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Lung and physical function in post COVID-19 and clinical and functional associations: a cross-sectional study in Brazil

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SUMMARY

OBJECTIVE: The purpose of this study was to assess exercise capacity, lung and physical function in COVID-19 survivors, and the association of lesion-level characteristics assessed by chest computed tomography, probable sarcopenia, and percentage of diffusing capacity of the lung for carbon monoxide with clinical and functional variables.

METHODS: This study was conducted in Salvador, Bahia, Brazil. All patients had a laboratory-confirmed SARS-CoV-2 infection. The sociodemographic characteristics, COVID-19 exposure history, pulmonary function, computed tomography, and functionality of the participants between 1 and 3 months of diagnosis of the disease were collected.

RESULTS: A total of 135 patients after COVID-19 recovery were included in this study. Probable sarcopenia, reduction in percentage of diffusing capacity of the lung for carbon monoxide, and a lower 6-min walk distance were observed after COVID-19 infection. Computed tomography>50% was associated with a longer length of stay and a lower percentage of diffusing capacity of the lung for carbon monoxide. Probable sarcopenia diagnosis was associated with a worse percentage of the predicted 6-min walk distance in relation to the predicted, absolute 6-min walk distance (m), percentage of diffusing capacity of the lung for carbon monoxide, and percentage of total lung capacity.

CONCLUSION: Muscle disability and lung dysfunction are common in COVID-19 survivors. Hospitalization was associated with the worst muscle force and diffusing capacity of the lung for carbon monoxide. Computed tomography characteristics could be a marker of prolonged hospital stay after the acute phase of COVID-19. Additionally, the probable diagnosis of sarcopenia could be a marker of impact on walking distance. These results highlight the need for long-term follow-up of those patients and rehabilitation programs.

KEYWORDS: COVID-19. Post-acute COVID-19 syndrome. Functional status. Respiratory function tests. Sarcopenia.

INTRODUCTION

Clinical and functional sequelae after COVID-19 have been described, including abnormalities in pulmonary function tests, chest imaging, and physical performance outcome measures in hospitalized and non-hospitalized patients[1,2]. Post-covid syndrome, which is not one condition, is defined by the National Institute for Health and Care Excellence (NICE) as "signs and symptoms that develop during or after an infection consistent with covid-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis[3]."

Based on this, Nalbandian et al.[4] reinforced the need that a comprehensive understanding of patient care needs beyond the acute phase will help in the development of infrastructure for COVID-19 clinics that will be equipped to provide integrated multispecialty care in the outpatient setting. Furthermore, decreased levels of physical function, muscle strength, and exercise capacity are associated with an increased risk of mortality in the general population and in people with chronic diseases[5].

In Brazil and around the world, there were a million confirmed cases of COVID-19. Most infected individuals remain asymptomatic or have a mild or moderate form of the disease (85%), with non-specific symptoms such as fever, cough, myalgia, sputum, and fatigue[6,7]. Thus, most available data focus on symptoms-related events data, and thus data about pulmonary and musculoskeletal functionality are scarce in the national and international literature. Thereby, we aimed to describe the characteristics of patients reporting prolonged symptoms after an infection with COVID-19 and examine the associations and correlations of computed tomography (CT) findings, probable sarcopenia, and percentage of diffusing capacity of

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the lung for carbon monoxide (%DLCO) with clinical and functional variables.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study design

The study was approved by the ethics committee of Bahia Medicine of Faculty, Bahia Federal University (FMB/UFBA), Brazil (CAEE: 41132020.4.0000.5577). A cross-sectional study was performed, and data were collected (from April 2020 to August 2021) from post-COVID patients. Written informed consent was obtained from all patients.

Setting and participants

This study was conducted in Salvador, Bahia, Brazil. The diagnosis of COVID-19 was based on CDC criteria. All patients had a laboratory-confirmed SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR). All adult patients, who were diagnosed with COVID-19 between 1 and 3 months and who underwent pulmonology treatment, were consecutively enrolled according to the World Health Organization (WHO) interim guidance. The inclusion criteria were as follows: (a) over 18 years of age; (b) positive RT-PCR assay; (c) no previous neurological sequelae; (d) inability to perform either the test (limited mobility or any joint/mobility pain); (e) hemodynamic stability; and (f) time for COVID-19 diagnosis≥3 months.

Variables/quantitative variable

Sociodemographic characteristics and medical history

The electronic medical record was used to extract the sociodemographic characteristics of the participants [age, gender, height, weight, body mass index (BMI), obesity or overweight (considering the WHO definition), smoking status, exercise activity, medical history (i.e., laboratory results – to help determine comorbidities, medication use, and chronic conditions), and chest imaging (chest CT scans)]. Comorbidities were included in the search. Exclusion criteria were as follows: (1) previous myopathy and (2) previous locomotor limitations.

COVID-19 exposure history

The diagnosis date, main symptoms, oxygen supplementation and/or invasive and noninvasive ventilation (NIV) support, COVID-19-specific therapies, hospitalization, if necessary, ICU admittance history, and outcomes were recorded. The severity of patients with COVID-19 infection was determined according to the WHO classification.

Clinical and functional variables

The specific questionnaire of symptoms-modified Medical Research Council (mMRC) dyspnea scale was used. The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4[8]. Lung function (spirometry and DLCO) and functionality variable were measured.

Data sources/measurement

Pulmonary function and chest computed tomography

The forced vital capacity, forced expiratory volume at 1 s, FEV1/FVC ratio, total lung capacity (TLC), and DLCO were measured during complete PFT. PFT data were collected as a percentage predicted based on previously published reference equations. FEV1/FVC was reported as the raw number ratio. Interpretation of the obtained values was based on the ATS-ERS criteria[9]. In addition, lesion-level characteristics were assessed by chest computed tomography (CT).

Five times sit-to-stand test

Participants were asked to stand up five times in a row as quickly as possible from a chair without stopping, keeping their arms folded across their chest. Participants had to come to a full standing position each time they stood up and to sit all the way down each time. Time (in seconds) or inability to perform the test was used for the present analyses[10]. The cutoff point to probable sarcopenia was ≥12 s[11].

Short physical performance battery

The lower extremity function was assessed using the short physical performance battery (SPPB) with the predicted normal values of Bergland et al.[12]. Following the Asian Working Group for Sarcopenia 2019[11] and considering that impaired mobility defined as SPPB score ≤9 was more predictive of all-cause mortality in a systematic review[13], SPPB score ≤9 was considered low physical performance.

6-min walking test and 6-min step test

All participants performed 6-min walking test (6MWT) based on the American Thoracic Society/European Respiratory Society

standards. The measured 6-min walk distance (6MWD) values were compared with the predicted values using a reference equation[14]. The absolute 6MWD was expressed as a percentage of the predicted 6MWD (%6MWD).

6-m gait speed

The gait speed was calculated for each participant using distance in meters and time in seconds. All studies used instructions to walk at a maximal pace and from a standing start. Two cones were placed 10 m apart and provided a 2 m acceleration zone, a 6 m timing area, and a 2 m deceleration zone. The subjects were instructed to "walk as fast as you can safely, without running" from one cone to the other. The time to walk 4 m was measured with a manual stopwatch[15]. Low physical performance is predicted when the gait speed is <1.0 m/s[11].

Time up and go test

The time up and go test (TUGT) assesses basic mobility skill as well as strength, balance, and agility. Time (in seconds) taken to rise from sitting in an armchair, walk 3 m, turn, walk back to the chair, and then sit down using regular footwear and a walking aid if required was measured[16]. Following EWGSOP2[17], sarcopenia cutoff point to TUG is ≥20 s.

Bias

Our results may be subject to selection bias.

Study size

The sample size was calculated using the Epi info statistical package version 7. Based on the following parameters for a cross-sectional study – expected post-COVID-19 cases 0.17, with an acceptable margin of error of 0.05, a design effect of 1, and a 95%CI, the required sample size will be 131 patients.

Statistical methods

Data were coded and analyzed using the Statistical Package of Social Science (SPSS) software program, version 22 (IBM SPSS 22 Statistics for Windows, Armonk, NY: IBM Corp). The statistical analysis plan was determined using the Shapiro-Wilk test. Continuous data were reported as mean±standard deviation (SD) or median and interquartile range. Frequency and percentage were used to denote qualitative variables. A comparison of quantitative variables was conducted using the Mann-Whitney test or Student's t-test. The relationships between 6MWD and functional variables were examined using Spearman correlation coefficients (r). P-value≤0.05 was considered substantially significant.

RESULTS

A total of 135 patients after recovery from COVID-19 (1.45±0.69 months after recovery) were included in this study. There were 69.6% men and 30.4% women, with a mean age of 56.9±13.3 years. Demographic, anthropometric, physiological, and clinical characteristics of patients are shown in Table 1.

Table 1. Demographic and clinical characteristics during post COVID-19.

Characteristics	Mean±SD (n)	Value % (n)
Age (years)	56.9±13.3 (135)	
Gender		
Female		30.4 (41)
Male		69.6 (94)
BMI	27.9±4.8 (135)	
Obese (BMI>30)		34.1 (45)
Overweight		37.9 (50)
Obesity or overweight		71.2 (94)
Comorbidities		
Hypertension		35.9 (47)
Diabetes		16 (21)
Cardiopathy		10.1 (13)
Other comorbities		67.9 (91)
Tabagism		1.5 (2)
Internation		
Yes		52.6 (71)
No		47.4 (64)
Internation (days)	16.3±15.9 (2–76 days) (135)	
ICU internation		
Yes		29.6 (40)
No		70.4 (95)
Mechanical ventilation (IV or NIV)		
Yes		12.6 (17)
No		87.4 (118)
ICU days	124.6±15.4 (1–64 days) (135)	
Percentage of lung disease		
Normal		5.2 (7)
25		15.6 (21)
25–50		28.1 (38)
50–75		14.1 (19)
>75		3.7 (5)
Corticosteroids		95 (132)
Dyspnea post COVID (MRC)		
0		53.3 (72)
1		29.6 (40)
2		11.1 (15)
3		1.5 (2)
4		4.4 (6)

BMI: body mass index; IV: invasive ventilation; NIV: noninvasive ventilation; MRC: Medical Research Council.

Hospitalization and ICU admission were observed in 52.6 and 29.6% of sample, respectively. The mean day of hospitalization was 16.3±15.9. Notably, 12.6% of sample used mechanical ventilation support. Table 2 shows the pulmonary function of the study patients, and 35.1% of sample presented DCLO lower than 80%.

Additionally, the mean of 6MWD in all subjects was 517.7±103.3 m (86.0%±14.0 of the predicted walking distance) (Table 2). It is important to highlight that probable sarcopenia was observed in 17.8% of patients. Four patients had the gait speed test lower than cutoff point (<1 m/s), one patient had SPPB lower cutoff point (≤9), and one and four patients had the TUG test>12 s and >10 s, respectively.

Spearman correlation coefficients were calculated from (1) hospital days and 6MWD (m) (r=-0.32, p=0.001); (2) hospital days and DLCO abs (r=-0.53, p<0.001); (3) hospital days and %DLCO (r=-0.76, p<0.001); (4) sit-to-stand test and 6MWD (m) (r=-0.495, p<0.0001); and (5) DLCO abs and 6MWD (m) (0.49, p<0001).

Differences in functional status were observed between hospitalized and non-hospitalized patients (Table 3). Hospital stay was significantly superior to CT>50% compared to CT<50% [median (IQ)=16.5 (23.5) *versus* 9.5 (10.5), p=0.015]. %DLCO was significantly lower to CT>50% compared to CT<50% [median (IQ)=77 (25) *versus* 66 (20.5), p=0.01]. No differences were observed to 6MWD (m), 6MWD, %-predicted, 6-m gait speed, 5xSTS, TUGT, and SPPB. Probable sarcopenia was associated with worse 6MWD, %-predicted in relation to predicted [70 (21.9) *versus* 90.5 (10.0), p<0.0001], 6MWD (m) [396 (174.5) *versus* 551 (103.3), p<0.0001], %DLCO [70(24) *versus* 77.5 (23.5), p=0.018], and percentage of TLC (%TLC) [72(28.5) *versus* 87(20.8), p=0.006].

Table 2. Lung function and functionality results during post COVID-19.

Characteristic	Mean±SD (n)	Value % (n)
FVC liters	3.5±1.0 (77)	
FVC%	81.8±15.5 (77)	
TLC liters	5.8±4.9 (74)	
%TLC	82.4±16.0 (74)	
FEV1 liters	2.8±0.8 (76)	
FEV1%	82.7±13.9 (76)	
FEV1/FVC %	81.3±8.3 (71)	
FEF 25–75%	104.8±39.9 (71)	
DLCO abs	18.4±6.2 (77)	
%DLCO	74±17.5 (77)	
DLCO<80%		
Yes		35.1 (26)
No		64.9 (48)
6MWD (m)	517.7±103.3 (124)	
Predictive 6MWTD (m)	598±65.4 (124)	
Predictive 6MWD (%)		86.0±14.0 (135)
6MWT or 6MST desaturation		
Yes		19.3 (26)
No		80.7 (109)
6MST	143.3±40.1 (11)	
TUG (s)	6.1±1.6 (135)	
TVM (m/s)	2.04±0.54 (135)	
SPPB	11.7±0.9 (135)	
FTSTST (s)	8.7±4.5 (125)	
Sarcopenia		
Yes		17.8 (24)
No		74.8 (101)

FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; DLCO: diffusing capacity of the lung for carbon monoxide; MWD: min walk distance; MWT: min walking test; TUG: time up and go; SPPB: short physical performance battery.

DISCUSSION

Although most people with COVID-19 get better within weeks of illness, some people experience post-COVID conditions. Post-COVID conditions are common and can involve sequelae, and other medical complications that last weeks to months after initial recovery.

Table 3. Functional status between hospitalized and non-hospitalized during post COVID-19.

Characteristics	Hospitalization (n=71)	Non-hospitalization (n=64)	p-value
6MWD (m)	502±113.2	538.4±86.8	>0.05
Predictive 6MWD (%)	82.2±15.3	90.6±10.5	**0.01***
TUG (s)	6.3±1.7	6.0±1.42	>0.05
TVM (m/s)	1.9±0.52	2.2±0.51	>0.05
FTSTST (s)	9.5±5.1	7.6 ±2.7	**0.04***
SPPB	11.6±1.1	11.9±0.47	>0.05
FEV1/FVC %	84.4±8.1	77.8±7.3	**<0.001***
%DLCO	69.0±16.5	80±17.4	**0.02***

*Differences between hospitalized and non-hospitalized patients (Mann-Whitney U test or Student's t-test). Statistically significant values are indicated in bold. MWD: min walk distance; TUG: time up and go; FVC: forced vital capacity; FEV: forced expiratory volume; SPPB: short physical performance battery; DLCO: diffusing capacity of the lung for carbon monoxide.

Thus, this study showed a high frequency (46.7%) of dyspnea (MRC score>0) in patients with post-COVID syndrome. Hospitalization and ICU admission were observed in 52.6 and 29.6% of sample, respectively. Notably, 35.1% of sample presented DCLO lower than 80%. Additionally, the mean of 6MWD in all subjects was 86.0%±14.0 of predicted walking distance. It is important to highlight that probable sarcopenia was observed in 17.8% of patients.

In addition, percentage of lesion-level characteristics, assessed by CT, was associated with a worse %DLCO. In this sense, in patients with emphysema, lesion-level chest CT is related to decreased PaO2 but cannot replace the measurements of diffusion capacity in the clinical evaluation of hypoxemia[18]. Moreover, multiple variable analysis showed that the visual extent of emphysema and 15th percentile HU were independent significant predictors of DLCO/VA[19]. It is also important to highlight that, in post-COVID patients, dyspnea was associated with both DLCO %-predicted and total CT score[1].

Furthermore, in this study, sarcopenia was associated with worse 6MWD, %-predicted, 6MWD (m), and %DLCO. These findings highlight that COVID-19 is a disease that also affects skeletal muscles[20] and patient's functionality. Specifically, post-COVID-19 patients showed reduced lung function, muscle strength, and exercise capacity. In this context, recent reviews showed that acute post-COVID-19 patients suffer from changes in respiratory function, fatigue, muscle weakness, and disability[21-25].

Considering the global scale of this pandemic, the sequelae of COVID-19 will continue to increase in the future[4]. There is a critical need to understand the disabilities of patients (in the acute and long-term), aiming to effectively improve the functionality of survivors of COVID-19[4]. We have identified persisting disability and functional and pulmonary abnormalities in a significant proportion of subjects. These data may assist with the detection of post-COVID complications and the identification of patients who could benefit from physical rehabilitation.

CONCLUSION

Physical disability and reduction in lung function are common in COVID-19 survivors. The impact of hospitalization on muscle force and DLCO was observed. Additionally, CT>50% was associated with longer length of stay (LOS) and lower %DLCO. Probable sarcopenia diagnosis was associated with a worse %6MWD in relation to predicted, 6MWD (m), %DLCO, and %TLC. These results highlight the need for a long-term follow-up of those patients and rehabilitation programs.

AUTHORS' CONTRIBUTIONS

IGNA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MGN:** Data curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **SFOJ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **DMM:** Investigation, Methodology, Validation, Visualization, Writing –review & editing. **WLCN:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **KDOA:** Investigation, Methodology, Validation, Visualization, Writing – review & editing.

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