Pulmonology 27 (2021) 563–565

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Predictors of reduced 6-minute walk distance after COVID-19: a cohort study in Mexico

Clinical sequelae after COVID-19 have been well described, including abnormalities in pulmonary function tests, chest imaging, and patient-reported outcome measures.[1,2] However, functional outcomes after COVID-19 are not well understood. We sought to identify the presence and underlying mechanisms of functional impairments after COVID-19. We hypothesized that patients with more severe COVID-19 would have a lower 6-minute walk distance (6MWD) at follow-up and that exertional dyspnea, fatigue, and hypoxemia would independently predict a lower 6MWD.

This was a consecutively-enrolled prospective cohort study. Patients who were seen in a hospital in Yucatan, Mexico with SARS-CoV-2 confirmed by real-time polymerase chain reaction were referred to a COVID-19 clinic for follow-up. Patients who were able to complete surveys, pulmonary function tests (PFTs), and 6-minute walk tests (6MWTs) were included. There were no exclusion criteria. PFTs and 6MWTs were conducted according to international guidelines.[3–5] Patients did not receive formal physical rehabilitation during their recovery. This study received institutional ethics approval.

COVID-19 severity was categorized as mild (no hypoxemia), moderate (hypoxemia without mechanical ventilation), or severe (hypoxemia with mechanical ventilation). The association between COVID-19 severity and 6MWD was determined using multivariable linear regression, and underlying mechanisms for reduced 6MWD were then explored. Unadjusted and adjusted linear regression models were used to determine the association between potential predictor variables (Borg dyspnea, Borg fatigue, and end-exercise SpO_2) and 6MWD, first in separate models and then in a final model with both Borg dyspnea and end-exercise SpO_2 as co-primary endpoints to explore the independent relationship of these two predictors with 6MWD. All models were adjusted for age, sex, smoking, body mass index (BMI), and time from symptom onset. Statistical analyses were performed using R version 3.6.3 (R Foundation).

A total of 295 patients were referred to the COVID-19 clinic between May and August 2020, of whom 225 were enrolled (65 patients declined and 5 were lost to follow-up). The overall cohort had 62% males and 19% ever-smokers, with a mean age of 47 ± 13 years and BMI of $32 \pm 7\,kg/m^2$ (Table 1). There were 63 patients with mild, 144 with moderate, and 18 with severe COVID-19. The median follow-up time was 61 days (interquartile range [IQR] 50–75), with fatigue on effort (68%) and dyspnea (39%) being the most common symptoms.

Patients with moderate or severe COVID-19 had a lower 6MWD compared to patients with mild disease (−51 m [95%CI −85, −17], $p = 0.004$ or −68 m [95%CI −134, −3], $p = 0.04$ respectively), with no difference between moderate and severe groups ($p = 0.55$). 6MWD was associated with both Borg dyspnea (coefficient −17 m per unit increase in Borg dyspnea [95%CI −27, −8]) and end-exercise SpO_2 (coefficient 8 m [95%CI 4, 12]) (both $p < 0.001$). A sensitivity analysis using the delta SpO_2 (i.e., end-exercise SpO_2 — baseline SpO_2) demonstrated similar results (coefficient 7 m per unit increase in delta SpO_2 [95%CI 2, 13; $p = 0.004$]). Borg fatigue was not associated with 6MWD. When Borg dyspnea and end-exercise SpO_2 were included as co-primary predictors in a single model, both variables remained independently associated with 6MWD with coefficients of −13 m (95%CI −22, −3) and 7 m (95%CI 3, 10), respectively, after adjusting for covariates (Table 2).

A lower 6MWD was independently associated with exertional dyspnea and hypoxemia, suggesting that dyspnea and hypoxemia may have distinct mechanisms through which they impact functional capacity. Of the patients who had exertional hypoxemia (i.e., SpO_2 decline $\geq$4%), 45% had a walk distance less than the lower limits of normal (LLN) and 100% had a $DL_{CO} < LLN$, which suggests that desaturation during exercise is associated with parenchymal and/or pulmonary vascular phenomena. Although dyspnea is typically accompanied by hypoxemia during acute COVID-19 illness,[6] our study found that exertional dyspnea predicted reduced functional capacity, regardless of whether end-exercise hypoxemia was present or not. The underlying mechanisms of persistent dyspnea after COVID-19 remain

https://doi.org/10.1016/j.pulmoe.2021.03.004

Table 1 Patient characteristics. Patients with mild (no hypoxemia), moderate (hypoxemia without mechanical ventilation), and severe (hypoxemia with mechanical ventilation) are shown. An obstructive pattern was defined as $FEV_1/FVC < LLN$. A restrictive pattern was defined as normal FEV_1/FVC with FVC-% predicted <LLN. Lung volumes using body plethysmography were unavailable.

	Overall (n = 225)	Mild (n = 63)	Moderate (n=144)	Severe (n = 18)
Age, years	47 ± 13	42 ± 11	49 ± 14	51 ± 8
Male sex, n (%)	139 (62)	31 (49)	92 (64)	16 (89)
BMI, kg/m^2	32 ± 7	30 ± 7	33 ± 7	33 ± 10
Current or former smoker, n (%)	43 (19)	17 (27)	24 (17)	9 (50)
Comorbidities, n (%)				
Obesity	115 (51)	24 (38)	82 (57)	9 (50)
Hypertension	47 (21)	8 (13)	32 (22)	7 (39)
Diabetes	32 (14)	3 (5)	27 (19)	2 (11)
Other[a]	15 (7)	3 (5)	11 (8)	1 (6)
Symptoms at follow-up, n (%)				
Fatigue on effort	153 (68)	37 (59)	102 (71)	14 (78)
Dyspnea	87 (39)	20 (32)	58 (40)	9 (50)
Chest pain	68 (30)	12 (19)	53 (37)	3 (17)
Myalgias	70 (31)	18 (29)	46 (32)	6 (33)
Cough	69 (31)	18 (29)	43 (30)	8 (44)
Sore throat	40 (18)	8 (13)	27 (19)	5 (28)
Sputum production	38 (17)	7 (11)	26 (18)	5 (28)
Headache	32 (14)	12 (19)	19 (13)	1 (6)
Rhinitis	32 (14)	10 (16)	22 (15)	0 (0)
Anosmia/ageusia	23 (10)	6 (10)	16 (11)	1 (6)
Dermatological symptoms	23 (10)	6 (10)	17 (12)	0 (0)
Diarrhea	6 (3)	2 (3)	4 (3)	0 (0)
Pulmonary function				
FVC, %-predicted	82 ± 19	95 ± 13	79 ± 18	61 ± 19
FEV_1, %-predicted	87 ± 19	97 ± 13	85 ± 19	68 ± 21
FEV_1/FVC, %	85 ± 7.4	83 ± 5	86 ± 8	88 ± 4
D_{LCO}, %-predicted	97 ± 29	112 ± 20	93 ± 27	65 ± 34
Restrictive pattern, n (%)	87 (39)	7 (11)	66 (46)	14 (78)
Obstructive pattern, n (%)	5 (2)	2 (3)	3 (2)	0 (0)
6- min walk test				
Distance, m	447 ± 104	491 ± 72	433 ± 111	425 ± 94
Distance, %-predicted	83 ± 20	83 ± 14	83 ± 21	86 ± 21
Baseline SpO_2, %	96 ± 2	97 ± 1	96 ± 2	96 ± 1
End-exercise SpO_2, %	95 ± 4	97 ± 2	95 ± 2	93 ± 5
Peak dyspnea, Borg 0–10	2 (1–3)	2 (1–3)	2 (1–3)	3 (2–4)
Peak fatigue, Borg 0–10	2 (0–3)	2 (1–4)	2 (0–3)	0 (0–2)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SpO_2, oxygen saturation by pulse oximetry.

[a] Other comorbidities include asthma, malignancy, dyslipidemia, and HIV. Values represent mean ± standard deviation or median (interquartile range), unless otherwise specified.

unclear; however, it is likely that physiologic sequelae contribute to this lingering symptom. In a previous study using the same cohort, we demonstrated that patients with persistent dyspnea had lower FVC, forced expiratory volume in 1 s, and higher proportion of restrictive ventilatory pattern compared to patients without persistent dyspnea.[6] Furthermore, patients with abnormal DL_{CO} at follow-up are more likely to have an elevated D-dimer on admission, suggesting that microangiopathies could contribute to dyspnea.[7]

This study had several limitations. First, our data did not include validated tools such as the Charlson Comorbidity Index to assess how comorbidities impact 6MWD. Second, this study was from a single Mexican center. However, this unique population adds to the understanding of COVID-19 recovery in diverse patient backgrounds. Third, we did not have information on treatment during the acute illness which could impact outcomes.

We demonstrate the impact that persistent dyspnea and hypoxemia have on functional capacity in patients after COVID-19. Further research to understand the underlying mechanisms of persistent symptoms, particularly dyspnea that is disproportionate to physiologic and radiologic findings, is needed in order to help patients recovering from COVID-19.

Table 2 Mechanisms of reduced 6-min walk distance after COVID-19 illness.

	Unadjusted analysis					Adjusted analysis			
Model	Outcome	Primary predictor(s)	Coefficient	95%CI	P-value	Coefficient	95%CI	P-value	Prespecified covariates
1a	6MWD	BORG dyspnea	−22	−33, −12	<0.001	−17	−27, −8	<0.001	Age, sex, smoker, BMI, time[a]
1b	6MWD	BORG fatigue	−5	−13, 4	0.277	−4	−11, 4	0.298	Age, sex, smoker, BMI, time
1c	6MWD	End-exercise SpO_2	8	4, 11	<0.001	8	4, 12	<0.001	Age, sex, smoker, BMI, time
2	6MWD	BORG dyspnea	−18	−29, −7	<0.001	−13	−22, −3	0.009	Age, sex, smoker, BMI, time
		End-exercise SpO_2	6	2, 10	0.004	7	3, 10	<0.001	

Abbreviations: 6MWD, 6-min walk distance; BMI, body mass index; CI, confidence interval, SpO_2, oxygen saturation by pulse oximetry.
[a] Time from symptom onset.

Funding

The authors received no funding for this work.

Conflict of interest

The authors have no conflicts of interest to declare.

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11 January 2021
Available online 26 March 2021