Safety of BNT162b2 or CoronaVac COVID-19 vaccines in patients with heart failure: A self-controlled case series study

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Summary

Background COVID-19 vaccines are important for patients with heart failure (HF) to prevent severe outcomes but the safety concerns could lead to vaccine hesitancy. This study aimed to investigate the safety of two COVID-19 vaccines, BNT162b2 and CoronaVac, in patients with HF.

Methods We conducted a self-controlled case series analysis using the data from the Hong Kong Hospital Authority and the Department of Health. The primary outcome was hospitalization for HF and the secondary outcomes were major adverse cardiovascular events (MACE) and all hospitalization. We identified patients with a history of HF before February 23, 2021 and developed the outcome event between February 23, 2021 and March 31, 2022 in Hong Kong. Incidence rate ratios (IRR) were estimated using conditional Poisson regression to evaluate the risks following the first three doses of BNT162b2 or CoronaVac.

Findings We identified 32,490 patients with HF, of which 3035 were vaccinated and had a hospitalization for HF during the observation period (BNT162b2 = 755; CoronaVac = 2280). There were no increased risks during the 0–13 days (IRR 0.64 [95% confidence interval 0.33–1.26]; 0.94 [0.50–1.78]; 0.82 [0.17–3.98]) and 14–27 days (0.73 [0.35–1.52]; 0.95 [0.49–1.84]; 0.60 [0.06–5.76]) after the first, second and third doses of BNT162b2. No increased risks were observed for CoronaVac during the 0–13 days (IRR 0.60 [0.41–0.88]; 0.71 [0.45–1.12]; 1.64 [0.40–6.77]) and 14–27 days (0.91 [0.63–1.32]; 0.79 [0.46–1.35]; 1.71 [0.44–6.62]) after the first, second and third doses. We also found no increased risk of MACE or all hospitalization after vaccination.

Interpretation Our results showed no increased risk of hospitalization for HF, MACE or all hospitalization after receiving BNT162b2 or CoronaVac vaccines in patients with HF.

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Research in context

Evidence before this study

We searched Pubmed and Embase on July 15, 2022, for articles published in English using the combination of search terms between vaccine types ("BNT162b2", "Comirnaty", "CoronaVac", "Sinovac") and outcomes of interest ("heart failure", "hospitalization"). No analytical study that focused on patients with heart failure (HF) was found. Two case reports of patients who developed HF after receiving BNT162b2 were found. Limited published articles explored the safety effects after receiving CoronaVac.

Added value of this study

This is the first population-based study in Hong Kong to investigate the safety of BNT162b2 and CoronaVac COVID-19 vaccines in patients with HF. We looked at hospitalization for HF, major adverse cardiovascular events and all hospitalization to provide a comprehensive analysis of the safety of these two vaccines. The modified self-controlled case series analysis showed no increased risk of these three outcomes after vaccination in patients with HF.

Implications of all the available evidence

Our results showed no evidence of increased risk of hospitalization for HF, major adverse cardiovascular events or all hospitalization after each dose of BNT162b2 or CoronaVac vaccination in patients with HF. The findings provide the safety profiles of COVID-19 vaccines for patients with HF and highlight the importance of vaccination to prevent potential severe outcomes if infected.

Introduction

Patients with pre-existing heart failure (HF) have a higher risk of complications and mortality if infected with coronavirus disease 2019 (COVID-19).[1–5] Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have highlighted the importance of COVID-19 vaccination in patients with HF to prevent severe outcomes.[1,6] In Hong Kong, the vaccination program began on February 23, 2021, with two authorized COVID-19 vaccines, BNT162b2 (Comirnaty) and CoronaVac (Sinovac). Although these vaccines have demonstrated efficacy against infection and severe outcomes with safety and tolerability profiles in clinical trials,[7,8] existing data were mainly from the general population and evidence of vaccine safety in patients with HF is limited.

It was reported that around 30% of hospitalized patients with HF had post-discharge readmission within 60–90 days post-discharge.[9] Studies also found that recurrent HF was associated with a higher risk of cardiovascular complications such as the major adverse cardiovascular events (MACE).[10–12] Based on current evidence, some patients who developed carditis after receiving mRNA-based COVID-19 vaccination experienced severe HF.[13] Although it is important for patients with HF to receive COVID-19 vaccines, the potential risks of hospitalization and cardiovascular complications including carditis can lead to vaccine hesitancy. In clinical practice, vaccine hesitancy generated from fear and uncertainty about the safety of COVID-19 vaccines can cause low vaccination rates and increase the risk of infection and severe illness, especially for patients with a disease history.[14] To date, no study has comprehensively evaluated the safety of BNT162b2 or CoronaVac COVID-19 vaccines in patients with HF. Therefore, we aimed to assess the risk of hospitalization for HF, MACE and all hospitalization after each dose of COVID-19 vaccination and provide insight into the safety profile of COVID-19 vaccines in patients with HF, utilizing the self-controlled case series (SCCS) study design.

Method

Data sources

This study was conducted by linking the electronic health records in the clinical management system from the Hong Kong Hospital Authority (HA) and vaccination records provided by the Department of Health (DH) of the government of Hong Kong Special Administrative Region. The HA serves as a statutory administrative body in Hong Kong and provides services to over 7.4 million Hong Kong residents, managing 43 public hospitals, 49 specialist outpatient clinics and 73 primary care clinics, and covering around 80% of all hospital admissions.[15] Individual patient-specific data include patients' demographic information, diagnoses, medication, laboratory tests, hospital admissions and discharges and emergency department admission records. Each patient has a unique identifier derived from their Hong Kong Identity Card Number in the clinical management system, which links up with all public hospitals, ambulatory clinics, specialist clinics, general

outpatient clinics and emergency rooms in the HA. The DH provided COVID-19 vaccination records of BNT162b2 and CoronaVac vaccines from February 23, 2021, when the mass COVID-19 vaccination program in Hong Kong was launched, until March 31, 2022. Individuals are not permitted to switch between vaccine types for the first two doses but can choose to switch vaccine types for the third dose. All the data are anonymized to protect patient confidentiality by using a unique identifier for each patient. These data have been used for prior COVID-19 vaccine safety studies.[16–19]

Patient identification

We identified all patients who had a diagnosis of HF from January 1, 2018 to February 22, 2021. HF was defined using the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM) codes of 428. Patients were followed up from February 23, 2021 until March 31, 2022 or the date of death, whichever was earlier. Those who had a hospitalization for HF as their primary inpatient diagnosis within the observation period were included in our primary SCCS analysis. Primary inpatient diagnosis means that HF is the primary medical diagnosis responsible for the patient's admission to hospitalization. Patients who developed MACE or patients who had a hospitalization for any reason were included in our secondary analyses, separately. Patients who had a heterogeneous vaccine type for their third dose were excluded.

Exposure and outcome

The exposure periods were defined as 0–13 and 14–27 days after the first three doses of vaccination with the vaccination date considered as day 0. As the interval between the first two doses might be less than 27 days, the exposure period was defined as day 14 to the day before the second dose in this case. The baseline non-exposure periods were defined as all other periods including before vaccination of the first dose, after the first dose plus 27 days and before the second dose, after the second dose plus 27 days and before the third dose, and after the third dose plus 27 days until March 31, 2022 or the date of death. The primary outcome was defined as the first admission of hospitalization for HF between February 23, 2021 and March 31, 2022. We also had two secondary outcomes as MACE and all hospitalization. MACE was defined as myocardial infarction (MI), stroke, carditis or cardiovascular death using ICD-9-CM codes (eTable S1). All hospitalization was defined as the inpatient admission for any reason during the observation period.

Study design

We conducted a population-based study using SCCS to evaluate the safety of BNT162b2 or CoronaVac regarding the potential risk of hospitalization for HF, MACE and all hospitalization after vaccination in patients with a history of HF during the ongoing COVID-19 vaccination program in Hong Kong. The SCCS is a within-individual study design that was developed to assess vaccine-related outcomes[20] and has been widely used for vaccine safety monitoring.[21–24] In SCCS analysis, an individual's observation period is fixed and follow-up is not censored at the event; hence all exposures occurring within the observation period, both before and after individuals have experienced the event, are included in the analysis.[20] The SCCS determines the relative incidence of the outcome by comparing the risks of outcome events between exposure and non-exposure baseline periods within the same individual (Fig. 1). Since each patient serves as their own control, this study design can inherently minimize all time-invariant confounding effects and other time-varying covariates can be manually adjusted.[20]

Three assumptions were required to be fulfilled to ensure the appropriate use of SCCS.[20] Firstly, the event should be independently recurrent such that each occurrence does not affect subsequent events. As the outcome events are likely to reoccur and thus increase the probability of future episodes, only the first event within the observation period was treated as the outcome of interest. Secondly, the occurrence of an event should not affect subsequent exposures. Patients who had the outcome events just before their vaccination appointments might be less likely to receive the vaccines. In this case, this assumption could be violated when applying the standard SCCS model, especially for the second and third dose vaccination. Histograms of the interval between vaccination and hospitalization for HF, for each dose, are shown in eFigure S1. It should be noticed that there is a dip in the number of events occurring just before each dose. This is because individuals who have had a hospitalization for HF are likely to delay vaccination until they have recovered sufficiently, and may even subsequently avoid vaccination completely, which is the situation of event-dependent exposure. Therefore, we applied a modified SCCS model, which was designed for investigating outcomes that can affect subsequent exposures.[25] The modified SCCS model included unvaccinated patients who developed the outcome events during the observation period to adjust the probability of receiving vaccination after the occurrence of the events. It is important to be aware that unvaccinated patients did not act as controls and inclusion of the unvaccinated group in the modified SCCS is essential as the lack of vaccination records may indicate cancellation of vaccination appointments and may tend to occur more often for earlier events (before they had the opportunity to be vaccinated). Thus, the absence of vaccination can be informative regarding the timing of the event. A comprehensive discussion on the use of modified SCCS for COVID-19 vaccine research can be found in a

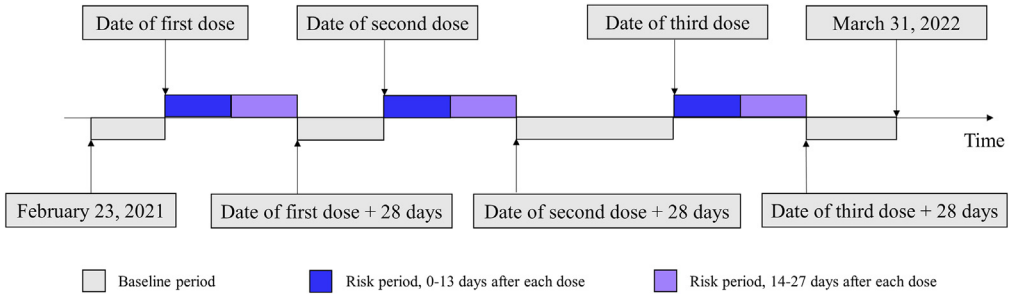

Fig. 1: Visualization of the self-controlled case series observation period (February 23, 2021 to March 31, 2022), baseline and risk periods following COVID-19 vaccination. The unvaccinated who had the outcome event during the observation period were also included to adjust seasonality and the probability of receiving vaccination after the event.

recent publication that highlights the important consideration of addressing event-dependent exposures.[25] The modified SCCS has been used in several high-quality studies on the association between COVID-19 vaccines and a series of outcomes.[21–25] Due to similar considerations, the use of modified SCCS and the inclusion of unvaccinated individuals are more appropriate for addressing our study objectives. Lastly, the occurrence of an event should not affect the subsequent period of observation. The modified SCCS was also proved to be valid when the outcome events can increase the risk of short-term mortality.[25] To test the robustness of our study design, we also conducted a sensitivity analysis by excluding patients who died during the observation period to avoid any potential violation of this assumption. In the within-individual design, only those patients who experienced an event are informative and the analyses were therefore based only on such patients.[20]

Statistical analysis

The R function "eventdepenexp" in the R-package "SCCS" was used to perform the modified SCCS for event-dependent exposure.[25] Conditional Poisson regression was used to estimate the incidence rate ratio (IRR) and its corresponding 95% confidence intervals (CI) by comparing the incidence rates of HF hospitalization in different exposure periods with the baseline non-exposure period. We adjusted the seasonal effect in monthly categories by modeling a piecewise constant with each month set as cut points.[20] All analyses were stratified by the type of vaccines, BNT162b2 and CoronaVac. We further conducted subgroup analyses to stratify individuals by sex and age groups for the primary outcome.

To evaluate the robustness of our results, three sensitivity analyses were conducted. First, we excluded patients who died during the observation period to test the assumption that the occurrence of an event should not affect the subsequent period of observation. Second, we excluded those who were diagnosed with COVID-19 before or during the observation period since COVID-19 can also increase the risk of HF.[26] Third, we excluded those who were hospitalized within three weeks before the observation period to ensure hospitalization for HF within the observation period was not the same episode as the hospitalization before the observation period. Fourth, we separated day 0 from the exposure periods after each dose. Fifth, to ensure that the inclusion of only the first event did not generate additional bias, we conducted a sensitivity analysis to include all recurrent events and modeled a parameter of dependence to analyze recurrences. Sixth, we defined the exposure periods as 28 or 21 days after each dose. All statistical tests were two sided and p values of less than 0.05 were considered significant in all statistical tests. Statistical analysis was conducted using R version 4.0.3 (http://www.R-project.org), by at least two investigators (X.Y. and C.H.) independently for quality assurance. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists were followed to guide transparent reporting of the analyses.

Ethical approval

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW21-149) and by the Department of Health Ethics Committee (LM21/2021). All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed written consent has been waived by the ethics committees as this is an observational study using de-identified electronic health records. This study does not contain any studies with animals performed by any of the authors.

Role of the funding source

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No.COVID19F01). F.T.T.L. (Francisco T.T. Lai) and I.C.K.W. (Ian C.K. Wong)'s posts were partly funded by the D24H; hence this work was partly supported by AIR@InnoHK administered by Innovation and Technology Commission. The study's sponsor was involved in the framework of study designs and data collection via the Department of Health. The corresponding author had full access to all data in the study and took final responsibility for the decision to submit for publication.

Results

A total of 32,490 patients with HF from January 1, 2018 to February 22, 2021 were identified. For the primary outcome, hospitalization for HF occurred in 8255 patients during the observation period. There were six patients who received BNT162b2 for the first and second doses but later received CoronaVac for the third dose, and 48 patients who received CoronaVac for the first and second doses but received BNT162b2 for the third dose, and these patients were excluded per-protocol (Fig. 2). We hence included 755 (9.2%) patients in the BNT162b2 group (mean age 75.0 years [SD 13.6], 60.1% male), 2280 (27.8%) in the CoronaVac group (mean age 81.0 years [SD 11.8], 46.4% male) and 5166 (63.0%) unvaccinated (mean age 84.2 years [SD 11.2], 43.8% male) for the SCCS study. Table 1 reported the patients' demographics, baseline comorbidities and medication history. The exact ICD-9-CM codes used in this study are shown in Supplementary eTable S1. The British National Formulary (BNF) used for identifying the drug history is shown in Supplementary eTable S2. In each vaccination group with hospitalization for HF during the observation period, 33 (4.3%) patients died in the BNT162b2 group (4 cardiovascular deaths, 3 other causes and 26 not recorded) and 169 (7.4%) patients died in the CoronaVac group (16 cardiovascular deaths, 21 other causes and 132 not recorded). There were 69 (9.1%) patients in the BNT162b2 group and 339 (14.9%) patients in the CoronaVac group who had a positive test for SARS-CoV-2 before or during the observation period. Three patients had a record of heart transplantation with one patient vaccinated with two doses of CoronaVac and two patients vaccinated with one dose of BNT162b2. None of them developed the outcome during the exposure periods or died during the observation period. The vaccine utilization uptake stratified by type of vaccine is shown in eFigure S2.

Primary analyses

Table 2 shows the risk of hospitalization for HF following the COVID-19 vaccination. In total, 52 patients in the BNT162b2 group and 166 in the

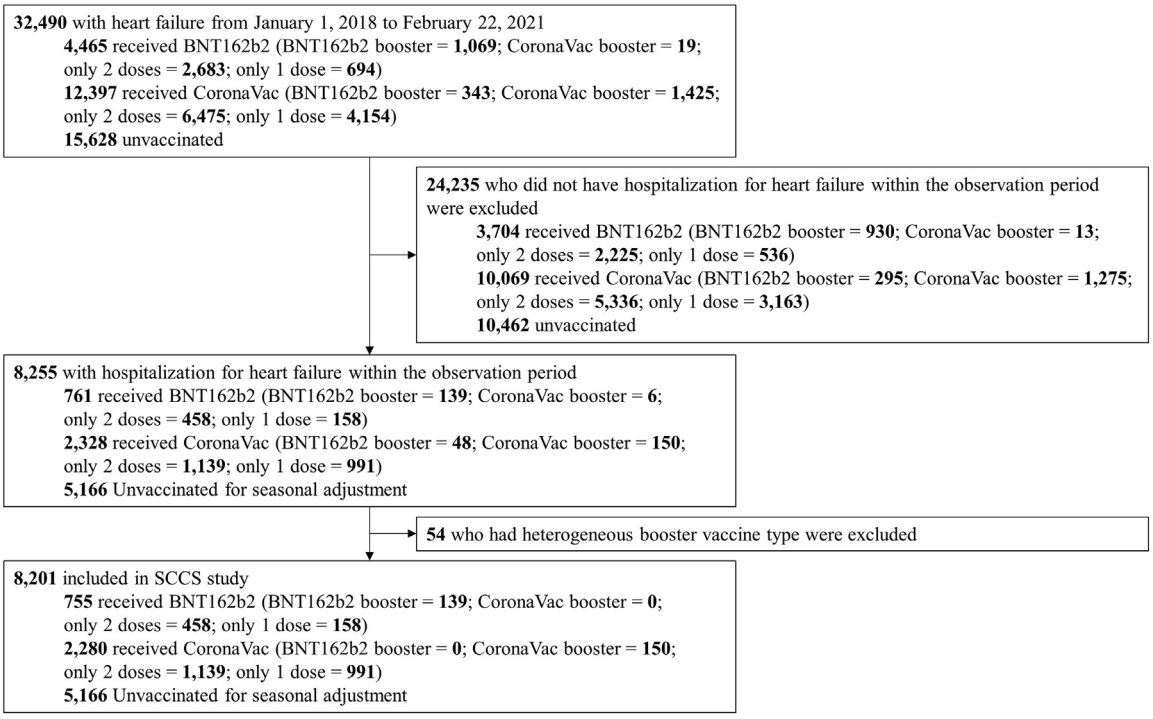

Fig. 2: Flowchart illustrating patient inclusion and reasons for exclusion in the primary analysis.

	BNT162b2	CoronaVac	Unvaccinated[a]
Number of patients	755	2280	5166
Age, years (mean (SD))	75.0 (13.6)	81.0 (11.8)	84.2 (11.2)
Sex, male (%)	454 (60.1)	1058 (46.4)	2265 (43.8)
Disease history			
Hypertension (%)	403 (53.4)	1388 (60.9)	3219 (62.3)
Diabetes (%)	261 (34.6)	797 (35.0)	1846 (35.7)
Ischemic stroke (%)	24 (3.2)	113 (5.0)	350 (6.8)
Transient ischemic attack (%)	11 (1.5)	29 (1.3)	58 (1.1)
Systemic embolism (%)	2 (0.3)	3 (0.1)	13 (0.3)
Vascular disease (%)	287 (38.0)	764 (33.5)	1892 (36.6)
Myocardial infarction (%)	94 (12.5)	247 (10.8)	732 (14.2)
Peripheral vascular disease (%)	26 (3.4)	50 (2.2)	183 (3.5)
Cerebrovascular disease (%)	95 (12.6)	357 (15.7)	1021 (19.8)
Chronic obstructive pulmonary disease (%)	105 (13.9)	345 (15.1)	946 (18.3)
Dementia (%)	7 (0.9)	62 (2.7)	181 (3.5)
Paralysis (%)	4 (0.5)	14 (0.6)	44 (0.9)
renal failure (%)	99 (13.1)	300 (13.2)	1000 (19.4)
liver disease (%)	7 (0.9)	21 (0.9)	97 (1.9)
Neoplasms (%)	30 (4.0)	76 (3.3)	255 (4.9)
Smoking history (%)	14 (1.9)	29 (1.3)	60 (1.2)
Medication use in the past year			
Renin-angiotensin-system agents (%)	580 (76.8)	1763 (77.3)	3722 (72.0)
Beta blockers (%)	492 (65.2)	1374 (60.3)	2919 (56.5)
Calcium channel blockers (%)	334 (44.2)	1157 (50.7)	2596 (50.3)
Diuretics (%)	632 (83.7)	1885 (82.7)	4418 (85.5)
Nitrates (%)	231 (30.6)	745 (32.7)	1900 (36.8)
Lipid lowering agents (%)	513 (67.9)	1475 (64.7)	3089 (59.8)
Insulins (%)	127 (16.8)	350 (15.4)	977 (18.9)
Antidiabetic drugs (%)	286 (37.9)	744 (32.6)	1539 (29.8)
Antiarrthymic drugs (%)	44 (5.8)	137 (6.0)	354 (6.9)
Oral anticoagulants (%)	296 (39.2)	840 (36.8)	1761 (34.1)
Antiplatelets (%)	360 (47.7)	1067 (46.8)	2535 (49.1)
Glucocorticoids (%)	82 (10.9)	185 (8.1)	636 (12.3)
Antidepressants (%)	66 (8.7)	203 (8.9)	457 (8.8)
Non-steroidal anti-inflammatory drugs (%)	35 (4.6)	84 (3.7)	133 (2.6)
Antiviral drugs (%)	22 (2.9)	50 (2.2)	136 (2.6)
Antibacterial drugs (%)	328 (43.4)	966 (42.4)	2711 (52.5)
Immunosuppressants (%)	8 (1.1)	14 (0.6)	38 (0.7)

[a]The unvaccinated individuals did not act as controls but were included for adjustment of seasonality and probability of receiving vaccination after the event, which is required by the modified SCCS methodology.

Table 1: **Baseline characteristics of patients in the self-controlled case series analysis.**

CoronaVac group had a hospitalization for HF within 27 days after the most recent dose of vaccination. The event-dependent SCCS model detected no evidence of an increased risk of hospitalization for HF during the 27 days after each dose of BNT162b2 or CoronaVac. There were no increased risks during the 0–13 days (IRR 0.64 [95% confidence interval 0.33–1.26]; 0.94 [0.50–1.78]; 0.82 [0.17–3.98]) and 14–27 days (0.73 [0.35–1.52]; 0.95 [0.49–1.84]; 0.60 [0.06–5.76]) after the first, second and third doses of BNT162b2. No increased risks were observed for CoronaVac during the 0–13 days (IRR 0.60 [0.41–0.88]; 0.71 [0.45–1.12]; 1.64 [0.40–6.77]) and 14–27 days (0.91 [0.63–1.32]; 0.79 [0.46–1.35]; 1.71 [0.44–6.62]) after the first, second and third doses. As the mean age of our included patients was around 80 years, we conducted subgroup analyses by looking at patients 80 years or older and patients under 80 years. The age and sex subgroup analyses showed no increased risk of hospitalization for HF after each dose of the COVID-19 vaccines (Supplementary eTable S3). The sensitivity analyses found similar results as the main analyses when we excluded patients who died during the observation period (Supplementary eTable S4), when we excluded those who were diagnosed with COVID-19 before or during the observation period (Supplementary eTable S5), when we excluded those

	Number of events	Patient-days	Crude incidence (per 1000 patient-days)	Incidence rate ratio (95% CI)	P value
BNT162b2 (n = 755) + unvaccinated (n = 5166)[a]					
Baseline	5869	1854311	3.2		
First dose					
0–13 days after	14	10369	1.4	0.64 (0.33–1.26)	0.20
14–27 days after	10	6391	1.6	0.73 (0.35–1.52)	0.40
Second dose					
0–13 days after	14	7815	1.8	0.94 (0.50–1.78)	0.85
14–27 days after	10	6509	1.5	0.95 (0.49–1.84)	0.88
Third dose					
0–13 days after	3	1715	1.7	0.82 (0.17–3.98)	0.81
14–27 days after	1	1164	0.9	0.60 (0.06–5.76)	0.66
CoronaVac (n = 2280) + unvaccinated (n = 5166)[a]					
Baseline	7280	2406616	3.0		
First dose					
0–13 days after	49	30870	1.6	0.60 (0.41–0.88)	0.0079
14–27 days after	62	27196	2.3	0.91 (0.63–1.32)	0.63
Second dose					
0–13 days after	30	15750	1.9	0.71 (0.45–1.12)	0.14
14–27 days after	19	11308	1.7	0.79 (0.46–1.35)	0.39
Third dose					
0–13 days after	3	1847	1.6	1.64 (0.40–6.77)	0.49
14–27 days after	3	1247	2.4	1.71 (0.44–6.62)	0.44

CI = confidence interval. [a]The unvaccinated individuals did not act as controls but were included for adjustment of seasonality and probability of receiving vaccination after the event, which is required by the modified SCCS methodology.

Table 2: **Results of self-controlled case series analysis on hospitalization for heart failure.**

who were hospitalized within three weeks before the observation period (Supplementary eTable S6) and when we separated day 0 from the exposure periods after each dose (Supplementary eTable S7). When we modeled a parameter of dependence to analyze recurrences, the results of patients with or without recurrent events both showed no increased risk of hospitalization for HF (Supplementary eTable S8). When we defined the exposure periods as 28 or 21 days after each dose, the results were also consistent with the main analysis (Supplementary eTables S9 and S10).

Secondary analyses

For the secondary outcomes, we identified 86 carditis, 1002 MI, 603 stroke and 1138 cardiovascular death in patients with HF during the observation period. There were 116 patients who received BNT162b2 and 18 experienced MACE 0–27 days after vaccination. For 325 patients who received CoronaVac, 47 experienced MACE 0–27 days after vaccination. Our results showed no increased risk of MACE after each dose of vaccination in patients with HF (Table 3). We also identified 19,475 cases of all hospitalization during the observation period in patients with HF, among whom 2231 received BNT162b2, 6266 received CoronaVac and 10,978 were unvaccinated. Table 3 showed no increased risk of all hospitalization in patients with HF after receiving each dose.

Discussion

Summary of results

In this study, we used hospitalization for HF as the primary outcome and MACE and all hospitalization as the secondary outcomes to fully assess the safety of BNT162b2, an mRNA vaccine or CoronaVac, an inactivated vaccine in patients with HF. We found no increased risk of hospitalization for HF as well as MACE and all hospitalization after receiving each dose of vaccination. Similar results were found in our subgroup analyses stratified by age and sex. Sensitivity analyses showed that the exclusion of patients who died during the observation period had little effect on our results. Excluding patients who were diagnosed with COVID-19 or patients who were hospitalized before the observation period also had consistent results as our primary analysis.

Comparison with other studies

Patients with HF were reported to have a high chance of rehospitalization.[9] In our data, among 32,490 patients with a history of HF, 19,475 had a record of

	Number of events	Patient-days	Crude incidence (per 1000 patient-days)	Incidence rate ratio (95% CI)	P value
Risk of major adverse cardiovascular events following COVID-19 vaccines					
BNT162b2 (n = 116) + unvaccinated (n = 2388)[a]					
Baseline	2486	557728	4.5		
First dose					
0–13 days after	3	1566	1.9	0.19 (0.05–0.72)	0.014
14–27 days after	5	1003	5	0.65 (0.19–2.20)	0.49
Second dose					
0–13 days after	6	1100	5.5	0.80 (0.26–2.48)	0.70
14–27 days after	4	984	4.1	1.00 (0.31–3.17)	0.99
Third dose					
0–13 days after	0	145	0	~	~
14–27 days after	0	79	0	~	~
CoronaVac (n = 325) + unvaccinated (n = 2388)[a]					
Baseline	2666	629360	4.2		
First dose					
0–13 days after	17	4317	3.9	0.10 (0.02–0.72)	0.021
14–27 days after	18	3658	4.9	0.23 (0.04–1.26)	0.090
Second dose					
0–13 days after	7	1963	3.6	0.10 (0.01–0.90)	0.040
14–27 days after	5	1552	3.2	0.17 (0.03–0.88)	0.034
Third dose					
0–13 days after	0	203	0	~	~
14–27 days after	0	171	0	~	~
Risk of all hospitalization following COVID-19 vaccines					
BNT162b2 (n = 2231) + unvaccinated (n = 10978)[a]					
Baseline	13064	4197513	3.1		
First dose					
0–13 days after	44	30532	1.4	0.81 (0.60–1.09)	0.16
14–27 days after	30	18769	1.6	0.93 (0.65–1.34)	0.70
Second dose					
0–13 days after	29	23652	1.2	0.70 (0.48–1.01)	0.059
14–27 days after	35	20290	1.7	0.98 (0.70–1.37)	0.90
Third dose					
0–13 days after	2	5624	0.4	0.24 (0.06–0.98)	0.046
14–27 days after	5	4186	1.2	0.82 (0.34–1.98)	0.66
CoronaVac (n = 6266) + unvaccinated (n = 10978)[a]					
Baseline	16846	5655635	3		
First dose					
0–13 days after	115	85141	1.4	0.84 (0.70–1.02)	0.073
14–27 days after	126	75847	1.7	1.02 (0.85–1.23)	0.81
Second dose					
0–13 days after	69	46402	1.5	0.90 (0.71–1.15)	0.42
14–27 days after	68	34411	2	1.15 (0.90–1.47)	0.26
Third dose					
0–13 days after	10	6930	1.4	0.99 (0.53–1.86)	0.98
14–27 days after	10	5050	2	1.36 (0.72–2.56)	0.34

[a]The unvaccinated individuals did not act as controls but were included for adjustment of seasonality and probability of receiving vaccination after the event, which is required by the modified SCCS methodology.

Table 3: **Results of self-controlled case series analysis on secondary outcomes.**

hospitalization during the observation period and 8255 were due to HF. However, when we compared the risk of hospitalization for HF or all hospitalization during the exposure periods and the non-exposure baseline periods, no increased risk was observed, suggesting that vaccination did not increase the risk of hospitalization

for HF or all hospitalization in patients with HF. It was reported that patients who developed myocarditis can experience severe HF after receiving mRNA vaccination.[13] Later studies showed that although patients who had myocarditis after vaccination can develop HF, myocarditis occurred mostly in young adults and adolescent males due to immune responses.[1,16,17,27–29] In our study of patients with HF where patients are generally old with a mean age over 80 years, we observed carditis including both myocarditis and pericarditis during the observation period in 86 patients with HF (10 received BNT162b2, 19 received Sinovac and 57 unvaccinated). No carditis occurred during the exposure periods after vaccination, suggesting the risk of carditis following vaccination among patients with a history of HF is very low. When we examined the risk of MACE as a composite outcome of MI, stroke, carditis and cardiovascular death after vaccination in patients with HF, no increased risk was observed. The results further support that the risk of MACE following BNT162b2 and CoronaVac COVID-19 vaccines in patients with HF is very low and are consistent with our earlier study of patients with coronary heart disease, cerebrovascular disease, peripheral vascular disease or cardiovascular surgery where no increased risk of MACE was detected after receiving BNT162b2 or CoronaVac.[24]

Clinical implications

In clinical practice, fear and uncertainty about the safety of COVID-19 vaccines can lead to vaccine hesitancy, causing low vaccination rates and increasing the risk of infection and severe illness, especially for patients with a disease history.[14] Our data showed that although 87.1% of the general population had received COVID-19 vaccines by March 31, 2022 in Hong Kong, only 16,862 (51.9%) had received the vaccines among 32,490 patients with a history of HF and 12,014 (37.0%) and 2856 (8.8%) had received two doses or third doses. Among the patients with HF who received the vaccination, the majority chose CoronaVac, an inactivated vaccine (12,397, 38.2%) rather than BNT162b2 from the mRNA platform (4,465, 13.7%). The low vaccination rate suggests vaccine hesitancy among patients with HF in Hong Kong. Despite evidence from clinical trials that focused mainly on healthy individuals,[7,8] specific vaccine safety data are needed for patients with a disease history. Patients with HF are at higher risk of complications and mortality if infected with COVID-19.[1–5] Based on current published evidence, vaccination is an important intervention to prevent severe outcomes.[6] Our results provided additional evidence of vaccine safety in patients with HF; hence the benefits of vaccination in this population must be emphasized to ease vaccine hesitancy in order to increase the vaccination rate. To the best of our knowledge, this is the first post-marketing study examining the safety of BNT162b2 and CoronaVac COVID-19 vaccines in patients with HF. This novel finding contributes to health professionals and the general public's understanding of the safety profiles of these two vaccines for patients with HF.

Strengths

The main strength of this study is the utilization of the SCCS study design. In vaccine surveillance studies, cohort and case–control studies are limited by confounding and residual healthy vaccine effects,[30] which means that healthier people are more willing to be vaccinated, and patients with disease history will be more cautious about vaccine safety and more hesitant to get vaccinated. The potential biases can only be overcome by utilizing a within-individual study design to compare the exposure periods versus other non-exposure baseline periods within the same individual to minimize the time-invariant confounding effects. The modified SCCS for event-dependent exposure can further adjust the probability of receiving vaccination after developing the outcome by including the unvaccinated patients.[25] The methodology was developed for event-dependent exposures and outcome events with a high risk of short-term mortality and had also been applied to many high-quality COVID-19 vaccine safety studies.[21–24] Other strengths include using a number of sensitivity analyses to test the robustness of our results, including the risk of hospitalization for HF, MACE and all hospitalization as the study outcomes, and having both BNT162b2, a mRNA vaccine and CoronaVac, an inactivated vaccine in our analyses.

Limitations

Despite the population-representativeness of data and important public health implications, this study has limitations. First, our dataset does not have ejection fraction recorded and we were unable to further stratify the analysis by the patients' ejection fraction, where future studies are needed to test vaccine safety in patients with reduced ejection fraction or preserved ejection fraction subgroups. Second, the majority of Hong Kong residents are of the Chinese population and therefore the generalizability of our results to other regions and ethnicities is limited. Third, although the data we used covers all public hospitalization records which are around 80% of the total number of hospital admissions in Hong Kong, we were unable to include data from private clinics and hospitals, where potential bias could exist. Fourth, our results of the 0–13 days risk period after the first dose of CoronaVac might indicate a healthy vaccine effect. However, as the study design is self-controlled and patients were compared with themselves, the healthy vaccine effect was unlikely to affect our results. Lastly,

patients who had HF before 1 January, 2018 were not included due to data availability.

Conclusions

In this SCCS study among patients with a history of HF in Hong Kong, we found no evidence of increased risk of hospitalization for HF, MACE or all hospitalization after each dose of BNT162b2 or CoronaVac vaccination. Our results provide the safety profiles of COVID-19 vaccines for patients with HF and highlight the importance of vaccination to prevent potential severe outcomes if infected.

Contributors

X.Y., K.Y., I.C.K.W., and E.W.C. designed the research; X.Y. and C.H. performed the research; X.Y., C.H. and V.K.C.Y., analyzed the data; Y.W., S.T.H.L., K.Y., H.T., T.M., X.Q., C.S.L.C., F.T.T.L., X.L., E.Y.F.W. and C.K.H.W. provided discussion and revision; I.C.K.W., and E.W.C. provided funding and supervision; X.Y. and C.H. prepared the manuscript with input from all co-authors.

Data sharing statement

Data will not be available for others as the data custodians have not given permission.

Declaration of interests

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Code availability

All the analysis codes support the findings are available from the corresponding author upon reasonable requests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100630.

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