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Original Article

Long-term cardiovascular outcomes after exercise-based cardiac rehabilitation among coronavirus disease 2019 survivors: A nationwide cohort study

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) is associated with poor cardiac outcomes and an increased risk of long-term cardiovascular disease. Long-term cardiovascular outcomes among patients with COVID-19 after exercise-based cardiac rehabilitation remain largely unknown. This study aimed to investigate the long-term cardiovascular outcomes of COVID-19 survivors after exercise-based cardiac rehabilitation using real-world data. **Materials and Methods:** We analyzed the data from the US Collaborative Network of the TriNetX Research Database. Adults aged ≥18 years who were diagnosed with COVID-19 between 2020 and 2022 were enrolled in this study. The comparison comprised a cohort of patients receiving exercise-based cardiac rehabilitation and 1:1 propensity score-matched controls. **Results:** The exercise-based cardiac rehabilitation group was found to have lower risks of developing several long-term cardiovascular outcomes than the controls, such as mortality (hazard ratio [HR] = 0.75 [0.63–0.89]), stroke (HR = 0.81 [0.68–0.94]), myocardial infarction (HR = 0.75 [0.61–0.89]), ischemic cardiomyopathy (HR = 0.86 [0.75–0.99]), heart failure (HR = 0.73 [0.65–0.83]), and nonischemic cardiomyopathy (HR = 0.78 [0.63–0.92]). **Conclusion:** Among COVID-19 survivors, those undergoing cardiac rehabilitation had lower risks of cardiovascular outcomes, including mortality, stroke, myocardial infarction, ischemic cardiomyopathy, heart failure, and nonischemic cardiomyopathy, than those of controls.

Keywords: *Cohort, Coronavirus disease 2019, Exercise-based cardiac rehabilitation*

Introduction

The coronavirus disease 2019 (COVID-19), resulting from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented significant challenges in over 200 countries [1]. Evidence increasingly indicates that many individuals recovering from COVID-19 face a broad spectrum of long-term health effects, including cardiovascular issues [2]. COVID-19 not only leads to viral

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pneumonia but is also associated with various complications outside the lungs, such as cardiovascular and cerebrovascular diseases [3]. This virus can overstimulate the sympathetic nervous system, trigger an inflammatory cytokine storm, and promote hypercoagulable states [4]. These processes can cause lasting damage to the cardiovascular and respiratory systems, potentially resulting in irreversible complications such as congestive heart failure and reduced lung function, which may, in turn, heighten the risk of cardiovascular or cerebrovascular diseases in COVID-19 survivors [5].

Exercise-based cardiac rehabilitation is a multifaceted approach designed to meet the unique needs of individuals with heart disease, incorporating exercise training, promotion of physical activity, health education, management of cardiovascular risk, and psychological support [6-8]. The substantial evidence supporting the benefits of this type of rehabilitation has led the American College of Cardiology and the American Heart Association to recommend it as a Class I indication for patients diagnosed with acute coronary syndrome, those undergoing percutaneous coronary intervention, or those receiving coronary artery bypass graft surgery [9]. In addition, they advocate that exercise-based cardiac rehabilitation can benefit clinically stable heart failure patients by enhancing functional capacity, extending exercise duration, improving health-related quality of life, and potentially reducing mortality, categorizing it as a Class IIa indication [10]. In patients with COVID-19, rehabilitation may have a role in functional improvement [11]. Exercise-based therapy can be conducted with different modules among COVID-19 survivors [12]. Rehabilitation interventions are associated with improved functional exercise capacity, dyspnea, and quality of life in patients with post-COVID-19 conditions [13].

Despite many studies related to exercise-based cardiac rehabilitation in patients diagnosed with heart disease, no study has focused on long-term cardiovascular outcomes after exercise-based cardiac rehabilitation among COVID-19 survivors. Thus, we aimed to analyze the long-term cardiovascular outcomes of COVID-19 survivors based upon a US Collaborative Network of 60 healthcare organizations within the TriNetX Research Network.

Materials and methods

Data source

To investigate cardiovascular outcomes among patients with COVID-19 under exercise-based cardiac rehabilitation, we analyzed the electronic medical records from the TriNetX Analytics Research Network (Cambridge, Massachusetts, USA). TriNetX is a multicenter patient database that provides de-identified aggregate healthcare data from approximately 100 million patients spanning 60 healthcare organizations across the United States at the time of data collection [11]. TriNetX offered access to electronic medical records containing valuable information, including demographic details, diagnoses (using International Classification of Diseases, Tenth Revision, Clinical Modification, [ICD-10] codes), procedures (coded in the ICD-10-Procedure Coding System, or Current Procedural Terminology), and medication data (coded in the Veterans psAffairs National Formulary) [12,13].

TriNetX includes analytical tools that enable analyses at the patient level, while reporting only aggregated population-level data to ensure patient anonymity. This study was designed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines [14]. There was no patient or public involvement in this study. This study was approved by Taichung Veterans General Hospital (IRB number: SE22220A-1). Informed consent was waived by the IRB. This study was conducted in accordance with the Declaration of Helsinki.

Study population

Adult patients newly diagnosed with COVID-19 aged ≥18 between January 1, 2019, and December 31, 2022, were considered eligible for inclusion. A diagnosis of COVID-19 was made using the ICD-10 Code U07.1 or a positive record of SARS-CoV-2 and related RNA (TNX: LAB: 9088, 41458-1, 94511-3, 94746-5). We included patients who had never undergone exercise-based cardiac rehabilitation therapy before the index date. We further categorized the enrollees into two cohorts: an exercise-based cardiac rehabilitation cohort and a control cohort. The exercise-based cardiac rehabilitation cohort comprised patients with the ICD-10 code Z71.82, Healthcare Common Procedure Coding System Code S9472, and current procedure terminology code 1013171. The index date (when follow-up started) was defined as the first record of exercise-based cardiac rehabilitation.

Patients with outcomes of interest recorded before their respective index dates were excluded. Patients with an outcome event before their index date were excluded from the analyses for that corresponding outcome; that is, patients with stroke before the index date were not excluded from the analysis for myocardial infarction.

Covariates and confounders

The baseline demographic data of the included participants were extracted from TriNetX. Preexisting comorbidities and baseline medication use, which were considered potential confounding factors, were guided by previous research. Any preexisting comorbidity was defined as a diagnosis ascertained at least twice within the year preceding the index date. Any baseline medication use was defined as a drug prescribed for at least 30 days within 3 months before the index date.

Outcome measures

The primary outcome of interest was the occurrence of incident cardiovascular diseases, including mortality, stroke (ICD-10 codes of I60–I69), myocardial infarction (ICD-10 codes of I21–I25), ischemic cardiomyopathy (ICD-10 code of I25.5), deep vein thrombosis (ICD-10 codes of I82.2, I82.4, I82.5, I82.60, I82.62, I82.89, and I82.9), pulmonary embolism (ICD-10 codes of I26), heart failure (ICD-10 code of I50), nonischemic cardiomyopathy (ICD-10 codes of I42, I43), myocarditis (ICD-10 codes of I40, I41), pericarditis (ICD-10 codes of I30, I32), and endocarditis (ICD-10 codes of I33, I38).

The diagnostic accuracy of the aforementioned codes was validated with the high positive predictive values. All the study participants were tracked from their respective index

dates until the occurrence of any cardiovascular outcome or their last medical visit.

Statistical analysis

We used propensity score matching to generate the study cohorts with balanced baseline characteristics. Each study group was matched in a 1:1 ratio using greedy nearest neighbor matching for the age, sex, ethnicity, race, medical utilization, overweight and obesity, smoking, comorbidities, and baseline medication use. The standardized mean difference was calculated to evaluate any disparities in baseline demographic data, with a value of <0.1 indicating a negligible difference.

Cumulative probability curves were constructed using the Kaplan–Meier method. For each outcome, hazard ratios (HRs) were estimated using Cox proportional hazard models to elucidate the temporal relationship between exercise-based cardiac rehabilitation and incident cardiac outcomes. Statistical significance was defined as a two-sided $P < 0.05$. A confidence interval (CI) that did not contain 1 was considered significant. The proportional hazard assumption was examined using the generalized Schoenfeld approach built on the TriNetX platform.

Results

A flowchart of the cohort construction from 1,753,058 participants enrolled between January 1, 2019 and December 31, 2022, is provided in Figure 1. Individuals aged >18 years who were newly diagnosed with COVID-19 were included in the cohort. Individuals diagnosed with cardiovascular diseases before the index date were excluded from the study. After applying the exclusion criteria, the original study population (n = 8025) was divided into the exercise-based cardiac rehabilitation (n = 6420) and control (n = 1605) groups. The exercise-based cardiac rehabilitation group consisted of patients who underwent exercise-based cardiac rehabilitation. Participants in the control group did not undergo exercise-based cardiac rehabilitation.

In the present cohort, propensity score matching 1:1 according to age, sex, ethnicity, race, medical utilization, overweight and obesity, smoking, comorbidities, and baseline medications was used. After propensity score matching, 1320 patients who underwent exercise-based cardiac rehabilitation and 1320 controls were selected for this study.

Demographic characteristics, comorbidities, procedures, and baseline medications of the enrolled patients before and after propensity score matching are presented in Table 1. After matching, the mean ages of the participants in the exercise-based cardiac rehabilitation and control groups were 66.1 and 66.2 years, respectively. Approximately 46.1% of the exercise-based cardiac rehabilitation group and 45.1% of the control group were women. The majority of patients were Caucasians (66.5% and 71.1% in the exercise-based cardiac rehabilitation and control groups, respectively). After matching, the standard mean differences in all covariates were negligible between the two groups.

The risks of multiple cardiovascular outcomes among COVID-19 survivors in the exercise-based cardiac rehabilitation and control groups are presented as HRs with their corresponding CIs in Table 2. Upon follow-up, the exercise-based cardiac rehabilitation group was found to have lower risks of developing several long-term

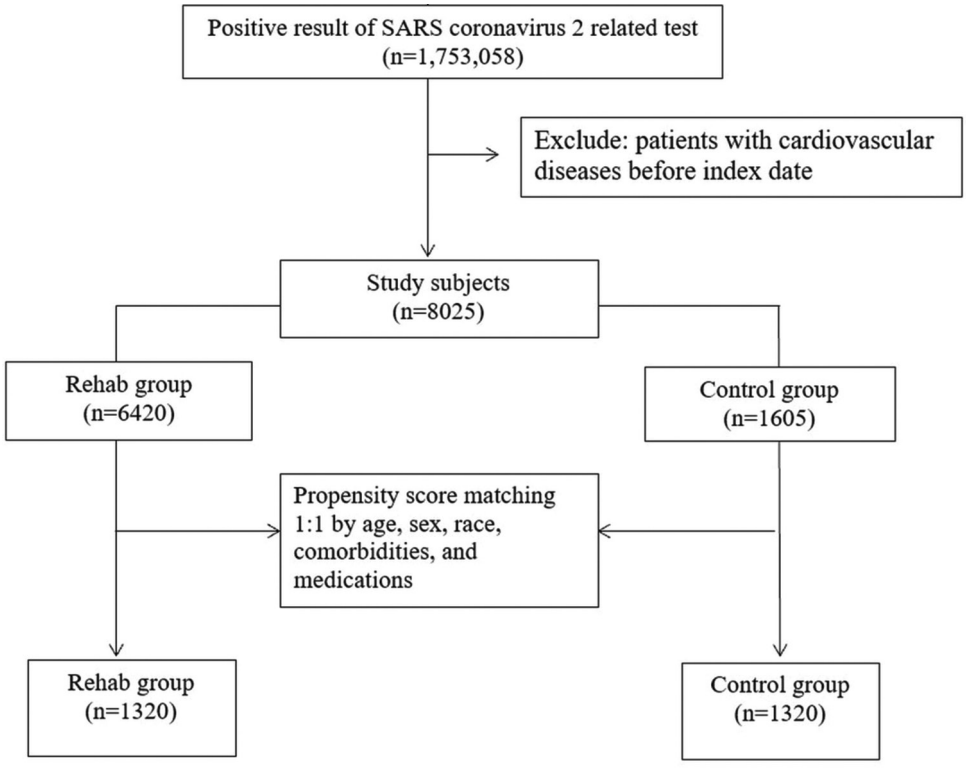

Figure 1: Study flow diagram

Table 1: Baseline characteristics of the study subjects

	Before matching			After matching		
	Rehabilitation group (*n*=6420), *n* (%)	Control group (*n*=1605), *n* (%)	SMD	Rehabilitation group (*n*=1320), *n* (%)	Control group (*n*=1320), *n* (%)	SMD
Age at index, mean±SD	66.5±14.7	66.3±15.1	0.017	66.1±15.3	66.2±15.6	0.006
Gender						
Female	2960 (46.1)	724 (45.1)	0.020	698 (44.0)	719 (45.3)	0.027
Male	3460 (53.9)	881 (54.9)	0.020	889 (56.0)	868 (54.7)	0.027
Race						
White	4269 (66.5)	1141 (71.1)	0.099	1102 (69.4)	1126 (71.0)	0.033
Unknown	957 (14.9)	248 (15.5)	0.015	246 (15.5)	245 (15.4)	0.002
Black or African American	1087 (16.9)	190 (11.8)	0.146	206 (13.0)	190 (12.0)	0.031
Asian	80 (1.2)	20 (1.2)	<0.001	25 (1.6)	20 (1.3)	0.027
American Indian	18 (0.3)	10 (0.6)	0.051	10 (0.6)	10 (0.6)	<0.001
Native Hawaiian	10 (0.2)	10 (0.6)	0.075	10 (0.6)	10 (0.6)	<0.001
Social economic status						
Housing/economic circumstances problem	54 (0.8)	20 (1.2)	0.040	13 (0.8)	17 (1.1)	0.026
Employment or unemployment problems	10 (0.2)	10 (0.6)	0.075	10 (0.6)	10 (0.6)	<0.001
Comorbidities						
Tobacco use	112 (1.7)	56 (3.5)	0.109	39 (2.5)	46 (2.9)	0.027
Nicotine dependence	272 (4.2)	69 (4.3)	0.003	64 (4.0)	66 (4.2)	0.006
Alcohol related disorders	99 (1.5)	34 (2.1)	0.043	25 (1.6)	29 (1.8)	0.019
Neoplasms	978 (15.2)	299 (18.6)	0.091	283 (17.8)	290 (18.3)	0.011
Dementia	145 (2.3)	41 (2.6)	0.019	42 (2.6)	39 (2.5)	0.012
Chronic kidney disease	606 (9.4)	186 (11.6)	0.070	197 (12.4)	181 (11.4)	0.031
Inflammatory polyarthropathies	395 (6.2)	134 (8.3)	0.085	134 (8.4)	130 (8.2)	0.009
Diseases of the liver	260 (4.0)	77 (4.8)	0.036	67 (4.2)	73 (4.6)	0.018
Chronic obstructive pulmonary disease	455 (7.1)	130 (8.1)	0.038	132 (8.3)	127 (8.0)	0.012
Procedure						
Cardiovascular procedures	1926 (30.0)	436 (27.2)	0.063	451 (28.4)	434 (27.3)	0.024
Medication						
Antivirals	620 (9.7)	142 (8.8)	0.028	138 (8.7)	137 (8.6)	0.002
Glucocorticoids	2412 (37.6)	571 (35.6)	0.041	556 (35.0)	563 (35.5)	0.009
ACE inhibitors	883 (13.8)	296 (18.4)	0.128	294 (18.5)	287 (18.1)	0.011
Angiotensin II inhibitors	768 (12.0)	198 (12.3)	0.011	187 (11.8)	196 (12.4)	0.017
Alpha-blockers	465 (7.2)	129 (8.0)	0.030	129 (8.1)	125 (7.9)	0.009
Beta-blockers	2101 (32.7)	531 (33.1)	0.008	512 (32.3)	521 (32.8)	0.012
Calcium channel blockers	1299 (20.2)	308 (19.2)	0.026	313 (19.7)	305 (19.2)	0.013
Diuretics	1655 (25.8)	506 (31.5)	0.127	471 (29.7)	493 (31.1)	0.030
Platelet aggregation inhibitors	1034 (16.1)	242 (15.1)	0.028	233 (14.7)	237 (14.9)	0.007
Blood glucose regulation agents	1624 (25.3)	384 (23.9)	0.032	392 (24.7)	374 (23.6)	0.027
Antiarrhythmics	1770 (27.6)	359 (22.4)	0.120	338 (21.3)	352 (22.2)	0.021
Antilipemic agents	1868 (29.1)	570 (35.5)	0.138	550 (34.7)	557 (35.1)	0.009
Cardiovascular agents, other	117 (1.8)	29 (1.8)	0.001	35 (2.2)	28 (1.8)	0.032
Hormones/synthetics/modifiers	3240 (50.5)	851 (53.0)	0.051	837 (52.7)	835 (52.6)	0.003
Gastric medications, other	1597 (24.9)	407 (25.4)	0.011	379 (23.9)	392 (24.7)	0.019
Antihypertensive combinations	53 (0.8)	10 (0.6)	0.024	10 (0.6)	10 (0.6)	<0.001

SD: Standard deviation, SMD: Standardized mean difference, ACE: Angiotensin-converting enzyme

cardiovascular outcomes than the controls, such as mortality (HR = 0.75 [0.63–0.89]), stroke (HR = 0.81 [0.68–0.94]), myocardial infarction (HR = 0.75 [0.61–0.89]), ischemic cardiomyopathy (HR = 0.86 [0.75–0.99]), heart failure (HR = 0.73 [0.65–0.83]), and nonischemic cardiomyopathy (HR = 0.78 [0.63–0.92]).

In addition, other cardiovascular outcomes showed no statistically significant differences in risks between the exercise-based cardiac rehabilitation group and the control group, including transient ischemic attack (TIA) (HR = 0.93 [0.65–1.27]), deep-vein thrombosis (HR = 0.93 [0.82–1.13]), pulmonary embolism (HR = 0.90 [0.38–2.21]), myocarditis (HR = 0.88 [0.71–1.04]), pericarditis (HR = 0.79 [0.22–2.83]), and endocarditis (HR = 0.73 [0.39–1.34]).

Discussion

In this study involving 1320 participants in the exercise-based cardiac rehabilitation group and 1320

Table 2: Long-term cardiovascular outcomes after exercise-based cardiac rehabilitation among coronavirus disease 2019 survivors

Outcome	HR (95% CI)
Mortality	0.75 (0.63–0.89)
Stroke	0.81 (0.68–0.94)
TIA	0.93 (0.65–1.27)
Myocardial infarction	0.75 (0.61–0.89)
Ischemic cardiomyopathy	0.86 (0.75–0.99)
Deep-vein thrombosis	0.93 (0.82–1.13)
Pulmonary embolism	0.90 (0.38–2.21)
Heart failure	0.73 (0.65–0.83)
Nonischemic cardiomyopathy	0.78 (0.63–0.92)
Myocarditis	0.88 (0.71–1.04)
Pericarditis	0.79 (0.22–2.83)
Endocarditis	0.73 (0.39–1.34)

HR: Hazard ratio, CI: Confidence interval, TIA: Transient ischemic attack

matched controls, we found that COVID-19 survivors under exercise-based cardiac rehabilitation had lower risks of cardiovascular outcomes, including mortality, stroke, myocardial infarction, ischemic cardiomyopathy, heart failure, and nonischemic cardiomyopathy, compared to the controls. To our knowledge, this is the first large-scale cohort study to examine the risk of cardiovascular outcomes after exercise-based cardiac rehabilitation in COVID-19 survivors.

Exercise-based cardiac rehabilitation programs typically include structured exercise training tailored to individual needs and abilities. Regular physical activity and exercise improve cardiovascular fitness, reduce cholesterol levels, lower blood pressure, and improve glucose metabolism, all of which contribute to a lower risk of cardiovascular events [6-8,15-19]. A recent cohort study revealed that exercise-based cardiac rehabilitation was associated with a lower risk of all-cause mortality among patients with cardiovascular disease, and this benefit was independent of sex, age, socioeconomic status, and comorbidities [20].

While patients with COVID-19 are associated with poor cardiac outcomes, we hypothesized that initiating exercise-based cardiac rehabilitation for such patients may have positive benefits. Regular exercise-based cardiac rehabilitation improves cardiovascular fitness, lowers blood pressure, reduces low-density lipoprotein cholesterol levels, and improves glucose metabolism. It may also improve respiratory function and help the patients to maintain oxygen saturation levels. Early mobilization also has benefits in improving respiratory symptoms, fatigue, functional capacity, and health-related quality of life in patients with COVID-19.

Although the risk factors for TIA are similar to those for stroke, the incidence of TIA is substantially more difficult to estimate. Owing to its transient nature, individuals who experience TIA may not seek medical attention or may delay seeking care if their symptoms resolve quickly [21]. In addition, many individuals who experience TIA may not recognize the significance of their symptoms or may attribute them to other causes, such as fatigue or stress [22]. Consequently, TIAs may be underreported in population-based studies or healthcare databases. Moreover, during the COVID-19 pandemic, a documented trend of patients being more hesitant to seek medical care was observed, including visiting hospitals or clinics for non-COVID-related issues [23]. Thus, the incidence of TIA may be even more difficult to estimate.

Although COVID-19 results in a unique prothrombotic milieu, leading to the arterial and venous thrombosis [4], evidence is lacking regarding whether exercise-based cardiac rehabilitation can reduce hypercoagulopathy. This may explain why the risk of deep vein thrombosis and pulmonary embolism did not decrease.

Several risk factors contribute to the development of inflammatory heart disease, including infections, autoimmune diseases, and toxic materials from the environment [24-28]. These risk factors may not be reduced by exercise-based cardiac rehabilitation.

Our study had certain limitations. First, we used validated outcome definitions; however, misclassification bias may not have been completely avoided. Second, despite the application of propensity score matching to balance the covariates between the study cohorts, residual confounding may still exist because the healthcare database we used has weaknesses inherent to electronic health record studies. Third, the propensity score-matched design used in this cohort study might result in a small group for comparison, which lacks the generalizability of the results. Finally, we were unable to evaluate the characteristics of exercise-based cardiac rehabilitation.

Conclusions

The exercise-based cardiac rehabilitation group had a lower risk of cardiovascular outcomes, including mortality, stroke, myocardial infarction, ischemic cardiomyopathy, heart failure, and nonischemic cardiomyopathy, than the controls among COVID-19 survivors. Further studies with a larger number of COVID-19 survivors are required to determine whether our results are universal or conclusive.

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Conflicts of interest

There are no conflicts of interest.

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