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### Article

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**Post-COVID-19 Outcomes and Exercise Rehabilitation**

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

36

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

48

49 This retrospective observational study was conducted in October 2020 with anonymised data  
50 provided by TriNetX, a global federated health research network with access to EMRs from  
51 participating academic medical centres, specialty physician practices, and community hospitals,  
52 predominantly in the United States. Patients with COVID-19 were identified via Centers for Disease  
53 Control and Prevention (CDC) coding using ICD-10-CM codes, or specific laboratory Logical  
54 Observation Identifiers Names and Codes.<sup>6</sup> All patients were aged  $\geq 18$  years with COVID-19 recorded  
55 in EMRs between January 20, 2020 (date COVID-19 first confirmed in the US)<sup>7</sup> and May 26, 2020 (to  
56 allow 4-month follow-up). CR was identified from ICD-10-CM codes Z71.82 (Exercise counselling),  
57 HCPCS code S9472 (CR program, non-physician provider, per diem), or CPT code 1013171 (Physician  
58 or other qualified health care professional services for outpatient CR). Correspondingly, these CR and  
59 exercise programme codes were excluded in the propensity score-matched controls. At the time of  
60 the search, 33 participating healthcare organisations had data available for patients meeting the study  
61 inclusion criteria. Thus, following propensity score matching, the cohort consisted of patients with  
62 cardiovascular disease and a diagnosis of COVID-19; who either were referred for CR and exercise

63 programmes (due to cardiovascular disease) within 3-months of a COVID-19 diagnosis (intervention)  
64 or were not referred (control).

65  
66 Baseline characteristics were compared using chi-squared tests or independent-sample t-tests. Using  
67 logistic regression, CR and exercise patients were 1:1 propensity score-matched with controls for age,  
68 sex, race, acute myocardial infarction (AMI), heart failure, hypertensive disease, diabetes mellitus,  
69 chronic kidney disease, cerebrovascular disease, cardiovascular procedures (e.g. cardiography,  
70 echocardiography, cardiac catheterisation, cardiac devices, electrophysiological procedures), and  
71 cardiovascular medications (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents,  
72 antianginals, calcium channel blockers, ACE inhibitors). These variables were chosen because they are  
73 established risk factors for AF and/or mortality or were significantly different between the two  
74 cohorts. Logistic regression produced odds ratios (OR) with 95% confidence intervals (CI) for mortality,  
75 hospitalisation, AMI, stroke, and heart failure at 4-months following a COVID-19 diagnosis, comparing  
76 CR and exercise with propensity score-matched controls. Statistical significance was set at  $P < 0.05$ .

77  
78 In total, 400,383 patients with COVID-19 met the inclusion criteria for the control group and 643  
79 patients with COVID-19 met the inclusion criteria for the CR and exercise cohort. Compared to  
80 controls, the CR and exercise cohort were generally older, had less females, and more cardiovascular  
81 comorbidities (Table 1). Following propensity score-matching, cohorts were well balanced for age,  
82 race, sex, comorbidities, cardiovascular medications and cardiovascular procedures ( $p > 0.05$ ; Table 1).

83  
84 Using the propensity score-matched cohort, and excluding patients with outcomes outside the  
85 measurement window, mortality at 4-months from COVID-19 diagnosis was proportionally lower with  
86 1.6% (n=10 of 639 patients) in the CR and exercise cohort compared to 6.4% (n=41 of 638 patients) in  
87 the controls (OR 0.23, 95% CI 0.12-0.47). Re-hospitalisations were also proportionally lower with  
88 15.1% (n=97 out of 643 patients) in the CR and exercise cohort compared to 30.8% (n=198 out of 643  
89 patients) in the controls (OR 0.4, 95% CI 0.3-0.53). No differences were found for AMI (OR 1, 95% CI  
90 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).

91  
92 Several limitations are of note. Firstly, the characterisation of COVID-19, health conditions, and CR and  
93 exercise programmes were based on ICD codes from EMRs, and reporting of conditions with ICD codes  
94 may vary by patient characteristics and healthcare organisations.<sup>8</sup> Indeed, we do not know the severity  
95 of individual COVID-19 cases, which may have affected the results. However, before propensity score  
96 matching, there was no difference in relative mortality between the cohorts. Thus, it may not be illness

97 severity that differentiated patients receiving CR or not within this cohort. We also do not know details  
98 of the CR interventions, including whether they were comprehensive, multicomponent or exercise-  
99 only, which limits the ability to identify active ‘intervention ingredients.’ Due to closures in many  
100 traditional (centre-based) CR programmes, evaluation of different types of CR is needed, particularly  
101 frameworks that are adapted to COVID-19 delivery such as ‘cardiac telerehabilitation’.<sup>9</sup> Another  
102 important caveat, an EMR of CR and exercise does not necessarily provide information as to whether  
103 a patient attended, the intervention type and dose, or intervention adherence. We could also not  
104 determine the influence of attending different healthcare organizations due to data privacy  
105 restrictions. Finally, although we were able to match patients for important co-morbidities and  
106 demographic factors, residual confounding may present.

107

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

114

115 **Disclosures**

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121

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124

125 **Authorship**

126 BJR and GYHL contributed to the conception or design of the work. BJR contributed to the  
127 acquisition, analysis, and interpretation of data for the work. BJR drafted the manuscript. SLH, EFE,  
128 PU, IGJ, NW, and GYHL critically revised the manuscript. All gave final approval and agree to be  
129 accountable for all aspects of work ensuring integrity and accuracy.

130

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**Table 1.** Baseline characteristics %(*n*)\* of the COVID-19 populations with and without CR and exercise 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)	<i>P</i> -value	COVID-19 without CR (n=643)	COVID-19 with CR (n=643)	<i>P</i> -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 <sup>a</sup>						
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 (5,016)	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 <sup>b</sup>	5.2 (20,806)	18.5 (119)	<0.001	18.2 (117)	18.5 (119)	0.885
Cardiovascular Medications <sup>c</sup>	38.3 (153,191)	90.7 (583)	<0.001	91 (585)	90.7 (583)	0.847

\*Values are % (*n*) unless otherwise stated. Baseline characteristics were compared using a chi-squared test for categorical variables and an independent-sample t-test for continuous variables. <sup>a</sup>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.

<sup>b</sup>Cardiovascular procedures include cardiography, echocardiography, catheterization, cardiac devices, electrophysiological procedures. <sup>c</sup>Cardiovascular medications include beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors.

CR; cardiac rehabilitation and exercise programmes, SD; standard deviation.