

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,^{e,h} Shioh-Ing Wang,^{c,e,†} and James Cheng-Chung Wei^{d,e,f,g,†*}

^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 [2.296-2.523]), 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).

[†] Shioh-Ing Wang and James Cheng-Chung Wei contribute equally.

eClinicalMedicine

2022;53: 101619

Published online xxx

[https://doi.org/10.1016/j.](https://doi.org/10.1016/j.eclinm.2022.101619)

[eclinm.2022.101619](https://doi.org/10.1016/j.eclinm.2022.101619)

Funding The Fundamental Research Funds for the Central public welfare research institutes and Young Elite Scientists Sponsorship Program by CACM.

Copyright © 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Keywords: COVID-19; Post-acute sequelae; Cardiovascular outcomes; TriNetX

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.¹ There is increasing evidence that many patients with COVID-19 could experience a wide range of post-acute sequelae, including cardiovascular complications.² COVID-19 not only causes viral pneumonia but also many extra-pulmonary complications, such as cardiovascular or cerebrovascular disease.³ 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.⁴ 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.^{5–7} 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-19.⁸ 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

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.^{9–11} 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], bradycardia [ICD10 = R00.1, I49.8, I49.5], and ventricular arrhythmia [ICD10 = I49].
- (3) Inflammatory heart disease: pericarditis [ICD10 = I30, I31, I32] and myocarditis [ICD10 = I40, I41, I51.4].
- (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, 80.2, I81, I82.0, 82.2, 82.3, 82.4, 82.5], and superficial vein thrombosis [ICD10 = I80.0, 80.3, 80.8, 80.9, I82.1, 82.6, 82.7, 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, I49.0], and sudden cardiac death [ICD9 = I46].
- (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 = Z55], 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 = K70–77], vitamin D deficiency [ICD10 = E55], 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.

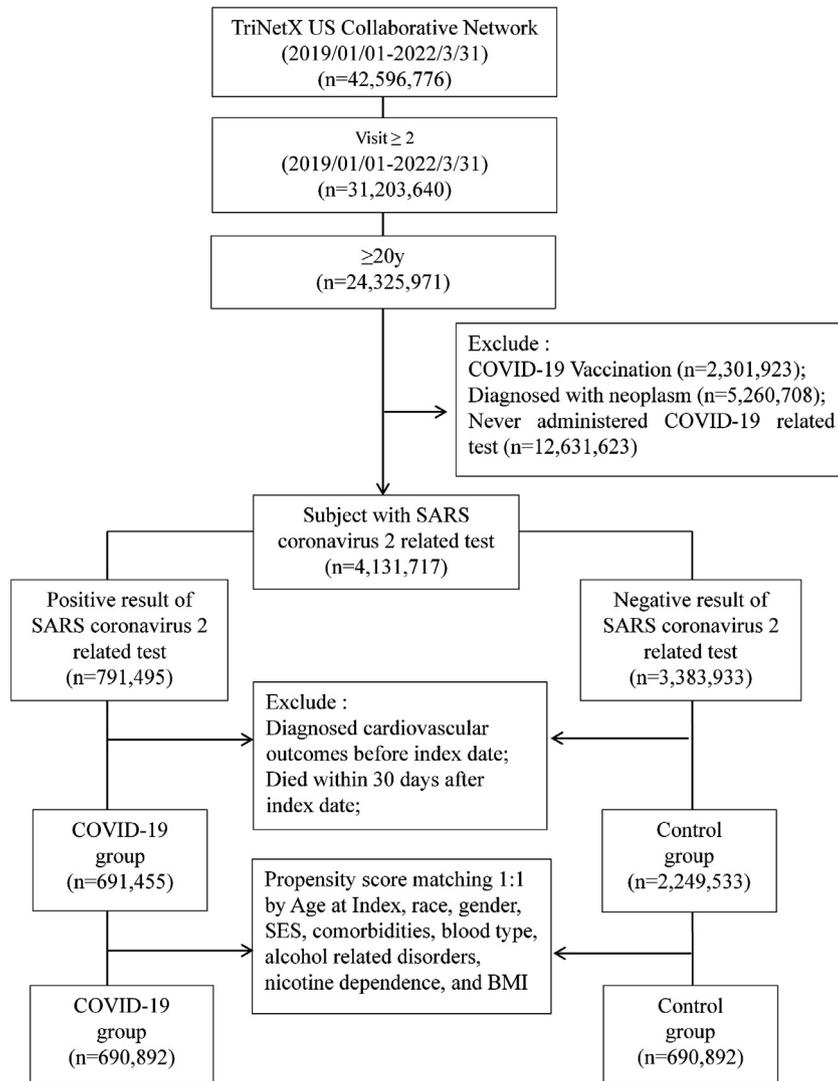


Figure 1. Flow chart of cohort construction.

The physical examination included BMI (obesity, $\geq 30 \text{ kg/m}^2$) and systolic and diastolic blood pressures. The laboratory tests analyzed in this study were, estimated glomerular filtration rate, and blood levels of triglyceride ($\geq 500 \text{ mg/dl}$), cholesterol in LDL ($\geq 190 \text{ mg/dl}$), cholesterol in HDL ($\geq 50 \text{ mg/dl}$), creatine kinase ($\geq 199 \text{ U/L}$), troponin I ($\geq 0.3 \text{ ng/ml}$), C-reactive protein (CRP) ($\geq 3.0 \text{ mg/L}$), creatinine ($\geq 1.5 \text{ mg/dl}$), and hemoglobin ($\geq 12 \text{ g/dL}$).

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 = 1.503 [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 [1.831–2.138]), ischemic cardiomyopathy (HR = 2.811 [2.477–3.190]) and angina (HR = 1.707 [1.545–1.885]) 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] = 3.145 [2.792–3.543])

	Before matching			After matching		
	COVID-19 group (n=691,455)	Control group (n=2,249,533)	Std diff	COVID-19 group (n=690,892)	Control group (n=690,892)	Std diff
Age at index						
Mean±SD	43.2 ± 16.2	44.5 ± 17.0	0.076	43.2 ± 16.2	43.1 ± 16.1	0.003
Gender						
Female	392628 (56.8)	1304888 (58.0)	0.025	392381 (56.8)	392613 (56.8)	0.001
Male	298538 (43.2)	942945 (41.9)	0.025	298223 (43.2)	297939 (43.1)	0.001
Race, n (%)						
White	389972 (56.4)	1310850 (58.3)	0.038	389767 (56.4)	389519 (56.4)	0.001
Unknown	155345 (22.5)	516848 (23.0)	0.012	155296 (22.5)	154260 (22.3)	0.004
Black or African American	129064 (18.7)	361545 (16.1)	0.069	128758 (18.6)	130205 (18.8)	0.005
Asian	13615 (02.0)	49896 (02.2)	0.017	13614 (02.0)	13563 (02.0)	0.001
American Indian	2518 (00.4)	8130 (00.4)	<0.001	2517 (00.4)	2600 (00.4)	0.002
Native Hawaiian	941 (00.1)	2264 (00.1)	0.010	940 (00.1)	745 (00.1)	0.008
Social economic status						
Housing/economic circumstances problem	7182 (01.0)	17549 (00.8)	0.027	7106 (01.0)	5441 (00.8)	0.025
Problems related to education and literacy	389 (00.1)	959 (00.0)	0.006	388 (00.1)	283 (00.0)	0.007
Employment or unemployment problems	2190 (00.3)	6868 (00.3)	0.002	2176 (00.3)	1746 (00.3)	0.012
Occupational exposure to risk factors	577 (00.1)	1319 (00.1)	0.009	576 (00.1)	431 (00.1)	0.008
Comorbidities						
Type 2 DM	58120 (08.4)	130368 (05.8)	0.102	57623 (08.3)	56880 (08.2)	0.004
Hyperlipidemia	61237 (08.9)	151755 (06.7)	0.079	60808 (08.8)	59639 (08.6)	0.006
Nicotine dependence (smoking)	50632 (07.3)	179867 (08.0)	0.025	50576 (07.3)	48296 (07.0)	0.013
Hypertension	122816 (17.8)	318182 (14.1)	0.099	122276 (17.7)	121967 (17.7)	0.001
CKD	20749 (03.0)	38428 (01.7)	0.085	20214 (02.9)	19327 (02.8)	0.008
COPD	14708 (02.1)	36884 (01.6)	0.036	14459 (02.1)	12019 (01.7)	0.026
Disease of liver	20183 (02.9)	55803 (02.5)	0.027	20032 (02.9)	17643 (02.6)	0.021
Vitamin D deficiency	37874 (05.5)	87465 (03.9)	0.075	37516 (05.4)	38016 (05.5)	0.003
Depression	54991 (08.0)	160713 (07.1)	0.031	54774 (07.9)	51998 (07.5)	0.015
Sleep disorder	52969 (07.7)	138161 (06.1)	0.060	52609 (07.6)	50714 (07.3)	0.010
Overweight and obesity	87865 (12.7)	198473 (08.8)	0.126	87336 (12.6)	87905 (12.7)	0.002
Alcohol related disorders (alcohol drinking)	12109 (01.8)	52404 (02.3)	0.041	12106 (01.8)	10119 (01.5)	0.023
Laboratory						
Type A blood	505 (00.1)	1957 (00.1)	0.005	505 (00.1)	488 (00.1)	0.001
BMI ≥ 30 kg/m ² , n (%)	105551 (15.3)	309604 (13.8)	0.043	105302 (15.2)	104417 (15.1)	0.004
Diastolic blood pressure, mean±SD, mmHg	76.5 ± 11.9	75.4 ± 12.3	0.091	76.5 ± 11.9	75.7 ± 12.4	0.062
Systolic blood pressure, mean±SD, mmHg	126.8 ± 18.3	125.9 ± 18.9	0.053	126.8 ± 18.3	126.1 ± 18.8	0.038
eGFR, Mean±SD, ml/min/1.73m ²	89.0 ± 29.4	90.3 ± 29.3	0.042	89.1 ± 29.4	90.2 ± 29.8	0.038
Triglyceride ≥ 500 mg/dl	3505 (00.5)	6736 (00.3)	0.033	3484 (00.5)	2700 (00.4)	0.017
Cholesterol in LDL≥190 mg/dl	4923 (00.7)	10766 (00.5)	0.030	4904 (00.7)	3798 (00.5)	0.020
Cholesterol in HDL≥50 mg/dl	87986 (12.7)	227066 (10.1)	0.083	87838 (12.7)	74314 (10.8)	0.061
Troponin I ≥ 0.3ng/ml	3761 (00.5)	4492 (00.2)	0.057	3713 (00.5)	1412 (00.2)	0.055
Hemoglobin ≥ 12 g/dL	327871 (47.4)	983928 (43.7)	0.074	327420 (47.4)	312261 (45.2)	0.044

Table 1: Baseline characteristics of study subjects (before and after Propensity score matching).

If the patient is less or equal to 10, results shows the count as 10.

Bold font represents a standardized difference > 0.1.

CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C reactive protein; BMI: Body mass index; GFR: glomerular filtration rate; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein.

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 [2.360–2.738]) than the sex-matched control subjects. (Supplementary Table 3 and Figure 4).

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)
Myocarditis	95	28	4.406 (2.890-6.716)
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)
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)
Cardiogenic shock	204	134	1.988 (1.599-2.473)
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 propensity score matching).

Note: TIA: Transient Ischemic Attack; MACE: major adverse cardiac event.

^a Proportionality ($P < 0.01$).

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).

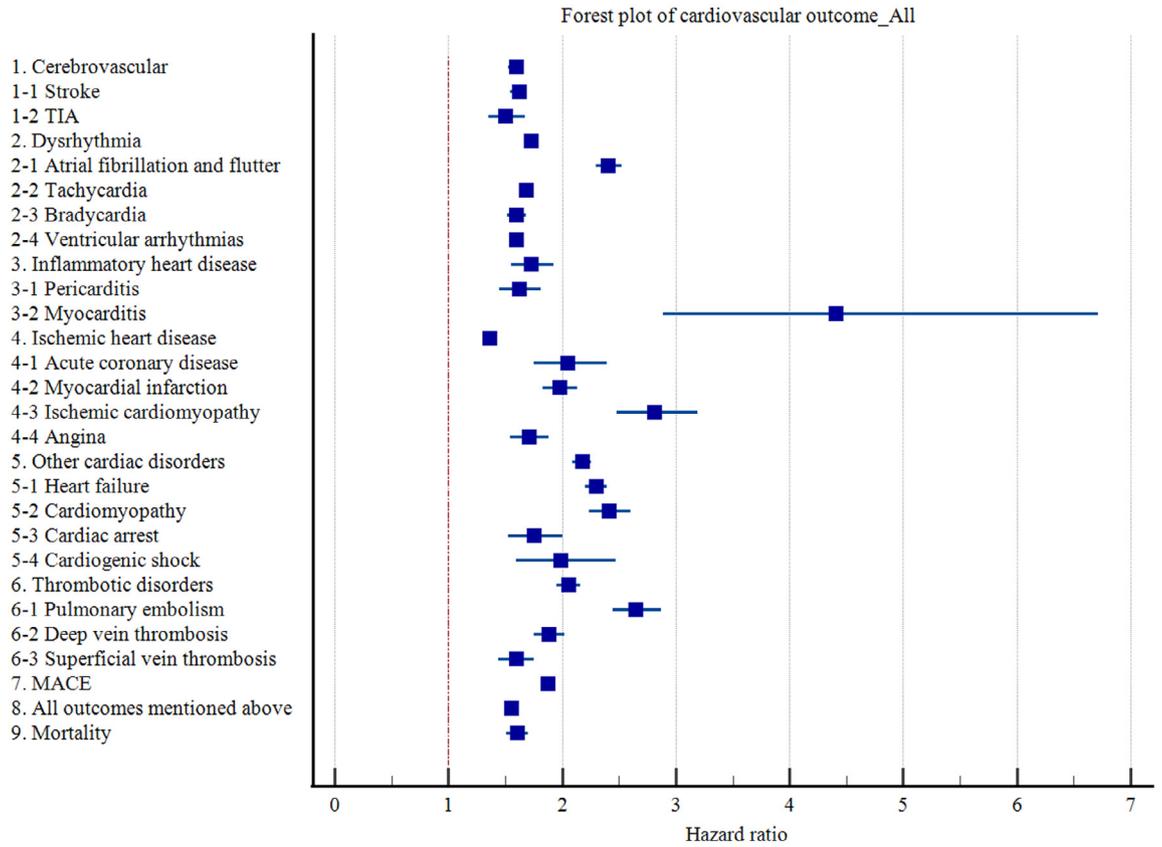


Figure 2. Forest plot of all cardiovascular outcomes.

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

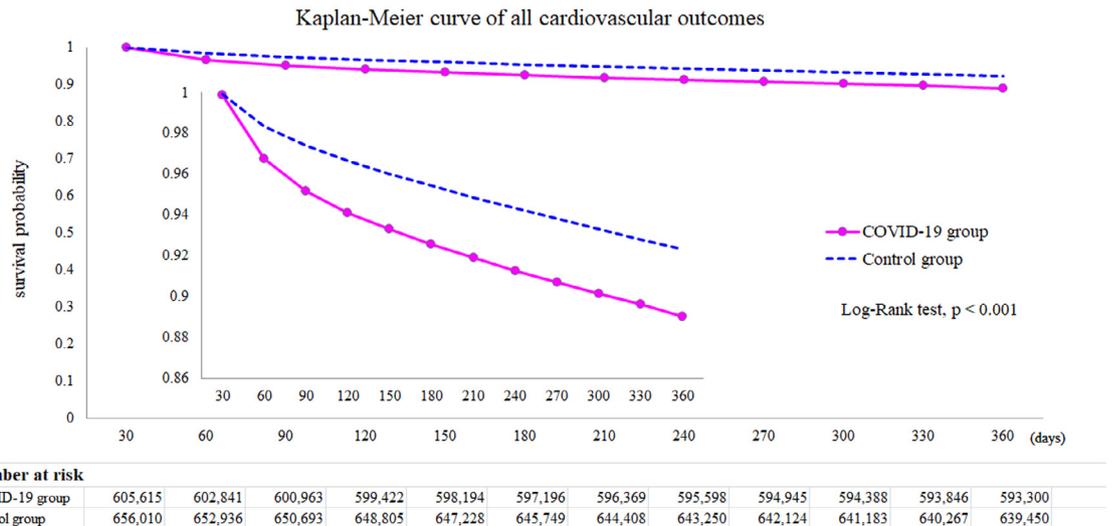


Figure 3. Kaplan-Meier curves of all cardiovascular outcomes.

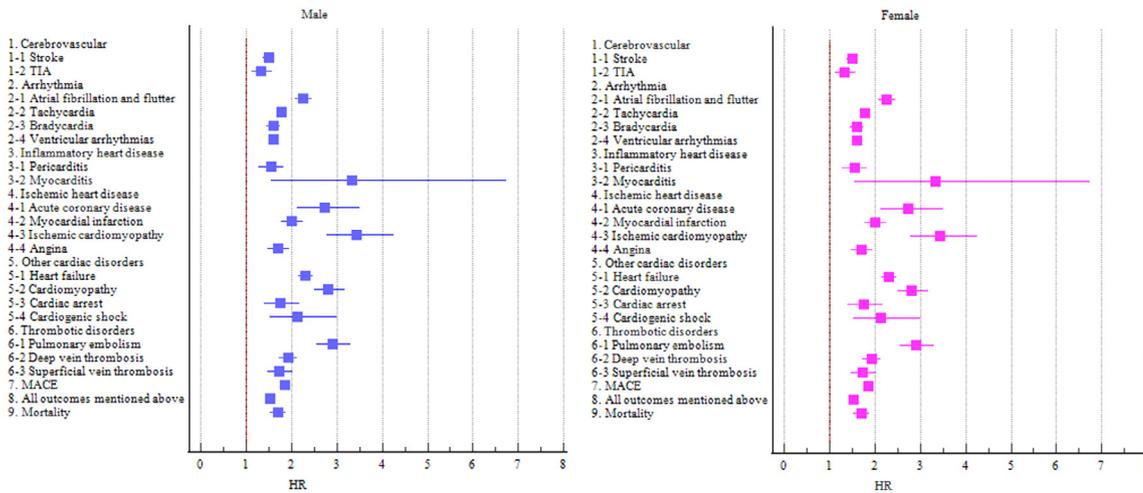


Figure 4. Forest plot of all cardiovascular outcomes stratified by gender.

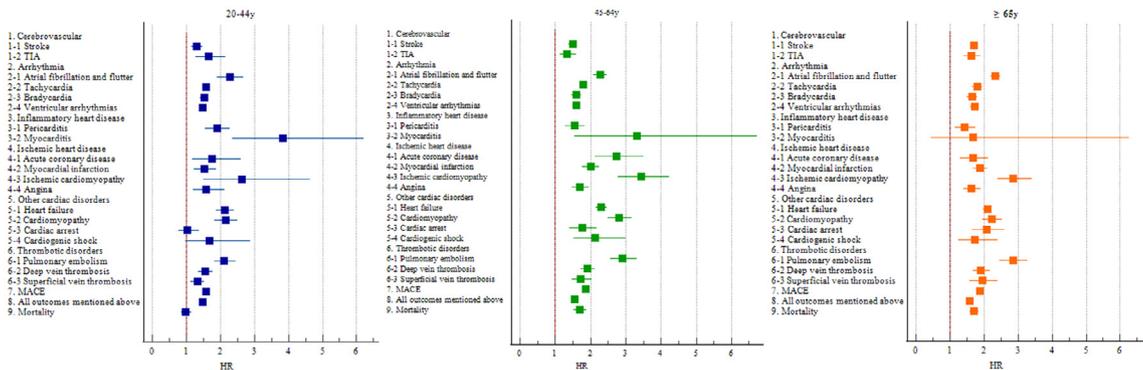


Figure 5. Forest plot of all cardiovascular outcomes stratified by age.

myocarditis (HR [95% CI] =6.119 [1.356-27.60]). In addition, compare 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-19¹⁴ and different mutant strains¹⁵ 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%.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.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.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.^{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.^{21,22} Furthermore, SARS-CoV-2 infection can trigger a cytokine storm; many pro-inflammatory cytokines and chemokines, such as TNF- α , IL-1 β , and IL-6, are overproduced, damaging various organs, including those in the cardiovascular system.^{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.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.²⁸ Finally, therapeutics for COVID-19, such as hydroxychloroquine and azithromycin, have adverse effects on the cardiovascular system.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. Secondly, 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.

Acknowledgments

This study was supported by National Nonprofit Institute Research Grant for Institute of Basic Theory for Chinese Medicine, CACMS (YZ-202014) and Young Elite Scientists Sponsorship Program by CACM (2021QNRC2-Bo1).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101619.

References

- 1 Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259–264.
- 2 Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ (Clin Res Ed)*. 2021;372:n693.
- 3 Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med*. 2020;35(5):1545–1549.
- 4 Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5(7):831–840.
- 5 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232.
- 6 Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ (Clin Res Ed)*. 2021;373:n1098.
- 7 Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603–605.
- 8 Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28(3):583–590.
- 9 Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. *PLoS Med*. 2020;17(9):e1003321.
- 10 Wang L, Wang Q, Davis PB, Volkow ND, Xu R. Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021. *World Psychiatry*. 2022;21(1):124–132.
- 11 Jorge A, D'Silva KM, Cohen A, et al. Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study. *Lancet Rheumatol*. 2021;3(2):e131–e1e7.
- 12 Vahia IV, Jeste DV, Reynolds 3rd CF. Older adults and the mental health effects of COVID-19. *JAMA*. 2020;324(22):2253–2254.
- 13 Hendren NS, de Lemos JA, Ayers C, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American heart association COVID-19 cardiovascular disease registry. *Circulation*. 2021;143(2):135–144.
- 14 Jamison DT, Wu KB. The east-west divide in response to COVID-19. *Engineering*. 2021;7(7):936–947.
- 15 Jain VK, Iyengar KP, Ish P. Elucidating causes of COVID-19 infection and related deaths after vaccination. *Diabetes Metabol Syndrome*. 2021;15(5):102212.
- 16 Ippolito M, Catalisano G, Marino C, et al. Mortality after in-hospital cardiac arrest in patients with COVID-19: a systematic review and meta-analysis. *Resuscitation*. 2021;164:122–129.
- 17 Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. *J Am Coll Cardiol*. 2020;75(22):2871–2872.
- 18 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
- 19 Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. *Heart Fail Rev*. 2021;26(1):1–10.
- 20 Wijeratne T, Sales C, Karimi L, Crewther SG. Acute ischemic stroke in COVID-19: a case-based systematic review. *Front Neurol*. 2020;11:1031.
- 21 Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J*. 2020;56(1).
- 22 Suh YJ, Hong H, Ohana M, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. *Radiology*. 2021;298(2):E70–e80.
- 23 Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543–558.
- 24 Ganguly M, Nandi A, Banerjee P, et al. A comparative study of IL-6, CRP and NT-proBNP levels in post-COVID multisystem inflammatory syndrome in children (MISC) and Kawasaki disease patients. *Int J Rheumatic Dis*. 2022;25(1):27–31.
- 25 De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J*. 2020;41(22):2083–2088.
- 26 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069.
- 27 Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811–818.
- 28 Bansal M. Cardiovascular disease and COVID-19. *Diabetes Metabol Syndrome*. 2020;14(3):247–250.
- 29 Ma L, Song K, Huang Y. Coronavirus disease-2019 (COVID-19) and cardiovascular complications. *J Cardiothorac Vasc Anesth*. 2021;35(6):1860–1865.