Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks

Weijie Wang, a,b Chi-Yen Wang, c,h Shiow-Ing Wang, c,e,1 and James Cheng-Chung Wei d,e,f,g,1*

aDepartment of Rheumatology, the Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China
bInstitute of Basic Theory for Chinese Medicine, China Academy of Chinese Medical Science, Beijing, China
cCenter for Health Data Science, Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan
dDepartment of Allergy, Immunology & Rheumatology, Chung Shan Medical University Hospital, Taichung, Taiwan
eInstitute of Medicine, Chung Shan Medical University, Taichung, Taiwan
fGraduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
gDepartment of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
hCardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan

Summary

Background The long-term cardiovascular outcomes in COVID-19 survivors remain largely unclear. The aim of this study was to investigate the long-term cardiovascular outcomes in COVID-19 survivors.

Methods This study used the data from the US Collaborative Network in TriNetX. From a cohort of more than 42 million records between 1 January 2019 and 31 March 2022, a total of 4,131,717 participants who underwent SARS-CoV-2 testing were recruited. Study population then divided into two groups based on COVID-19 test results. To avoid reverse causality, the follow-up initiated 30 days after the test, and continued until 12 months. Hazard ratios (HRs) and 95% Confidence intervals (CIs) of the incidental cardiovascular outcomes were calculated between propensity score−matched patients with versus without SARS-CoV-2 infection. Subgroup analyses on sex, and age group were also conducted. Sensitivity analyses were performed using different network, or stratified by hospitalization to explore the difference of geography and severity of COVID-19 infection.

Findings The COVID-19 survivors were associated with increased risks of cerebrovascular diseases, such as stroke (HR [95% CI] = 1.618 [1.545-1.694]), arrhythmia related disorders, such as atrial fibrillation (HR [95% CI] = 2.407 [2.296-2.533]), inflammatory heart disease, such as myocarditis (HR [95% CI] = 4.406 [2.890-6.716]), ischemic heart disease (IHD), like ischemic cardiomyopathy (HR [95% CI] = 2.811 [2.477-3.190]), other cardiac disorders, such as heart failure (HR [95% CI] = 2.296 [2.200-2.396]) and thromboembolic disorders (e.g. pulmonary embolism: HR [95% CI] = 2.648 [2.443-2.870]). The risks of two composite endpoints, major adverse cardiovascular event (HR [95% CI] = 1.871 [1.816-1.927]) and any cardiovascular outcome (HR [95% CI] = 1.552 [1.526-1.578]), were also higher in the COVID-19 survivors than in the controls. Moreover, the survival probability of the COVID-19 survivors dramatically decreased in all the cardiovascular outcomes. The risks of cardiovascular outcomes were evident in both male and female COVID-19 survivors. Furthermore, the risk of mortality was higher in the elderly COVID-19 survivors (age ≥ 65 years) than in the young ones. Sensitivity analyses presented roughly similar results globally. Furthermore, the impact of COVID-19 on cardio-related outcomes appeared to be more pronounced in inpatients than in outpatients.

Interpretation The 12-month risk of incidental cardiovascular diseases is substantially higher in the COVID-19 survivors than the non-COVID-19 controls. Clinicians and patients with a history of COVID-19 should pay attention to their cardiovascular health in long term.

*Corresponding author at: No. 110, Sec. 1, Jianguo N. Rd., South District, Taichung City 40201, Taiwan.
E-mail address: jccwei@gmail.com (J.C.-C. Wei).
1 Shiow-Ing Wang and James Cheng-Chung Wei contribute equally.
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Research in context

Evidence before this study

We searched PubMed for follow-up studies regarding post-acute sequelae of COVID-19 especially cardiovascular complications up to April 30, 2022. A few studies have reported the short-term cardiovascular outcomes in COVID-19 survivors.

Added value of this study

In this study, we used the data from the US Collaborative Network in TriNetX. Our findings showed that the COVID-19 survivors exhibited higher cardiovascular risk outcomes, including cerebrovascular diseases, arrhythmia, inflammatory heart disease, ischemic heart disease (IHD), and thromboembolic disorders. The risks of two composite endpoints, major adverse cardiovascular events and any cardiovascular complication, were also higher in the COVID-19 survivors than in the controls. Moreover, the survival probability of the COVID-19 survivors dramatically decreased in all cardiovascular outcomes among non-vaccinated population.

Implications of all the available evidence

The 12-month risk of incidental cardiovascular diseases is substantially higher in the COVID-19 survivors than the non-COVID controls. Clinicians and patients with a history of COVID-19 should pay attention to their cardiovascular health in long term.

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has brought crucial challenges to more than 200 countries. There is increasing evidence that many patients with COVID-19 could experience a wide range of post-acute sequelae, including cardiovascular complications. COVID-19 not only causes viral pneumonia but also many extra-pulmonary complications, such as cardiovascular or cerebrovascular disease. COVID-19 can overstimulate the sympathetic system and induce an inflammatory cytokine storm and hypercoagulopathy status. These mechanisms may induce irreversible damage to the cardiovascular or respiratory system even after recovery from COVID-19. These irreversible complications, such as congestive heart failure or decreased lung function, are expected to increase the incidence of cardiovascular or cerebrovascular disease among COVID-19 survivors in the future. At present, the data on the real incidence and relative risk of cardiovascular disease (CVD) after COVID-19 infection are limited.

A few studies have reported the short-term cardiovascular outcomes in COVID-19 survivors. A recent report by Yan Xie et al. has provided substantial evidence from the US Department of Veterans Affairs National Healthcare Databases (VHA) that the risk and 1-year burden of CVD are high in both hospitalized and non-hospitalized survivors of acute COVID-19. Although the comprehensive and detailed design of the study provided robust evidence, the study conclusions cannot be extrapolated to general populations due to the limitations of the database used such as the demographic composition (majority White and male).

Here, we analyzed the long-term cardiovascular outcomes in COVID-19 survivors based on a US Collaborative Network from 48 healthcare organizations (HCOs) in the TriNetX Research Network.

Methods

Setting

We used the US Collaborative Network from 48 HCOs in the TriNetX Research Network. The available data included information about the demographics, diagnoses (based on the International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM codes), procedures (coded in The International Classification of Diseases, Tenth Revision, Procedure Coding System, ICD-10-PCS or Current Procedural Terminology, CPT), medication (coded in Veterans Affairs National Formulary), laboratory tests (coded in Logical Observation Identifiers Names and Codes, LOINC), genomics (coded in Human Genome Variation Society, HGVS), and healthcare utilization. The HCOs were hospitals, primary-care units, or specialists, providing data from uninsured or insured patients.

The TriNetX database, which is a global health-collaborative clinical-research platform collecting real-time articles
informed consent was waived. Due to the anonymous nature of the data, informed consent was waived.

| Articles |
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Electronic medical data from a network of HCOs, currently holds the largest global COVID-19 dataset. Multiple studies have used TriNetX to study the risk, trends, and outcomes of COVID-19 infection. In this study, we used the US Collaborative Network in TriNetX to build a cohort out of the more than 42 million participants between 1 January 2019 and 31 March 2022. Due to the anonymous nature of the data, informed consent was waived.

### Ethics statement

The TriNetX platform is compliant with the Health Insurance Portability & Accountability Act and General Data Protection Regulation. The Western Institutional Review Board has granted TriNetX a waiver of informed consent since this platform only aggregated counts and statistical summaries of de-identified information. In addition, the use of TriNetX for the present study was approved under the authority of the Institutional Review Board of Chung Shan Medical University Hospital (No: CS2-21176).

### Cohort

A flowchart of the cohort construction from 42,596,776 participants enrolled between 1 January 2019 and 31 March 2022 is provided in Figure 1. People who were older than 20 years and had more than 2 visits to HCOs were included in the cohort. People vaccinated against COVID-19 were excluded. Additionally, people with neoplasm [ICD10 = C00–D49], or any cardiovascular complication before the index date, and people who died within 30 d after the index date were excluded. After exclusion, the study population (n = 4,131,717) was divided into the COVID-19 (n = 691,455) and control (n = 2,249,533) groups. The COVID-19 group consisted of people who tested positive for SARS-CoV-2. The people in the control group tested negative for SARS-CoV-2 and did not show any symptoms of COVID-19.

In our cohort, propensity score matching 1:1 by age at index, race, gender, socioeconomic status (SES), comorbidities, blood type, alcohol-related disorders, nicotine dependence, and body mass index (BMI) was used. After propensity score matching, 690,892 COVID-19 survivors and 690,892 controls were selected for the study. The people from the cohort were longitudinally followed after 30 d after the index time to 12 months to estimate the risk of incident cardiovascular disease.

### Pre-specified outcomes

Incident cardiovascular disease in the post-acute phase of COVID-19 was assessed during the follow-up period between 30 d after the index time until the end of follow-up (1 year). The cardiovascular complications in the study were:

1. Cerebrovascular complications: stroke [ICD10 = I60–I69] and transient ischemic attack (TIA) [ICD10 = G45].
2. Arrhythmia: atrial fibrillation and flutter [ICD10 = I48], tachycardia [ICD10 = R00.0, I47], bradyarrhythmia [ICD10 = R00.1, I49.8, I49.5], and ventricular arrhythmia [ICD10 = I49].
3. Inflammatory heart disease: pericarditis [ICD10 = I30, I31, I32] and myocarditis [ICD10 = I14.0, I14.1, I15.1, I15.4].
4. Ischemic heart disease (IHD): acute coronary disease [ICD10 = I24], myocardial infarction [ICD10 = I21, I22], ischemic cardiomyopathy [ICD10 = I25.5], and angina [ICD10 = I20].
5. Other cardiac disorders: Heart failure [ICD10 = I50], non-ischemic cardiomyopathy [ICD10 = I42], cardiac arrest [ICD10 = I46], and cardiogenic shock [ICD10 = R57.0].
6. Thrombotic disorders: pulmonary embolism [ICD10 = I26], deep vein thrombosis [ICD10 = I80.1, I80.2, I81, I82.0, 82.2, 82.3, 82.4, 82.5], and superficial vein thrombosis [ICD10 = I80.0, I80.3, I80.8, I80.9, I82.1, I82.6, I82.7, 82.8, 82.9].
7. Major adverse cardiac events (MACEs): myocardial infarction [ICD10 = I21–I22], ischemic stroke [ICD10 = I63, I65, I66, I67.89], hemorrhagic stroke [ICD10 = I61–I62], heart failure [ICD10 = I50], ventricular arrhythmia [ICD10 = I47.0, I47.2, I49.3, I49.9], and sudden cardiac death [ICD9 = 436].
8. The composite of any cardiovascular outcome was defined as the first incident of any cardiovascular complication investigated in this study.

### Covariates

To adjust for the difference in baseline characteristics between the two groups, we incorporated the following covariate factors: demographic covariates (age, sex, and race) and problems related to housing and SES [ICD10 = Z59]. problems related to education and literacy [ICD10 = Z53], problems related to employment/unemployment [ICD10 = Z56], and occupational exposure to risk factors [ICD10 = Z57]. The comorbidities analyzed in this study were type 2 diabetes [ICD10 = E11], hyperlipidemia [ICD10 = E78.5], nicotine dependence [proxy code for smoking] [ICD10 = F17], essential hypertension [ICD10 = I10], chronic kidney disease [ICD10 = N18], chronic obstructive pulmonary disease [ICD10 = J44], liver diseases [ICD10 = K70–K77], vitamin D deficiency [ICD10 = E35], depression [ICD10 = F32], sleep disorders [ICD10 = G47], obesity [ICD10 = E66], type A blood [ICD10 = Z67.1], and alcohol-related disorders [proxy code for alcohol drinking] [ICD10 = F10].

We also selected additional potential confounders, such as physical examination and laboratory test results.
The physical examination included BMI (obesity, $\geq 30$ kg/m²) and systolic and diastolic blood pressures. The laboratory tests analyzed in this study were, estimated glomerular filtration rate, and blood levels of triglyceride ($\geq 500$ mg/dl), cholesterol in LDL ($\geq 190$ mg/dl), cholesterol in HDL ($\geq 50$ mg/dl), creatine kinase ($\geq 199$ U/L), troponin I ($\geq 0.3$ ng/ml), C-reactive protein (CRP) ($\geq 3.0$ mg/L), creatinine ($\geq 1.5$ mg/dl), and hemoglobin ($\geq 12$ g/dL).

**Statistical analyses**

To reduce the effect of confounding factors, we used propensity scores matching to generate groups with matched baseline characteristics. We adopted TriNetX built-in function and matched the two groups at a 1:1 ratio by greedy nearest neighbor matching for age at index, sex, race, adverse socioeconomic status (such as problems related to housing and economic circumstances, problems related to education and literacy et al.), lifestyle related proxy variables (Nicotine dependence, alcohol related disorders, BMI), and comorbidities. Standardized difference (Std diff) was used to evaluate the balance of baseline characteristics in the propensity score-matched populations. Generally, Std diff $< 0.1$ is considered a small difference. To avoid reverse causality, the follow-up initiated 30 days after the test, and continued until 12 months. The hazard ratio (HR) of incident cardiovascular disease was calculated for the COVID-19 and control groups. The proportional hazard assumption was tested using the generalized Schoenfeld approach built in the TriNetX platform. If the assumptions are not met, we then calculate the hazard.
ratios separately for different time periods. In all the analyses, a 95% confidence interval (95% CI) was considered evidence of statistical significance. The Kaplan-Meier method was used for the survival probability. Statistical significance was defined as P-value < 0.05.

Subgroup analyses investigated how the risks for cardiovascular outcomes in COVID-19 patients differed by sex, and age group. In addition, as there may be geographical differences between countries regarding the prevalence of COVID-19, and availability of health care resources, sensitivity analysis was also performed with EMEA (Europe, Middle East and Africa) and global research network to examine the consistency of results. We also attempted to explore whether differences in the severity of COVID-19 infection could lead to different outcomes. Thus, a sensitivity analysis was also performed on hospitalized patients (defined as those hospitalized within 1 month on or after the SARS-CoV-2 test) and outpatients (defined as patients using outpatient services and never hospitalized within 1 month on or after the SARS-CoV-2 test).

Role of the funding source
The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The corresponding author James Cheng-Chung Wei and the co-author show-Ing Wang had full access to all data in the study and had the final responsibility to submit it for publication.

Results

Baseline characteristics of the study subjects
The demographic characteristics, co-morbidities, and laboratory measurements of the COVID-19 and control groups before and after propensity score matching is presented in Table 1. The mean age of the participants in the COVID-19 group was approximately 43 years at index after matching which may be more universe than 61 years for the people in VAH database. Approximately 56.8% of the COVID-19 survivors were women. The major race was Caucasian (56.4%). After matching, the differences in socioeconomic status, comorbidities, and laboratory results between the two groups were small and well-matched.

Incidence of cardiovascular complications in the COVID-19 and control groups

We estimated the risks of pre-specified cardiovascular complications in the COVID-19 and control groups (Table 2 and Figure 2 and Supplementary Table 1). Upon 12-month follow-up, the COVID-19 survivors were found to have higher risks of developing these cardiovascular complications than the controls, as detailed below.

The COVID-19 survivors exhibited higher risks of cerebrovascular complications, such as stroke (HR = 1.52 [1.43–1.62]) and TIA (HR = 1.593 [1.353–1.670]).

There were increased risks of arrhythmia outcomes, such as atrial fibrillation and flutter (HR = 2.407 [2.296–2.523]), tachycardia (HR = 1.682 [1.626–1.740]), bradycardia (HR = 1.599 [1.521–1.681]), and ventricular arrhythmias (HR = 1.600 [1.535–1.668]).

The COVID-19 survivors exhibited higher risks of inflammatory heart disease, especially myocarditis (HR = 4.406 [2.890–6.716]) and pericarditis (HR = 1.621 [1.452–1.810]).

Ischemic heart disease (IHD), such as acute coronary disease (HR = 2.048 [1.752–2.393]), myocardial infarction (HR = 1.979 [1.831–2.118]), ischemic cardiomyopathy (HR = 2.811 [2.477–3.190]) and angina (HR = 1.707 [1.545–1.883]) have higher risk in COVID-19 survivors.

There were increased risks of other cardiac disorders, namely heart failure (HR = 2.296 [2.200–2.396]), cardiomyopathy (HR = 2.413 [2.235–2.606]), cardiac arrest (HR = 1.751 [1.526–2.008]) and cardiogenic shock (HR = 1.988 [1.599–2.473]).

Thrombotic disorders, including pulmonary embolism (HR = 2.648 [2.443–2.870]), deep vein thrombosis (HR = 1.879 [1.751–2.017]), and superficial vein thrombosis (HR = 1.592 [1.442–1.756]) were increased risk in COVID-19 survivors.

Compared to the control group, there were increased risks of composite endpoints, namely MACE (HR [95% CI] = 1.871 [1.816–1.927]) and any cardiovascular complication (HR [95% CI] = 1.552 [1.526–1.578]).

Additionally, the mortality rate in the COVID-19 group was higher than that in the control group (HR = 1.604 [1.510–1.703]). The Kaplan-Meier curve of survival probability of cardiovascular complication is presented in Figure 3. Since many of the outcomes did not meet the proportionality assumption for hazard ratios, we divided the follow-up period into 90 days intervals (Supplementary Table 2). It can be seen that the results for the different time periods are similar and also met the proportionality assumption, except for those variables that mix multiple diseases (such as MACEs, or any cardiac outcome mentioned above).

Subgroup analyses
We examined the risk of incident cardiovascular disease in subgroups based on sex and age. The risks of cardiovascular complications were evident in both the male and female COVID-19 survivors. Risks of myocarditis (HR [95% CI] = 4.116 [2.344–7.229]), ischemic cardiomyopathy (HR [95% CI] = 3.189 [2.734–3.719]), and pulmonary embolism (HR [95% CI] = 3.415 [2.792–3.543])...
ranked the top three risks in the male COVID-19 survivors. However, the female COVID-19 survivors had higher risks of myocarditis (HR [95% CI] = 3.329 [1.901–5.829]), ischemic cardiomyopathy (HR [95% CI] = 3.169 [2.459–4.085]), and atrial fibrillation and flutter (HR [95% CI] = 2.542 [2.160–2.718]) than the sex-matched control subjects. (Supplementary Table 3 and Figure 4).
The risks of myocarditis (HR [95% CI] = 3.829 [2.361–6.211]) and ischemic cardiomyopathy (HR [95% CI] = 2.632 [1.494–4.636]) ranked the top two risks in younger COVID-19 survivors (aged 20–44 years). In addition, the risks of ischemic cardiomyopathy (HR [95% CI] = 3.435 [2.777–4.249]) and myocarditis (HR [95% CI] = 3.237 [1.554–6.743]) ranked the top two risks in the middle-aged survivors (aged 45–64 years). However, the elderly COVID-19 survivors (aged ≥65 years) had higher risks of ischemic cardiomyopathy (HR [95% CI] = 2.869 [2.406–3.420]) and pulmonary embolism (HR [95% CI] = 2.849 [2.464–3.295]) than the age-matched control subjects. Furthermore, the risk of mortality was higher in the middle-aged (HR [95% CI] = 1.694 [1.519–1.890]) and elderly COVID-19 survivors (HR [95% CI] = 1.708 [1.575–1.852]) than in the age-matched control subjects. There was no significant difference in the risk of mortality between the young COVID-19 survivors and age-matched control subjects (Supplementary Table 4 and Figure 5).

Sensitivity analyses
Because our cohort was based on the US Collaborative Network in TriNetX, we examined the risk of incident cardiovascular disease worldwide, and in Europe, Middle East and Africa (EMEA), by using TriNetX Global and EMEA network. The risks of incident composite cardiovascular outcomes were evident worldwide. In addition, we found that the risks of myocarditis (HR [95% CI] = 3.178 [2.192–4.606]) and ischemic cardiomyopathy (HR [95% CI] = 3.003 [2.637–3.419]) ranked the top two risks in the global cohort, consistent with the results of the US Collaborative Network. However, in the EMEA cohort, only the risks of cerebrovascular complications, atrial fibrillation and flutter, tachycardia, myocardial infarction, and pulmonary embolism were higher in the COVID-19 survivors than in the controls. Among these outcomes, TIA (HR [95% CI] = 2.581 [1.239–5.373]) and pulmonary embolism (HR [95% CI] = 2.265 [1.275–4.022]) were found to be twice likely to develop in COVID-19 survivors vs. the controls (Supplementary Table 5).

| Outcome                          | Patients with outcome | Hazard ratio (95% CI) | COVID-19 group | Control group |
|---------------------------------|-----------------------|-----------------------|----------------|---------------|
| **Cerebrovascular**             |                       |                       |                |               |
| Stroke                          | 4054                  | 3297                  | 1.618 [1.545–1.694]a |               |
| TIA                             | 739                   | 655                   | 1.503 [1.353–1.670]a |               |
| **Arrhythmia**                  |                       |                       |                |               |
| Atrial fibrillation and flutter | 4980                  | 2673                  | 2.407 [2.296–2.523]a |               |
| Tachycardia                     | 7659                  | 6047                  | 1.682 [1.626–1.740]a |               |
| Bradycardia                     | 3403                  | 2835                  | 1.599 [1.521–1.681]a |               |
| Ventricular arrhythmias         | 4885                  | 4063                  | 1.600 [1.535–1.668]a |               |
| **Inflammatory heart disease**  |                       |                       |                |               |
| Pericarditis                    | 711                   | 574                   | 1.621 [1.452–1.810]a |               |
| Myocarditis                     | 95                    | 28                    | 4.406 [2.890–6.716]a |               |
| **Ischemic heart disease**      |                       |                       |                |               |
| Acute coronary disease          | 402                   | 261                   | 2.048 [1.752–2.393]a |               |
| Myocardial infarction           | 1601                  | 1071                  | 1.979 [1.831–2.138]a |               |
| Ischemic cardiomyopathy         | 760                   | 351                   | 2.811 [2.477–3.190]a |               |
| Angina                          | 888                   | 692                   | 1.707 [1.545–1.885]a |               |
| **Other cardiac disorders**     |                       |                       |                |               |
| Heart failure                   | 5831                  | 3298                  | 2.296 [2.200–2.396]a |               |
| Cardiomyopathy                  | 1865                  | 1007                  | 2.413 [2.235–2.606]a |               |
| Cardiac arrest                  | 474                   | 358                   | 1.751 [1.526–2.008]a |               |
| Cardiogenic shock               | 204                   | 134                   | 1.988 [1.599–2.473]a |               |
| **Thrombotic disorders**        |                       |                       |                |               |
| Pulmonary embolism              | 1822                  | 882                   | 2.648 [2.443–2.870]a |               |
| Deep vein thrombosis            | 1898                  | 1310                  | 1.879 [1.751–2.017]a |               |
| Superficial vein thrombosis     | 879                   | 725                   | 1.592 [1.442–1.756]a |               |
| MACE                            | 10530                 | 7385                  | 1.871 [1.816–1.927]a |               |
| Any cardiac outcome mentioned above | 29357                 | 25050                 | 1.552 [1.526–1.578]a |               |
| Mortality                       | 2370                  | 1937                  | 1.604 [1.510–1.703]a |               |

Table 2: Incidence of outcomes among COVID-19 group compared to control subjects (after prosperity score matching).
Note: TIA:Transient Ischemic Attack; MACE: major adverse cardiac event.

* Proportionality (P<0.01).
Supplementary Table 6 provides stratification of the severity of the COVID-19 infection and subsequent outcomes. Similar results can be found from the comparison of hospitalized patients, except myocarditis (HR [95% CI] = 1.451 [0.487-4.321]) and ischemic heart related diseases. In outpatients, the impact of COVID-19 on cardio-related outcomes appears to be less pronounced than in hospitalized patients, except...
myocarditis (HR [95% CI] = 6.119 [1.356-27.60]). In addition, compared to non-COVID-19 group, non-hospitalized COVID-19 cohort has significantly lower risk of mortality-related outcomes, such as cardiac arrest (HR [95% CI] = 0.387 [0.164-0.915]), or mortality (HR [95% CI] = 0.460 [0.327-0.646]).

Discussion
In this study involving 690,892 COVID-19 survivors and matched 690,892 controls, we found that the COVID-19 survivors have higher risks of cardiovascular complications, including cerebrovascular complications, arrhythmia, inflammatory or ischemic heart disease, and thromboembolic disorders than the controls. The risks of two composite endpoints, MACE and any cardiovascular complication, were also higher in the COVID-19 survivors. The risks of cardiovascular complications were evident in both the male and female COVID-19 survivors.

The risks of myocarditis and pulmonary embolism were higher than the risks of most of the other cardiovascular complications, and this observation is consistent with the results of the VHA database. However, the risk of TIA ranked the top in the COVID-19 survivors in the EMEA region. This regional difference may necessitate different cardiovascular healthcare strategies. Substantial evidence indicates that old people infected with SARS-CoV-2 experience more severe COVID-19 and higher mortality than young people.12,13 In our study, the risks of the MACE (HR [95% CI] = 1.879 [1.799-1.963]), any cardiac outcome (HR [95% CI] = 1.589 [1.545-1.635]), and mortality (HR [95% CI] = 1.708 [1.575-1.852]) of the elderly COVID-19 survivors (aged > 65 years) were higher than those of the young survivors. When addressing the myocarditis in sensitivity analysis, our very small sample of hospitalized COVID-19 patients (<=10) and the patients in outpatient (<=10) may be a limiting factor in our analysis. Concerning the mortality in sensitivity analysis, different control
strategies for COVID-19\textsuperscript{14} and different mutant strains\textsuperscript{15} in pandemic between different regions including EMEA and US may lead to the result that the mortality rate was lower in the COVID-19 group than the control group in the EMEA group. In addition, the COVID-19 survivors in outpatient group (mean age 44) were much younger than that in inpatient group (mean age 51), which would probably lead to lower mortality rate. A recent meta-analysis also indicated that the estimated overall mortality rate of cardiac arrest in patients with COVID-19 (in-hospital or at 30 days) was 89.9%.\textsuperscript{16} Thus, cardiac arrest (HR [95% CI] = 0.387 [0.164-0.915]) in outpatient group could also underestimate the mortality in outpatients with COVID-19. Moreover, the pandemic might have induced an attitude towards postponement of less urgent cases, at both the patients and the healthcare system levels. These results are in line with recent finding, where an estimated 38% reduction in STEMI activations was reported by US cardiac catheterization laboratories.\textsuperscript{17}

Several underlined mechanisms between COVID-19 and development of cardiovascular diseases are presented and presumed. A previous study that used real-world data suggested that COVID-19 infection causes irreversible damage to the cardiovascular or cerebrovascular system, such as congestive heart failure and decreased lung function.\textsuperscript{18} Congestive heart failure increases the incidence of atrial or ventricular arrhythmia, cardiomyopathy, and even cardiogenic shock. The irreversible damage to the respiratory system is expected to impair lung function and increase systemic hypoxic stress, thereby provoking ischemic heart disease, including coronary artery disease, acute coronary syndrome, and ischemic stroke.\textsuperscript{19-20} Furthermore, the hyper-coagulopathy status caused by COVID-19 may last even after the recovery from COVID-19. The hyper-coagulopathy status presumably increases the risks of venous thromboembolic events, such as acute pulmonary embolism.\textsuperscript{21-22} Furthermore, SARS-CoV-2 infection can trigger a cytokine storm; many pro-inflammatory cytokines and chemokines, such as TNF-\alpha, IL-1\beta, and IL-6, are overproduced, damaging various organs, including those in the cardiovascular system.\textsuperscript{23-24} Additionally, cardiovascular risk factors, such as hypertension and diabetes, have been reported to be significant in COVID-19 patients and the mortality rate in former studies.\textsuperscript{25-27} COVID-19 itself can also induce cardiovascular complications. Moreover, electrolyte imbalances can occur in COVID-19 and may increase vulnerability to various tachyarrhythmias.\textsuperscript{28} Finally, therapeutics for COVID-19, such as hydroxychloroquine and azithromycin, have adverse effects on the cardiovascular system.\textsuperscript{29}

Our study had many strengths to make the evidence robust. First, we restricted the COVID-19 diagnoses to individuals who tested positive with an RNA or antigen test (and used the antigen test as an index event), to avoid misclassification bias. Second, for control group, they all had tests related to COVID-19, which could reduce detection bias caused by not seeking medical service. Moreover, the study population was racially diverse and included Caucasian, Black or African American, Asian, American Indian, Native Hawaiian, and others. Furthermore, the laboratory measurements, such as blood levels of triglyceride, cholesterol in LDL and HDL, CRP, creatine kinase, and troponin I, were also presented. Moreover, it represents a more diverse population than that presented in the VHA studies. Furthermore, we excluded all the mortal cases in the follow-up time.

Our study has several limitations. First, although we evaluated the cardiovascular risks in the US as well as the global network in TriNetX, almost 80% of the HCOs were American, and thus the generalizability of our conclusions to Eastern countries is limited. Second, we used validated outcome definitions and the propensity score-matching to avoid bias, but misclassification bias and residual confounding could not be completely avoided because the healthcare database we used has weaknesses inherent to an electronic health records study. Finally, treatments for COVID-19, such as hydroxychloroquine and azithromycin, may have side effects on the cardiovascular system and thus underlie our observations.

In summary, the 12-month risk of incident cardiovascular diseases is substantially higher in the COVID-19 survivors than the controls. Clinicians and patients with a history of COVID-19 should pay extra attention to their cardiovascular health in long term.

Contributors
WJ-W wrote the draft of the manuscript; SI-W have performed data analysis; SI-W and CY-W revised the manuscript critically. James Cheng-Chung Wei designed and supervised the study. All authors contributed to manuscript revision, read and approved the submitted version.

Data sharing statement
The data that support the findings of this study are available from the TriNetX Analytics Network. https://trinetx.com.

Declaration of interests
The authors declare no competing interests.

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Supplementary materials

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