Assessment of Exercise Capacity of Individuals with Long COVID: A Cross-sectional Study

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ABSTRACT **Background:** Clinical investigations of long-term effects of coronavirus disease 2019 (COVID-19) are rarely translated to objective findings.

Objectives: To assess the functional capacity of individuals reported on deconditioning that hampered their return to their pre-COVID routine.

Methods: Assessment included the 6-minute walk test (6MWT) and the 30-second sit-to-stand test (30-STST). We compared the expected and observed scores using the Wilcoxon signed-rank test. Predictors of test scores were identified using linear regression models.

Results: We included 49 individuals, of whom 38 (77.6%) were recovering from mild COVID-19. Twenty-seven (55.1%) individuals had a 6MWT score lower than 80% of expected. The average 6MWT scores were 129.5 ± 121.2 meters and 12.2 ± 5.0 repeats lower than expected scores, respectively ($P < 0.001$ for both). The 6MWT score was 107.3 meters lower for individuals with severe COVID-19 ($P = 0.013$) and rose by 2.7 meters per each 1% increase in the diffusing capacity of carbon monoxide ($P = 0.007$). The 30-STST score was 3.0 repeats lower for individuals who reported moderate to severe myalgia ($P = 0.038$).

Conclusions: Individuals with long COVID who report on deconditioning exhibit significantly decreased physical capacity, even following mild acute illness. Risk factors include severe COVID-19 and impaired diffusing capacity or myalgia during recovery.

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A significant proportion of individuals recovering from coronavirus disease 2019 (COVID-19) continues to experience effects (long COVID), even following mild acute illness [1]. In most cases, these symptoms tend to abate over time. Still, a group of individuals may present with debilitating long lasting symptoms that prevent them from returning to their pre-COVID-19 functional state and impair their quality of life [2]. It is likely that rehabilitation programs facilitate their recovery [3,4]; however, the medical literature evaluating patient assessment and potential interventions is still scarce [5].

To be able to consider possible interventions, researchers must assess the physical capacity of individuals with debilitating long COVID. Long COVID is diagnosed based on patient reports of symptoms, combined with exclusion of other possible causes. Thus far, the clinical assessment of these individuals mainly relied on quality-of-life questionnaires and other self-reported functional measures [5], which were limited by their subjective nature.

Physical exercise assessment provides objective measures for the functional capacity of an individual. Of the several validated tests, the 6-minute walk test (6MWT), an easy-to-perform tool that can be conducted at time of clinic visit, is commonly used for objectively assessing the functional capacity of individuals with moderate-to-severe pulmonary disease [6]. The 6MWT has been shown to elicit maximal oxygen consumption like that evoked by cardiopulmonary exercise stress test (CPET) [7]. The two tests also highly correlate with respect to the peak work [8]. These findings remained consistent across different sub-populations [8].

In the current study, we assessed the exercise capacity of individuals with overtly symptomatic long COVID by implementing the 6MWT and additional exercise assessment tests.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

Rabin Medical Center (Beilinson Campus) operates a COVID-19 recovery clinic, which provides comprehensive as-

sessment and care for individuals recovering from COVID-19. To be eligible for a visit, one must have been diagnosed with COVID-19 by either polymerase chain reaction. These individuals were invited for evaluation at least 4 weeks following their diagnosis. During a visit, they were examined by an infectious diseases physician, a pulmonologist, and a social worker. They completed pulmonary function testing. Those with debilitating symptoms that hampered their attempts to return to their pre-COVID routine were referred for functional assessment and physical therapy. We conducted a cross-sectional study, which included consecutive individuals who were referred to physical therapy, and assessed their physical capacity, including possible clinical correlates for poorer functioning.

DATA COLLECTION

Information on demographics (age and sex), co-morbidities, smoking status, body mass index, and the acute COVID-19 illness was retrieved from patient medical charts. Acute COVID-19 severity was defined in accordance with the World Health Organization (WHO) guidelines [9]. During their clinic visit, the patients reported on their long COVID symptoms using a designated questionnaire, in which they were asked to rank each symptom on a 0–3 scale. Symptoms that were ranked as 2 to 3 were interpreted as moderate to severe. The case managing physician used this questionnaire during the assessment and documented the symptoms as well as other clinical and sociodemographic parameters, such as the degree of pre-COVID physical activity and pre- and post-COVID employment status.

We used the WHO guidelines on physical activity and sedentary behavior to define the individual's physical activity. Physically active individuals were those who undertook aerobic activity of more than 75 minutes or more than 150 minutes per week for moderate or vigorous activities, respectively [10].

We documented the employment status based on three levels: full-time job, part-time job, and unemployed. We defined post-COVID employment or physical activity status decline whenever the employment level or activity level was lower during the post-COVID period compared to the pre-COVID period.

PHYSICAL ASSESSMENT TESTS

The physical assessment was conducted by experienced physiotherapists. In the current study, we extracted data from patient physical therapy files. The assessment included four main tests: the 6MWT, reported as the distance (in meters) traversed within 6 minutes; the 30-second sit-to-stand test (30-STST), reported as the number of sit-to-stand transitions conducted during 30 seconds; the timed-up-and-go test (TUGT), reported as and the time (in seconds) that passed until completion of the task; and the dominant handgrip test, expressed in kilograms.

We implemented validated equations to calculate the individual's expected result for the 6MWT [11] and 30-STST [12]. For the TUGT, we calculated the proportion of individuals with an extremely poor performance, those above the 95th percentile [13,14]. We measured the hand grip of the dominant hand and calculated the proportion of individuals who scored below the lower limit for the right hand, based on the manufacturer's guidance [15].

PULMONARY FUNCTION TESTING

Pulmonary function testing was performed in accordance with the American Thoracic Society recommendations [16]. We assessed the diffusing capacity of carbon monoxide (DLCO) of all participating individuals and defined impaired DLCO as a result < 80% of the expected value, standardized for age, sex, and height.

STATISTICAL ANALYSIS

We used descriptive statistics with measures of central tendency and dispersion to describe the study population. Comparisons of subgroups based on the results of the physical assessment tests or on demographics and clinical parameters were implemented using the Mann-Whitney U test and Fisher's exact for continuous and categorical variables, respectively. We compared the expected and observed results of the 6MWT and 30-STST using the Wilcoxon signed-rank test. Linear regression models were implemented to identify predictors of physical assessment test scores. Variables were introduced to the models based on the univariate analysis ($P < 0.10$). We used Spearman's rank correlation coefficient to evaluate collinearity (variables for which the correlation coefficient was > 0.6 were assessed in separate models). Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

ETHICS APPROVAL

The local Research Ethics Committee at Rabin Medical Center approved the study protocol (RMC-0485-2020). All participating individuals signed informed consent forms.

RESULTS

Between July 2020 and March 2021, 50 (7.9%) of the 635 symptomatic individuals who were evaluated at our COVID recovery clinic were referred to our department of physical therapy and completed exercise assessments. Of this group, one individual (2%) had no documented 6MWT; therefore, a total of 49 individuals were included for analysis.

The mean age of the study population was 48.3 years ± 10.2 (range 28–71 years) and 36 (73.5%) were female. These individuals were recovering from mild (n=38, 77.6%), moderate (n=2, 4.1%), severe (n=7; 14.3), or critical (n=2, 4.1%) COVID-19. Their post-COVID medical evaluation was conducted on average 3 months following their acute COVID-19 diagnosis (89 days ± 36); their physical therapy assessment occurred approximately one month later (127 days from diagnosis ± 55).

PHYSICAL ASSESSMENT

Twenty-seven (55.1%) individuals had a 6MWT score lower than 80% of expected. These individuals were younger (45.0 vs. 52.4 years, $P = 0.009$) and tended to have a sedentary lifestyle prior to COVID-19 (92.0% [n=23] vs. 61.9% [n=22], $P = 0.028$). In addition, among those with poorer 6MWT scores, a higher proportion was incapable of returning to their pre-COVID employment level (18/25 [72.0%] vs. 6/22 [27.3%], $P = 0.003$), reported on myalgia (18/27 [66.7%] vs. 7/22 [31.8%], $P = 0.022$), and experienced pathological pulmonary diffusion capacity (16/26 [61.5%] vs. 4/22 [18.2%], $P = 0.003$) [Table 1].

The study population had a significantly reduced physical capacity, compared to that expected for their age and sex, as reflected by the results of the physical assessment tests [Table 2]. The mean 6MWT result was 429 ± 115 meters, in average 20% or 130 meters lower than the expected result of 559 ± 85 meters ($P < 0.001$). The group of individuals who were physically active prior to COVID-19 tended to traverse a slightly greater distance than those who were not (86% vs. 78% of the expected result, $P = 0.158$). However, the result of this group remained significantly reduced when compared to the expected distance (average 82 ± 101 meters lower than expected, $P = 0.047$).

The study population also exhibited a low performance in the 30-STST. The mean result for the total sample was 12 ± 5 repeats, only 50% of the expected average value of 25 ± 3, $P < 0.001$. No significant differences were noted based on the pre-COVID physical activity.

Poorer performance was also noted for the TUGT and dominant hand grip. For 9 individuals (19.6%), the duration to accomplish the TUGT was extremely prolonged, above the 95th percentile of the healthy population. The dominant hand grip strength of 26 (55.3%) individuals was found to be below the lower limit of normal.

RISK FACTORS ASSESSMENT

Based on the univariate analyses of the different physical assessment tests (see the supplementary material included with the electronic version), we implemented linear regression models to assess risk factors for poorer physical capacity. We found that the 6MWT score was 107.3 meters lower for individuals with severe acute COVID-19 ($P = 0.013$). No other statistically significant risk factors were noted for the other physical assessment tests (severe acute COVID-19 was associated with poorer functioning: 3.0 repeats lower for 30-STST and 1.7 seconds longer for TUGT, $P = 0.109$ and $P = 0.071$, respectively). The time interval between the diagnosis and physical assessment did not correlate with the 6MWT score [Table 2].

Additional linear regression models were performed to assess possible associations between the symptoms and clinical findings at the time of the first evaluation and the scores of the different physical assessment tests. The 6MWT score rose by 2.7 meters per each 1% increase in the DLCO ($P = 0.007$) and the 30-STST score was 3.0 repeats lower for individuals who reported on moderate to severe myalgia ($P = 0.038$). No statistically significant correlates were found for the TUGT and the dominant grip strength.

Table 1. Characteristics of participants based on their 6-minute walk test score

	Total, N=49	Observed/expected 6MWT score		*P*-value*
		< 80%, n=27 (55.1%)	≥ 80%, n=22 (44.9%)	
Females, n (%)	36 (73.5)	21 (77.8)	15 (68.2)	0.525
Age, mean	48.3 ± 10.2	45.0 ± 10.1	52.4 ± 8.8	0.009
Body mass index, mean kg/m²	28.8 ± 6.3	29.1 ± 5.6	28.5 ± 7.2	0.521
Pre-COVID co-morbidities				
Smoking (current or past), n (%)	5 (10.4)	2 (7.7)	3 (13.6)	0.649
Obesity, n (%)	16 (32.7)	8 (29.6)	8 (36.4)	0.761
Sedentary lifestyle, n (%)**	36 (78.3)	23 (92.0)	13 (61.9)	0.028
Diabetes mellitus, n (%)	6 (12.2)	3 (11.1)	3 (13.6)	1.000
Hypertension, n (%)	6 (12.2)	3 (11.1)	3 (13.6)	1.000
Hypothyroidism, n (%)	4 (8.2)	1 (3.7)	3 (13.6)	0.314
Acute COVID				
Severe or critical illness, n (%)	9 (18.4)	5 (18.5)	4 (18.2)	1.000
Post-COVID employment				
Unable to maintain their pre-COVID employment, n (%)***	24 (51.1)	18 (72.0)	6 (27.3)	0.003
Long-COVID symptoms**				
Fatigue, n (%)	42 (85.7)	22 (81.5)	20 (90.9)	0.436
Insomnia, n (%)*****	20 (41.7)	13 (50.0)	7 (31.8)	0.249
Dyspnea, n (%)	22 (44.9)	14 (51.9)	8 (36.4)	0.388
Myalgia, n (%)	25 (51.0)	18 (66.7)	7 (31.8)	0.022
Arthralgia, n (%)*****	6 (12.5)	5 (19.2)	1 (4.5)	0.199
Pulmonary function testing				
DLCO, mean	82.2 ± 15.4	79.0 ± 15.1	86.0 ± 15.2	0.006
DLCO < 80% of expected, n (%)	20 (41.7)	16 (61.5)	4 (18.2)	0.003

*Calculated using Mann Whitney U test or Fisher's exact test

**Data for three individuals were missing

***Data for two individuals were missing

****Only moderated-to-severe symptoms were counted as positive Symptoms were mentioned whenever relevant and present for ≥ 5 individuals

*****Data for 1 individual were missing

6MWT = 6-minute walk test, DLCO = diffusing capacity of the lung for carbon monoxide, SD = standard deviation, WHO = world health organization

Table 2. Physical assessment test results of individuals with long COVID, according to their pre-COVID physical activity status

	Total population, N=49	Pre-COVID physical activity		*P*-value*
		Non active, n=36	Active, n=10	
6-minute walk test				
Expected result, mean	558.5 ± 84.8	557.9 ± 86.9	555.4 ± 78.9	0.790
Observed result, mean	429.0 ± 114.9	430.4 ± 105.8	473.4 ± 86.3	0.456
Difference (Exp-Obs), mean	129.5 ± 121.2	127.5 ± 109.4	82.0 ± 101.3	0.201
% Observed/expected, mean	80.0 ± 21.7	78.4 ± 20.1	86.3 ± 16.6	0.158
P-value**	< 0.001	< 0.001	0.047	
30-second sit-to-stand-test				
Expected result, mean	24.7 ± 2.6	24.6 ± 2.4	25.3 ± 3.3	0.638
Observed result, mean	12.4 ± 5.0	12.3 ± 5.2	13.3 ± 3.9	0.462
Difference (Exp-Obs), mean	12.2 ± 5.0	12.3 ± 5.4	12.0 ± 4.0	0.915
% Observed/expected, mean	50.4 ± 19.3	50.3 ± 19.9	52.6 ± 14.7	0.594
P-value**	< 0.001	< 0.001	0.005	
Timed-up-and go test, seconds				
Observed, mean	7.9 ± 2.4	7.9 ± 2.3	7.1 ± 1.7	0.497
Extremely impaired (> 97.5%), n (%)	9 (19.6)	8 (22.2)	1 (10.0)	0.659
Dominant hand grip, kg				
Observed, mean	20.4 ± 9.4	20.0 ± 8.1	24.5 ± 12.6	0.423
Extremely impaired (below the lower limit), n (%)	25 (54.3)	21 (58.3)	4 (40.0)	0.475

*Comparison based on their pre-COVID physical activity was calculated for the 46 individuals for whom the pre-COVID physical activity status was known, using Mann-Whitney U test or chi-square test

**Within group comparison of the observed and expected values was calculated using Wilcoxon signed-rank test

DISCUSSION

We implemented validated formal tests to assess the physical capacity of individuals with debilitating long COVID symptoms. The majority (82%) had recovered from non-severe acute COVID-19. We found that in line with subjective complains, these individuals exhibited poorer physical functioning compared to what was expected based on their age and sex.

Their mean 6MWT score (429 ± 115 meters), at an average of 4 months following disease onset, was similar [17,18] or lower [19], than the scores reported for individuals with moderate to severe COVID-19 at approximately 1 [19], 1.6 [18], and 3 [17] months following discharge. Likewise, while 55.1% of our population had a 6MWT score < 80% of the expected value, the proportion of individuals with similar scores among intensive care unit (ICU) survivors was only 34% at 5 months following discharge [20].

The poorer functional capacity of the study population probably reflects our selection for evaluation of patients who were unable to return to work and/or usual physical activity. However, these patients were mostly recovering from mild acute COVID-19, suggesting that even mild disease may be associated with subsequent severe deconditioning. Nonetheless, as one might expect, severity of acute COVID-19 was identified in our study as a risk factor for poorer 6MWT score.

In this study of individuals recovering from COVID-19, we identified two clinical correlates for reduced physical capacity. Impaired DLCO (DLCO < 80%) of expectancy, was associated with decreased 6MWT results. Individuals with decreased diffusing capacity tended to experience effort intolerance. Moreover, impaired DLCO was the most prevalent pulmonary function test abnormality reported among recovering individuals [21]. Accordingly, individuals with long COVID and impaired DLCO should be considered for physical therapy and rehabilitation.

Myalgia, one of the most common long COVID symptoms [1], was associated with decreased 30-STST scores. The 30-STST is a functional test that indirectly measures lower limb strength [22]. Poorer performance is expected for ICU survivors, who tended to have diminished muscle strength [23]. However, most participants in the current study were recovering from mild COVID-19, which did not necessitate hospitalization. It seems unlikely that their poor functional lower limb strength was related to the relative immobilization while quarantined during the acute phase, approximately 3–4 months prior to testing. The pathophysiology by which COVID-19 affects the muscles needs further clarification. Still, regardless of the mechanism, long COVID myalgia seems to be an indicator for impaired muscle strength. Accordingly, clinicians may consider referring recovering individual who report on myalgia for physical assessment and therapy.

The clinical evidence gathered so far implies that rehabilitation programs may improve the physical capacity of individuals recovering from severe COVID-19. A 3-weeks multidisciplinary rehabilitation program initiated at time of discharge improved the 6MWT score of individuals recovering from severe-critical COVID-19 (from 323 ± 196 meters to 499 ± 103 meters, $P < 0.001$) [24]. Similarly, a 2-week pulmonary rehabilitation program improved the 6MWT scores of individuals recovered after mechanical ventilation for COVID-19 (from 332.6 ± 34.5 meters to 376.5 ± 39.4 meters, $P < 0.001$) [25]. Similar interventions among individuals with long COVID recovering from mild disease remains to be evaluated in further prospective studies.

LIMITATIONS

The major limitations of the current study concern to the absence of a comparison group and lack of data on baseline physical capacity of the participating individuals. However, by using validated equations we can confidently assert that these individuals, who reported on decreased functioning and prolonged symptoms following their diagnosis with COVID-19, exhibited poorer scores on objective measures. Moreover, the fact that the sub-population

of individuals who were physically active prior to their diagnosis with COVID-19 also performed worse than expected, reinforces that our results reflect a realistic trend among those facing long COVID. In the absence of a comparison group, one may argue that the impaired physical capacity of the study population resulted from isolation, quarantine, and social distancing policies implemented during COVID-19 pandemic and are not related to the disease itself. However, the study period spanned beyond lockdown periods, and the effect of quarantine, if existed at all, is unlikely to entirely explain the observed deconditioning.

CONCLUSIONS

We assessed a group of individuals with debilitating long COVID at an average time of 4 months following their acute illness. The participants had substantially decreased functional capacity, even those with mild acute disease. This finding reinforces that the subjective report of individuals with long COVID on deconditioning translates into impaired physical capacity, as reflected in the 6MWT and other assessment tests. Physical therapy and rehabilitation were found to benefit patients recovering from severe COVID-19. Such interventions should be also evaluated in patients recovering from mild illness, with objective findings of impaired functional capacity. In addition to rehabilitation programs, incorporating objective measures into the routine assessment of individuals recovering from mild disease may mitigate the distress of long COVID patients yearning that their suffering would be recognized by the medical establishment.

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Mistakes are the portals of discovery.
James Joyce (1882–1941), Irish novelist, poet, and literary critic