe liver disease	3666 (0.1)	3509 (0.1)	2822 (0.1)	4673 (0.1)	6894 (0.2)	0.014
Ulcers	37,358 (1.0)	41,500 (1.1)	39,446 (1.0)	42,146 (1.1)	46,942 (1.2)	0.011
Rheumatoid arthritis and other inflammatory polyarthropathies	15,516 (0.4)	17,100 (0.4)	16,950 (0.4)	16,209 (0.4)	18,742 (0.5)	0.006
Acquired immune deficiency syndrome (AIDS)	8 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.001
Malignancy	110,554 (2.9)	94,420 (2.5)	99,599 (2.6)	112,459 (2.9)	172,683 (4.5)	0.048
Metastatic solid tumor	18,870 (0.5)	9,682 (0.3)	11,332 (0.3)	21,434 (0.6)	56,238 (1.5)	0.062
Medication history						
Renin-angiotensin system agents	543,451 (14.2)	535,752 (14.1)	550,713 (14.5)	544,896 (14.3)	561,725 (14.6)	0.007
Beta-blockers	343,990 (9.0)	354,237 (9.3)	354,979 (9.3)	345,695 (9.1)	362,166 (9.4)	0.008
Calcium channel blockers	764,595 (20.0)	732,992 (19.2)	766,221 (20.2)	764,390 (20.0)	782,898 (20.3)	0.012
Diuretics	118,650 (3.1)	117,662 (3.1)	122,698 (3.2)	120,500 (3.2)	129,769 (3.4)	0.008
Nitrates	85,421 (2.2)	85,906 (2.3)	87,713 (2.3)	86,476 (2.3)	90,767 (2.4)	0.004
Lipid-lowering agents	781,588 (20.4)	765,893 (20.1)	784,093 (20.6)	785,049 (20.6)	803,700 (20.9)	0.008
Insulins	66,414 (1.7)	71,182 (1.9)	69,032 (1.8)	67,438 (1.8)	76,617 (2.0)	0.009
Antidiabetic drugs	415,093 (10.8)	421,824 (11.1)	423,609 (11.1)	416,006 (10.9)	431,842 (11.2)	0.006
Oral anticoagulants	46,658 (1.2)	48,834 (1.3)	48,463 (1.3)	47,388 (1.2)	51,978 (1.3)	0.005
Antiplatelets	305,831 (8.0)	296,699 (7.8)	309,166 (8.1)	310,017 (8.1)	321,256 (8.3)	0.009
Immunosuppressants	18,178 (0.5)	20,464 (0.5)	19,832 (0.5)	18,872 (0.5)	20,145 (0.5)	0.004
Number of past healthcare visits						
Hospital admission	0.4 (3.80)	0.5 (2.07)	0.4 (2.11)	0.4 (2.81)	0.6 (6.78)	0.036
Doctor consultation	2.8 (4.48)	2.9 (5.95)	2.9 (3.69)	2.8 (3.59)	2.9 (3.79)	0.015
Doses of COVID-19 vaccines received						
0	632,151 (16.5)	3,809,700 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	286,526 (7.5)	0 (0.0)	3,801,677 (100.0)	0 (0.0)	0 (0.0)	
2	1,328,800 (34.7)	0 (0.0)	0 (0.0)	3,818,571 (100.0)	0 (0.0)	
3 or above	1,580,598 (41.3)	0 (0.0)	0 (0.0)	0 (0.0)	3,854,149 (100.0)	

SMD standard mean difference, COPD chronic obstructive pulmonary disease.

The number of individuals presented represents the pseudo-population of each stratum of patients with COVID-19 after propensity-score weighting; Age, Charlson Comorbidity Index, Inpatient hospital and Specialist and general outpatient visits are presented in mean  $\pm$  SD; SMD  $\leq$  0.1 is considered a good balance between cohorts.



The risk of all-cause mortality reduced progressively over one year between patients with SARS-CoV-2 infection and non-COVID-19 controls [0–30 d: 18.89 (18.07, 19.74); 31–90 d: 3.79 (3.56, 4.03); 91–180 d: 2.11 (1.97, 2.26); 181–270 d: 1.97 (1.83, 2.13); 271–365 d: 2.12 (1.92, 2.33)]. A sharp decline in the risks of the outcomes were observed during the post-acute phase between 31 and 90 days of infection compared to the acute phase especially in patients who received complete and booster dose of vaccination. Nevertheless, the risk of several clinical sequelae including heart failure (dose=2: 1.43; 1.13, 1.81; dose ≥3: 1.35; 1.05, 1.75) and all-cause mortality (dose=2: 1.11; 1.02, 1.21) remained significantly greater in patients with SARS-CoV-2 infection. The risk of clinical sequelae further reduced in the subsequent observation period with no significant greater risk of clinical sequelae observed among completely vaccinated and patients with booster dose of vaccines from 271 and 91 days onwards, respectively. Meanwhile, the increased risk of certain clinical sequelae including all-cause mortality (2.12; 1.92, 2.33) continued to persist for up to a year amongst unvaccinated patients. (Tables 3–7 and Fig. 2) The cumulative incidence plots for individual observation windows were shown in Supplementary Fig. 1. Sensitivity analyses reported largely consistent findings for the aforementioned outcomes (Supplementary Tables 2–11). A moderate increase in risk of lung cancer and lymphoma was observed during the first 30 days of infection. (Supplementary Table 12).

Patients aged above 65 or with a CCI of four or above are at a greater risk of clinical sequelae during the acute and post-acute phase of SARS-CoV-2 infection especially amongst unvaccinated or incompletely vaccinated patients. Male and female incurred broadly comparable risk of acute and post-acute sequelae with respect to their vaccination status. (Supplementary Tables 13–18).

## Discussion

This study examined the risk of long-term health consequences of SARS-CoV-2 infection involving multiple organ systems between patients with a history of SARS-CoV-2 infection and non-infected controls over the course of 365 days. The findings of this study showed a reduction in the risk of the majority of clinical sequelae over the course of the observation window suggesting the gradual subside of the risk of long-term health consequences over a year. COVID-19 vaccination, especially the uptake of the booster dose, was found to be effective in reducing the risk of health consequences. Patients who received three or more doses of vaccines did not incur any significant risk increased in clinical sequelae from 91 days onwards from their initial infection. On the other hand, unvaccinated patients were at a greater risk of several clinical sequelae including all-cause mortality up to one year following infection. Such findings provided evidence to support the potential protection from vaccination in reducing the risk of long-term health consequences following SARS-CoV-2 infection.

Previous studies that characterized and evaluated the risk of post-acute sequelae have reported a considerable increase in risk of clinical sequelae involving multiple organ systems<sup>1,2,7,8,10</sup>. In particular, patients with a severe SARS-CoV-2 infection during the acute phase were reported to incur further risk of post-acute clinical sequelae following infection<sup>23</sup>. Nevertheless, evidence that emerged in the early stage of the pandemic has been generated based on data with limited representation of the general population such as discharged hospitalized and older patients with SARS-CoV-2 infection. Since these factors were indicative of patients with more severe disease outcomes compared to the general population, the findings from these studies have shown great discrepancies in the prevalence and risk of clinical sequelae following infection<sup>11,24</sup>. More recent evidence from several large-scale, nationwide population-based studies have indicated a gradual improvements in their recovery status characterized by the reduction in prevalence of self-reported symptoms and proportion of infected individuals reporting non-recovery from health outcomes associated

with SARS-CoV-2 infection<sup>25,26</sup>. A reduction in risk of post-infection clinical sequelae was also reported 6 months following their initial infection amongst individuals with a mild SARS-CoV-2 infection<sup>13</sup>. With consideration of the comparable disease severity induced by the dominant XBB variant to the other sublineages of the omicron strain of SARS-CoV-2, the current body of evidence may indicate the gradual subside and lesser clinical burden on the long-term health consequences caused by such milder strain of SARS-CoV-2 virus than that reported in the earlier stage of the pandemic<sup>27</sup>. Nonetheless, high-risk patients including older people, lack of vaccination, immunosuppression, and individuals with certain underlying comorbidities may still be more vulnerable to poor clinical prognosis from the adverse clinical outcomes following SARS-CoV-2 infection. This emphasizes the need for closer monitoring for these patient groups and provide timely treatment if necessary.

As the pandemic evolved, the global COVID-19 vaccination campaigns have shown to be effective in preventing serious illness and death associated with SARS-CoV-2 infection. Recent research on the booster dose of COVID-19 vaccination has reported substantial extra protection against initial, severe SARS-CoV-2 infection and the rate of mortality by over 80% with a greater risk reduction estimated amongst high-risk population with multi-morbidity, in addition to that conferred by the first and second doses<sup>28–31</sup>. The bivalent omicron-containing booster vaccine was also shown to confer broader immunity against the Omicron variant of SARS-CoV-2 and reduce hospitalizations or deaths due to SARS-CoV-2 infection<sup>32,33</sup>. Previous studies investigating the impact of COVID-19 vaccines on the risk of developing clinical sequelae associated with SARS-CoV-2 infection have reported inconsistent findings due to the difference in the methodological approach employed to evaluate two key aspects: the effect of vaccination on the risk of incident clinical sequelae following SARS-CoV-2 infection and the prevalence of post-infection sequelae outcomes among COVID-19 survivors<sup>19,20</sup>. Further to the current evidence supporting the protection against both acute and post-acute health consequences of SARS-CoV-2 infection conferred by COVID-19 vaccination, the findings of this study demonstrated a graded reduction in the incidence and the persistence in risk according to the number of vaccines doses received prior to infection. The protective effect was more pronounced among the older people and patients with a greater degree of morbidity. Nevertheless, further studies are warranted to evaluate the effect of COVID-19 vaccination in reducing the prevalence of clinical sequelae and understand the potential protective effect of COVID-19 vaccination in patients who have developed onset of clinical sequelae associated with SARS-CoV-2 infection.

Despite the recapitulation of evidence demonstrating the association of COVID-19 vaccination with a reduced risk of clinical sequelae and adverse clinical outcomes during the acute phase of SARS-CoV-2 infection, its protective effect against clinical sequelae in the post-acute phase of infection remained largely unknown. One putative mechanism for the protection effects against the long-term health consequences from vaccination observed could be attributed to the protection against severe SARS-CoV-2 infection during the acute infection may subsequently reduce the risk of long-term health outcomes. The most common COVID-19 vaccines development approach was based on the spike protein of the virus as an antigen accessible by antibodies and immunological cells in the body. The BioNTech COVID-19 vaccines contains mRNA molecules carrying the information for the SARS-CoV-2 spike protein whilst the CoronaVac consisted of whole attenuated SARS-CoV-2 virus capable of provoking an immune response upon administration. The spike proteins attracts antibodies and provoke a high response of sub-types CD8+ killer and CD4 helper T cells, signaling the production of cytokines and proliferations of T memory cells to mediate a lasting immunity, preventing severe health consequences from SARS-CoV-2 infection and the associated irreversible damage to vital organ systems in our body, constituting to a

**Table 3 | Incidence rate and hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 cohort after weighting during 0–30 days of SARS-CoV-2 infection**

0-30 days												
Controls (REF)			COVID-19									
Clinical sequelae	Unvaccinated			Received single dose			Received two doses			Received booster dose(s)		
	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio
Major CVD	1312	4.37 (4.14, 4.61)	5941	20.38 (19.87, 20.90)	4.64 (4.00, 5.38)	3.13 (2.60, 3.76)	3300	11.05 (10.68, 11.43)	2.53 (2.21, 2.89)	2612	8.67 (8.35, 9.01)	1.99 (1.72, 2.29)
Stroke	818	2.61 (2.44, 2.79)	3605	11.90 (11.52, 12.29)	4.52 (3.74, 5.48)	3.03 (2.40, 3.83)	2287	7.35 (7.05, 7.65)	2.81 (2.39, 3.31)	1702	5.41 (5.15, 5.67)	2.07 (1.71, 2.51)
Myocardial infarction	300	0.93 (0.83, 1.04)	1895	6.00 (5.74, 6.28)	6.42 (4.99, 8.26)	5.27 (3.88, 7.16)	980	3.06 (2.87, 3.25)	3.29 (2.53, 4.27)	925	2.85 (2.67, 3.04)	3.07 (2.38, 3.96)
Heart failure	272	0.84 (0.75, 0.95)	1326	4.22 (4.00, 4.46)	4.99 (3.72, 6.68)	3.41 (2.36, 4.93)	643	2.01 (1.86, 2.17)	2.38 (1.75, 3.25)	354	1.09 (0.98, 1.21)	1.30 (0.88, 1.92)
Atrial fibrillation	154	0.48 (0.41, 0.56)	668	2.14 (1.98, 2.31)	4.43 (2.95, 6.65)	3.93 (2.51, 6.15)	425	1.34 (1.22, 1.47)	2.77 (1.89, 4.06)	509	1.58 (1.45, 1.72)	3.28 (2.34, 4.60)
Coronary artery disease	483	1.55 (1.41, 1.69)	2116	6.88 (6.60, 7.18)	4.43 (3.50, 5.60)	3.49 (2.62, 4.63)	1267	4.07 (3.85, 4.30)	2.63 (2.11, 3.27)	1098	3.51 (3.30, 3.72)	2.27 (1.82, 2.82)
Deep vein thrombosis	41	0.13 (0.09, 0.17)	288	0.91 (0.81, 1.02)	7.18 (3.53, 14.60)	6.78 (3.19, 14.39)	110	0.34 (0.28, 0.41)	2.70 (1.25, 5.81)	72	0.22 (0.17, 0.27)	1.75 (0.77, 3.96)
Cardiovascular mortality	1092	3.36 (3.17, 3.57)	6361	20.00 (19.51, 20.49)	5.92 (5.17, 6.78)	3.19 (2.65, 3.84)	2118	6.55 (6.28, 6.84)	1.95 (1.63, 2.32)	1057	3.23 (3.04, 3.43)	0.96 (0.74, 1.26)
Chronic pulmonary disease	115	0.36 (0.30, 0.43)	361	1.16 (1.05, 1.29)	3.22 (1.88, 5.50)	6.10 (3.65, 10.21)	399	1.26 (1.14, 1.39)	3.51 (2.33, 5.27)	234	0.73 (0.64, 0.83)	2.03 (1.30, 3.16)
Acute respiratory distress syndrome	189	0.58 (0.50, 0.67)	1405	4.45 (4.23, 4.69)	7.58 (5.44, 10.55)	3.83 (2.53, 5.80)	449	1.40 (1.27, 1.53)	2.39 (1.66, 3.43)	431	1.33 (1.20, 1.45)	2.27 (1.59, 3.23)
Seizure	103	0.32 (0.26, 0.38)	741	2.37 (2.20, 2.54)	7.40 (4.68, 11.69)	5.67 (3.20, 10.06)	233	0.73 (0.64, 0.82)	2.28 (1.43, 3.65)	296	0.91 (0.81, 1.02)	2.86 (1.51, 5.43)
End-stage renal disease	37	0.11 (0.08, 0.16)	238	0.75 (0.66, 0.85)	6.50 (2.86, 14.76)	1.50 (0.37, 6.06)	94	0.29 (0.24, 0.35)	2.54 (1.02, 6.30)	87	0.27 (0.21, 0.33)	2.33 (0.63, 8.62)
Acute kidney injury	87	0.27 (0.22, 0.33)	803	2.54 (2.37, 2.73)	9.45 (6.26, 14.27)	9.57 (6.02, 15.20)	313	0.97 (0.87, 1.09)	3.63 (2.24, 5.86)	387	1.19 (1.07, 1.31)	4.43 (2.77, 7.09)
Pancreatitis	56	0.17 (0.13, 0.22)	270	0.85 (0.76, 0.96)	4.89 (2.41, 9.93)	2.47 (0.80, 7.62)	146	0.45 (0.38, 0.53)	2.61 (1.38, 4.92)	133	0.41 (0.34, 0.48)	2.35 (1.31, 4.22)
All-cause mortality	5379	16.56 (16.12, 17.00)	99,819	313.79 (311.85, 315.74)	18.89 (18.07, 19.74)	8.96 (8.46, 9.48)	21,135	65.40 (64.52, 66.28)	3.95 (3.71, 4.20)	9418	28.81 (28.23, 29.40)	1.74 (1.50, 2.02)

CI confidence interval, REF reference group, Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or < 1) indicates patients with COVID-19 had a higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Unvaccinated, incomplete vaccinated, fully vaccinated and received booster dose of COVID-19 vaccines refers to patients who have received 0 dose, 1 doses, 2 doses and ≥3 doses of BioNTech or CoronaVac COVID-19 vaccines, respectively.



**Table 4 | Incidence rate and hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 cohort after weighting during 31–90 days of SARS-CoV-2 infection**

31–90 days												
Controls (REF)			COVID-19									
Clinical sequelae	Unvaccinated			Incompletely vaccinated			Fully vaccinated			Received booster dose		
	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio
Major CVD	3124	5.31 (5.12, 5.50)	1.93 (1.67, 2.22)	4397	7.60 (7.38, 7.83)	1.43 (1.21, 1.70)	3294	5.63 (5.44, 5.82)	1.06 (0.94, 1.20)	3455	5.87 (5.68, 6.07)	1.11 (0.98, 1.25)
Stroke	1775	2.89 (2.76, 3.03)	1.67 (1.37, 2.05)	2400	3.99 (3.83, 4.15)	1.38 (1.09, 1.74)	1759	2.89 (2.75, 3.02)	1.00 (0.85, 1.18)	1597	2.60 (2.47, 2.73)	0.90 (0.75, 1.08)
Myocardial infarction	695	1.10 (1.02, 1.18)	1.72 (1.29, 2.29)	683	1.10 (1.02, 1.18)	1.00 (0.64, 1.55)	716	1.14 (1.06, 1.22)	1.04 (0.80, 1.34)	701	1.11 (1.03, 1.19)	1.01 (0.78, 1.31)
Heart failure	724	1.15 (1.07, 1.24)	3.22 (2.61, 3.98)	1223	1.97 (1.86, 2.08)	1.71 (1.29, 2.28)	1027	1.64 (1.54, 1.74)	1.43 (1.13, 1.81)	982	1.56 (1.46, 1.66)	1.35 (1.05, 1.75)
Atrial fibrillation	474	0.76 (0.69, 0.83)	2.43 (1.80, 3.28)	706	1.14 (1.06, 1.23)	1.51 (1.01, 2.26)	633	1.02 (0.94, 1.10)	1.34 (1.01, 1.78)	507	0.81 (0.74, 0.88)	1.07 (0.78, 1.45)
Coronary artery disease	1227	2.00 (1.90, 2.12)	1.95 (1.57, 2.42)	1533	2.53 (2.41, 2.66)	1.26 (0.94, 1.69)	1343	2.20 (2.09, 2.32)	1.10 (0.91, 1.33)	1606	2.63 (2.50, 2.76)	1.31 (1.11, 1.55)
Deep vein thrombosis	118	0.19 (0.15, 0.22)	3.76 (2.19, 6.44)	221	0.35 (0.31, 0.40)	1.90 (0.96, 3.73)	237	0.38 (0.33, 0.43)	2.02 (1.25, 3.28)	106	0.17 (0.14, 0.20)	0.90 (0.48, 1.68)
Cardiovascular mortality	1324	2.08 (1.97, 2.20)	1.97 (1.63, 2.39)	1570	2.50 (2.38, 2.63)	1.20 (0.93, 1.55)	1254	1.98 (1.87, 2.09)	0.95 (0.77, 1.18)	693	1.09 (1.01, 1.17)	0.52 (0.38, 0.72)
Chronic pulmonary disease	308	0.49 (0.44, 0.55)	2.94 (2.03, 4.26)	633	1.03 (0.95, 1.11)	2.09 (1.26, 3.45)	385	0.62 (0.56, 0.69)	1.26 (0.88, 1.81)	276	0.44 (0.39, 0.50)	0.90 (0.60, 1.33)
Acute respiratory distress syndrome	539	0.85 (0.78, 0.93)	1.80 (1.26, 2.57)	892	1.43 (1.34, 1.52)	1.68 (1.14, 2.48)	625	0.99 (0.92, 1.07)	1.16 (0.88, 1.55)	715	1.13 (1.05, 1.21)	1.32 (0.97, 1.81)
Seizure	290	0.46 (0.41, 0.51)	2.51 (1.62, 3.89)	537	0.86 (0.79, 0.94)	1.89 (1.09, 3.27)	351	0.56 (0.50, 0.62)	1.22 (0.84, 1.77)	197	0.31 (0.27, 0.36)	0.68 (0.40, 1.15)
End-stage renal disease	62	0.10 (0.08, 0.13)	1.65 (0.58, 4.73)	139	0.22 (0.19, 0.26)	2.27 (0.86, 5.95)	63	0.10 (0.08, 0.13)	1.02 (0.42, 2.47)	21	0.03 (0.02, 0.05)	0.34 (0.10, 1.10)
Acute kidney injury	203	0.32 (0.28, 0.37)	3.74 (2.53, 5.52)	513	0.82 (0.75, 0.89)	2.55 (1.54, 4.23)	252	0.40 (0.35, 0.45)	1.24 (0.77, 2.00)	258	0.41 (0.36, 0.46)	1.27 (0.76, 2.10)
Pancreatitis	145	0.23 (0.19, 0.27)	3.37 (1.93, 5.88)	265	0.42 (0.37, 0.48)	1.86 (0.90, 3.83)	154	0.24 (0.21, 0.28)	1.07 (0.60, 1.92)	176	0.28 (0.24, 0.32)	1.22 (0.75, 1.97)
All-cause mortality	7708	12.12 (11.85, 12.39)	3.79 (3.56, 4.03)	13,463	21.43 (21.07, 21.79)	1.77 (1.61, 1.94)	8539	13.49 (13.21, 13.78)	1.11 (1.02, 1.21)	6728	10.55 (10.30, 10.80)	0.87 (0.76, 0.99)

CI confidence interval, REF reference group, Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or < 1) indicates patients with COVID-19 had a higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Unvaccinated, incomplete vaccinated, fully vaccinated and received booster dose of COVID-19 vaccines refers to patients who have received 0 dose, 1 doses, 2 doses and ≥ 3 doses of BioNTech or CoronaVac COVID-19 vaccines, respectively.

**Table 5 | Incidence rate and hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 cohort after weighting during 91–180 days of SARS-CoV-2 infection**

Clinical sequelae	Controls (REF)		COVID-19									
			Unvaccinated					Fully vaccinated				
	Event	Incidence per 1000 person-years	Event	Hazard ratio	Incidence per 1000 person-years	Event	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years
Major CVD	4239	5.58 (5.42, 5.75)	6525	8.24 (8.04, 8.44)	1.48 (1.29, 1.70)	5820	6.91 (6.74, 7.09)	4709	5.63 (5.47, 5.79)	1.01 (0.92, 1.12)	3223	5.00 (4.83, 5.18)
Stroke	2461	3.11 (2.99, 3.23)	3270	3.96 (3.83, 4.10)	1.28 (1.05, 1.56)	3196	3.65 (3.52, 3.77)	2637	3.03 (2.92, 3.15)	0.98 (0.86, 1.12)	1561	2.33 (2.21, 2.44)
Myocardial infarction	913	1.12 (1.05, 1.19)	1499	1.74 (1.65, 1.83)	1.55 (1.16, 2.07)	1156	1.27 (1.20, 1.35)	938	1.05 (0.98, 1.11)	0.93 (0.74, 1.17)	899	1.30 (1.22, 1.39)
Heart failure	834	1.03 (0.96, 1.10)	2135	2.49 (2.39, 2.60)	2.44 (1.95, 3.05)	1516	1.68 (1.59, 1.76)	1299	1.45 (1.38, 1.53)	1.43 (1.16, 1.75)	716	1.04 (0.97, 1.12)
Atrial fibrillation	676	0.84 (0.77, 0.90)	1047	1.23 (1.16, 1.31)	1.47 (1.07, 2.02)	1071	1.19 (1.12, 1.26)	956	1.08 (1.01, 1.14)	1.28 (1.02, 1.61)	800	1.17 (1.09, 1.25)
Coronary artery disease	1699	2.15 (2.05, 2.25)	2688	3.20 (3.09, 3.33)	1.49 (1.21, 1.84)	2403	2.72 (2.62, 2.83)	1856	2.13 (2.04, 2.23)	0.99 (0.85, 1.16)	1514	2.27 (2.16, 2.39)
Deep vein thrombosis	149	0.18 (0.15, 0.21)	263	0.30 (0.27, 0.34)	1.66 (0.87, 3.16)	343	0.38 (0.34, 0.42)	98	0.11 (0.09, 0.13)	0.60 (0.30, 1.17)	135	0.19 (0.16, 0.23)
Cardiovascular mortality	1557	1.90 (1.80, 1.99)	2870	3.30 (3.18, 3.42)	1.74 (1.44, 2.10)	1673	1.83 (1.74, 1.92)	1214	1.34 (1.27, 1.42)	0.71 (0.58, 0.87)	397	0.57 (0.52, 0.63)
Chronic pulmonary disease	432	0.54 (0.49, 0.59)	955	1.13 (1.06, 1.20)	2.12 (1.46, 3.09)	864	0.97 (0.90, 1.03)	559	0.63 (0.58, 0.69)	1.19 (0.89, 1.59)	425	0.63 (0.57, 0.69)
Acute respiratory distress syndrome	714	0.87 (0.81, 0.94)	1447	1.68 (1.59, 1.77)	1.92 (1.43, 2.58)	1017	1.12 (1.05, 1.19)	1022	1.14 (1.07, 1.21)	1.30 (1.04, 1.62)	594	0.86 (0.79, 0.93)
Seizure	389	0.48 (0.43, 0.53)	1046	1.22 (1.15, 1.30)	2.59 (1.81, 3.71)	936	1.03 (0.97, 1.10)	412	0.46 (0.42, 0.50)	0.97 (0.70, 1.36)	300	0.43 (0.39, 0.48)
End-stage renal disease	77	0.09 (0.08, 0.12)	132	0.15 (0.13, 0.18)	1.62 (0.58, 4.52)	182	0.20 (0.17, 0.23)	39	0.04 (0.03, 0.06)	0.47 (0.16, 1.34)	0	NA
Acute kidney injury	355	0.43 (0.39, 0.48)	638	0.74 (0.68, 0.80)	1.71 (1.14, 2.57)	498	0.55 (0.50, 0.60)	441	0.49 (0.45, 0.54)	1.14 (0.80, 1.61)	144	0.21 (0.18, 0.25)
Pancreatitis	181	0.22 (0.19, 0.25)	205	0.24 (0.21, 0.27)	1.07 (0.52, 2.21)	186	0.20 (0.18, 0.23)	194	0.22 (0.19, 0.25)	0.97 (0.58, 1.63)	104	0.15 (0.12, 0.18)
All-cause mortality	9958	12.13 (11.89, 12.37)	22,224	25.56 (25.23, 25.90)	2.11 (1.97, 2.26)	13,014	14.22 (13.98, 14.47)	8752	9.69 (9.49, 9.90)	0.80 (0.74, 0.87)	5537	7.98 (7.77, 8.19)

CI confidence interval, REF reference group, Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression. HR > 1 (or < 1) indicates patients with COVID-19 had higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Unvaccinated, incomplete vaccinated, fully vaccinated, and received booster dose of COVID-19 vaccines refers to patients who have received 0 dose, 1 doses, 2 doses and ≥3 doses of BioNtech or CoronaVac COVID-19 vaccines, respectively.

Table 6 | Incidence rate and hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 cohort after weighting during 181–270 days of SARS-CoV-2 infection

Clinical sequelae	Controls (REF)		COVID-19					
			Unvaccinated			Incomplete vaccination		
	Event	Incidence per 1000 person-years	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio
Major CVD	3462	5.79 (5.60, 5.99)	4973	8.28 (8.05, 8.51)	1.43 (1.23, 1.66)	4720	7.54 (7.33, 7.76)	1.30 (1.12, 1.52)
Stroke	1927	3.09 (2.96, 3.23)	2865	4.57 (4.41, 4.74)	1.48 (1.22, 1.80)	2277	3.49 (3.35, 3.64)	1.13 (0.91, 1.40)
Myocardial infarction	826	1.29 (1.20, 1.37)	893	1.36 (1.28, 1.45)	1.06 (0.78, 1.44)	1223	1.81 (1.71, 1.91)	1.40 (1.04, 1.89)
Heart Failure	769	1.20 (1.12, 1.29)	1889	2.90 (2.77, 3.04)	2.42 (1.94, 3.02)	1501	2.23 (2.12, 2.34)	1.86 (1.44, 2.40)
Atrial fibrillation	544	0.85 (0.79, 0.93)	969	1.50 (1.41, 1.60)	1.76 (1.29, 2.40)	748	1.12 (1.04, 1.20)	1.31 (0.91, 1.90)
Coronary Artery Disease	1462	2.35 (2.23, 2.47)	1706	2.68 (2.55, 2.81)	1.14 (0.90, 1.44)	2019	3.08 (2.94, 3.21)	1.31 (1.04, 1.65)
Deep vein thrombosis	114	0.18 (0.15, 0.21)	118	0.18 (0.15, 0.21)	1.02 (0.51, 2.05)	86	0.13 (0.10, 0.16)	0.72 (0.30, 1.73)
Cardiovascular mortality	984	1.52 (1.43, 1.62)	1761	2.67 (2.54, 2.79)	1.76 (1.41, 2.19)	1155	1.70 (1.60, 1.80)	1.12 (0.85, 1.47)
Chronic pulmonary disease	361	0.57 (0.51, 0.63)	822	1.28 (1.19, 1.37)	2.25 (1.56, 3.23)	635	0.95 (0.88, 1.03)	1.68 (1.11, 2.53)
Acute respiratory distress syndrome	562	0.87 (0.80, 0.95)	859	1.31 (1.23, 1.40)	1.50 (1.06, 2.13)	582	0.86 (0.79, 0.93)	0.98 (0.65, 1.49)
Seizure	320	0.50 (0.45, 0.55)	1036	1.59 (1.50, 1.69)	3.21 (2.27, 4.53)	781	1.16 (1.08, 1.24)	2.33 (1.54, 3.53)
End-stage renal disease	52	0.08 (0.06, 0.11)	98	0.15 (0.12, 0.18)	1.83 (0.74, 4.51)	109	0.16 (0.13, 0.19)	1.98 (0.88, 4.44)
Acute kidney injury	302	0.47 (0.42, 0.52)	452	0.69 (0.63, 0.75)	1.47 (0.97, 2.22)	351	0.52 (0.47, 0.58)	1.11 (0.67, 1.84)
Pancreatitis	173	0.27 (0.23, 0.31)	296	0.45 (0.40, 0.50)	1.68 (0.91, 3.10)	163	0.24 (0.21, 0.28)	0.90 (0.37, 2.18)
All-cause mortality	8058	12.45 (12.18, 12.72)	16,197	24.53 (24.15, 24.91)	1.97 (1.83, 2.13)	9673	14.20 (13.92, 14.48)	1.14 (1.04, 1.26)

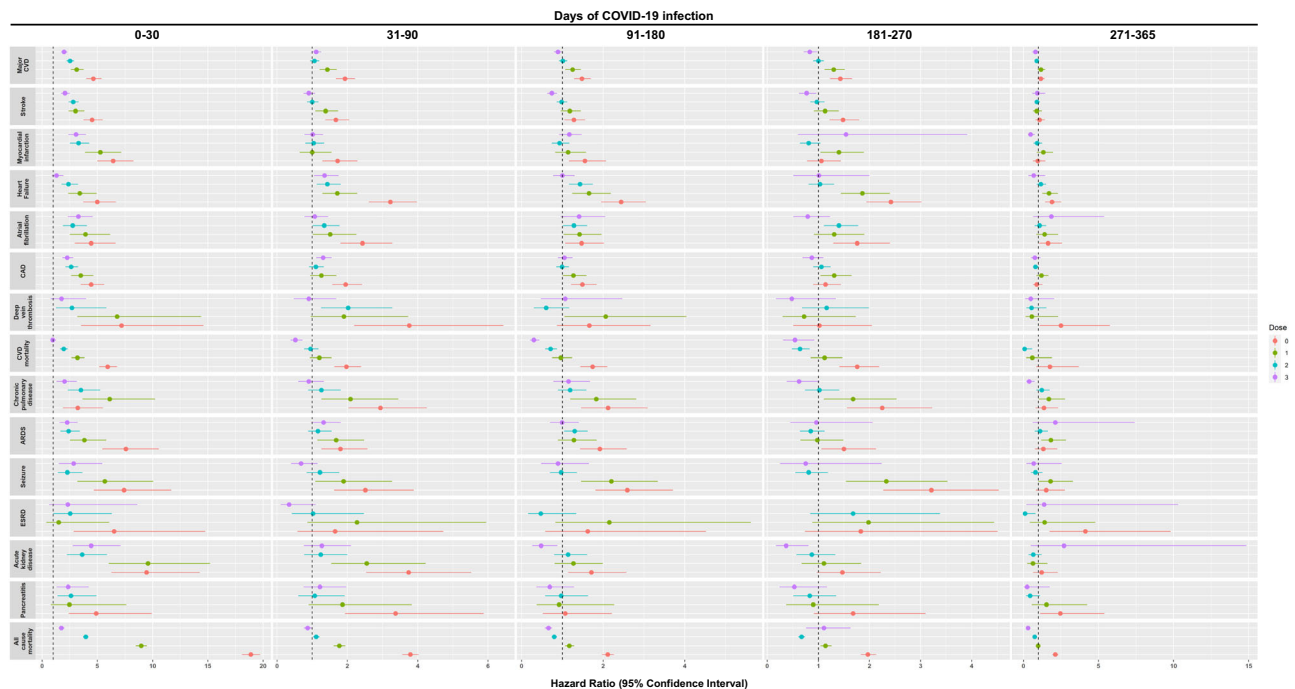
CI confidence interval, REF reference group, Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or < 1) indicates patients with COVID-19 had a higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Unvaccinated, incomplete vaccinated, fully vaccinated and received booster dose of COVID-19 vaccines refers to patients who have received 0 dose, 1 doses, 2 doses and ≥3 doses of BioNTech or CoronaVac COVID-19 vaccines, respectively.

**Table 7 | Incidence rate and hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 cohort after weighting during 271–365 days of SARS-CoV-2 infection**

Clinical sequelae	Controls (REF)		COVID-19						Received booster dose					
			Unvaccinated			Incomplete vaccination			Fully vaccinated			Event		
	Event	Incidence per 1000 person-years	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio	Event	Incidence per 1000 person-years	Hazard ratio
Major CVD	2090	6.02 (5.77, 6.29)	2405	6.59 (6.33, 6.86)	1.16 (0.95, 1.42)	2370	7.13 (6.85, 7.42)	1.17 (0.95, 1.45)	1833	5.36 (5.12, 5.61)	0.89 (0.77, 1.02)	1642	4.88 (4.65, 5.12)	0.80 (0.59, 1.07)
Stroke	1099	3.04 (2.86, 3.22)	1180	3.12 (2.94, 3.30)	1.07 (0.80, 1.43)	934	2.70 (2.53, 2.88)	0.88 (0.63, 1.23)	973	2.74 (2.57, 2.91)	0.90 (0.74, 1.09)	1014	2.86 (2.69, 3.04)	0.93 (0.59, 1.45)
Myocardial infarction	509	1.37 (1.25, 1.49)	482	1.22 (1.12, 1.34)	0.96 (0.63, 1.46)	656	1.83 (1.70, 1.98)	1.32 (0.89, 1.98)	463	1.27 (1.16, 1.39)	0.92 (0.68, 1.25)	245	0.67 (0.59, 0.75)	0.48 (0.30, 0.77)
Heart Failure	573	1.54 (1.42, 1.68)	1070	2.73 (2.57, 2.90)	1.90 (1.44, 2.52)	946	2.65 (2.49, 2.83)	1.70 (1.25, 2.30)	659	1.81 (1.67, 1.95)	1.16 (0.89, 1.52)	395	1.08 (0.98, 1.19)	0.69 (0.33, 1.45)
Atrial fibrillation	305	0.83 (0.74, 0.92)	504	1.30 (1.19, 1.41)	1.64 (1.05, 2.57)	413	1.17 (1.06, 1.29)	1.41 (0.86, 2.31)	321	0.88 (0.79, 0.98)	1.07 (0.75, 1.52)	565	1.55 (1.43, 1.68)	1.86 (0.64, 5.37)
Coronary Artery Disease	864	2.40 (2.24, 2.56)	783	2.04 (1.90, 2.19)	0.89 (0.63, 1.26)	1004	2.89 (2.72, 3.07)	1.20 (0.86, 1.67)	684	1.93 (1.79, 2.08)	0.80 (0.63, 1.01)	651	1.85 (1.71, 1.99)	0.76 (0.51, 1.14)
Deep vein thrombosis	56	0.15 (0.12, 0.19)	140	0.35 (0.30, 0.42)	2.50 (1.08, 5.76)	31	0.09 (0.06, 0.12)	0.56 (0.14, 2.31)	30	0.08 (0.06, 0.11)	0.54 (0.19, 1.53)	28	0.08 (0.05, 0.11)	0.49 (0.12, 2.04)
Cardiovascular mortality	95	0.25 (0.21, 0.31)	194	0.49 (0.43, 0.56)	1.77 (0.85, 3.69)	52	0.14 (0.11, 0.19)	0.59 (0.18, 1.90)	8	0.02 (0.01, 0.04)	0.08 (0.01, 0.59)	0	NA	NA
Chronic pulmonary disease	287	0.78 (0.69, 0.87)	385	0.99 (0.90, 1.10)	1.37 (0.81, 2.31)	470	1.33 (1.22, 1.46)	1.69 (1.03, 2.77)	345	0.95 (0.86, 1.06)	1.22 (0.85, 1.75)	109	0.30 (0.25, 0.36)	0.38 (0.19, 0.75)
Acute respiratory distress syndrome	278	0.75 (0.66, 0.84)	361	0.92 (0.83, 1.01)	1.32 (0.77, 2.26)	499	1.39 (1.27, 1.52)	1.83 (1.19, 2.83)	305	0.83 (0.74, 0.93)	1.11 (0.75, 1.63)	596	1.63 (1.50, 1.76)	2.12 (0.61, 7.41)
Seizure	180	0.48 (0.42, 0.56)	268	0.69 (0.61, 0.77)	1.51 (0.83, 2.76)	316	0.88 (0.79, 0.99)	1.81 (0.99, 3.30)	143	0.39 (0.33, 0.46)	0.80 (0.51, 1.27)	126	0.34 (0.28, 0.40)	0.69 (0.19, 2.55)
End-stage renal disease	41	0.11 (0.08, 0.15)	162	0.41 (0.35, 0.48)	4.12 (1.73, 9.80)	56	0.16 (0.12, 0.20)	1.41 (0.42, 4.79)	4	0.01 (0.00, 0.03)	0.11 (0.01, 0.81)	58	0.16 (0.12, 0.20)	1.38 (0.19, 10.30)
Acute kidney injury	150	0.40 (0.34, 0.47)	179	0.45 (0.39, 0.52)	1.21 (0.64, 2.29)	93	0.26 (0.21, 0.32)	0.63 (0.25, 1.60)	96	0.26 (0.21, 0.32)	0.65 (0.34, 1.22)	419	1.14 (1.03, 1.25)	2.70 (0.49, 14.84)
Pancreatitis	79	0.21 (0.17, 0.26)	190	0.48 (0.42, 0.55)	2.46 (1.12, 5.39)	118	0.33 (0.27, 0.39)	1.53 (0.55, 4.25)	34	0.09 (0.07, 0.13)	0.44 (0.17, 1.11)	20	0.05 (0.03, 0.08)	0.24 (0.03, 1.75)
All-cause mortality	4615	12.32 (11.97, 12.68)	9718	24.52 (24.04, 25.01)	2.12 (1.92, 2.33)	4411	12.25 (11.89, 12.61)	0.98 (0.86, 1.13)	3398	9.22 (8.92, 9.54)	0.75 (0.66, 0.84)	1440	3.88 (3.68, 4.09)	0.31 (0.20, 0.47)

CI confidence interval, REF reference group, Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or < 1) indicates patients with COVID-19 had a higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Unvaccinated, incomplete vaccinated, fully vaccinated and received booster dose of COVID-19 vaccines refers to patients who have received 0 dose, 1 doses, 2 doses and ≥ 3 doses of BioNTech or CoronaVac COVID-19 vaccines, respectively.





**Fig. 2 | Hazard ratio (and 95% confidence interval) of clinical sequelae compared to the control groups between 0 and 30, 31 and 90, 91 and 180, 181 and 270, 271 and 365 days of SARS-CoV-2 infection.** Note: Major CVD major cardiovascular disease, Composite outcome of stroke, heart failure and coronary artery disease, ARDS acute respiratory distress syndrome, CAD coronary artery disease, ESRD end-stage renal disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or < 1) indicates patients with COVID-19 had higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. Dose 0, 1, 2, 3 refers to study population who have received 0 dose, 1 dose, 2 doses, and ≥ 3 doses of BioNtech or CoronaVac COVID-19 vaccines, respectively.

reduced risk of subsequent clinical sequelae beyond the acute phase of SARS-CoV-2 infection<sup>34</sup>.

The findings of this study demonstrated a gradual reduction in the risk of long-term health consequences associated with SARS-CoV-2 over one year, indicating a lesser disease burden compared to that reported in earlier studies as well as the effect of COVID-19 vaccination in reducing the risk of clinical sequelae beyond the acute phase of SARS-CoV-2 infection. The comprehensive records of vaccination records provided by the Department of Health ensures the accuracy of information on the vaccination status of individuals reported in this study. As the pandemic progresses, our findings provided real-world evidence supporting the effectiveness of the COVID-19 vaccines in the prevention of long-term health consequences following SARS-CoV-2 infection. Nevertheless, our study is subject to several limitations. First, detection bias might be inherent in this study due to the potential under-reporting of existing underlying conditions prior to a diagnosis of SARS-CoV-2 infection. In addition, the increased healthcare contacts from receiving further examination amongst patients diagnosed with SARS-CoV-2 infection could result in the increased diagnosis of condition which could have persisted prior to infection. For instance, patients presenting with sequelae may have developed certain diseases prior to their diagnosis of SARS-CoV-2 infection; yet they did not receive a diagnosis for those conditions until a confirmed diagnosis of SARS-CoV-2 infection, resulting in the over-attribution of disease diagnosis as post-infection sequelae. Nevertheless, the history of chronic diseases in the HKHA has been recorded with high completeness as demonstrated in previous study, thus ensuring the accuracy and reliability of data to distinguish existing comorbidities and sequelae of SARS-CoV-2 infection<sup>35</sup>. Given the sufficiently long observation period, any existing comorbidities of subjects that were not captured is considered unlikely. Such error would also have a minimal effect on sequelae observed during the post-acute phase of infection. Furthermore, sequelae reported in this study including stroke, MI and seizure were largely of great disease severity which would typically

result in distinct symptoms upon the onset of disease. Thus, the incidence of such sequelae would not be affected by the increased surveillance on patients following SARS-CoV-2 infection. Second, potential selection bias may also arise from the increased SARS-CoV-2 testing amongst individuals with prevalent comorbidities. Third, the emergence of novel variant of SARS-CoV-2 is strongly correlated with better vaccination coverage and booster dose of vaccination. Given the lower severity and risk of health consequences associated with Delta and Omicron variant emerged later in the pandemic, this could lead to potential confounding bias in our findings. Nevertheless, sensitivity analysis which adjusted for the likely variant of SARS-CoV-2 amongst the infected patients have reported a largely consistent result as the main analysis suggesting that such potential confounding bias should not impact the study's overall conclusions. Fourth, the estimation of period-specific HR is subjected to possible built-in selection bias from the censoring of patients upon the incident of clinical sequelae and the systematic difference in distribution of unknown ubiquitous factors between survivors from separate cohorts exist generally especially toward the later stage of follow-up. This could contribute to the reduction in the magnitude of HR estimated in the later observation windows. Further study is warranted to evaluate the effect of the built-in selection bias described<sup>36,37</sup>. Lastly, residual confounding bias can remain even after weighing subjects according to their propensity scores. Several important unmeasured confounders, namely obesity, smoking, socioeconomic status, educational level and strains of SARS-CoV-2 virus found in individual patients, could not be accounted for in this study owing to data availability, which may have introduced bias to our results.

This study examined the progressive risk of acute and post-acute sequelae following SARS-CoV-2 infection at 3 monthly intervals up to a year amongst patients with different vaccination status. The risk of clinical sequelae was observed to reduce gradually over the observation period. Complete vaccination and the uptake of booster dose of COVID-19 vaccines were found to further reduce the risk and

persistence in risk of long-term health consequences of SARS-CoV-2 infection. The findings of this study indicated a lesser disease burden caused by health consequences of SARS-CoV-2 infection compared to that reported in earlier study and provided real-world evidence supporting the effectiveness of COVID-19 vaccines in reducing the risk of long-term health consequences following infection.

## Methods

### Data source

In this retrospective cohort study, routine electronic medical records were retrieved from the Hong Kong Hospital Authority (HKHA). The Hospital Authority is a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong. The service is available to all HK residents (>7.2 million) covering ~80% of all routine hospital admissions<sup>38</sup>. Electronic medical records from the HKHA database consisted of disease diagnoses recorded in planned or unplanned doctor consultations from in- and outpatient hospitals and emergency visits, thus allowing timely capture of all medical records of all users of the public health services in HK. Records were obtained from the Hong Kong Deaths Registry to identify mortality in this study. Information on vaccination status was provided by the Department of Health, The Government of Hong Kong Special Administrative Region whilst records of confirmed cases of SARS-CoV-2 infection were obtained from the Centre for Health Protection of the Government, the Hong Kong Special Administrative Region and HKHA. Anonymized unique patient identifiers were used to integrate these databases. These population-based databases have been used in previous studies on the long-term sequelae of COVID-19 infection, COVID-19 vaccines safety surveillance and effectiveness<sup>3,6,38–42</sup>.

### Study design and population

Individuals with data linkage to electronic medical records of Hong Kong Hospital Authority from January 1, 2018 to January 23, 2023 were eligible for this study. A cohort study was conducted to evaluate the risk of health consequences between patients with and without SARS-CoV-2 infection aged 18 years or above. Patients with an incident SARS-CoV-2 infection (confirmed by rapid antigen test [RAT] or polymerase chain reaction [PCR] test in throat swab, nasopharyngeal aspirate, or deep throat sputum specimens) between April 1, 2020 and October 31, 2022 were matched to non-infected controls without a positive SARS-CoV-2 test record throughout the study period with the exact birth-year and sex. All individuals without a record of positive test record of the same birth-year and sex were selected as matched controls. Patients with SARS-CoV-2 infection were further stratified into (1) unvaccinated (0 dose), (2) incompletely vaccinated (1 dose), (3) completely (2 doses), and (4) vaccinated with booster doses ( $\geq 3$  doses) according to the number of BioNtech or CoronaVac vaccines received prior to first SARS-CoV-2 infection. The index date of patients with SARS-CoV-2 infection was defined as the date of first diagnosis date of SARS-CoV-2 infection. The identical index date was assigned to randomly selected corresponding matched controls as the pseudo-index date.

All subjects were followed up from the index date until the date of death, the occurrence of outcome, SARS-CoV-2 re-infection or the end of the separate observation periods at 30, 90, 180, 270, and 365 days after the index date or the end of the study period January 31, 2023, whichever occurred earlier.

Anonymized longitudinal clinical healthcare data since 2016 and the earliest date of data availability were obtained for all subjects from HKHA. Relevant data included baseline demographic (sex, age and Charlson Comorbidity Index); pre-existing morbidities captured by clinical diagnosis codes (cardiovascular, cerebrovascular, respiratory, chronic kidney, liver diseases, rheumatoid arthritis and malignancy; Supplementary Table 1), history of long-term medication (renin-angiotensin-system agents, beta-blockers, calcium channel

blockers, diuretics, nitrates, lipid-lowering agents, insulins, anti-diabetic drugs, oral anticoagulants, antiplatelets and immunosuppressants) and COVID-19 vaccination status before index date.

This study was reported according to the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD), extended from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

### Outcomes of clinical diagnosis

The outcomes of this study were selected based on previous evidence on the risk of clinical sequelae associated with SARS-CoV-2 infection which includes incidences of major cardiovascular diseases (a composite outcome of stroke, heart failure and coronary heart disease), stroke, myocardial infarction (MI), heart failure, atrial fibrillation, coronary artery disease, deep vein thrombosis (DVT), chronic pulmonary disease, acute respiratory distress syndrome, seizure, end-stage renal disease, acute kidney injury, pancreatitis, cardiovascular and all-cause mortality<sup>1,8–10,43</sup>. Outcomes were identified based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; Supplementary Table 1).

### Statistical analyses

Inverse Probability Treatment Weighting (IPTW)<sup>44</sup> based on age, sex, Charlson Comorbidity index (CCI), history of separate class of medication (renin-angiotensin system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, antiplatelets and immunosuppressants), the number of hospital admission and doctor consultation within one year of index date was applied to account for potential confounding factors. Standardized mean difference (SMD) between cases and controls was estimated,  $SMD \leq 0.1$  was regarded as sufficient balance between case and control groups<sup>45</sup>. Subjects with a history of outcome of interest were excluded from the analysis of the specific conditions whilst continued to be considered at risk for other disease outcomes. The incidence rate (per 1000 person-years), hazard ratio (HR) and 95% confidence interval (CI) of each outcome were estimated between COVID and non-COVID-19 cohorts separately for each of the observation period using Cox proportional hazard regressions. Sensitivity analysis was performed by only including individuals with a positive PCR SARS-CoV-2 screening test results, cases of SARS-CoV-2 infection from the Omicron wave in Hong Kong<sup>46</sup>, unvaccinated patients with COVID-19 and matched control with the same vaccination status, adjusting for the likely variant of SARS-CoV-2 responsible for the infection, excluding patients who received their last dose of vaccine more than 6 months before SARS-CoV-2 infection owing to the waning of immunity following vaccination<sup>47,48</sup>, and controlling for the false discovery rate at 0.05 through Benjamin-Hochberg procedure<sup>49</sup>. Lung cancer, brain cancer, and lymphoma which were considered to have a prolonged latent period for their development were included as negative control outcomes to detect possible testing bias. Subgroup analyses were predefined taking account of the risk factors of post-COVID-19 condition<sup>50</sup>. Patients were stratified by (1) age ( $\leq 65$ ,  $>65$ ), (2) sex, (3) Charlson Comorbidity index (CCI;  $<4$ ,  $\geq 4$ ).

All statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All significance tests were two-tailed. A *P* value less than 0.05 or 95% CI excluding 1.0 were taken to indicate statistical significance. At least two investigators (ICHL, RZ, and EYFW) conducted each of the statistical analyses independently for quality assurance.

### Data access

EYFW and ICKW had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.



## Ethical approval

Ethical approval for this study was granted by the Institutional Review Board of the University of HK/HA HK West Cluster (UW20-556 and UW21-149) and Department of Health, HK (L/M21/2021 and L/M175/2022) with an exemption for informed consent from participants as patients' confidentiality was maintained in this retrospective cohort study.

## Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

## Data availability

The data contains confidential information and hence cannot be shared with the public due to third-party use restrictions. Local academic institutions, government departments, or non-governmental organizations may apply for the access to data through the Hospital Authority's data-sharing portal (<https://www3.ha.org.hk/data>).

## Code availability

The code used in this study is available on Zenodo (<https://doi.org/10.5281/zenodo.10132693>).

## References

- Daugherty, S. E. et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* **373**, n1098 (2021).
- Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* **594**, 259–264 (2021).
- Lam, I. C. H. et al. Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK. *eClinicalMedicine* **60**, 102000 (2023).
- Chaichana, U. et al. Definition of post-COVID-19 condition among published research studies. *JAMA Netw. Open* **6**, e235856–e235856 (2023).
- Thaweethai, T. et al. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA* **329**, 1934–1946 (2023).
- Wan, E. Y. F. et al. Association of COVID-19 with short- and long-term risk of cardiovascular disease and mortality: a prospective cohort in UK Biobank. *Cardiovasc. Res.* **119**, 1718–1727 (2023).
- Taquet, M. et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry* **9**, 815–827 (2022).
- Xie, Y. & Al-Aly, Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* **10**, 311–321 (2022).
- Xie, J. et al. Clinical and genetic risk factors for acute incident venous thromboembolism in ambulatory patients with COVID-19. *JAMA Intern. Med.* **182**, 1063–1070 (2022).
- Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. *Nat. Med.* **28**, 2406–2415 (2022).
- Wu, Q., Ailshire, J. A. & Crimmins, E. M. Long COVID and symptom trajectory in a representative sample of Americans in the first year of the pandemic. *Sci. Rep.* **12**, 11647 (2022).
- Wu, X. et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir. Med.* **9**, 747–754 (2021).
- Mizrahi, B. et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. *BMJ* **380**, e072529 (2023).
- Dagan, N. et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New Engl. J. Med.* **384**, 1412–1423 (2021).
- Polack, F. P. et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New Engl. J. Med.* **383**, 2603–2615 (2020).
- Tanriover, M. D. et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* **398**, 213–222 (2021).
- Menni, C. et al. COVID-19 vaccine waning and effectiveness and side-effects of boosters: a prospective community study from the ZOE COVID Study. *Lancet Infect. Dis.* **22**, 1002–1010 (2022).
- Andrews, N. et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. *New Engl. J. Med.* **386**, 1532–1546 (2022).
- Byambasuren, O., Stehlik, P., Clark, J., Alcorn, K. & Glasziou, P. Effect of covid-19 vaccination on long covid: systematic review. *BMJ Med.* **2**, e000385 (2023).
- Notarte, K. I. et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. *eClinicalMedicine* **53**, 101624 (2022).
- Al-Aly, Z., Bowe, B. & Xie, Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat. Med.* **28**, 1461–1467 (2022).
- Ayoubkhani, D. et al. Risk of long COVID in people infected with severe acute respiratory syndrome coronavirus 2 after 2 doses of a coronavirus disease 2019 vaccine: community-based, matched cohort study. *Open Forum Infect. Dis.* **9**, ofac464 (2022).
- Xie, Y., Bowe, B. & Al-Aly, Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. *Nat. Commun.* **12**, 6571 (2021).
- Ballering, A. V., van Zon, S. K. R., olde Hartman, T. C. & Rosmalen, J. G. M. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* **400**, 452–461 (2022).
- Ballouz, T. et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ* **381**, e074425 (2023).
- Hastie, C. E. et al. Natural history of long-COVID in a nationwide, population cohort study. *Nat. Commun.* **14**, 3504 (2023).
- Mahase, E. Covid-19: what do we know about XBB.1.5 and should we be worried? *BMJ* **380**, p153 (2023).
- Arbel, R. et al. BNT162b2 vaccine booster and mortality due to Covid-19. *New Engl. J. Med.* **385**, 2413–2420 (2021).
- Bar-On, Y. M. et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *New Engl. J. Med.* **385**, 1393–1400 (2021).
- Magen, O. et al. Fourth dose of BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. *New Engl. J. Med.* **386**, 1603–1614 (2022).
- Barda, N. et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* **398**, 2093–2100 (2021).
- Arbel, R. et al. Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study. *Lancet Infect. Dis.* **23**, 914–921 (2023).
- Moreira, E. D. et al. Safety and efficacy of a third dose of BNT162b2 Covid-19 vaccine. *New Engl. J. Med.* **386**, 1910–1921 (2022).
- Mascellino, M. T., Di Timoteo, F., De Angelis, M. & Oliva, A. Overview of the main anti-SARS-CoV-2 vaccines: mechanism of action, efficacy and safety. *Infect. Drug Resist.* **14**, 3459–3476 (2021).
- Wong, M. C. S. et al. Health services research in the public healthcare system in Hong Kong: an analysis of over 1 million anti-hypertensive prescriptions between 2004–2007 as an example of the potential and pitfalls of using routinely collected electronic patient data. *BMC Health Serv. Res.* **8**, 138 (2008).
- Hernán, M. A. The hazards of hazard ratios. *Epidemiology* **21**, 13–15 (2010).
- Bartlett, J. W. et al. The hazards of period specific and weighted hazard ratios. *Stat. Biopharm. Res.* **12**, 518–519 (2020).
- Lai, F. T. T. et al. Carditis after COVID-19 vaccination with a messenger RNA vaccine and an inactivated virus vaccine. *Ann. Intern. Med.* **175**, 362–370 (2022).

39. Wan, E. Y. F. et al. Safety of an inactivated, whole-virion COVID-19 vaccine (CoronaVac) in people aged 60 years or older in Hong Kong: a modified self-controlled case series. *Lancet Healthy Longev.* **3**, e491–e500 (2022).
40. Yan, V. K. C. et al. Effectiveness of BNT162b2 and CoronaVac vaccinations against mortality and severe complications after SARS-CoV-2 Omicron BA.2 infection: a case-control study. *Emerg. Microbes Infect.* **11**, 2304–2314 (2022).
41. Yan, X. et al. Follow-up study of pulmonary function among COVID-19 survivors 1 year after recovery. *J. Infect.* **83**, 381–412 (2021).
42. Wan, E. Y. F. et al. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. *Lancet Infect. Dis.* **22**, 64–72 (2022).
43. Cohen, K. et al. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* **376**, e068414 (2022).
44. Ruth, C. et al. *Long-Term Outcomes Of Manitoba's Insight Mentoring Program: A Comparative Statistical Analysis* (Manitoba Centre for Health Policy, Winnipeg, MB, 2015).
45. Austin, P. C. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun. Stat. Simul. Comput.* **38**, 1228–1234 (2009).
46. Xie, R. et al. Resurgence of Omicron BA.2 in SARS-CoV-2 infection-naïve Hong Kong. *Nat. Commun.* **14**, 2422 (2023).
47. Feikin, D. R. et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* **399**, 924–944 (2022).
48. Ponticelli, D. et al. Dynamics of antibody response to BNT162b2 mRNA COVID-19 vaccine after 6 months. *J. Travel Med.* **28**, taab173 (2021).
49. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B (Methodol.)* **57**, 289–300 (1995).
50. Subramanian, A. et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat. Med.* **28**, 1706–1714 (2022).

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## Author contributions

I.C.H.L., E.Y.F.W., and I.C.K.W. had the original idea for the study, contributed to the development of the study, extracted data from the source database, constructed the study design and the statistical model, reviewed the literature, and act as guarantors for the study. I.C.H.L., R.Z., and E.Y.F.W. accessed and verified the data, and performed statistical analysis. I.C.H.L., R.Z., E.Y.F.W., and I.C.K.W. wrote the first draft of the manuscript. I.C.K.W. is the principal investigator and provided oversight for all aspects of this project. K.K.C.M., C.K.H.W., C.S.L.C., F.T.T.L., X.L., E.W.Y.C., C.S.L., E.Y.F.W., and I.C.K.W.

provided critical input to the analyses, study design, and discussion. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript to be submitted.

## Competing interests

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## Additional information

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## 添付資料 2：生成 AI による日本語解説

この論文は、COVID-19 ワクチン接種が SARS-CoV-2 感染後の長期的な健康影響に与える効果とリスクの持続性に関する研究を扱っています。以下はその詳細です。

**タイトル（英語・日本語）：**Persistence in risk and effect of COVID-19 vaccination on long-term health consequences after SARS-CoV-2 infection / SARS-CoV-2 感染後の長期的健康影響に対する COVID-19 ワクチン接種の効果とリスクの持続性

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**アブストラクト：**本研究では、SARS-CoV-2 感染後の長期的健康影響の持続するリスクと、COVID-19 ワクチン接種がこのリスクに対して提供する保護の明確さについて、香港の広範な公衆衛生データベースと人口ベースのワクチン接種記録を用いた後ろ向きコホート研究を通じて検証しました。1 年間にわたり、SARS-CoV-2 感染者と非感染者のコントロールとの間で全原因死亡リスクの漸進的な減少が観察されました。完全にワクチン接種を受けた患者やブースター接種を受けた患者は、ワクチン未接種者や不完全なワクチン接種を受けた患者に比べて、主要な心血管疾患や全原因死亡のリスクが低かったです。

**背景：**COVID-19 パンデミックの発生以来、SARS-CoV-2 感染による健康影響とその後の長期的な影響に関する研究が行われてきました。COVID-19 ワクチンの普及により、感染のリスク、病気の重症度、および入院のリスクが低減されましたが、ワクチン接種が感染後の長期的な健康影響に与える影響は明確ではありませんでした。

**方法：**本研究では、1175277 人の SARS-CoV-2 感染者（ワクチン接種状況によって分類）と非感染のコントロールを含む、香港の地域全体の公衆衛生データベースを用いた後ろ向きコホート研究を実施しました。臨床的な後遺症、心血管疾患、全原因死亡のリスクを評価しました。

**結果:** ワクチン接種を完了した患者やブースター接種を受けた患者は、ワクチン未接種者や不完全接種者に比べて、健康影響のリスクが低かったことが観察されました。時間が経つにつれて、全原因死亡のリスクは全ての群で減少しましたが、完全接種およびブースター接種を受けた群で特に顕著でした。

**議論:** COVID-19 ワクチン接種、特にブースター接種は、SARS-CoV-2 感染後の長期的な健康影響のリスクを軽減する効果があると結論付けられます。この研究は、ワクチン接種の長期的な利益を支持する実世界の証拠を提供します。

**新規性:** この研究は、COVID-19 ワクチン接種が SARS-CoV-2 感染後の長期的な健康影響に及ぼす影響を地域全体の人口ベースのデータを用いて評価した最初の研究の一つです。

**限界:** 研究は後ろ向きコホート研究であり、因果関係を確立することはできません。また、分析に使用されたデータは香港に限定されており、他の地域や国における結果の一般化には注意が必要です。

**潜在的応用:** この研究の結果は、COVID-19 ワクチン接種プログラムの設計と政策立案に役立つ可能性があります。(以下、省略)