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ORIGINAL INVESTIGATIONS

Prognosis of Myocarditis Developing After mRNA COVID-19 Vaccination Compared With Viral Myocarditis

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ABSTRACT

BACKGROUND Association between messenger RNA (mRNA) COVID-19 vaccines and myocarditis has aroused public concern over vaccine safety.

OBJECTIVES The goal of this study was to compare the prognosis of this condition with viral infection–related myocarditis over 180 days.

METHODS A territory-wide electronic public health care database in Hong Kong linked with population-based vaccination records was used to conduct a retrospective cohort study. Since the roll-out of BNT162b2 (Pfizer-BioNTech), patients aged ≥12 years hospitalized with myocarditis within 28 days after BNT162b2 vaccination were compared against viral infection–related myocarditis recorded before the pandemic (2000-2019), over a 180-day follow-up period (starting from diagnosis of myocarditis). All-cause mortality, heart failure, dilated cardiomyopathy, heart transplant, and postdischarge health care utilization were examined with Cox proportional hazards models.

RESULTS A total of 866 patients were included for analysis. Over the follow-up period, 1 death (1.0%) of 104 patients with postvaccination myocarditis and 84 deaths (11.0%) of 762 patients with viral infection–related myocarditis were identified. One case (1.0%) of dilated cardiomyopathy and 2 cases (1.9%) of heart failure were identified in the postvaccination group, compared with 28 (3.7%) and 93 (12.2%) in the viral infection–related myocarditis group, respectively. Adjusted analysis showed that the postvaccination myocarditis group had a 92% lower mortality risk (adjusted HR: 0.08; 95% CI: 0.01-0.57). No significant differences in other prognostic outcomes were seen.

CONCLUSIONS This study found a significantly lower rate of mortality among individuals with myocarditis after mRNA vaccination compared with those with viral infection–related myocarditis. Prognosis of this iatrogenic condition may be less severe than naturally acquired viral infection–related myocarditis. (J Am Coll Cardiol 2022;80:2255–2265)

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ABBREVIATIONS AND ACRONYMS

A&E = accident and emergency department

CDARS = clinical data analysis and reporting system

cMRI = cardiac magnetic resonance imaging

EHR = electronic health record

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

ICU = intensive care unit

mRNA = messenger ribonucleic acid

With accruing evidence showing an association of messenger RNA (mRNA) COVID-19 vaccines with myocarditis worldwide,[1-6] myocarditis is increasingly acknowledged as one of the rare potential adverse events that follow COVID-19 vaccination.[7] An Israeli retrospective cohort study of 0.9 million individuals found a 3-fold elevated risk of myocarditis associated with the use of BNT162b2, an mRNA vaccine developed by Pfizer and BioNTech.[1] Subsequent research studies from the United Kingdom,[5] Nordic countries,[2,8] and Hong Kong[3] all suggest similar associations.

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Despite this evident relationship, it has been observed that the demographic characteristics and prognosis of patients presenting with this condition are noticeably different from previously seen cases of myocarditis arising from pathomechanisms other than mRNA vaccines.[9,10] In general, there are more male and younger patients, particularly adolescents, identified with myocarditis than those of other demographic characteristics.[11] The prognosis of postvaccination myocarditis has been reported to be mostly mild and self-limiting compared with previously seen cases of otherwise acquired myocarditis, such as those arising from an influenza infection.[11,12] Although the younger age of the patients is one of the obvious reasons for the better prognosis, there may also be a distinct etiology underlying this post-mRNA vaccination iatrogenic acute condition.

Amid the pandemic, nonpharmaceutical infection control strategies such as social/physical distancing measures have significantly suppressed the circulation of other pathogens that may induce myocarditis such as influenza.[13] For adolescents and children, in particular, the incidence of otherwise acquired myocarditis, mainly from a viral infection, has essentially dropped to near zero in many developed countries with strict measures.[13,14] Hence there are few data to facilitate a fair comparison of the prognosis between myocarditis cases following mRNA vaccination and those related to a viral infection. Using a territory-wide electronic public health care database in Hong Kong, the aim of the current study was to examine the potential differences in a range of prognostic outcomes between patients with myocarditis following the use of BNT162b2 and a historical cohort of patients with viral infection–related myocarditis.

METHODS

STUDY DESIGN AND DATA SOURCE. We adopted a retrospective cohort study design following the statement on Strengthening the Reporting of Observational Studies in Epidemiology.[15] Routine health care records provided by the Hospital Authority of Hong Kong were linked with population-based vaccination records at the Department of Health to identify myocarditis cases following mRNA vaccination. Matching between inpatient and vaccination records was based on the pseudo-identification numbers provided by the Hospital Authority and the Department of Health.

The Hospital Authority serves as the sole provider of public inpatient services and a major provider of outpatient services in Hong Kong, with a comprehensive electronic health record (EHR) system in the facilitation of clinical management. Each Hong Kong resident has a unique Hong Kong Identity Number that allows the Hospital Authority to create a unique EHR for each patient to link attendances to all health care facilities. Data from the Hospital Authority's EHR are de-identified and transferred daily to the Clinical Data Analysis and Reporting System (CDARS), a nonclaims-based clinical management database with the EHRs of all patients who used the Hospital Authority's health care services. The EHRs in CDARS include demographic characteristics, diagnoses, medication dispensing records, outpatient and primary care clinics, accident and emergency department (A&E) attendances, laboratory tests, and hospitalization details. The database has frequently been used for high-quality pharmacovigilance studies to evaluate the safety of medicines and vaccines at the population level.[3,16-22] A previous study showed high coding accuracy for major cardiovascular diagnosis in CDARS, with positive predictive values estimated at >85% based on the International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM).[23]

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ETHICAL CONSIDERATIONS. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West (UW 21-149 and UW 21-138) and the Department of Health Ethics Committee (LM 21/2021).

COHORT IDENTIFICATION AND FOLLOW-UP. Starting from March 6, 2021, the day on which BNT162b2 was first rolled out in Hong Kong for emergency use, all patients diagnosed with myocarditis (ICD-9-CM: 422.x, 429.0) aged ≥12 years within 28 days after receiving BNT162b2 (first, second, or booster doses) were examined for inclusion in the BNT162b2-related myocarditis cohort (up to March 31, 2022). All other patients aged ≥12 years with a myocarditis diagnosis from January 1, 2000, to December 31, 2019, were examined for inclusion in the viral infection-related myocarditis cohort for comparison. The adopted ICD-9-CM codes represent conditions most typically induced by a viral infection in the Hospital Authority setting. Those patients with a COVID-19 infection indicated by a positive polymerase chain reaction test result within the current episode were removed. Cases without elevated troponin levels during indexed hospitalization were excluded; Supplemental Table 1 provides details of troponin reference.[3] Patients with a history of any examined disease outcome before the respective index date were also excluded. Concerning multiple episodes within individuals, only the most recent episode for each individual was selected for inclusion. Stratified according to age group (12-17, 18-59, and ≥60 years), patients were followed up from the date of the myocarditis diagnosis (index date) until the occurrence of the outcome of interest, death (for outcomes other than all-cause mortality), 180 days of follow-up, or March 31, 2022 (ie, the end of data availability), whichever came first. For A&E attendance, intensive care unit (ICU) admission, and subsequent hospitalization outcomes, the date of discharge, instead of the date of myocarditis diagnosis, was used as the index date, with those who died within the current episode excluded. This approach was to ensure everyone included in the cohort belonged with the population at risk at the commencement of observation.

PROGNOSTIC OUTCOMES. The incidence of a variety of prognostic outcomes was investigated,[24] including all-cause mortality, heart failure (ICD-9-CM: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428; International Classification of Primary Care, 2nd edition: K77), dilated cardiomyopathy (ICD-9-CM: 425.4),[25] heart transplant (ICD-9-CM: 37.51), ICU admission, A&E attendance, and subsequent hospitalization. All ranks of diagnosis (ie, regardless of primary or secondary diagnoses) were considered for ICD-9-CM–operationalized outcomes.

COVARIATES. These covariates were included for multivariable adjustment: sex, age, Charlson Comorbidity Index,[26] health care utilization in the past year (including the number of outpatient visits, the number of A&E attendances, and the number of hospitalizations), and cardiovascular disease medications prescribed within the past year before the current episode, which were treated as a composite binary variable. These medications included anticoagulants, antiplatelet medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, digoxin, diuretics, and statins. Supplemental Table 2 presents the specific medications included.

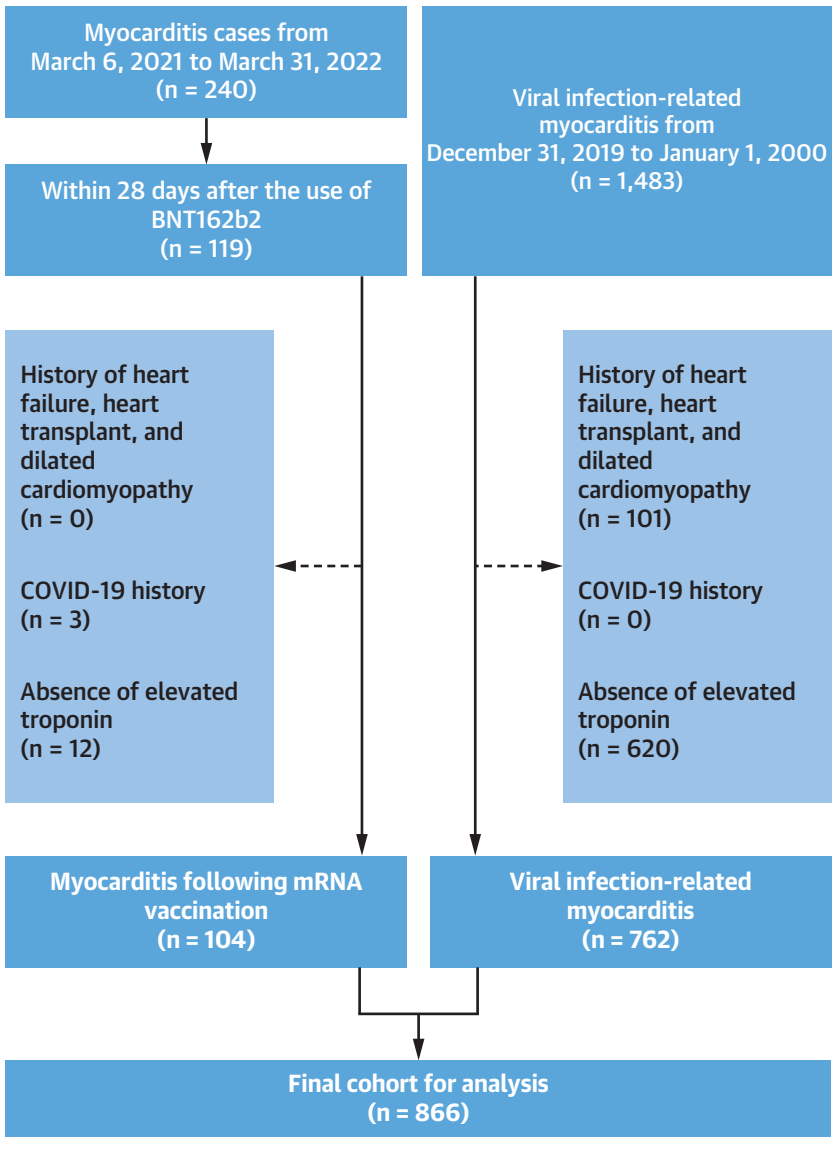
STATISTICAL ANALYSIS. Descriptive statistics, including 180-day cumulative incidence and incidence rate, were generated for a comparison between the 2 types of myocarditis stratified according to age group (12-17, 18-59, and ≥60 years). Upon confirming no violation of the assumption of proportional hazard, multivariable Cox proportional hazards models were used to examine the association of post-mRNA vaccination myocarditis (vs viral infection-related myocarditis) with the aforementioned prognostic outcomes. Adjusted HRs were estimated considering the included covariates as specified earlier. For sensitivity analysis, we confined the BNT162b2-related myocarditis patients to those only diagnosed within 14 days after receiving BNT162b2 and repeated the analysis. We also repeated the analysis with this interval extended to 56 days.

All statistical tests were 2-sided, and P values <0.05 were considered statistically significant. Statistical analysis was conducted using R version 4.0.3 (R Foundation for Statistical Computing). Two investigators (E.W.W.C. and L.H.) conducted the statistical analyses independently for quality assurance.

RESULTS

Up to March 31, 2022, a total of 8,896,843 doses of BNT162b2 were administered in 3,979,103 individuals aged ≥12 years in Hong Kong. There were 119 cases of myocarditis within 28 days after the use of BNT162b2 according to electronic diagnostic codes. From January 1, 2000, to December 31, 2019, there were 1,483 cases of myocarditis. After application of the aforementioned exclusion criteria, our eventual cohort included a total of 866 patients. One hundred four (12.0%) were patients with myocarditis following mRNA vaccination, and 762 (88.0%) were viral

FIGURE 1 Flowchart of Cohort Selection



Arrows indicate the narrowing selection of participants from earlier to later stages. **Dark blue boxes** represent selected participants or potential participants for selection. **Light blue boxes** represent excluded individuals. mRNA = messenger RNA.

infection related. Incidence of myocarditis following mRNA vaccination according to our adopted operational definition was 2.61 (95% CI: 2.14-3.17) per 100,000 vaccinated persons. Details of the cohort selection are described in **Figure 1**. The frequencies of each unique myocarditis ICD-9-CM code in each group are tabulated in Supplemental Table 3.

COHORT CHARACTERISTICS. In the cohort of myocarditis cases following mRNA vaccination, 96 (92.3%) patients had received at least 1 of the 2 priming doses (68 [65.4%] received the second dose), whereas only 8 (7.7%) individuals had received a booster third dose. There were more male patients than female patients in both the post-mRNA vaccination and viral infection-related myocarditis groups except for older adults. Across age groups, a higher proportion of cardiovascular medication use, higher average Charlson Comorbidity Index scores, and higher health care utilization in the past year (including hospitalization, outpatient consultation, and A&E attendances) were observed among patients

TABLE 1 Characteristics of Viral Infection–Related Cases and Myocarditis Cases After mRNA Vaccination According to Age Group

	Aged 12 to 17 Years			Aged 18 to 59 Years			Aged ≥60 Years		
	Viral Infection–Related (n = 105)	Post–mRNA Vaccination (n = 47)	SMD[a]	Viral Infection–Related (n = 548)	Post–mRNA Vaccination (n = 52)	SMD[a]	Viral Infection–Related (n = 109)	Post–mRNA Vaccination (n = 5)	SMD[a]
Male	79 (75.2)	42 (89.4)	0.14	327 (59.7)	39 (75.0)	0.15	51 (46.8)	1 (20.0)	0.27
Age at diagnosis, y	15.30 ± 1.54	14.79 ± 1.47	0.34	36.36 ± 12.37	31.42 ± 10.40	0.43	70.70 ± 7.79	68.80 ± 5.85	0.28
Statin	0	0	0.00	105 (19.2)	2 (3.8)	0.15	48 (44.0)	0	0.44
Angiotensin-converting enzyme inhibitors	5 (4.8)	0	0.05	156 (28.5)	0	0.29	63 (57.8)	0	0.58
Angiotensin receptor blockers	0	0	0.00	18 (3.3)	1 (1.9)	0.01	11 (10.1)	1 (20.0)	0.10
Digoxin	2 (1.9)	0	0.02	18 (3.3)	0	0.03	11 (10.1)	0	0.10
Diuretics	11 (10.5)	0	0.11	108 (19.7)	1 (1.9)	0.18	57 (52.3)	0	0.52
Anticoagulants	0	0	0.00	18 (3.3)	0	0.03	4 (3.7)	0	0.04
Antiplatelets	6 (5.7)	0	0.06	259 (47.3)	0	0.47	80 (73.4)	0	0.73
Beta-blockers	2 (1.9)	0	0.02	148 (27.0)	2 (3.8)	0.23	54 (49.5)	0	0.50
Calcium-channel blockers	3 (2.9)	0	0.03	46 (8.4)	3 (5.8)	0.03	36 (33.0)	0	0.33
Cardiovascular medication[b]	19 (18.1)	0	0.18	364 (66.4)	6 (11.5)	0.55	99 (90.8)	1 (20.0)	0.71
Charlson Comorbidity Index	0.15 ± 0.48	0.00 ± 0.00	0.45	0.25 ± 0.69	0.12 ± 0.43	0.23	0.69 ± 1.14	0.00 ± 0.00	0.85
Hospitalization in the past year	1.05 ± 0.86	0.09 ± 0.35	1.47	1.36 ± 2.20	0.19 ± 1.01	0.69	2.11 ± 2.73	0.20 ± 0.45	0.98
Outpatient visit in the past year	3.03 ± 6.05	0.60 ± 1.19	0.56	2.55 ± 6.18	2.08 ± 4.70	0.09	6.46 ± 6.78	3.00 ± 2.92	0.66
A&E attendance in the past year	1.20 ± 0.92	0.28 ± 0.50	1.24	1.48 ± 1.09	0.38 ± 0.72	1.18	1.88 ± 2.09	1.00 ± 0.71	0.56

Values are n (%) or mean ± SD. [a]Standardized mean difference (SMD) for continues variables; proportion difference for categorical variables. [b]Statin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, digoxin, anticoagulants, antiplatelets, beta-blockers, calcium-channel blockers, and diuretics.

A&E = accident and emergency department; mRNA = messenger RNA.

with viral infection–related myocarditis than among the patients with myocarditis after mRNA vaccination. Notably, among adults aged ≥18 years, more patients with viral myocarditis had been using a statin typically for lowering cholesterol, beta-blocker and angiotensin-converting enzyme inhibitors most often used for abnormal heart rhythm and hypertension, respectively, and antiplatelets for preventing blood clots and strokes. Specifically, among older people, those with a viral myocarditis were more often found using digoxin, typically for atrial fibrillation, and calcium-channel blocker most often used for hypertension. Across all age groups, diuretics used for hypertension were more commonly used by patients with viral myocarditis. More cohort characteristics are presented according to age group in Table 1.

INCIDENCE OF PROGNOSTIC OUTCOMES. Over the follow-up period (tabulated in Supplemental Table 4 for each outcome), 1 death (1.0%) was identified among the patients with myocarditis after mRNA vaccination, and 84 (11.0%) among those with viral infection–related myocarditis died. A zero incidence of heart transplant surgery was seen in both groups. One case (1.0%) of dilated cardiomyopathy and 2 cases (1.9%) of heart failure were identified in the post-mRNA vaccination myocarditis group, compared with 28 (3.7%) and 93 (12.2%) in the viral infection–related myocarditis group, respectively. For health care utilization outcomes, 21 (20.4%), 33 (32.0%), and 1 (1.0%) patient with myocarditis after mRNA vaccination had at least 1 subsequent A&E attendance, hospitalization, and ICU admission respectively, compared with 196 (28.4%), 224 (32.5%), and 6 (0.9%) patients among those with viral infection–related myocarditis.

Overall, a lower incidence of adverse prognostic outcomes (including mortality, heart failure, and dilated cardiomyopathy) was observed among the patients with myocarditis following mRNA vaccination, but the rates of subsequent health care utilization were similar. Similar patterns across age groups were also identified, with the frequencies and incidence estimates according to age group illustrated in Table 2 and Figure 2.

COX REGRESSIONS. Results of the adjusted Cox model (Table 2) showed that the post-mRNA vaccination myocarditis group had a 92% lower mortality risk (adjusted HR: 0.08; 95% CI: 0.01-0.57) compared with the viral infection–related myocarditis group. Analysis conducted specifically among the patients aged 18 to 59 years yielded a similar result (adjusted

TABLE 2 Incidence Rates (per 100 Person-Days) and HRs of Prognostic Outcomes Among All Examined Cases

	Post-mRNA Vaccination Group		Viral Infection-Related Group		HR (95% CI)[a]	
	No. of Events	Incidence Rate	No. of Events	Incidence Rate	Crude	Adjusted[b]
Overall						
Mortality	1 (1.0)	0.01	84 (11.0)	0.07	0.08 (0.01-0.61)[c]	0.08 (0.01-0.57)[c]
Heart failure	2 (1.9)	0.01	93 (12.2)	0.08	0.15 (0.04-0.60)[d]	0.34 (0.08-1.45)
Dilated cardiomyopathy	1 (1.0)	0.01	28 (3.7)	0.02	0.26 (0.04-1.94)	0.38 (0.05-3.14)
Heart transplant surgery	0	0.00	0	0.00	-	-
Subsequent A&E attendance	21 (20.4)	0.16	196 (28.4)	0.20	0.80 (0.51-1.25)	1.38 (0.84-2.27)
Subsequent ICU admission	1 (1.0)	0.01	6 (0.9)	0.00	1.22 (0.15-10.11)	1.12 (0.11-11.26)
Subsequent hospitalization	33 (32.0)	0.30	224 (32.5)	0.24	1.12 (0.77-1.61)	1.40 (0.92-2.11)
Aged 12-17 y						
Mortality	0	0.00	3 (2.9)	0.02	-	-
Heart failure	0	0.00	6 (5.7)	0.03	-	-
Dilated cardiomyopathy	0	0.00	3 (2.9)	0.02	-	-
Heart transplant surgery	0	0.00	0	0.00	-	-
Subsequent A&E attendance	8 (17.0)	0.13	25 (24.5)	0.16	0.77 (0.35-1.70)	0.62 (0.23-1.67)
Subsequent ICU admission	0	0.00	0	0.00	-	-
Subsequent hospitalization	22 (46.8)	0.54	41 (40.2)	0.34	1.32 (0.79-2.22)	1.25 (0.65-2.41)
Aged 18 to 59 y						
Mortality	1 (1.9)	0.01	56 (10.2)	0.06	0.18 (0.02-1.30)	0.13 (0.02-0.98)[c]
Heart failure	2 (3.8)	0.03	67 (12.2)	0.08	0.30 (0.07-1.22)	0.62 (0.14-2.72)
Dilated cardiomyopathy	1 (1.9)	0.01	22 (4.0)	0.03	0.48 (0.06-3.56)	1.00 (0.11-8.88)
Heart transplant surgery	0	0.00	0	0.00	-	-
Subsequent A&E attendance	12 (23.5)	0.19	136 (27.3)	0.19	0.98 (0.54-1.77)	0.59 (0.94-3.47)
Subsequent ICU admission	1 (2.0)	0.01	5 (1.0)	0.01	2.10 (0.25-18.02)	1.91 (0.18-20.32)
Subsequent hospitalization	10 (19.6)	0.16	114 (22.8)	0.21	0.98 (0.54-1.77)	1.12 (0.56-2.26)
Aged ≥60 y						
Mortality	0	0.00	25 (22.9)	0.16	-	-
Heart failure	0	0.00	20 (18.3)	0.15	-	-
Dilated cardiomyopathy	0	0.00	3 (2.8)	0.02	-	-
Heart transplant surgery	0	0.00	0	0.00	-	-
Subsequent A&E attendance	1 (20.0)	0.24	35 (39.3)	0.30	0.66 (0.09-4.81)	0.51 (0.05-4.81)
Subsequent ICU admission	0	0.00	1 (1.1)	0.01	-	-
Subsequent hospitalization	1 (20.0)	0.24	39 (43.8)	0.37	0.49 (0.07-3.60)	0.56 (0.06-5.44)

Values are n (%) unless otherwise indicated. [a]Viral infection-related group as reference group; HRs involving zero events were not estimated. [b]Covariates include age, sex, Charlson Comorbidity Index, prior health care utilization, and dichotomized history of cardiovascular disease medication use (composite binary indicator). [c]$P < 0.05$. [d]$P < 0.01$.
ICU = intensive care unit; other abbreviations as in Table 1.

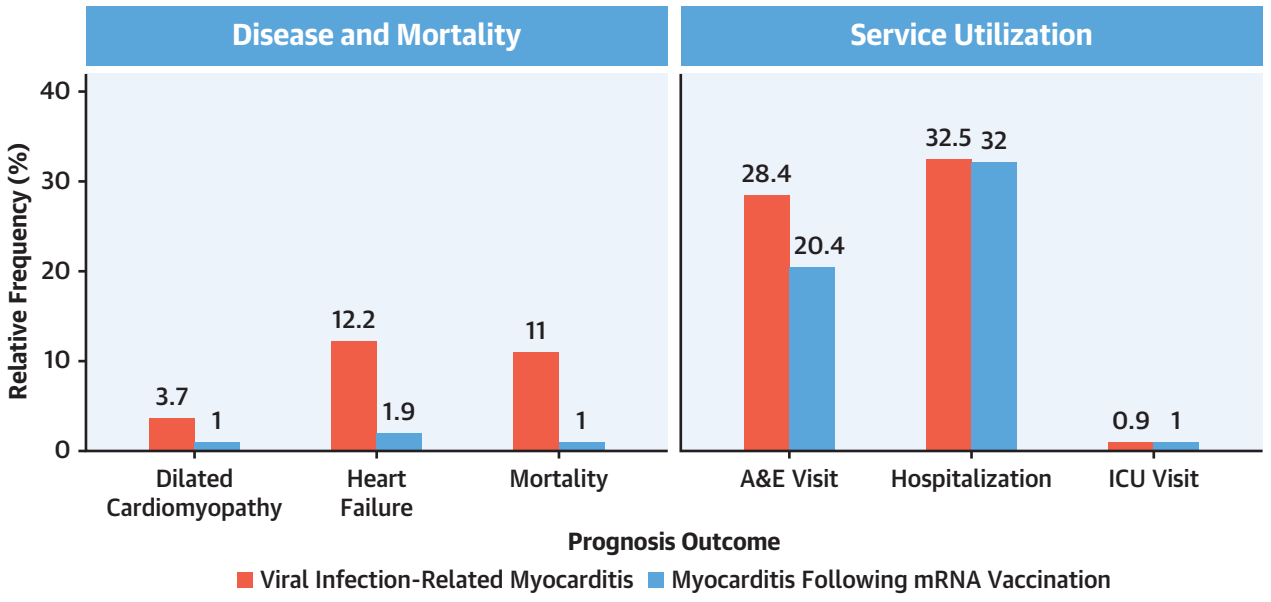
HR: 0.13; 95% CI: 0.02-0.98), but nonsignificant results were obtained for analyses among those aged 12 to 17 years and those aged ≥60 years. No significant differences in the occurrence of the other prognostic outcomes were identified.

Results of sensitivity analyses (Supplemental Tables 5 and 6) indicated that if myocarditis after mRNA vaccination was confined to those cases occurring within 14 days after receiving BNT162b2, a significant adjusted association with increased hospitalization was observed (adjusted HR: 1.77; 95% CI: 1.13-2.77), but the association with a lower mortality rate became inestimable due to zero mortality recorded. When extending this period to 56 days, the mortality results were highly similar to those of the main analysis (adjusted HR: 0.21; 95% CI: 0.06-0.70).

DISCUSSION

In this territory-wide retrospective cohort study, we found a significantly lower rate of mortality among the myocarditis cases after mRNA vaccination within 180 days of diagnosis, compared with viral infection-related cases in a historical cohort. We observed very low incidence rates (<1 per 10,000 person-days) of mortality, heart failure, and dilated cardiomyopathy following myocarditis after mRNA vaccination, in contrast with incidence rates of 7, 8, and 2 per 10,000 person-days, respectively, among the viral infection-related myocarditis patients. Zero incidences of heart transplant surgery were recorded for both groups. The Central Illustration exemplifies the findings graphically with a cumulative incidence plot of

FIGURE 2 Bar Chart Showing the Proportion of the Incidence of Prognostic Outcomes



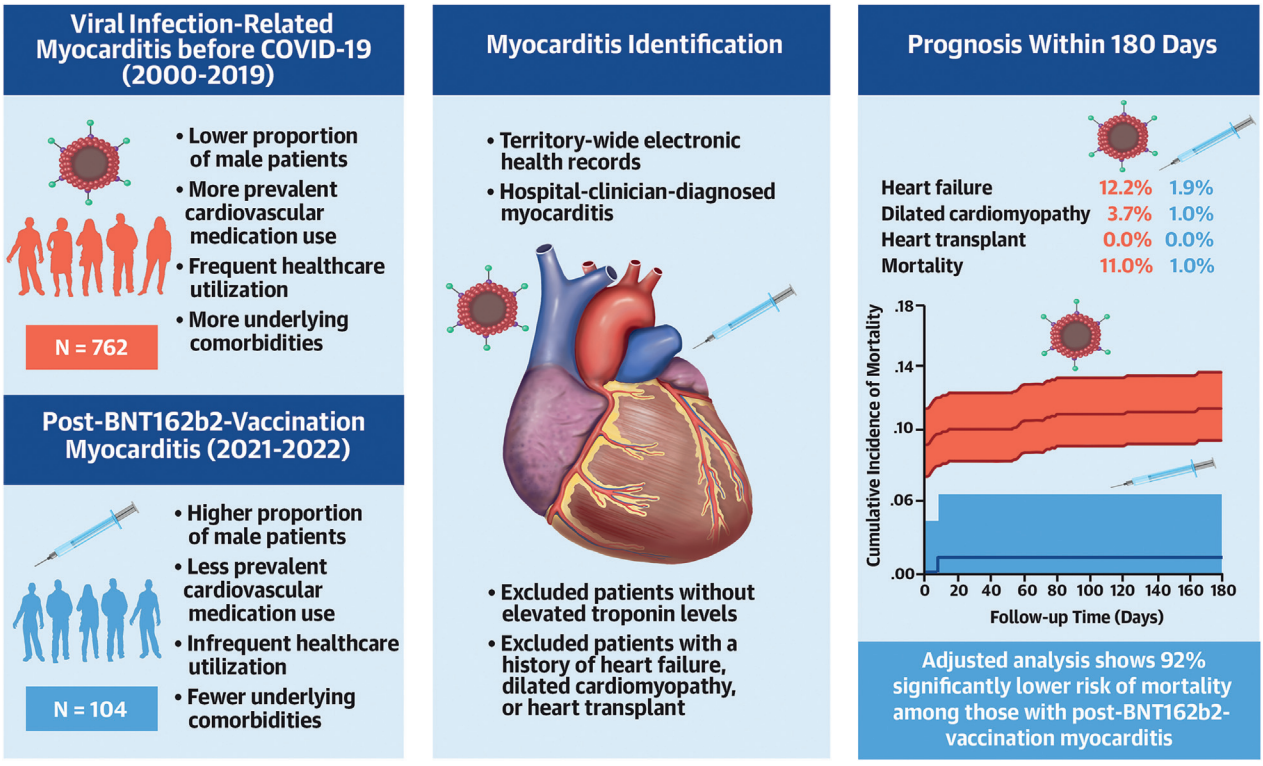
The **left panel** shows the frequencies of prognostic outcomes, including dilated cardiomyopathy, heart failure, and mortality, in each of the 2 myocarditis groups; that is, viral infection–related myocarditis vs myocarditis following messenger RNA vaccination. Heart transplant was zero for both myocarditis groups and was omitted. The **right panel** shows the postdischarge frequencies of service utilization. A&E = accident and emergency department; ICU = intensive care unit.

mortality to highlight the significant risk difference between the 2 groups.

Among nearly 4 million individuals having been vaccinated with BNT162b2 in Hong Kong, a total of 104 myocarditis cases (2.61 per 100,000 persons) were captured, constituting a highly comparable estimate with previous research in other populations such as Israel (ie, 2.13; 95% CI: 1.56-2.70).[27] In addition, this study's findings are consistent with the existing literature in 2 other main aspects. First, the demographic features of the cohort of patients with myocarditis following mRNA vaccination were characterized by a higher proportion of male subjects and were generally younger, although we identified many more cases from those aged 18 to 59 years than those aged 12 to 17 years, likely due to the fact that the total population of the latter is much smaller to begin with.[7] Second, the prognosis was typically mild among those with myocarditis following mRNA vaccination, with very few deaths and other adverse prognostic outcomes recorded.[28] For instance, a study examining myocarditis cases from the United States and Canada reported on 139 adolescents and young adults with vaccine-related myocarditis who typically had abnormal cardiac magnetic resonance imaging (cMRI) findings but rapid resolution of symptoms.[29] Nevertheless, this study is the first, to the best of our knowledge, comparing the prognostic outcomes of myocarditis related to mRNA vaccines and viral infection-related ones.

Importantly, a significant and substantially lower rate of mortality (ie, >90%) was found among the patients with myocarditis following mRNA vaccination compared with those with viral infection-related myocarditis. Because this difference has already been adjusted for a certain variety of clinical histories and medication use, as well as demographic information, this finding may suggest a potentially distinct etiology of myocarditis conditions related to mRNA vaccines as distinguished from those otherwise acquired such as viral infection. Considering immunology, it may be sensible to anticipate a milder prognosis because of typically brief exposure to stimuli that triggered the immune responses (ie, vaccine vs viruses). In fact, for viral infection-related myocarditis, there may be a direct invasion of myocardial cells, constituting a direct cardiomyocyte injury caused by the infection.[30] A greater extent of damage and

CENTRAL ILLUSTRATION **Myocarditis Prognosis Post-BNT162b2 COVID-19 Vaccination May Be Less Severe Than Viral Infection-Related Myocarditis**



Lai FTT, et al. J Am Coll Cardiol. 2022;80(24):2255–2265.

This illustration visualizes the design and findings of the study, showing that the prognosis of myocarditis after BNT162b2 COVID-19 vaccination (symbolized by the virus logo) may be less severe than viral infection–related myocarditis (symbolized by the syringe logo). The plot of cumulative incidence with 95% CIs represented by the **shaded areas** indicates the mortality risk difference between the 2 groups.

inflammation to the heart would then be anticipated, and this may explain our observation of a potentially more severe prognosis in the current study.

We also observed that the underlying health conditions, particularly cardiovascular health status, of the patients with myocarditis following mRNA vaccination were apparently better than the patients with viral infection-related myocarditis, across the age groups. This finding potentially implies that the incidence of myocarditis related to viral infections is typically higher among those with an underlying medical condition. It therefore also reflects the iatrogenicity of the myocarditis cases that were related to mRNA vaccines,[22] which could apparently occur in otherwise healthy individuals. The low incidence of mortality, heart failure, and cardiomyopathy may be partly explained by this observation.

There are clear strengths to the current study. First, it is the first study comparing myocarditis prognosis after mRNA COVID-19 vaccination vs viral myocarditis. We made use of comprehensive clinical data from a large sample with a follow-up period of up to 180 days. To the best of our knowledge, no comparable data of a similar quality and quantity have been published. Second, all diagnoses in our database were made and entered by registered hospital doctors based on standard clinical work-up, including cMRI, with previous validation studies suggesting high accuracy of the data.[23,31] Third, the selection of a historical cohort of viral myocarditis

ensured that the cases were neither related to COVID-19 nor mRNA vaccination.

STUDY LIMITATIONS. First, we were not able to double confirm the myocarditis diagnoses with clinical investigative data such as cMRI, which are unavailable in our database.[32] Second, there was also the possibility of overdiagnosis of myocarditis in mRNA vaccine recipients due to the increased awareness (ie, surveillance bias) about myocarditis as an adverse event after COVID-19 vaccination. Third, the sample may be biased toward more severe cases because the included patients were all hospitalized rather than treated in the community, although typically all suspected myocarditis cases are admitted in the public health care setting in Hong Kong. Fourth, the etiology of myocarditis cases categorized as viral infection related was not all confirmed by laboratory test results although viral infection has been the most common cause of myocarditis.[25] Fifth, we did not investigate the impacts of potentially different specific treatments between the 2 cohorts in our study. For instance, the treatment of viral myocarditis would typically involve the use of antiviral agents upon confirmation of a viral infection. Nevertheless, such treatment is highly collinear with the type of myocarditis (ie, viral infection- vs vaccine-related myocarditis) and thus would be very challenging to delineate. Sixth, troponin levels were measured with various kits of different technologies that were independently calibrated. Thus, these levels could not be directly compared between the groups. Seventh, the follow-up time was confined by the data availability of the databases. Further studies should investigate longer term outcomes. Eighth, we were not able to further compare vs patients with myocarditis following a COVID-19 infection due to a much lower infection rate than most other populations in 2020 to 2021. Also, partly due to the less severe infections and complications associated with the Omicron variant, which dominated the large outbreak in 2022, there was a very low incidence of COVID-19-related myocarditis.[33] In addition, we did not have a sufficient follow-up period amid the Omicron outbreak starting from January 2022,[34] with more than two-thirds of the cases occurring in March. Ninth, because the event rate of some of the outcomes was low, we have only been able to include a limited number of covariates in the model, and cardiovascular medications were operationalized as some vs none. Tenth, because the Hong Kong population is predominantly Chinese, this comparison should be conducted in other populations to test for the generalizability of the results to other ethnicities. Eleventh, the timing of viral infection is less clear than that of mRNA vaccination. It is possible that the viral condition resolved in some patients without hospitalization but grew more severe in the hospitalized sample over this unknown duration, thus potentially causing a selection bias. Last but not least, given the nature of the disease, the rare incidence number of myocarditis, especially among the exposure group, also limited our sample size and small numbers of events, resulting in substantially wide CIs for some estimates.

We observed a very low incidence of mortality, heart failure, heart transplant, dilated cardiomyopathy, and similar postdischarge health care utilization among patients with myocarditis following mRNA vaccines in contrast with those with viral infection-related myocarditis. If this potential difference is substantiated by future data, it will affect the risk-benefit assessment of the use of mRNA vaccines for both society and individuals. Specifically, if proven to be milder in prognosis, less weight should be given to this particular risk, and mRNA vaccination could be more strongly encouraged given a lesser impact of this established side effect of the vaccines. In addition, as the prognosis of myocarditis after vaccination is apparently mild, our data favor the current clinical management approaches for myocarditis to be largely appropriate for most people. Nevertheless, further longer-term follow-up data need to be accumulated to inform the postdischarge care in the medium to long term. Close monitoring of patients with myocarditis after mRNA vaccination, therefore, is still strongly recommended for clinicians worldwide.

CONCLUSIONS

This study found a significantly lower rate of mortality among the myocarditis cases following mRNA vaccination compared with those with viral infection-related myocarditis. The incidence of mortality, heart failure, heart transplant, and dilated cardiomyopathy within 180 days of myocarditis diagnosis among the former group is very rare.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with cases of myocarditis before the COVID-19 pandemic, cases arising within 28 days of mRNA COVID-19 vaccination have been associated with a generally milder course and lower risk of mortality.

TRANSLATIONAL OUTLOOK: Longitudinal data from a larger number of cases with longer follow-up in varied populations are needed to better assess the prognosis associated with myocarditis following mRNA vaccination.

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APPENDIX For supplemental tables, please see the online version of this paper.