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Post-acute sequelae of hospitalised COVID-19 re-infection compared with hospitalised first-time infection: a population-based retrospective cohort study in Hong Kong

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ABSTRACT

Introduction COVID-19 infection is associated with post-acute adverse outcomes affecting multiple organ systems. Although preliminary studies have suggested that COVID-19 re-infection may have a cumulative effect on long-term outcome, differential effects of COVID-19 re-infection severe enough to be hospitalised on post-acute sequelae compared with hospitalised first-time infection have not been explored.

Methods Retrospective cohort study using territory-wide electronic medical records databases in Hong Kong. Adults hospitalised with COVID-19 between 1 January and 30 November 2022, who survived the first 28 days after infection and was discharged, were categorised into re-infection and first-time infection groups. Individuals with reinfection were compared with those with first-time infection for all-cause mortality, all-cause hospital readmission, attendance to the emergency department and complications during the post-acute period using propensity-score-weighted Cox regression. Subgroup analyses were conducted by age (<65 and ≥65 years), sex, Charlson Comorbidity Index (0–4, ≥5), COVID-19 vaccination (0–1, 2+doses) and hospitalisation status of previous infection.

Results 2244 patients with hospitalised COVID-19 re-infection and 58 894 patients with hospitalised first-time COVID-19 infection were included. After a median follow-up of 170 days, re-infection was associated with a significantly higher risk of post-acute all-cause mortality compared with first-time infection (adjusted HR (95% CI): 1.366 (1.166 to 1.600); incidence rate (95% CI): 7.3 (7.1 to 7.5) vs 4.6 (4.4 to 4.7) per 10 000 person-days), all-cause hospital readmission (1.297 (1.200 to 1.403); 50.5 (49.8 to 51.1) vs 28.1 (27.8 to 28.5)), and attendance to emergency departments (1.307 (1.199 to 1.425); 35.4 (34.8 to 35.9) vs 21.9 (21.6 to 22.2)). Findings were consistent across subgroups of age, sex, health status and vaccination status. A greater magnitude of increased risk was observed especially among those hospitalised during a previous infection.

Conclusion Among patients with COVID-19 infection requiring hospitalisation, COVID-19 re-infection was associated with increased post-acute mortality and

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Evidence remains scant regarding post-acute sequelae associated with hospitalised COVID-19 re-infection versus hospitalised first-time infection, especially during the Omicron dominant period.

WHAT THIS STUDY ADDS

⇒ Hospitalised COVID-19 re-infection was associated with a significantly higher risk of post-acute all-cause mortality, all-cause hospital readmission and attendance to emergency departments, compared with hospitalised first-time infection.

⇒ Both re-infection groups and first-time infection groups had comparable COVID-19 severity requiring hospitalisation during the acute-phase, thus reducing potential bias arising from different COVID-19 severity between groups when evaluating post-acute outcomes.

⇒ This study was conducted using territory-wide electronic health records data during an Omicron-dominant period; thus the findings confer high population representativeness and relevance to the current landscape of SARS-CoV-2 variants worldwide.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings from this and previous studies suggest that COVID-19 reinfection is associated with an increased risk of mortality and adverse health outcomes.

⇒ Strategies targeting patients with COVID-19 infection history as a high-risk group to reduce the risk of re-infection requiring hospitalisation and subsequent post-acute morbidity and mortality are warranted.

morbidity compared with first-time infection. Further studies are warranted to delineate the effects on complications.

INTRODUCTION

SARS-CoV-2 re-infection is increasingly common, with an estimated 4.2% of the global population infected more than once.[1 2] While there is no consensus on the definition, SARS-CoV-2 re-infection is generally defined as a new infection episode 90 days after the primary infection.[1 3] An infection is typically considered severe if it results in hospitalisation, intensive care unit (ICU) admission, mechanical ventilation or death from COVID-19. Understanding the characteristics of post-acute sequelae specifically associated with hospitalised re-infection provides a basis for formulating public health policies and clinical guidelines, thereby facilitating the prevention of adverse re-infection outcomes and the development of effective treatment strategies for COVID-19-related complications. However, existing research on the post-acute sequelae of SARS-CoV-2 re-infection is scant and inconsistent.

Few studies reported that the risk of persistent symptoms, sequela and long-term adverse outcomes of re-infection was lower than first-time infection, which is partly contributed by hybrid immunity from the primary infection.[4] Preliminary research using primary care electronic health record (EHR) data sets in the UK and Spain found that persistent symptoms, including fatigue, dyspnoea, olfactory or gustatory changes, headache and cough, were less likely to occur after re-infection compared with the first infection.[5] Data from the UK on new-onset, self-reported post-acute symptoms after COVID-19 re-infection showed a 28% lower risk after the second COVID-19 infection compared with the first.[6]

Conversely, an increased risk of post-acute sequelae after re-infection has been reported in other studies. Bowe *et al*[7] postulated that the risk of sequelae associated with COVID-19 re-infection accumulates even after complete vaccination with two or more doses. Using data from the US Veterans Affairs (VA) system, they found that the risk and burden of sequelae across multiple organ systems were increased in individuals who experienced re-infection compared with those who were either never infected or had a single episode of infection. Preliminary data from EHRs of more than 1.5 million patients in the USA (N3C RECOVER) also suggested that primary infection may not stimulate strong immunological protection against subsequent infection, especially in the Omicron era.[8] This suggests that the incidence of post-acute sequela following re-infection with the Omicron variant may be greater than the incidence following the primary infection.

Current literature is largely focused on comparing the acute severity of re-infection versus first-time infection, or evaluating the post-acute sequelae of first-time COVID-19 infection. Few studies have evaluated the risk of post-acute sequela after re-infection compared with first-time infection, and those studies did not differentiate the severity of the re-infection episode (for instance, hospitalised or not) which could have contributed to the inconsistent findings. This population-based retrospective cohort study aims to focus on hospitalised re-infection cases and compare them with hospitalised primary infection cases to provide epidemiological evidence on the association between SARS-CoV-2 re-infection and post-acute outcomes among patients severe enough to be hospitalised.

MATERIALS AND METHODS

Data sources

We obtained clinical data from the routine EHRs database of the Hospital Authority (HA), COVID-19 vaccination records from the Department of Health (DH) and COVID-19 confirmed case records from the Centre of Health Protection (CHP) of the Government of the Hong Kong Special Administrative Region. The HA is a statutory organisation that manages all public inpatient services and the majority of public outpatient services in Hong Kong. HA's EHRs database contains data on patients' demographics, diagnoses, procedures, prescriptions, laboratory tests, hospitalisation, outpatient clinic and emergency department attendance records, providing real-time information to support clinical management across all clinics and hospitals in the HA. DH maintains a database of COVID-19 vaccination records for all individuals in Hong Kong. CHP maintains a database of all confirmed COVID-19 cases, based on both mandatory and voluntary reporting of positive PCR and rapid antigen test (RAT) test results. Anonymised unique patient identifiers were used to integrate these databases. These territory-wide databases have been frequently applied in previous studies assessing vaccine effectiveness and risk of adverse events following COVID-19 vaccinations.[9–17] The Hong Kong government has implemented extensive PCR testing for SARS-CoV-2 in public hospitals and clinics for close contacts with confirmed cases. Territory-wide community testing centres were also in place to screen asymptomatic individuals and provide regular testing to various staff groups with a high risk of exposure, such as those working in nursing homes. Reporting of positive RAT results was mandatory during the study period. Routine verification on reported RAT results were conducted and it is an offence to declare false information. Thus it is expected that the possibility of false-positives is minimal while the proportion of missed asymptomatic infections remains relatively small compared with other regions relying solely on voluntary testing.

Study design and population

This is a population-based retrospective cohort study. Patients aged ≥18 years, who were hospitalised with COVID-19 (defined as inpatient admission on or within 28 days after a positive PCR/RAT result confirmed by

DH), whose date of infection was between 1 January 2022 and 30 November 2022, were included. The study population was restricted to only patients hospitalised in the acute phase to ensure the homogeneity of the study population in terms of severity of the acute phase of the COVID-19 infection episode, as a SARS-CoV-2 infection is considered severe if it results in hospitalisation, ICU admission, the requirement for ventilatory support or death.[18–21] Patients who died or had not been discharged from hospital within 28 days after the date of infection were excluded. This excludes those with prolonged hospitalisations (>28 days) due to acute severe complications, which allowed us to better distinguish between the ongoing health effects of acute-phase complications and longer-term sequelae. The index date was defined as the 28th day after the date of infection to assess post-acute sequelae, as this time point is commonly used in clinical studies to define the post-acute phase of COVID-19.[22 23] Patients were followed-up from the index date until the earliest outcome occurrence, death or the end of data availability (31 January 2023).

Exposure

Patients were categorised based on their COVID-19 infection history into the re-infection group (exposed group) and the first-time infection group (control group). The first-time infection group included patients with one COVID-19 infection during the study period and had no previous COVID-19 infection before the study period. A COVID-19 re-infection is defined as a positive PCR/RAT result with a gap of at least 90 days from a previous positive PCR/RAT result. A 90-day gap was used to define re-infection to minimise the inclusion of repeat positive tests which may be part of a previous infection episode.[1 3] The re-infection group included patients with one or more reinfection.

Outcomes

We defined post-acute phase outcomes as health outcomes more than 28 days after infection, as most of the patients recovered within 4 weeks,[23 24] such that outcomes after 28 days could often be considered post-acute phase manifestations and not complications of infection/re-infection itself. Primary outcomes include (1) all-cause mortality, (2) all-cause hospital readmission and (3) attendance to emergency department. Secondary outcomes were a prespecified list of organ system complications (cardiovascular, respiratory, neurological, gastrointestinal and renal) listed in detail in online supplemental table 1. Information regarding all-cause mortality was extracted from the Hong Kong Deaths Registry, which is the official government registry that documents all registered deaths in Hong Kong. Organ system complications were defined as an incident diagnosis identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (online supplemental table 1), from the inpatient diagnosis records with primary ranking. Patients who had a history of an outcome before the index date were excluded during the analyses of each outcome to evaluate new health issues potentially caused by COVID-19 itself, rather than natural recurrence or worsening of pre-existing conditions.

Statistical analysis

Inverse probability of treatment weighting (IPTW) using propensity score was employed to minimise confounding across comparison groups. Covariates included in the propensity score model were age, sex, Charlson Comorbidity Index (CCI), number of COVID-19 vaccine doses received, time since last vaccine dose or infection (for analyses of the vaccinated subpopulation only since this is not defined for the unvaccinated), pre-existing comorbidities (cancer, chronic kidney disease, respiratory disease, diabetes mellitus, cardiovascular disease, dementia), medication use within 90 days before infection (renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, antiplatelets and immunosuppressants) and severity of the COVID-19 episode (admission to intensive care unit, use of ventilatory support; within 28 days of infection), and medications received during the COVID-19 episode (remdesivir, molnupiravir, nirmatrelvir-ritonavir, tocilizumab, baricitinib, corticosteroids; within 28 days of infection). Medications did not include monoclonal antibodies because only very few patients in Hong Kong have received monoclonal antibody treatments during the study period. A standardised mean difference of less than 0.2 between comparison groups post-weighting was considered negligible.[25]

The risks of outcomes were compared between groups using IPTW-weighted Cox proportional hazards regression. HRs with 95% CIs were reported. IPTW-weighted Kaplan-Meier (KM) curves were plotted. Schoenfeld residuals test was used to test the proportional hazards assumption for the primary outcomes. Subgroup analyses stratified by age (<65 and ≥65 years), sex, CCI (0–4, ≥5), COVID-19 vaccination (0–1, 2+doses) and hospitalisation status of previous infection were conducted. Sensitivity analyses were also conducted: (1) individuals with hospitalised first-time infection who subsequently had non-hospitalised re-infection were also included in the first-time infection group and censored on non-hospitalised re-infection; (2) repeating the analyses among only the vaccinated individuals with additional adjustment for time since last vaccination or infection in the propensity score model, to account for the potential effect of waning immunity among the vaccinated population.

All statistical tests were two-sided, and p values<0.05 were considered statistically significant. Statistical analysis was conducted using R V.4.0.3 (www.R-project.org). Two investigators (VKCY and YZ) conducted the statistical analyses independently for quality assurance. STROBE (Strengthening the Reporting of Observational Studies

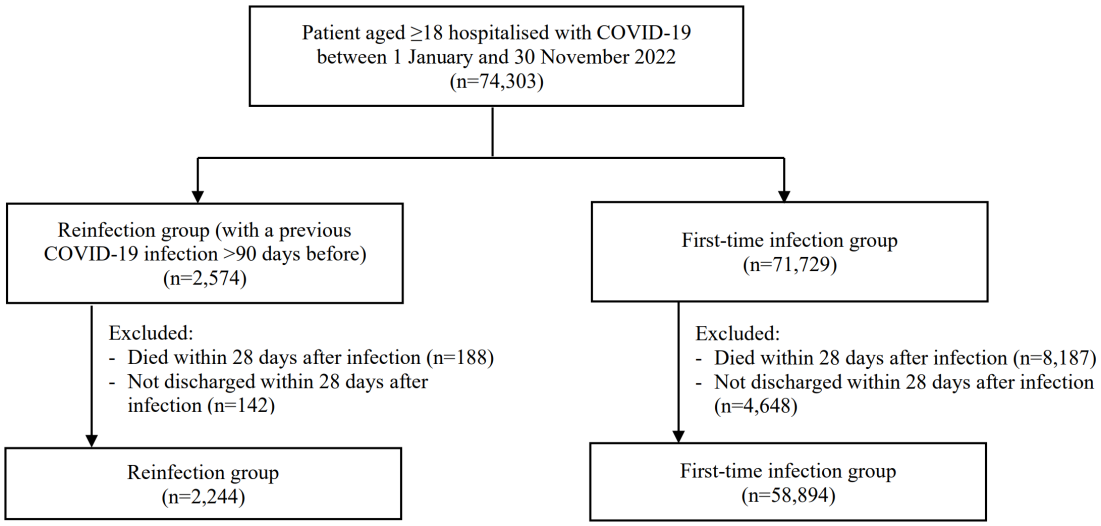


Figure 1 Cohort selection.

in Epidemiology) statement checklists were followed to guide transparent reporting of the cohort study.

Ethics approval

This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW21-149), the DH Ethics Committee (LM171/2021 and LM175/2022) and the Central Institutional Review Board of the Hospital Authority of Hong Kong (CIRB-2021-005-4). The principal investigator's institution is The University of Hong Kong. Approval was obtained from all listed local ethics committees for this study.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

A total of 74303 hospitalised COVID-19 patients were identified from 1 January 2022 to 30 November 2022. After exclusion, 2244 patients with COVID-19 re-infection and 58894 patients with first-time COVID-19 infection were included in the study (figure 1). During the study period, first-time infection cases peaked around March 2022 whereas re-infection cases were spread across June to November 2022 (figure 2). Baseline characteristics before IPTW weighting are presented in table 1. A higher proportion of the re-infection group were vaccinated with two doses and few were unvaccinated, compared with the first-time infection group. The re-infection group generally had more comorbidities but required less ventilatory support, ICU admission and remdesivir treatment. The mean (SD) time since previous vaccination or infection was 109 (74) days in the re-infection group and 110 (84) days in the first-time infection group. After IPTW weighting, all baseline characteristics were well-balanced with standardised mean differences below 0.2 (table 1). Additionally, 814 of 2244 patients in the reinfection group were hospitalised during the first episode of COVID-19 infection, and a higher proportion had comorbidities and or were unvaccinated compared with both re-infection and first-time infection groups (online supplemental table 2).

After a median (IQR) follow-up period of 170 (93–301) days, a total of 231 and 5171 events of all-cause mortality were observed in the re-infection (adjusted incidence rate (95% CI): 7.32 (7.11 to 7.53) per 10000 person-days) and first-time infection (4.56 (4.44 to 4.68)) groups, respectively. Re-infection was associated with a significantly higher risk of post-acute all-cause mortality compared with first-time infection (adjusted HR (95% CI): 1.366 (1.166 to 1.600)) (figure 3). For post-acute all-cause hospital readmission, 969 and 22558 events were observed in the re-infection and first-time infection groups, respectively, and re-infection was associated with significantly increased risk (1.297 (1.200 to 1.403)). The most common reasons (>1% occurrence) for hospital readmission include pneumonia, chronic kidney disease, urinary tract infection, fever, congestive heart failure, fluid overload disorder, chronic airway obstruction, septicaemia and chest pain in both re-infection and first-time infection groups (online supplemental table 3). The re-infection group was also commonly readmitted for cancers (breast, liver, multiple myeloma, lymphoma) and anaemia, whereas the first-time infection group was also commonly readmitted for dizziness and giddiness, essential hypertension and intestinal disorders.

Similarly, re-infection significantly increased the risk of post-acute attendance to emergency departments ((95% CI): 1.307 (1.199 to 1.425)), with 774 and 19312 events observed in the re-infection and first-time infection groups, respectively (figure 3). IPTW-weighted KM curves for primary outcomes are presented in online supplemental figure 1. No significant difference was observed for all secondary outcomes possibly due to the limited number of events.

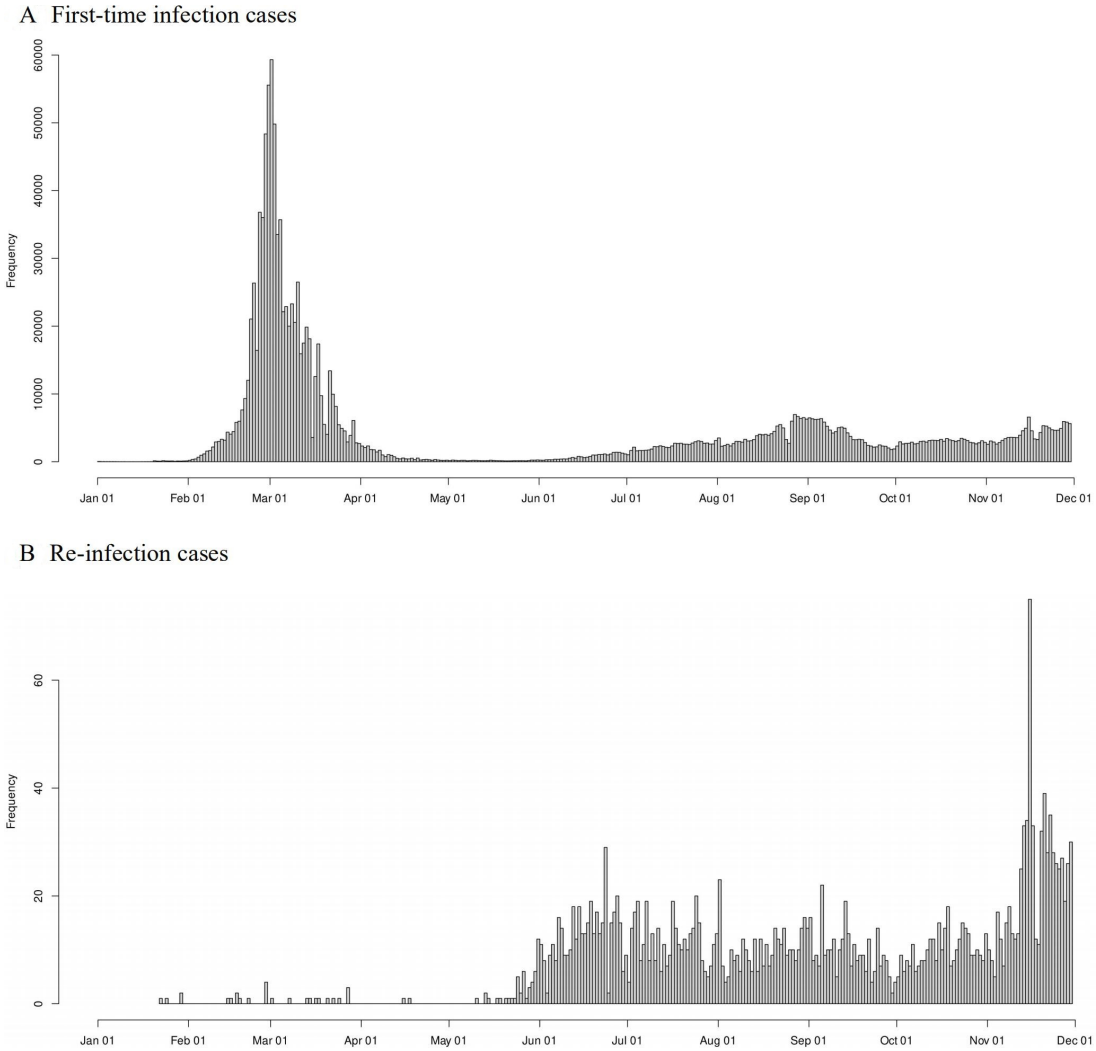


Figure 2 Distribution of COVID-19 first time infection and re-infection cases during the study period (1 January 2022 to 30 November 2022).

The findings of the subgroup analyses were generally consistent with the main analyses (table 2). Significantly increased risk of post-acute all-cause hospital readmission and attendance to the emergency department in the re-infection group were observed across all subgroups of age, sex, CCI and COVID-19 vaccination status. Increased risk of post-acute all-cause mortality was also observed across subgroups except for age <65 years, male and CCI≥5, which were not statistically significant possibly due to reduced sample size. We also observed a significantly increased risk of post-acute respiratory distress syndrome among those with CCI≥5 (adjusted HR (95% CI): 3.274 (1.460 to 7.338)). The observed increased risks of myocardial infarction and heart failure in those aged <65 years, and psychotic disorders in males should be interpreted with caution considering the wide CI of the estimate due to the limited number of events (table 2). Notably, a greater magnitude of increased risks of post-acute all-cause mortality, hospital readmission and attendance to the emergency department were observed when restricting the re-infection group to those hospitalised during a previous infection. No significant difference in these primary outcomes were observed when restricting the re-infection group to those who were not hospitalised during the previous infection (table 2). Results from sensitivity analyses were consistent with the main analyses (online supplemental tables 4,5). Schoenfeld residuals test showed no evidence of a violation of the proportional hazards assumption (p value=0.99, 0.74 and 0.96 for mortality, hospital readmission and emergency department attendance, respectively).

DISCUSSION

Summary of findings

In this territory-wide study of 74 303 patients with hospitalised COVID-19 infection (58 894 with first-time infection and 2244 with re-infection), we found that patients with hospitalised re-infection, who survived the acute phase, experienced significantly higher risks of post-acute all-cause mortality, all-cause hospital readmission and attendance to emergency departments, compared with patients with hospitalised first-time infection. This is the first study focusing on hospitalised COVID-19 re-infection

Table 1 Baseline characteristics before and after inverse probability of treatment weighting

	Before weighting			After weighting		
	Reinfection	First time infection	SMD	Reinfection	First time infection	SMD
Number of individuals	2244	58894		60049	61137	
Age, years - mean (SD)	71.02 (17.70)	68.73 (18.99)	0.124	67.92 (19.20)	68.82 (18.95)	0.047
Sex, male (%)	1264 (56.3)	28954 (49.2)	0.144	29519 (49.2)	30217 (49.4)	0.005
Charlson Comorbidity Index - mean (SD)	4.32 (2.58)	3.66 (2.50)	0.260	3.63 (2.45)	3.69 (2.51)	0.022
Number of vaccine doses received (%)			0.230			0.027
0	341 (15.2)	13778 (23.4)		13299 (22.1)	14119 (23.1)	
1	272 (12.1)	6746 (11.5)		6804 (11.3)	7017 (11.5)	
2	746 (33.2)	15386 (26.1)		15816 (26.3)	16130 (26.4)	
3+	885 (39.4)	22984 (39.0)		24130 (40.2)	23871 (39.0)	
Pre-existing comorbidities before infection (%)						
Cancer	345 (15.4)	6332 (10.8)	0.138	7130 (11.9)	6679 (10.9)	0.030
Chronic kidney disease	259 (11.5)	4240 (7.2)	0.149	4609 (7.7)	4498 (7.4)	0.012
Respiratory disease	213 (9.5)	4360 (7.4)	0.075	4795 (8.0)	4574 (7.5)	0.019
Diabetes	597 (26.6)	14094 (23.9)	0.062	13854 (23.1)	14690 (24.0)	0.023
Cardiovascular disease	1344 (59.9)	29527 (50.1)	0.197	30002 (50.0)	30870 (50.5)	0.011
Dementia	111 (4.9)	1693 (2.9)	0.107	1617 (2.7)	1803 (3.0)	0.016
Medication use within 90 days before infection (%)						
Renin-angiotensin-system agents	766 (34.1)	17639 (30.0)	0.090	17834 (29.7)	18404 (30.1)	0.009
Beta blockers	617 (27.5)	12759 (21.7)	0.136	12967 (21.6)	13375 (21.9)	0.007
Calcium channel blockers	989 (44.1)	22762 (38.6)	0.110	23003 (38.3)	23751 (38.8)	0.011
Diuretics	515 (23.0)	8316 (14.1)	0.229	8586 (14.3)	8829 (14.4)	0.004
Nitrates	211 (9.4)	4828 (8.2)	0.043	4966 (8.3)	5038 (8.2)	0.001
Lipid lowering agents	919 (41.0)	23518 (39.9)	0.021	23879 (39.8)	24437 (40.0)	0.004
Insulins	271 (12.1)	3991 (6.8)	0.182	3922 (6.5)	4261 (7.0)	0.017
Antidiabetic drugs	511 (22.8)	12988 (22.1)	0.017	12379 (20.6)	13497 (22.1)	0.036
Oral anticoagulants	183 (8.2)	3467 (5.9)	0.089	3343 (5.6)	3649 (6.0)	0.017
Antiplatelets	687 (30.6)	14546 (24.7)	0.133	15112 (25.2)	15233 (24.9)	0.006
Immunosuppressants	93 (4.1)	1128 (1.9)	0.130	1551 (2.6)	1223 (2.0)	0.039
Treatments within 28 days after infection (%)						
ICU admission	22 (1.0)	984 (1.7)	0.060	859 (1.4)	1006 (1.6)	0.017
Ventilatory support	32 (1.4)	928 (1.6)	0.012	711 (1.2)	959 (1.6)	0.033
Remdesivir	88 (3.9)	4403 (7.5)	0.154	4010 (6.7)	4491 (7.3)	0.026
Molnupiravir	385 (17.2)	8998 (15.3)	0.051	9885 (16.5)	9385 (15.4)	0.030
Paxlovid	319 (14.2)	9800 (16.6)	0.067	10864 (18.1)	10120 (16.6)	0.041
Tocilizumab	1 (0.0)	38 (0.1)	0.009	43 (0.1)	39 (0.1)	0.003
Baricitinib	1 (0.0)	334 (0.6)	0.095	70 (0.1)	335 (0.5)	0.075
Corticosteroids	319 (14.2)	11949 (20.3)	0.161	11563 (19.3)	12269 (20.1)	0.020

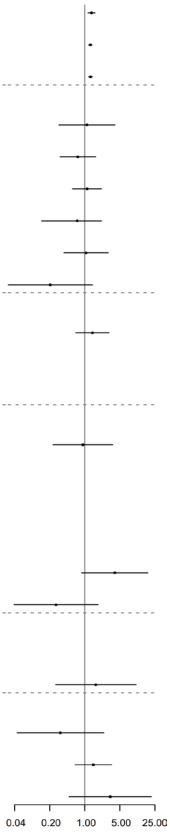
ICU, intensive care unit; SMD, standardised mean difference.

and the associated post-acute health outcomes during a period of Omicron dominance.

Comparison with previous studies

Few studies had compared the outcomes of patients with first-time COVID-19 infection to those with multiple infection episodes. A previous study by Bowe and colleagues using data from the US Department of VA database to compare people with a reinfection to those who had survived a previous infection without ever being reinfected. Their study showed that COVID-19 re-infection was associated with increased risks of acute and post-acute all-cause mortality and hospitalisation. During

Outcome	Group	No. of Patients	No. of Events	Follow-up (person-days)	Adjusted Incidence Rate (95% CI) (per 10000 person-days)	Adjusted hazard ratio (95% CI)
Primary Outcomes						
All-cause mortality	First-time infection	58,894	5,171	11,400,811	4.56 (4.44-4.68)	-
	Reinfection	2,244	231	248,079	7.32 (7.11-7.53)	1.366 (1.166, 1.600)
All-cause hospital readmission	First-time infection	58,894	22,558	8,073,976	28.13 (27.77-28.49)	-
	Reinfection	2,244	969	159,725	50.45 (49.80-51.12)	1.297 (1.200, 1.403)
Emergency department attendance	First-time infection	58,894	19,312	8,873,804	21.86 (21.56-22.17)	-
	Reinfection	2,244	774	190,000	35.35 (34.84-35.87)	1.307 (1.199, 1.425)
Cardiovascular disorders						
Myocardial infarction	First-time infection	56,573	162	10,964,762	0.15 (0.13-0.17)	-
	Reinfection	2,136	4	235,294	0.16 (0.13-0.19)	1.103 (0.305, 3.991)
Stroke	First-time infection	50,011	280	9,711,465	0.29 (0.26-0.32)	-
	Reinfection	1,756	7	196,772	0.24 (0.20-0.28)	0.727 (0.322, 1.643)
Heart failure	First-time infection	54,528	331	10,560,946	0.31 (0.28-0.35)	-
	Reinfection	1,991	11	218,145	0.36 (0.31-0.41)	1.115 (0.573, 2.167)
Atrial fibrillation	First-time infection	53,738	101	10,453,517	0.10 (0.08-0.12)	-
	Reinfection	1,979	2	218,698	0.08 (0.06-0.10)	0.707 (0.138, 2.167)
Coronary artery disease	First-time infection	51,494	230	10,025,622	0.23 (0.20-0.26)	-
	Reinfection	1,931	6	212,365	0.24 (0.20-0.28)	1.065 (0.385, 2.946)
Deep vein thrombosis	First-time infection	58,407	38	11,303,501	0.03 (0.02-0.05)	-
	Reinfection	2,210	1	243,657	0.01 (0.00-0.02)	0.206 (0.030, 1.435)
Respiratory disorders						
Acute respiratory distress syndrome	First-time infection	55,886	169	10,831,348	0.16 (0.13-0.18)	-
	Reinfection	2,061	8	227,358	0.27 (0.23-0.31)	1.419 (0.661, 3.042)
Chronic pulmonary disease	First-time infection	54,245	110	10,526,903	0.10 (0.09-0.13)	-
	Reinfection	2,028	0	222,956	0.00 (0.00-0.01)	-
Interstitial lung disease	First-time infection	58,800	4	11,382,442	0.00 (0.00-0.01)	-
	Reinfection	2,241	0	247,759	0.00 (0.00-0.01)	-
Neurological disorders						
Seizure	First-time infection	57,245	94	11,057,765	0.08 (0.07-0.10)	-
	Reinfection	2,142	2	237,311	0.08 (0.06-0.11)	0.921 (0.234, 3.628)
Bell"s palsy	First-time infection	58,603	8	11,348,441	0.01 (0.00-0.01)	-
	Reinfection	2,230	0	246,424	0.00 (0.00-0.01)	-
Encephalitis and encephalopathy	First-time infection	58,848	3	11,393,227	0.00 (0.00-0.01)	-
	Reinfection	2,244	0	248,079	0.00 (0.00-0.01)	-
Anxiety	First-time infection	58,379	10	11,306,028	0.01 (0.00-0.02)	-
	Reinfection	2,229	0	246,689	0.00 (0.00-0.01)	-
Psychotic disorder	First-time infection	58,209	28	11,262,982	0.02 (0.02-0.04)	-
	Reinfection	2,200	2	243,235	0.14 (0.11-0.17)	3.965 (0.863, 18.208)
Post-traumatic stress disorder	First-time infection	57,873	42	11,198,236	0.04 (0.03-0.05)	-
	Reinfection	2,189	1	241,767	0.01 (0.00-0.02)	0.268 (0.039, 1.849)
Gastrointestinal disorders						
Acute liver injury	First-time infection	57,748	13	11,189,860	0.01 (0.01-0.02)	-
	Reinfection	2,198	0	243,399	0.00 (0.00-0.01)	-
Pancreatitis	First-time infection	58,511	25	11,323,162	0.02 (0.01-0.03)	-
	Reinfection	2,219	1	244,868	0.05 (0.03-0.07)	1.662 (0.262, 10.523)
Renal disorders						
Acute kidney injury	First-time infection	56,636	98	10,972,276	0.09 (0.07-0.11)	-
	Reinfection	2,093	1	231,399	0.03 (0.02-0.05)	0.327 (0.045, 2.402)
Chronic kidney disease	First-time infection	54,481	89	10,543,077	0.09 (0.07-0.10)	-
	Reinfection	1,995	6	217,858	0.15 (0.12-0.18)	1.487 (0.639, 3.465)
End-stage renal disease	First-time infection	58,411	26	11,307,460	0.02 (0.02-0.03)	-
	Reinfection	2,208	2	243,785	0.05 (0.03-0.07)	3.218 (0.488, 21.222)



CI: confidence interval. Hazard ratios of outcomes in some subgroups could not be estimated due to limited number of events.

Figure 3 Risk of post-acute outcomes associated with severe COVID-19 re-infection compared with severe first-time infection.

the fourth to sixth month after infection, patients with re-infection had around 1.3 times risk of mortality and 1.6 times risk of hospitalisation compared with patients with no re-infection.[7] However, no further analyses stratified by the severity of infection was conducted, thus it remains unclear whether the increased risk of post-acute outcomes were due to a difference in the severity of the infection episode, or indeed associated with infection history. Further, their study population were predominantly male (~90%), which may lack representativeness and generalisability.[7] Moreover, their findings primarily highlight the additional risks of reinfection compared with no reinfection, rather than comparing risk after reinfection with risk after a first infection. Potential survivor bias may exist, as individuals in the no reinfection group needed to survive until the assigned time point for comparison. Our study compared hospitalised re-infection with hospitalised first-time infection groups and found that re-infection was associated with 1.3 times risk of post-acute mortality and hospitalisation, which aligns with the general trend observed by Bowe and colleagues. On the other hand, some studies have reported dissimilar results. Data from a UK-based survey reported a 28% lower risk of post-acute sequelae after a second infection compared with a first infection,[6] however this could be an underestimate as self-reported survey data could have non-response and misclassification biases. A European study showed that all persistent symptoms were less common after re-infection than after the first-time infection,[5] but the study was conducted at an earlier period when variants other than Omicron were dominant. Our study complements current evidence by focusing on patients with hospitalised infection (or re-infection) during the Omicron period, and show that patients with hospitalised re-infection are indeed more vulnerable to post-acute health risks.

Potential mechanisms

Some possible mechanisms support the increased risk of adverse health effects after hospitalised re-infection. First, re-infection in this study occurred during an Omicron-dominant period. Immune enhancement by Omicron infection appeared to be low due to the immune evasion increased by Omicron,[26] and protection against re-infection from previous infection decreased over time.[27] The Omicron variant is capable of escaping from recognition by virus-specific adaptive immune response, including the neutralising antibodies and T-cell response against SARS-CoV-2 virus. On the other hand, this variant is associated with prolonged activation of the innate response, that is, non-SARS-CoV-2 specific inflammation, mediated by the interferon signalling pathway.[28] Therefore, patients in the re-infection group, who had previous exposure to SARS-CoV-2 antigens, mounted earlier

Table 2 Subgroup analyses

	Adjusted HR (95% CI)					
	Age <65	Age ≥65	Male	Female	CCI 0–4	CCI≥5
Outcome	(N=20919)	(N=40219)	(N=30218)	(N=30920)	(N=40110)	(N=21028)
Primary outcomes						
All-cause mortality	1.198 (0.757 to 1.898)	1.409 (1.185 to 1.674)	1.148 (0.927 to 1.422)	1.614 (1.275 to 2.043)	1.794 (1.367 to 2.353)	1.176 (0.971 to 1.424)
All-cause hospital readmission	1.242 (1.075 to 1.435)	1.332 (1.213 to 1.464)	1.258 (1.134 to 1.395)	1.316 (1.169 to 1.482)	1.234 (1.102 to 1.382)	1.404 (1.267 to 1.556)
Emergency department attendance	1.320 (1.106 to 1.574)	1.330 (1.203 to 1.470)	1.273 (1.136 to 1.427)	1.336 (1.171 to 1.524)	1.292 (1.137 to 1.467)	1.331 (1.187 to 1.492)
Cardiovascular disorders						
Myocardial infarction	7.040 (1.030 to 48.127)	0.533 (0.163 to 1.740)	2.208 (0.599 to 8.135)	–	1.711 (0.202 to 14.504)	0.795 (0.251 to 2.521)
Stroke	0.334 (0.050 to 2.259)	0.811 (0.330 to 1.991)	0.280 (0.091 to 0.856)	1.203 (0.428 to 3.380)	0.611 (0.173 to 2.164)	0.803 (0.286 to 2.252)
Heart failure	4.815 (1.190 to 19.474)	0.940 (0.436 to 2.029)	1.582 (0.738 to 3.391)	0.641 (0.156 to 2.642)	1.337 (0.436 to 4.102)	0.947 (0.417 to 2.150)
Atrial fibrillation	–	0.689 (0.132 to 3.584)	0.387 (0.044 to 3.373)	1.090 (0.140 to 8.477)	1.277 (0.167 to 9.776)	0.295 (0.035 to 2.514)
Coronary artery disease	2.737 (0.512 to 14.630)	0.640 (0.215 to 1.905)	2.036 (0.729 to 5.683)	–	1.286 (0.288 to 5.751)	0.926 (0.253 to 3.390)
Deep vein thrombosis	–	0.229 (0.033 to 1.598)	0.485 (0.070 to 3.343)	–	–	0.208 (0.030 to 1.464)
Respiratory disorders						
Acute respiratory distress syndrome	–	1.812 (0.818 to 4.013)	0.716 (0.204 to 2.519)	2.148 (0.847 to 5.448)	–	3.274 (1.460 to 7.338)
Chronic pulmonary disease	–	–	–	–	–	–
Interstitial lung disease	–	–		–	–	
Neurological disorders						
Seizure	–	1.345 (0.340 to 5.323)	0.934 (0.150 to 5.821)	1.101 (0.137 to 8.851)	0.855 (0.111 to 6.618)	0.912 (0.142 to 5.871)
Bell's palsy	–	–	–	–	–	–
Encephalitis and encephalopathy	–	–	–	–	–	
Anxiety	–	–	–	–	–	–
Psychotic disorder	2.184 (0.330 to 14.449)	2.098 (0.313 to 14.091)	6.192 (1.306 to 29.363)	–	5.202 (1.194 to 22.662)	–
Post-traumatic stress disorder	–	0.455 (0.065 to 3.191)	–	0.712 (0.105 to 4.856)	–	0.533 (0.074 to 3.862)

Continued

Table 2 Continued

Outcome	Adjusted HR (95% CI) Age <65 (N=20 919)	Age ≥65 (N=40 219)	Male (N=30 218)	Female (N=30 920)	CCI 0–4 (N=40 110)	CCI≥5 (N=21 028)
Gastrointestinal disorders						
Acute liver injury	–	–	–	–	–	–
Pancreatitis	–	1.792 (0.282 to 11.394)	–	3.748 (0.590 to 23.806)	2.862 (0.413 to 19.835)	–
Renal disorders						
Acute kidney injury	–	0.425 (0.057 to 3.163)	0.687 (0.095 to 4.968)	–	–	0.625 (0.085 to 4.598)
Chronic kidney disease	0.636 (0.098 to 4.115)	1.612 (0.618 to 4.205)	1.614 (0.571 to 4.557)	1.639 (0.383 to 7.013)	1.035 (0.241 to 4.442)	1.640 (0.572 to 4.705)
End stage renal disease	–	4.543 (0.666 to 31.004)	6.513 (0.658 to 64.475)	1.685 (0.197 to 14.433)	–	4.219 (0.687 to 25.913)

Outcome	Adjusted HR (95% CI) COVID-19 vaccination: 0 or 1 dose (n=21 137)	COVID-19 vaccination: 2 or more doses (n=40 001)	Hospitalised during previous infection (N=59 708)	Not hospitalised during previous infection (N=60 324)
Primary outcomes				
All-cause mortality	1.342 (1.049 to 1.718)	1.639 (1.328 to 2.023)	1.986 (1.585 to 2.489)	1.022 (0.807 to 1.296)
All-cause hospital readmission	1.330 (1.157 to 1.529)	1.271 (1.153 to 1.402)	1.940 (1.707 to 2.204)	1.081 (0.976 to 1.196)
Emergency department attendance	1.316 (1.135 to 1.525)	1.295 (1.159 to 1.447)	1.879 (1.634 to 2.16)	1.092 (0.974 to 1.225)
Cardiovascular disorders				
Myocardial infarction	0.695 (0.134 to 3.61)	1.928 (0.378 to 9.823)	0.478 (0.094 to 2.443)	0.934 (0.203 to 4.297)
Stroke	0.199 (0.028 to 1.422)	1.148 (0.493 to 2.672)	0.163 (0.024 to 1.135)	1.078 (0.464 to 2.505)
Heart failure	0.864 (0.306 to 2.435)	1.577 (0.637 to 3.906)	1.471 (0.582 to 3.716)	0.836 (0.335 to 2.087)
Atrial fibrillation	–	1.87 (0.351 to 9.962)	–	1.125 (0.234 to 5.418)
Coronary artery disease	1.151 (0.384 to 3.451)	1.004 (0.202 to 4.987)	0.678 (0.185 to 2.487)	0.816 (0.228 to 2.923)
Deep vein thrombosis	–	0.472 (0.068 to 3.283)	–	0.363 (0.053 to 2.469)
Respiratory disorders				

Continued

Table 2 Continued

Outcome	Adjusted HR (95% CI)					
	Age <65 (N=20 919)	Age ≥65 (N=40 219)	Male (N=30 218)	Female (N=30 920)	CCI 0–4 (N=40 110)	CCI≥5 (N=21 028)
Acute respiratory distress syndrome	1.563 (0.541 to 4.513)	0.851 (0.275 to 2.634)	2.516 (1.017 to 6.222)	0.775 (0.162 to 3.711)		
Chronic pulmonary disease	–	–	–	–		
Interstitial lung disease	–	–	–	–		
Neurological disorders						
Seizure	1.531 (0.398 to 5.892)	–	0.733 (0.098 to 5.487)	0.868 (0.137 to 5.496)		
Bell's palsy	–	–	–	–		
Encephalitis and encephalopathy	–	–	–	–		
Anxiety	–	–	–	–		
Psychotic disorder	2.887 (0.448 to 18.616)	1.638 (0.242 to 11.092)	–	5.329 (1.105 to 25.687)		
Post-traumatic stress disorder	–	0.65 (0.093 to 4.543)	0.348 (0.051 to 2.363)	–		
Gastrointestinal disorders						
Acute liver injury	–	–	–	–		
Pancreatitis	–	3.008 (0.4 to 22.604)	7.55 (1.189 to 47.946)	–		
Renal disorders						
Acute kidney injury	0.429 (0.059 to 3.13)	–	–	0.807 (0.109 to 5.949)		
Chronic kidney disease	0.422 (0.06 to 2.985)	2.329 (0.909 to 5.969)	3.183 (0.935 to 10.837)	1.074 (0.34 to 3.393)		
End stage renal disease	4.183 (0.439 to 39.854)	1.634 (0.154 to 17.305)	0.999 (0.116 to 8.58)	5.217 (0.524 to 51.964)		

HRs of outcomes in some subgroups could not be estimated due to limited number of events.
CI, confidence interval.

antiviral responses but simultaneously provoked exaggerated bystander inflammation (online supplemental figure 2). Moreover, adverse health consequences from the first-time infection may have a cumulative effect on re-infection.[7] Indeed, our findings showed that those who required hospitalisation during a previous COVID-19 infection episode had much worse clinical outcomes with re-infection compared with those with first-time infection, whereas those who were not hospitalised during the previous infection had a relatively small increased risk of adverse outcomes on re-infection compared with those with first-time infection. This suggests that the irreversible end-organ injury resulting from previous exposure to the virus could have predisposed to a higher risk of adverse clinical outcomes from re-infection. For instance, post-COVID-19 pulmonary fibrosis which affects >40% of people recovering from COVID-19 would be a risk factor for severe pneumonia requiring inpatient management (as seen in 8.46% re-infection group and 6.94% first-time infection group online supplemental table 3).[29] Patients surviving COVID-19 are at higher risk of developing chronic kidney disease,[30] and haemodialysis would be required for those who progress to end-stage renal disease. Online supplemental figure 2 illustrates the above two potential mechanisms that contribute to the higher risk of adverse clinical outcomes in the re-infection group, which is characterised by pre-existing host end-organ damage and exaggerated immune response. In our study, two-thirds of the reinfection group had received two or more doses of COVID-19 vaccination, indicating that even those who developed hybrid immunity were still at significant risk of adverse health outcomes following hospitalised re-infection. We cannot rule out other explanations; however, regardless of the underlying mechanism, those reinfected hospitalised patients should be considered as a population at higher risk for adverse outcomes, particularly in terms of long-term health prognosis.

Clinical implications

As a significant proportion of the population has been infected with COVID-19 once and re-infection is expected to be common due to waning immunity and emerging novel variants, it is imperative to understand if re-infection poses additional health risks and burden to the healthcare system in the long run. Although acute outcomes of COVID-19 re-infection could be less severe than the first infection, our study suggests that the additional risks of hospitalisation and mortality after a hospitalised re-infection in the post-acute phase are higher than that after hospitalised first-time infection, therefore re-infection should not be taken lightly. Further, considering some studies have shown that the severity of re-infection correlates with the severity of the first infection,[8] strategies to reduce re-infection in patients with hospitalised first infection are meaningful to prevent the adverse consequences of hospitalised re-infection. Additionally, with COVID-19 expected to become endemic, the burden of a large number of patients with mild or asymptomatic illnesses is less significant,[31] but for patients with re-infection severe enough to require hospitalisation, this study emphasises that their long-term health burden is still remarkable. Thus, it is necessary to rationalise and allocate more healthcare resources for patients with hospitalised re-infection. Strategies such as regular booster vaccination targeting patients with hospitalised COVID-19 infection as a high-risk group to reduce the risk of hospitalised re-infection and subsequent post-acute hospitalisation and mortality are warranted.[32]

Strengths and limitations

To our knowledge, this is the first study to evaluate the long-term sequelae after hospitalised COVID-19 re-infection compared with hospitalised first-time COVID-19 infection. This study has several strengths. First, in our cohort, both re-infection groups and first-time infection groups had comparable COVID-19 severity requiring hospitalisation during the acute-phase, thus reducing potential bias arising from different COVID-19 severity between groups when evaluating post-acute outcomes. Second, this population-based study used territory-wide EHR databases which covered close to 90% of the Hong Kong population, thus conferring high population representativeness. High diagnostic coding accuracy of HA EHR data had also been demonstrated in previous research.[33–35] Third, this study was conducted at a period when the Omicron variant was dominant, and thus findings from this study are more relevant to the current landscape of SARS-CoV-2 infections worldwide and supplements previous studies conducted in earlier periods.

Nevertheless, this study had several limitations. First, the number of events observed for organ system disorders were limited. Further studies with a larger sample of re-infection patients would be warranted to confirm our findings relating to the secondary outcomes. Second, we cannot rule out the possibility that some previous asymptomatic COVID-19 infections were not reported. Nevertheless, at the time of the study, the Hong Kong government had implemented extensive PCR testing for SARS-CoV-2 in public hospitals and clinics for close contacts with confirmed cases. Territory-wide community testing centres were also in place to screen asymptomatic individuals and provide regular testing to various staff groups with a high risk of exposure, such as those working in nursing homes. Thus, the proportion of missed asymptomatic infections remains relatively small compared with other regions relying solely on voluntary testing. Given that our definition of COVID-related hospitalisation is based on PCR/RAT test results, we cannot ascertain the cause of hospitalisation is indeed due to COVID-19. However, many other EHR-based studies also use laboratory tests to determine hospitalised COVID-19 cases.[36 37] Third, individual-level data on SARS-CoV-2 variants is not available. Nevertheless, our study was conducted during a time period when the Omicron variant was dominant. Future studies with detailed variant data would be valuable

in accurately assessing the impacts of specific subvariants on health outcomes. Fourth, events may not be fully captured for the patients enrolled near the end of the study period (eg, November 2022) due to their shorter follow-up period. Lastly, as with other retrospective observational studies using electronic medical record data, the effects of potential residual confounding, such as those related to patient vulnerability, could not be ruled out. Also, whether a particular hospital admission episode is directly caused by a previous COVID-19 diagnosis could not be ascertained from electronic medical records data, thus the population we included were all-cause hospitalisations in patients with SARS-CoV-2 positivity. Further studies with causal assessment may be warranted. It was not possible to determine solely from the electronic database whether a hospital readmission or mortality outcome was COVID-19-related, since this would require formal causative assessment by clinicians on a case-by-case basis. Nevertheless, we had listed out the most common reasons for hospital readmission in our main results and online supplemental table 3, which hopefully provided some insights on the post-acute sequelae among re-infection versus first-time infection groups.

CONCLUSION

Among patients with COVID-19 requiring hospitalisation, those who had a previous COVID-19 infection (ie, re-infection group) were at significantly higher risk of post-acute all-cause mortality, all-cause hospital readmission and attendance to emergency departments, compared with those who were infected for the first time. Such increased risks were consistently observed in both unvaccinated and fully vaccinated individuals. The magnitude of increased risks on re-infection were greater in those who were also hospitalised during their previous infection episode.

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