

Omicron SARS-CoV-2 outcomes in vaccinated individuals with heart failure and ischaemic heart disease

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ABSTRACT

Introduction: Outcomes after SARS-CoV-2 Omicron infection in patients with heart failure (HF) and ischaemic heart disease (IHD) remain poorly defined.

Method: In a highly vaccinated cohort of adult Singapore citizens and permanent residents, we used Cox proportional hazards models (adjusted for sociodemographic variables and comorbidities) to compare the risks of Omicron infection, COVID-19-related hospitalisation, and severe COVID-19 between individuals with HF or IHD and matched controls without these conditions.

Results: From national databases, we identified 15,426 HF patients matched 1:~3 to 41,221 controls, and 110,442 IHD patients matched 1:~2 to 223,843 controls. Over 80% of HF and IHD patients had received at least 3 vaccine doses. During the Omicron-predominant period, both HF and IHD cohorts demonstrated higher adjusted risks of COVID-19 hospitalisation compared with matched controls (HF: adjusted hazard ratio [aHR] 1.77, 95% confidence interval [CI] 1.65–1.90; IHD: aHR 1.21, 95% CI 1.17–1.26). Among those with at least 1 HF- or IHD-related admission in the prior year, hospitalisation risk was further elevated (HF: aHR 1.27, 95% CI 1.13–1.42; IHD: aHR 1.11, 95% CI 1.01–1.23). Receipt of ≥3 vaccine doses was associated with substantially lower risk of severe COVID-19 versus only 2 doses (HF: aHR 0.35, 95% CI 0.28–0.43; IHD: aHR 0.27, 95% CI 0.23–0.32). A fourth dose conferred additional reductions in infection and adverse outcomes, though CIs for infection overlapped with those for 3 doses.

Conclusion: During Omicron predominance, HF and IHD patients experienced greater risk of COVID-19

hospitalisation and severe COVID-19 versus matched controls. Booster vaccinations attenuated these risks. Individuals with recent HF/IHD admissions should be prioritised for receipt of booster vaccine doses.

Keywords: boosters, cardiology, COVID-19, heart failure, infectious diseases, Omicron, SARS-CoV-2, vaccination

CLINICAL IMPACT

What is New

- This is the first population-based, matched case-control analysis in Singapore to examine how vaccination status influences COVID-19 outcomes in patients with heart failure (HF) or ischaemic heart disease (IHD) during the Omicron wave.
- Patients with HF or IHD faced higher rates of COVID-19-related hospitalisation and severe COVID-19 versus matched controls, but booster doses significantly mitigated these risks.

Clinical Implications

- Even in the Omicron-dominant and endemic phase of COVID-19, booster vaccination continues to provide meaningful protection for individuals with HF or IHD, underscoring the need to prioritise regular receipt of booster doses in this high-risk group.

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INTRODUCTION

Respiratory viral infections are a relatively common cause of heart failure (HF) exacerbations, with higher risk of adverse outcomes observed in HF episodes precipitated by infection.¹ Multiple reports from the initial phase of the COVID-19 pandemic reported higher mortality and in-hospital complications associated with a history of HF and ischaemic heart disease (IHD) among hospitalised patients with concurrent SARS-CoV-2 infection.^{2,3,4} In a multicentre cohort study of critically ill adult patients hospitalised for COVID-19, one-fourth had pre-existing cardiovascular conditions.⁵ This association is not just observed in hospitalised cohorts; in a population-based study involving >6 million English adults, marked gradients were still seen in the incidence of adverse COVID-19 outcomes by cardiovascular risk profile.⁶ Increased risk of adverse COVID-19 outcomes has been documented in HF regardless of left ventricular ejection fraction; in a cohort of HF patients with mildly reduced or preserved ejection fraction recruited into a large clinical trial spanning the pandemic period, ~10% of cases contracted SARS-CoV-2 infection on follow-up, with >50% of infections leading to hospitalisation or death.⁷

However, a significant limitation is that most studies on COVID-19 outcomes among HF/IHD patients were based on data from the early pre-Delta stages of the pandemic.¹⁻⁷ In a multicentre US registry of adults hospitalised with cardiovascular complications and concurrent SARS-CoV-2 infection, rates of in-hospital mortality progressively declined during the transition from pre-Delta to Delta-predominant transmission.⁸ Newer SARS-CoV-2 variants, such as Omicron, are associated with milder symptoms and higher proportions of non-severe disease;⁹ individuals hospitalised during the Omicron-predominant period were less likely to experience severe respiratory disease compared to those hospitalised during circulation of earlier SARS-CoV-2 variants.¹⁰ Data on COVID-19 outcomes among individuals with HF/IHD who were infected with SARS-CoV-2 during Omicron-predominant transmission remains lacking. Additionally, most studies pre-dated the rollout of vaccination or did not systematically record vaccination status.^{1-6,8} A single population-based cohort of adults with HF who were infected with SARS-CoV-2 during Omicron-predominant transmission reported significant reduction in risk of severe COVID-19 following receipt of a single booster dose, though restriction to only polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infections meant that a substantial proportion of mild infections may have been missed, thus limiting generalisability.¹¹ Additional studies are required in order to guide recommendations for vaccination and boosting in

patients with HF/IHD during COVID-19 endemicity. We contrasted outcomes of SARS-CoV-2 infection in a highly-vaccinated cohort of adults in Singapore with HF/IHD versus matched population controls, during waves of transmission driven by successive Omicron subvariants, including Omicron XBB.

METHOD

Study population, period and design

Population-wide national records of all confirmed SARS-CoV-2 infections, hospitalisations and vaccines administered in Singapore, a multi-ethnic Southeast Asian city state, were linked with national healthcare claims records for the study period of 1 January 2022 to 20 December 2023, corresponding to the wave of infections predominated by the SARS-CoV-2 Omicron variant. Omicron emerged in late 2021 to displace Delta as the predominant strain, and subsequently predominated community transmission by January 2022, with ≥90% of sequenced cases on national surveillance.¹² The Omicron XBB subvariant first emerged in Singapore at the end of 2022,¹³ replacing earlier Omicron subvariants in circulation; as such, 18 September 2022 was used as the cut-off date to further separate the Omicron period into XBB and pre-XBB (Omicron BA.1/2/3/4) transmission.

A retrospective case-control study design was utilised to match controls from the general population to every patient with HF/IHD in the study population (matched by age strata; sex; ethnicity; socioeconomic status [SES] based on housing type; cardiovascular risk factors including diabetes, hypertension, dyslipidaemia; and COVID-19 vaccination timing [respective months in which an individual was fully vaccinated, boosted and received a second booster dose]), during the Omicron wave in Singapore (Fig. 1). Data collected was capped at 20 December 2023. The study population included all adult Singapore citizens and permanent residents aged ≥18 years. Three controls from the general population were included for every patient with HF/IHD in each period for comparison, using exact matching with replacement. History of HF/IHD and other comorbidities such as cardiovascular risk factors, were defined based on International Classification of Diseases, Tenth Revision codes recorded in the national healthcare claims database. The national healthcare claims database encompasses all public and private healthcare providers in inpatient and outpatient settings; participation in the national government-administered medical-savings scheme (i.e. Medisave) is compulsory for all Singaporeans.¹⁴ Under the Chronic Disease Management Scheme, Medisave can be used to claim expenses for inpatient and outpatient treatment of various chronic diseases, including HF/

IHD, hypertension, diabetes and dyslipidaemia;¹⁴ this enabled comprehensive capture of diagnoses across different healthcare settings. Individuals with missing sociodemographic data, who demised or were infected prior to study start date, developed HF/IHD during the study period, or had no matching controls were excluded from the final study population (Fig. 1). Individuals vaccinated with non-messenger ribonucleic acid (mRNA) vaccines were also excluded as they formed a very small minority (<5%).

COVID-19 outcomes

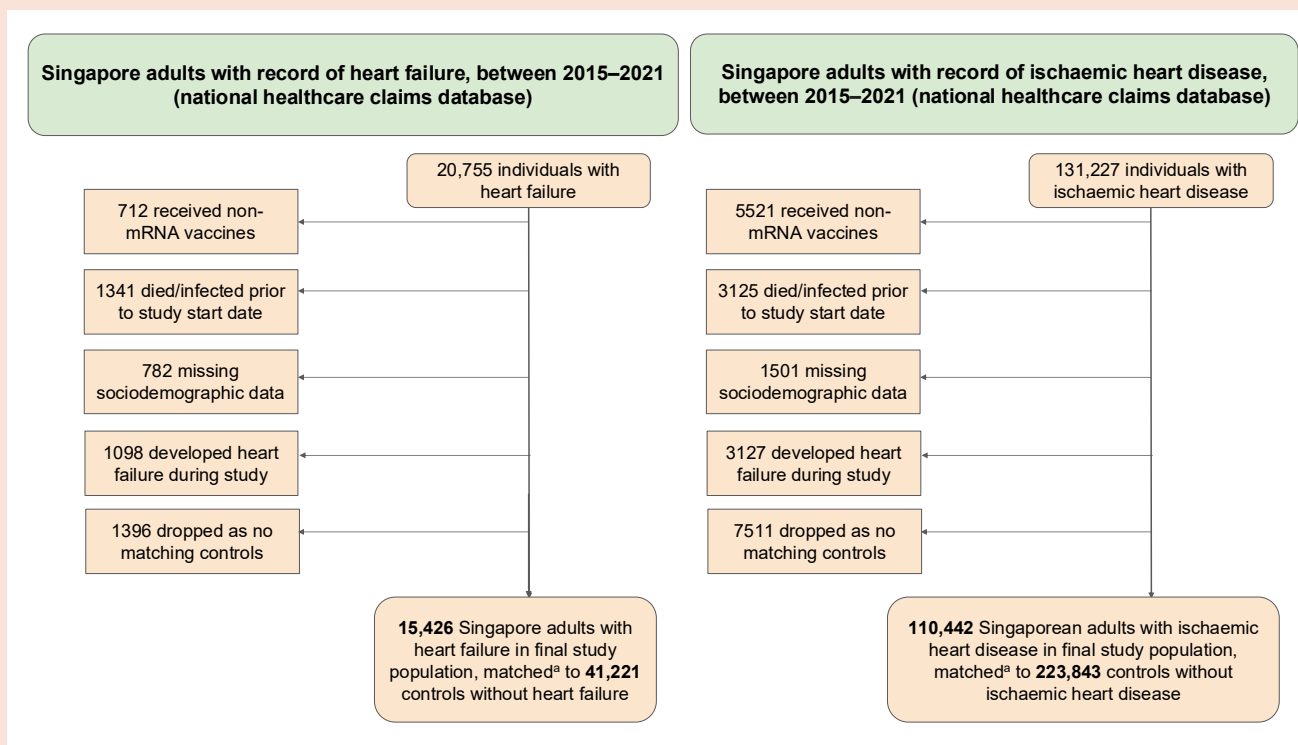
SARS-CoV-2 infection, COVID-19-related hospitalisation and severe COVID-19 disease were defined using the national COVID-19 registry. SARS-CoV-2 infection was defined as either a positive PCR test or rapid antigen test (RAT) result recorded in the national testing registry. During the study period, SARS-CoV-2 testing was widely available across all healthcare providers, including both public and private hospitals, public primary care clinics (polyclinics) and Public Health Preparedness Clinics, which formed a nationwide network of more than 1000 private general-practitioner clinics activated during pandemics to provide subsidised testing.¹⁵ By law, MOH was notified of all test-positive cases up to 1 March 2024, beyond the end of the study period.¹⁶ COVID-19-related hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive

COVID-19 result. Severe COVID-19 disease was defined as those requiring oxygen supplementation or intensive care unit admission, or that resulting in death. Singapore's Ministry of Health (MOH) was notified of all COVID-19 hospitalisations and severe COVID-19 infections.^{15,16}

Covariates

The following covariates were extracted from national databases: demographics (age, sex, ethnicity), vaccination status, comorbidities and SES. SES was classified by housing type based on postal code. Most Singaporeans (≥90%) live in subsidised public housing; smaller-sized flats attract higher subsidy, with purchase eligibility linked to household income.¹⁷ SES has been shown to affect COVID-19 vaccination uptake and oral antiviral utilisation in the Singapore context,^{17,18} which can potentially affect risk of adverse COVID-19 outcomes. Vaccination status was defined by the number of mRNA vaccination doses recorded in the National Immunisation Registry, at the point of SARS-CoV-2 infection. In Singapore, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) were first approved for use in the national vaccination programme as a 2-dose primary series; ≥90% of the population received mRNA vaccines.¹⁹ Booster vaccinations (third and fourth vaccine doses) were concurrently rolled out in September 2021 during emergence of the Delta wave.¹⁹ From December 2022

Fig. 1. Cohort construction flowchart.



^a Matched by age, sex, ethnicity, socioeconomic status, cardiovascular risk factors and vaccination status.

onwards, bivalent vaccine formulations fully replaced their monovalent predecessors;²⁰ updated monovalent XBB1.5 vaccines in turn replaced bivalent boosters in October 2023.²⁰

Statistical analysis

Differences in proportions were compared using chi-square test. Cox regressions were conducted to compare risks of SARS-CoV-2 infection, COVID-19-related hospitalisations, and severe COVID-19 disease between HF/IHD patients and population-based controls without a diagnosis of HF/IHD, adjusting for demographics, SES and comorbidities as covariates. Estimates of risk were grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose and ≥ 4 -dose groups). Hospitalisation for HF/IHD in the preceding year was taken as an indicator of disease severity in supplementary analyses. As an additional analysis, risk estimates for COVID-19 outcomes in individuals with HF/IHD infected during Omicron were stratified into XBB-predominant transmission and pre-XBB periods. Data were analysed using Python version 3.11.5 (Python Software Foundation, Wilmington, DE, US) and R statistical software version 4.3.1 (R Core Team 2023, R Foundation for Statistical Computing, Vienna, Austria). Python was used for data preprocessing, while R was used for statistical analysis; $P < 0.05$ was considered statistically significant.

This study was performed as part of national public health research under Singapore's Infectious Diseases Act. Separate individual informed consent and ethics review by an institutional review board was not required by law.

RESULTS

Overall, after applying inclusion and exclusion criteria, 15,426 HF patients were matched to 41,221 controls without HF, and 110,442 IHD patients were matched to 223,843 controls without IHD (Fig. 1). Sociodemographic characteristics of IHD/HF cases and controls, stratified by vaccination doses received, are reported in Tables 1 and 2. Around one-third of IHD/HF cases were female (IHD: 28.2%, 31,124/110,442; HF: 41.3%, 6364/15,426). The majority were aged ≥ 60 years (IHD: 75.9%, 83,824/110,442; HF: 81.7%, 12,603/15,426). Booster uptake (≥ 3 vaccine doses) was high in both IHD/HF cases aged ≥ 60 years (IHD: 92.9%, 77,904/83,824; HF: 83.8%, 10,567/12,603), as well as in those aged < 60 years (IHD: 95.0%, 25,279/26,618; HF: 87.9%, 2482/2823). Rates of vaccination throughout the Omicron wave among HF/IHD patients, compared against vaccination rates in controls and in the whole population, are reflected in Supplementary Table S1. At the onset

of Omicron, the majority (IHD: 74.4%; HF: 59.1%) had already received a booster dose; this rose to 94.8% of IHD patients and 88.1% of HF patients by the end of the study period (Supplementary Table S1).

The adjusted hazard ratio (aHR) for risk of SARS-CoV-2 infection, COVID-19-related hospitalisations and severe COVID-19 disease in HF/IHD patients grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose and ≥ 4 -dose groups) are shown in Table 3, with unadjusted incidence rates reported in Supplementary Table S2. During Omicron, significantly decreased risk of SARS-CoV-2 infection, but not COVID-19 hospitalisation or severe COVID-19, was noted in unvaccinated or partially-vaccinated patients compared with fully-vaccinated individuals, across both HF/IHD cases and healthy controls (Table 3). Risk of SARS-CoV-2 infection, COVID-19-related hospitalisation and severe COVID-19 disease was significantly lower in boosted HF/IHD patients (≥ 3 doses), compared against HF/IHD patients who had only completed a 2-dose primary vaccination series. Hazard ratios (HRs) of SARS-CoV-2 infection, hospitalisation and severe disease were lower in the ≥ 4 -dose group compared with the 3-dose group, though the confidence intervals (CIs) for infection overlapped (Table 3).

Compared with matched controls, higher risks of SARS-CoV-2 infection (HF: aHR 1.05 [95% CI 1.01–1.08]; IHD: aHR 1.10 [95% CI 1.09–1.12]) and COVID-19-related hospitalisation (HF: aHR 1.77 [95% CI 1.65–1.90]; IHD: aHR 1.21 [95% CI 1.17–1.26]) were observed among HF/IHD patients infected during Omicron (Table 4). Risk of COVID-19 hospitalisation remained elevated during both XBB-predominant transmission and prior circulation of other Omicron subvariants (BA.1/2/4/5). During the period of Omicron predominance, those with at least 1 HF/IHD-related admission in the preceding year had higher risk of COVID-19-related hospitalisation (IHD: aHR 1.11 [95% CI 1.01–1.23]; HF: aHR 1.27 [95% CI 1.13–1.42]) (Supplementary Table S3).

DISCUSSION

In a highly vaccinated/boosted population-based cohort of HF/IHD cases, elevated risk of COVID-19-related hospitalisation relative to matched population controls was still observed during Omicron-predominant transmission, persisting even into the XBB-predominant period. While risk of infection in the unvaccinated may have diminished during Omicron-predominant transmission due to the introduction of vaccine-differentiated social distancing measures, with greater restrictions placed on unvaccinated individuals,^{17,21} vaccination and boosting

Table 1. Characteristics of heart failure cases (n=15,426) and control populations without heart failure (n=41,221), stratified by total number of vaccine doses.

Sex, no. (%)	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double-boosted)	
	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control
Female	442 (43.8)	1153 (44.7)	613 (44.8)	1455 (46.1)	3064 (41.3)	8313 (41.3)	2245 (39.9)	6124 (39.9)
Male	566 (56.2)	1426 (55.3)	756 (55.2)	1698 (53.9)	4354 (58.7)	11,839 (58.7)	3386 (60.1)	9213 (60.1)
Age, no. (%)								
18–29 years	3 (0.3)	9 (0.3)	3 (0.2)	9 (0.3)	27 (0.4)	79 (0.4)	5 (0.1)	13 (0.1)
30–39 years	7 (0.7)	18 (0.7)	15 (1.1)	39 (1.2)	127 (1.7)	353 (1.8)	44 (0.8)	118 (0.8)
40–49 years	31 (3.1)	82 (3.2)	31 (2.3)	62 (2.0)	431 (5.8)	1202 (6.0)	171 (3.0)	447 (2.9)
50–59 years	106 (10.5)	266 (10.3)	145 (10.6)	313 (9.9)	1080 (14.6)	2969 (14.7)	597 (10.6)	1615 (10.5)
60–69 years	203 (20.1)	536 (20.8)	322 (23.5)	743 (23.6)	2095 (28.2)	5758 (28.6)	1527 (27.1)	4230 (27.6)
70–79 years	224 (22.2)	585 (22.7)	392 (28.6)	899 (28.5)	1957 (26.4)	5348 (26.5)	1545 (27.4)	4256 (27.7)
≥80 years	434 (43.1)	1083 (42.0)	461 (33.7)	1088 (34.5)	1701 (22.9)	4443 (22.0)	1742 (30.9)	4658 (30.4)
Ethnicity, no. (%)								
Chinese	635 (63.0)	1712 (66.4)	843 (61.6)	2082 (66.0)	4841 (65.3)	13,459 (66.8)	4244 (75.4)	11,881 (77.5)
Indian	166 (16.5)	397 (15.4)	223 (16.3)	453 (14.4)	927 (12.5)	2376 (11.8)	428 (7.6)	1026 (6.7)
Malay	191 (18.9)	438 (17.0)	296 (21.6)	606 (19.2)	1590 (21.4)	4177 (20.7)	904 (16.1)	2295 (15.0)
Others	16 (1.6)	32 (1.2)	7 (0.5)	12 (0.4)	60 (0.8)	140 (0.7)	55 (1.0)	135 (0.9)
Socioeconomic status by housing type, no. (%) ^b								
Public, 1–2 rooms	165 (16.4)	406 (15.7)	231 (16.9)	492 (15.6)	945 (12.7)	2434 (12.1)	634 (11.3)	1609 (10.5)
Public, 3 rooms	266 (26.4)	652 (25.3)	337 (24.6)	799 (25.3)	1823 (24.6)	4923 (24.4)	1260 (22.4)	3462 (22.6)
Public, 4 rooms	255 (25.3)	675 (26.2)	443 (32.4)	1016 (32.2)	2536 (34.2)	6972 (34.6)	1876 (33.3)	5169 (33.7)
Public, 5 rooms	229 (22.7)	603 (23.4)	274 (20.0)	644 (20.4)	1770 (23.9)	4906 (24.3)	1490 (26.5)	4151 (27.1)
Others	13 (1.3)	32 (1.2)	9 (0.7)	20 (0.6)	19 (0.3)	44 (0.2)	87 (1.5)	181 (1.2)
Private housing	80 (7.9)	211 (8.2)	75 (5.5)	182 (5.8)	325 (4.4)	873 (4.3)	284 (5.0)	765 (5.0)

Table 1. Characteristics of heart failure cases (n=15,426) and control populations without heart failure (n=41,221), stratified by total number of vaccine doses. (Cont'd)

	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double-boosted)	
	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control
Types of comorbidities no. (%)								
Ischaemic heart disease	654 (64.9)	488 (18.9)	944 (69.0)	662 (21.0)	4900 (66.1)	3772 (18.7)	3691 (65.5)	2737 (17.8)
Chronic obstructive pulmonary disease	137 (13.6)	188 (7.3)	229 (16.7)	306 (9.7)	861 (11.6)	1350 (6.7)	677 (12.0)	967 (6.3)
Cerebrovascular disorders	205 (20.3)	438 (17.0)	260 (19.0)	498 (15.8)	1127 (15.2)	2157 (10.7)	871 (15.5)	1414 (9.2)
Cancer	95 (9.4)	251 (9.7)	144 (10.5)	454 (14.4)	539 (7.3)	1489 (7.4)	464 (8.2)	1159 (7.6)
Chronic kidney disease	288 (28.6)	354 (13.7)	506 (37.0)	607 (19.3)	2126 (28.7)	2497 (12.4)	1481 (26.3)	1886 (12.3)
Chronic liver disease	39 (3.9)	36 (1.4)	41 (3.0)	64 (2.0)	192 (2.6)	271 (1.3)	135 (2.4)	182 (1.2)
Diabetes	538 (53.4)	1312 (50.9)	799 (58.4)	1749 (55.5)	4165 (56.1)	11,052 (54.8)	3008 (53.4)	8056 (52.5)
Hypertension	794 (78.8)	1974 (76.5)	1168 (85.3)	2637 (83.6)	6226 (83.9)	16,769 (83.2)	4815 (85.5)	13,071 (85.2)
Hyperlipidaemia	596 (59.1)	1483 (57.5)	886 (64.7)	2029 (64.4)	5069 (68.3)	13,743 (68.2)	3939 (70.0)	10,822 (70.6)
No. of comorbidities, no. (%)								
0 comorbidity	44 (4.4)	334 (13.0)	35 (2.6)	272 (8.6)	267 (3.6)	1628 (8.1)	188 (3.3)	1150 (7.5)
1 comorbidity	87 (8.6)	285 (11.1)	82 (6.0)	262 (8.3)	563 (7.6)	2278 (11.3)	408 (7.2)	1663 (10.8)
2 comorbidities	145 (14.4)	496 (19.2)	156 (11.4)	503 (16.0)	989 (13.3)	4206 (20.9)	752 (13.4)	3399 (22.2)
3–4 comorbidities	439 (43.6)	1120 (43.4)	577 (42.1)	1570 (49.8)	3517 (47.4)	10,151 (50.4)	2786 (49.5)	7821 (51.0)
≥5 comorbidities	293 (29.1)	344 (13.3)	519 (37.9)	546 (17.3)	2082 (28.1)	1889 (9.4)	1497 (26.6)	1304 (8.5)
COVID-19, no. (%)								
Infected ^c	398 (39.5)	735 (28.5)	626 (45.7)	1509 (47.9)	3162 (42.6)	8427 (41.8)	2432 (43.2)	6278 (40.9)
Hospitalised ^d	291 (28.9)	402 (15.6)	349 (25.5)	522 (16.6)	970 (13.1)	1111 (5.5)	589 (10.5)	615 (4.0)
Severe disease ^e	134 (13.3)	178 (6.9)	128 (9.3)	145 (4.6)	300 (4.0)	223 (1.1)	128 (2.3)	95 (0.6)
Death	42 (4.2)	72 (2.8)	28 (2.0)	47 (1.5)	31 (0.4)	26 (0.1)	5 (0.1)	6 (0.0)

^a Among cases of heart failure (n=15,426), 10,189 (66.1%) had a concurrent diagnosis of ischaemic heart disease.

^b Housing type was used as an indicator of socioeconomic status.

^c SARS-CoV-2 infection defined as positive test result (polymerase chain reaction [PCR] test or rapid antigen test [RAT]) recorded in the national COVID-19 registry.

^d COVID-19 hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive COVID-19 result (PCR/RAT).

^e Severe disease was defined as COVID-19 infection with the resulting need for supplemental oxygen, intensive care admission or death.

Table 2. Characteristics of ischaemic heart disease cases (n=110,442) and control populations without ischaemic heart disease (n=223,843), stratified by total number of vaccine doses.

		0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double boosted)	
		Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control
Sex, no. (%)									
Female		1173 (35.1)	2556 (39.8)	1479 (37.8)	2826 (43.0)	14,569 (28.8)	34,850 (33.9)	67,850 (26.5)	38,633 (31.3)
Male		2173 (64.9)	3868 (60.2)	2434 (62.2)	3744 (57.0)	36,078 (71.2)	67,850 (66.1)	38,633 (73.5)	74,333 (68.7)
Age, no. (%)									
18–29 years		2 (0.1)	6 (0.1)	4 (0.1)	12 (0.2)	59 (0.1)	167 (0.2)	17 (0.0)	47 (0.0)
30–39 years		19 (0.6)	48 (0.7)	31 (0.8)	79 (1.2)	631 (1.2)	1660 (1.6)	191 (0.4)	507 (0.5)
40–49 years		123 (3.7)	286 (4.5)	196 (5.0)	374 (5.7)	3801 (7.5)	9134 (8.9)	1660 (3.2)	4037 (3.7)
50–59 years		437 (13.1)	873 (13.6)	527 (13.5)	916 (13.9)	10,754 (21.2)	22,909 (22.3)	8166 (15.5)	17,841 (16.5)
60–69 years		848 (25.3)	1642 (25.6)	916 (23.4)	1521 (23.2)	17,134 (33.8)	33,759 (32.9)	18,564 (35.3)	38,094 (35.2)
70–79 years		865 (25.9)	1674 (26.1)	1094 (28.0)	1760 (26.8)	12,017 (23.7)	23,352 (22.7)	15,248 (29.0)	30,668 (28.4)
≥80 years		1052 (31.4)	1895 (29.5)	1145 (29.3)	1908 (29.0)	6251 (12.3)	11,719 (11.4)	8690 (16.5)	16,955 (15.7)
Ethnicity, no. (%)									
Chinese		2250 (67.2)	4532 (70.5)	2535 (64.8)	4583 (69.8)	35,455 (70.0)	75,130 (73.2)	41,756 (79.5)	88,599 (81.9)
Indian		570 (17.0)	925 (14.4)	698 (17.8)	958 (14.6)	6943 (13.7)	11,952 (11.6)	4265 (8.1)	7074 (6.5)
Malay		434 (13.0)	771 (12.0)	659 (16.8)	988 (15.0)	7772 (15.3)	14,732 (14.3)	5775 (11.0)	10,982 (10.2)
Others		92 (2.7)	196 (3.1)	21 (0.5)	41 (0.6)	477 (0.9)	886 (0.9)	740 (1.4)	1494 (1.4)
Socioeconomic status by housing type, no. (%)^b									
Public, 1–2 rooms		392 (11.7)	684 (10.6)	567 (14.5)	877 (13.3)	4283 (8.5)	8075 (7.9)	3710 (7.1)	7109 (6.6)
Public, 3 rooms		734 (21.9)	1360 (21.2)	938 (24.0)	1589 (24.2)	9796 (19.3)	19,732 (19.2)	9463 (18.0)	19,461 (18.0)
Public, 4 rooms		993 (29.7)	1862 (29.0)	1270 (32.5)	2104 (32.0)	17,008 (33.6)	34,756 (33.8)	16,239 (30.9)	33,561 (31.0)
Public, 5 rooms		833 (24.9)	1646 (25.6)	918 (23.5)	1576 (24.0)	16,285 (32.2)	33,494 (32.6)	18,630 (35.5)	38,926 (36.0)
Others		114 (3.4)	258 (4.0)	17 (0.4)	37 (0.6)	105 (0.2)	228 (0.2)	250 (0.5)	476 (0.4)
Private housing		280 (8.4)	614 (9.6)	203 (5.2)	387 (5.9)	3170 (6.3)	6415 (6.2)	4244 (8.1)	8616 (8.0)

Table 2. Characteristics of ischaemic heart disease cases (n=110,442) and control populations without ischaemic heart disease (n=223,843), stratified by total number of vaccine doses. (Cont'd)

	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double boosted)	
	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control
Types of comorbidities no. (%)								
Heart failure	650 (19.4)	155 (2.4)	914 (23.4)	196 (3.0)	4848 (9.6)	942 (0.9)	3629 (6.9)	663 (0.6)
Chronic obstructive pulmonary disease	289 (8.6)	351 (5.5)	477 (12.2)	552 (8.4)	3597 (7.1)	5250 (5.1)	3640 (6.9)	5398 (5.0)
Cerebrovascular disorders	536 (16.0)	871 (13.6)	643 (16.4)	971 (14.8)	5040 (10.0)	8640 (8.4)	4947 (9.4)	8509 (7.9)
Cancer	297 (8.9)	612 (9.5)	504 (12.9)	950 (14.5)	2999 (5.9)	6194 (6.0)	3523 (6.7)	7134 (6.6)
Chronic kidney disease	609 (18.2)	635 (9.9)	987 (25.2)	963 (14.7)	6534 (12.9)	8642 (8.4)	6645 (12.6)	9747 (9.0)
Chronic liver disease	81 (2.4)	98 (1.5)	99 (2.5)	129 (2.0)	750 (1.5)	1162 (1.1)	750 (1.4)	1139 (1.1)
Diabetes	1504 (44.9)	2482 (38.6)	2040 (52.1)	2946 (44.8)	22,285 (44.0)	41,523 (40.4)	22,996 (43.8)	44,042 (40.7)
Hypertension	2433 (72.7)	4113 (64.0)	3180 (81.3)	4876 (74.2)	38,573 (76.2)	71,864 (70.0)	41,288 (78.6)	79,618 (73.6)
Hyperlipidaemia	2003 (59.9)	3243 (50.5)	2701 (69.0)	3961 (60.3)	37,407 (73.9)	69,387 (67.6)	40,139 (76.4)	77,229 (71.4)
No. of comorbidities, no. (%)								
0 comorbidity	349 (10.4)	1369 (21.3)	247 (6.3)	952 (14.5)	4426 (8.7)	14,950 (14.6)	4231 (8.1)	13,667 (12.6)
1 comorbidity	526 (15.7)	1076 (16.7)	383 (9.8)	815 (12.4)	7392 (14.6)	16,950 (16.5)	6964 (13.3)	16,066 (14.9)
2 comorbidities	707 (21.1)	1364 (21.2)	732 (18.7)	1286 (19.6)	13,630 (26.9)	27,969 (27.2)	14,582 (27.8)	30,659 (28.3)
3–4 comorbidities	1296 (38.7)	2162 (33.7)	1705 (43.6)	2797 (42.6)	21,256 (42.0)	39,088 (38.1)	23,279 (44.3)	44,139 (40.8)
≥5 comorbidities	468 (14.0)	453 (7.1)	846 (21.6)	720 (11.0)	3943 (7.8)	3743 (3.6)	3480 (6.6)	3618 (3.3)
COVID-19, no. (%)								
Infected ^c	1062 (31.7)	1567 (24.4)	1990 (50.9)	3155 (48.0)	22,977 (45.4)	43,344 (42.2)	22,773 (43.3)	43,673 (40.4)
Hospitalised ^d	617 (18.4)	788 (12.3)	799 (20.4)	972 (14.8)	2865 (5.7)	3506 (3.4)	2143 (4.1)	2731 (2.5)
Severe disease ^e	242 (7.2)	363 (5.7)	244 (6.2)	282 (4.3)	555 (1.1)	642 (0.6)	318 (0.6)	396 (0.4)
Death	83 (2.5)	139 (2.2)	70 (1.8)	95 (1.4)	71 (0.1)	95 (0.1)	20 (0.0)	35 (0.0)

^a Among cases of ischaemic heart disease (n=110,422), 10,041 (9.09%) had a concurrent diagnosis of heart failure.
^b Housing type was used as an indicator of socioeconomic status.
^c SARS-CoV-2 infection was defined as positive test result (polymerase chain reaction [PCR] test or rapid antigen testing [RAT]) recorded in the national COVID-19 registry
^d COVID-19 hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive COVID-19 result (PCR/RAT).
^e Severe disease was defined as COVID-19 infection with resulting need for supplemental oxygen, intensive care admission or death.

Table 3. Risk of Omicron SARS-CoV-2 infection, COVID-19 related-hospitalisation and severe disease by vaccination status, among heart failure/ischemic heart disease cases and matched controls.

No. of mRNA vaccine doses ^c	SARS-CoV-2 infection, aHR (95% CI) ^a		COVID-19 hospitalisation, aHR (95% CI) ^{a,b}		Severe COVID-19 disease, aHR (95% CI) ^{a,b}	
	Heart failure	Controls	Heart failure	Controls	Heart failure	Controls
Unvaccinated/partially vaccinated	0.81 (0.71–0.94)	0.54 (0.49–0.59)	0.98 (0.82–1.18)	0.90 (0.78–1.04)	1.18 (0.88–1.58)	1.51 (1.17–1.96)
Fully vaccinated, not boosted	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Boosted	0.81 (0.75–0.87)	0.89 (0.85–0.94)	0.42 (0.37–0.48)	0.31 (0.28–0.35)	0.35 (0.28–0.43)	0.25 (0.20–0.31)
Double boosted (≥4 doses)	0.79 (0.71–0.88)	0.92 (0.86–0.99)	0.28 (0.23–0.34)	0.18 (0.16–0.22)	0.19 (0.13, 0.27)	0.15 (0.10, 0.21)
No. of mRNA vaccine doses ^c	Ischaemic heart disease	Controls	Ischaemic heart disease	Controls	Ischaemic heart disease	Controls
Unvaccinated/partially vaccinated	0.57 (0.52–0.62)	0.51 (0.48, 0.54)	0.92 (0.81, 1.04)	0.85 (0.78, 0.93)	1.07 (0.85, 1.35)	1.23 (1.04–1.44)
Fully vaccinated, not boosted	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Boosted	0.91 (0.87–0.95)	0.98 (0.95–1.00)	0.37 (0.34–0.40)	0.34 (0.32–0.36)	0.27 (0.23–0.32)	0.25 (0.22–0.28)
Double boosted (≥4 doses)	0.91 (0.87–0.96)	0.98 (0.95–1.01)	0.23 (0.20–0.25)	0.19 (0.18–0.21)	0.15 (0.12–0.19)	0.14 (0.12–0.17)

aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable

^a Calendar-time scale cox regression, controlling for age, sex, ethnicity, socioeconomic status (housing type), comorbidities, vaccination status.

^b Restricted to infected individuals only.

^c Individuals who received 0 mRNA vaccine dose were considered unvaccinated; individuals who received 1 mRNA vaccine dose only were considered partially vaccinated; full vaccination was defined as having completed a primary 2-dose vaccine series (either BNT162b2 or mRNA-1273, at least 8 weeks apart). Fully-vaccinated individuals who received additional mRNA vaccine doses at least 6 to 9 months after the second dose were considered boosted. Unvaccinated and partially vaccinated individuals were consolidated in the same category due to the small number of unvaccinated/partially vaccinated cases in our population.

Table 4. Comparing risk of SARS-CoV-2 infection and COVID-19-related hospitalisation and severe disease between individuals with heart failure/ ischaemic heart disease and matched controls who were infected during Omicron-predominant transmission.

Heart failure cases versus matched population controls (period of transmission)	SARS-CoV-2 infection, aHR (95% CI) ^a	COVID-19 hospitalisation, aHR (95% CI) ^{a,b}	Severe COVID-19 disease, aHR (95% CI) ^{a,b}
Population controls (reference category)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Heart failure cases (entire Omicron period) ^c	1.05 (1.01–1.08)	1.77 (1.65–1.90)	2.40 (2.10–2.75)
Heart failure cases (pre-Omicron XBB transmission) ^d	1.02 (0.98–1.06)	1.92 (1.76, 2.09)	2.56 (2.18, 2.99)
Heart failure cases (Omicron XBB transmission) ^d	1.14 (1.06–1.22)	1.58 (1.40–1.80)	2.17 (1.66–2.85)
Ischaemic heart disease cases versus matched population controls (period of transmission)	SARS-CoV-2 infection, aHR (95% CI) ^a	COVID-19 hospitalisation, aHR (95% CI) ^{a,b}	Severe COVID-19 disease, aHR (95% CI) ^{a,b}
Population controls (reference category)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Ischaemic heart disease cases (entire Omicron period) ^c	1.10 (1.09–1.12)	1.21 (1.17–1.26)	1.12 (1.03–1.21)
Ischaemic heart disease cases (pre-Omicron XBB transmission) ^d	1.09 (1.08–1.10)	1.24 (1.19–1.30)	1.14 (1.03–1.25)
Ischaemic heart disease cases (Omicron XBB transmission) ^d	1.15 (1.12–1.18)	1.15 (1.08–1.22)	0.98 (0.84–1.14)

aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable

^a Calendar-time scale cox regression, controlling for age, sex, ethnicity, socioeconomic status (housing type), comorbidities and vaccination status.^b Restricted to infected individuals only.^c Entire Omicron period refers to Omicron-predominant transmission period.^d 18 September 2022 was used as the cut-off date to further separate the Omicron period into XBB-predominant and pre-XBB (Omicron BA.1/2/3/4) transmission.

unequivocally attenuated risks of adverse COVID-19 outcomes in HF/IHD cases during the Omicron wave.

Elevated risk of infection, hospitalisation and severe COVID-19 among adults with HF/IHD compared to matched population controls was still observed during Omicron predominance, even though the Omicron variant was associated with relatively milder symptoms and lower risk of respiratory complications.^{9,10} Adverse COVID-19 outcomes in acute infection may arise not just from respiratory complications, but also cardiac damage sustained during viral infection of cardiomyocytes, which differentially express angiotensin-converting enzyme 2 required for SARS-CoV-2 viral entry. In an in-vitro study evaluating differential response of engineered human cardiac tissues to Delta and Omicron variants, Omicron pseudoviruses were still able to efficiently infect cardiomyocytes in a tissue-engineered cardiac muscle bundle model.²² Up to one-third of older adults infected with Omicron sustained concurrent myocardial injury (elevated troponin); myocardial injury was associated with higher risk of requiring intensive care.²³ Elevated risk of adverse COVID-19 outcomes in HF/IHD patients infected with Omicron is of concern, given that increased transmissibility of the Omicron variant results in a much greater number of infected individuals. Elevated risk of COVID-19

hospitalisation persisted even into XBB-predominant transmission, compared with other Omicron subvariants in historical circulation. In a population-based study of adults who tested positive for SARS-CoV-2 over successive pandemic phases, pre-existing cardiovascular conditions remained a significant predictor for adverse COVID-19 outcomes even during Omicron transmission, with HF being the most significant predictor for progression to severe COVID-19.²⁴

Our findings highlight the continued benefit of COVID-19 vaccination for patients with HF/IHD in the current era of COVID-19 endemicity and Omicron-predominant transmission. The majority of studies that documented adverse COVID-19 outcomes in patients with HF/IHD were conducted in the early pre-Omicron stages of the pandemic, prior to vaccination rollout.^{1–6} Improved outcomes for COVID-19 patients with elevated troponin and myocardial injury during Omicron was ascribed to the protective effect of vaccination, not available in earlier pandemic waves.²⁵ A single population-based cohort of adults in the Czech Republic with HF who were infected during Omicron-predominant transmission reported vaccine effectiveness estimates against severe COVID-19 of 41.9% in the fully vaccinated group and 76.6% in those who had received a single booster.¹¹ However,

generalisability was significantly limited by restriction to PCR-confirmed cases of SARS-CoV-2 infection, which may have introduced bias as milder RAT-confirmed infections may not have been recorded. Indeed, the reported infection rate (approx. 5%) in the Czech study was surprisingly low.¹¹ Significantly lower HRs against hospitalisation and severe disease in the 4-dose group compared with the 3-dose group suggests that regular boosting is beneficial for additional protection in individuals with HF/IHD. Hospitalisation for HF/IHD in the preceding year was associated with higher risk of COVID-19-related hospitalisation attributed to the Omicron variant, suggesting that individuals with recurrent admissions remain at-risk and should be prioritised for vaccination/boosting. However, vaccine hesitancy remains an issue in this at-risk population,²⁶ despite multiple studies unequivocally demonstrating the safety of mRNA COVID-19 vaccines for patients with HF/IHD.^{27–29} For instance, in a Danish cohort of HF patients matched to population-based controls, receipt of an mRNA COVID-19 vaccine was not associated with an increased risk of worsening heart failure, myocarditis, venous thromboembolism or all-cause mortality.²⁷ Similarly, in a population-based cohort of 32,490 adults in Hong Kong with HF, analysis using a self-controlled case series design did not demonstrate risk of hospitalisation for HF, major adverse cardiovascular events or all-cause hospitalisation after receiving the BNT162b2 mRNA vaccine.²⁸ COVID-19 vaccination in HF patients was associated with significant subsequent reduction in all-cause hospitalisation and mortality rates.²⁹ In our Singapore population, no increased risk of cardiovascular events was observed up to 180 days after any mRNA vaccination dose administered in the Omicron era,³⁰ and myocarditis cases reported post-COVID-19 vaccination were rare and clinically mild.³¹ Continued prioritisation of patients with HF/IHD for booster doses is crucial during COVID-19 endemicity. Such individuals at increased risk of severe COVID-19 should receive updated vaccine doses at an interval of around 1 year from the last vaccine dose,³² given that updated booster doses have been shown to decrease risk of severe COVID-19 in the acute phase of illness,²⁰ as well as long-term risk of cardiovascular complications (eg. thrombosis),³³ compared to ancestral vaccine doses.

Our study has the following strengths: usage of a comprehensive nationwide vaccination and testing database (PCR/RAT) during a period when diagnostic tests were widely available, subsidised and strongly encouraged, resulting in minimal misclassification bias for SARS-CoV-2 infection/vaccination status. National healthcare claims data were used to comprehensively

identify patients with HF/IHD. However, our study also has the following limitations. Unmeasured confounders could still have influenced estimates; in particular, several important comorbidities (e.g. smoking history) were not adjusted for, as this information was unavailable in the national electronic health records. Corroborative test data (e.g. echocardiography) was not available in the national electronic health record, hence we were unable to further stratify HF patients into groups with preserved or reduced ejection fraction for further comparison. This analysis was focused on outcomes of COVID-19 in the acute phase; post-acute long-term cardiovascular sequelae following SARS-CoV-2 infection was not evaluated, although increased long-term risk of dysrhythmias has been observed after Omicron infection in the general adult Singaporean population.^{34,35} Finally, our results may not be immediately generalisable to other populations with differing uptake of COVID-19 boosters/vaccination doses.

CONCLUSION

Persistently elevated risk of COVID-19-related hospitalisation was observed among patients with HF/IHD compared with matched population controls, during successive Omicron waves, including Omicron XBB. Boosting attenuated risk of serious COVID-19 outcomes, with lower risk of hospitalisation and severe disease in the double-boosted group compared to those who only received a single booster. Patients with HF/IHD would benefit from continued enrolment in vaccination programmes during the Omicron era.

Supplementary materials

Supplementary Table S1. Vaccination rates in patients with ischaemic heart disease/heart failure compared to controls and the general adult population.

Supplementary Table S2. Incidence rate of COVID-19 infection, hospitalisation and severe disease, by unvaccinated or partially vaccinated, fully vaccinated, and boosted subgroups.

Supplementary Table S3. Incidence rate of COVID-19 infection, hospitalisation and severe disease, by unvaccinated or partially vaccinated, fully vaccinated, and boosted subgroups.

Ethics statement

Not applicable.

Declaration

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Data sharing

The databases with individual-level information used for this study are not publicly available due to personal data protection. De-identified data can be made available for research, subject to approval by the Ministry of Health, Singapore. All inquiries should be sent to the corresponding author.

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