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RESEARCH LETTER

Exercise rehabilitation associates with lower mortality and hospitalisation in cardiovascular disease patients with COVID-19

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The COVID-19 pandemic has caused global health, social, and economic system challenges. In an effort to try and reduce transmission rates, most countries have varying levels of societal 'lockdowns' and social restrictions in place. This creates a unique challenge for the promotion of physical activity and exercise, which we know has profound physical and mental health benefits. Although there was initial promise of increased population *interest* in physical activity and exercise at the beginning of the COVID-19 pandemic,[1] recent large-scale data from over 455 000 people has demonstrated a 27% decrease in average daily steps within 30 days of the pandemic declaration.[2]

It may therefore be more important now than ever to facilitate physical activity and exercise promotion during and post-COVID-19. Despite, recent collaborative efforts developing post-COVID-19 guidelines for athletes returning to exercise,[3] limited evidence is available for the impact of exercise and cardiac rehabilitation (CR) on clinical outcomes following-COVID-19. Secondary prevention through comprehensive CR has been recognized as the most cost-effective intervention to ensure favourable outcomes across a wide spectrum of cardiovascular diseases.[4] Given there is a high prevalence of cardiovascular disease among patients with COVID-19, and >7% experience COVID-19 induced myocardial injury,[5] CR following COVID-19 infection warrants investigation. The objective of this study was therefore to compare mortality, hospitalization, and cardiovascular comorbidity between patients with cardiovascular disease and COVID-19 with and without an electronic medical record (EMR) of CR or exercise programmes.

This retrospective observational study was conducted in October 2020 with anonymized data provided by TriNetX, a global federated health research network with access to EMRs from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the USA. Patients with COVID-19 were identified via Centers for Disease Control and Prevention (CDC) coding using ICD-10-CM codes, or specific laboratory Logical Observation Identifiers Names and Codes.[6] All patients were aged ≥18 years with COVID-19 recorded in EMRs between 20 January 2020 (date COVID-19 first confirmed in the USA)[7] and 26 May 2020 (to allow 4-month follow-up). Cardiac rehabilitation was identified from ICD-10-CM codes Z71.82 (Exercise counselling), HCPCS code S9472 (CR programme, non-physician provider, per diem), or CPT code 1013171 (physician or other qualified healthcare professional services for outpatient CR). Correspondingly, these CR and exercise programme codes were excluded in the propensity score-matched controls. At the time of the search, 33 participating healthcare organizations had data available for patients meeting the study inclusion criteria. Thus, following propensity score matching, the cohort consisted of patients with cardiovascular disease and a diagnosis of COVID-19; who either were referred for CR and exercise programmes (due to cardiovascular disease) within 3 months of a COVID-19 diagnosis (intervention) or were not referred (control).

Baseline characteristics were compared using χ^2 tests or independent-sample *t*-tests. Using logistic regression, CR and exercise patients were 1:1 propensity score matched with controls for age, sex, race, acute myocardial infarction (AMI), heart failure, hypertensive disease, diabetes mellitus, chronic kidney disease, cerebrovascular disease, cardiovascular procedures (e.g. cardiography, echocardiography, cardiac catheterization, cardiac devices, electrophysiological procedures), and cardiovascular medications (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, angiotensin-converting enzyme inhibitors). These variables were chosen because they are established risk factors for cardiovascular disease and/or mortality or were significantly different between the two cohorts. Logistic regression produced odds ratios (OR) with 95% confidence intervals (CI) for mortality, hospitalization, AMI, stroke, and heart failure at 4 months following a COVID-19 diagnosis, comparing exercise-based CR with propensity score-matched controls. Statistical significance was set at $P < 0.05$.

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Table 1 Baseline characteristics % (*n*)[a] of the COVID-19 populations with and without exercise-based CR before and after propensity score matching

	Initial populations			Propensity score-matched populations		
	COVID-19 without CR (*n* = 400 383)	**COVID-19 with CR (*n* = 643)**	***P*-value**	**COVID-19 without CR (*n* = 643)**	**COVID-19 with CR (*n* = 643)**	***P*-value**
Age (years); mean (SD)	47.8 (20.2)	59.4 (18.5)	<0.001	60.3 (18.4)	59.4 (18.5)	0.348
Female	57.2 (229 022)	36.7 (236)	<0.001	37.9 (244)	36.7 (236)	0.645
Race[b]						
White	63.1 (252 745)	76.8 (494)	<0.001	76.8 (494)	76.8 (494)	1
Black or African American	17 (68 120)	17.3 (111)	0.867	17.7 (114)	17.3 (111)	0.826
Unknown	16.7 (66 945)	4.2 (27)	<0.001	3.9 (25)	4.2 (27)	0.777
Hypertensive diseases	6.7 (26 774)	72 (463)	<0.001	53.3 (343)	72 (463)	<0.001
Diabetes mellitus	21.6 (86 335)	70.5 (453)	<0.001	74.8 (481)	70.5 (453)	0.08
Heart failure	4.6 (18 513)	38.4 (247)	<0.001	40.9 (263)	38.4 (247)	0.362
Acute myocardial infarction	1.3 (5016)	35.9 (231)	<0.001	34.5 (222)	35.9 (231)	0.599
Chronic kidney disease	9.9 (39 515)	33.1 (213)	<0.001	33.7 (217)	33.1 (213)	0.813
Cerebrovascular diseases	3.4 (13 784)	18.5 (119)	<0.001	18.1 (117)	18.5 (119)	0.829
Cardiovascular procedures[c]	5.2 (20 806)	18.5 (119)	<0.001	18.2 (117)	18.5 (119)	0.885
Cardiovascular medications[d]	38.3 (153 191)	90.7 (583)	<0.001	91 (585)	90.7 (583)	0.847

CR, cardiac rehabilitation; SD, standard deviation.
[a]Values are % (*n*) unless otherwise stated. Baseline characteristics were compared using a χ^2 test for categorical variables and an independent-sample *t*-test for continuous variables.
[b]Data are taken from structured fields in the electronic medical record systems of the participating healthcare organizations, therefore, there may be regional or country-specific differences in how race categories are defined.
[c]Cardiovascular procedures include cardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures.
[d]Cardiovascular medications include beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and angiotensin-converting enzyme inhibitors.

In total, 400 383 patients with COVID-19 met the inclusion criteria for the control group and 643 patients with COVID-19 met the inclusion criteria for the exercise-based CR cohort. Compared with controls, the exercise-based CR cohort were generally older, had less females, and more cardiovascular comorbidities (*Table 1*). Following propensity score matching, cohorts were well balanced for age, race, sex, comorbidities, cardiovascular medications, and cardiovascular procedures ($P > 0.05$; *Table 1*).

Using the propensity score-matched cohort, mortality at 4 months from COVID-19 diagnosis was proportionally lower with 1.6% (*n* = 10 of 639 patients) in the exercise-based CR cohort compared with 6.4% (*n* = 41 of 638 patients) in the controls (OR 0.23, 95% CI 0.12–0.47). Re-hospitalizations were also proportionally lower with 15.1% (*n* = 97 out of 643 patients) in the exercise-based CR cohort compared with 30.8% (*n* = 198 out of 643 patients) in the controls (OR 0.4, 95% CI 0.3–0.53). No differences were found for AMI (OR 1, 95% CI 0.42–2.48), stroke (0.95, 95% CI 0.39–2.31), or heart failure (OR 0.96. 95% CI 0.4–2.34).

Several limitations are of note. Firstly, the characterization of COVID-19, health conditions, and CR and exercise programmes were based on ICD codes from EMRs, and reporting of conditions with ICD codes may vary by patient characteristics and healthcare organizations.[8] Indeed, we do not know the severity of individual COVID-19 cases, which may have affected the results. However, before propensity score matching, there was no difference in relative mortality between the cohorts. Thus, it may not be illness severity that differentiated patients receiving CR or not within this cohort. We also do not know details of the CR interventions, including whether they were comprehensive, multicomponent or exercise-only, which limits the ability to identify active 'intervention ingredients'. Due to closures in many traditional (centre-based) CR programmes, evaluation of different types of CR is needed, particularly frameworks that are adapted to COVID-19 delivery such as 'cardiac telerehabilitation'.[9] Another important caveat, an EMR of CR and exercise does not necessarily provide information as to whether a patient attended, the intervention type and dose, or intervention adherence. We could also not determine the influence of attending different healthcare organizations due to data privacy restrictions. Finally, although we were able to match patients for important comorbidities and demographic factors, residual confounding may present.

In summary, the present study of over 1200 patients with cardiovascular disease demonstrated that exercise-based CR programmes following COVID-19 associated with significantly lower odds of mortality and re-hospitalization at 4 months, when compared to propensity score-matched patients without CR. The provision of exercise rehabilitation for cardiovascular patients following a COVID-19 diagnosis is therefore a promising entity and warrants further investigation.

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