Respiratory and functional outcomes in post-hospitalized COVID-19 patients

Repercussões respiratórias e funcionais de indivíduos após hospitalização por COVID-19

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Abstract

Introduction: COVID-19 is a disease with systemic manifestations that can result in respiratory and functional sequelae. Understanding these consequences is crucial for developing effective preventive and rehabilitative strategies. **Objective:** To assess the short- and long-term respiratory and functional repercussions following hospitalization for COVID-19. **Methods:** This observational, longitudinal, multicenter study evaluated individuals post-hospitalization for COVID-19 at 15, 90, and 180 days post-hospital discharge using the follow-ing measures: spirometry, maximal inspiratory pressure (MIP), mMRC dyspnea scale, six-minute step test (6MST), handgrip strength, 30-second sit-to-stand test (30sSTS) and physical activity in daily life. **Results:** Sixty-five participants (54.8 ± 12.5 years, 54% male) were assessed at 15, 90, and 180 days post-hospital discharge. The results showed, respectively: forced vital capacity (FVC): 67.6 ± 25.4%, 76.7 ± 20.5%, and 70.1 ± 22.6% predicted; MIP: 77.4 ± 49.8%, 76.5 ± 48.8%, and 84.0 ± 54.1% predicted; mMRC: 2.0 (0.0 – 3.0), 1.0 (0.0 – 2.5), and 1.0 (0.0 – 3.0) points; 6MST: 70.7 ± 25.9%, 80.2 ± 29.8%, and 84.8 ± 31.3% predicted; 30sSTS: 61.3 ± 23.8%, 65.6 ± 19.5%, and 71.7 ± 20.0% predicted; handgrip strength: 101.3 ± 40.1%, 99.8 ± 35.5%, and 101.7 ± 31.2% predicted; physical activity: 23.1%, 10.8%, and 23.1% of participants were sedentary. **Conclusion:** Individuals post-hospitalization for COVID-19 exhibited persistent dyspnea, reductions in FVC, MIP, functional capacity, peripheral muscle strength, and low levels of physical activity. Dyspnea, reduced FVC, peripheral muscle strength, and low physical activity levels persisted even 180 days post- discharge.

Keywords: COVID-19. Exercise test. Post-acute COVID-19 syndrome. Respiratory function tests.

Resumo

Introdução: *A COVID-19 é uma doença com manifestações sistêmicas que podem resultar em sequelas respiratórias e funcionais. Compreender essas consequências é importante para desenvolver estratégias preventivas e reabilitadoras eficazes.* ***Objetivo:*** *Avaliar as repercussões respiratórias e funcionais a curto e longo prazo após a hospitalização por COVID-19.* ***Métodos:*** *Trata-se de um estudo observacional, longitudinal e multicêntrico, que avaliou indivíduos após hospitalização por COVID-19 aos 15, 90 e 180 dias após a alta hospitalar. As avaliações utilizadas foram: espirometria, pressão inspiratória máxima (PIM), escala de dispneia mMRC, teste de degrau de seis minutos (TD6), força de preensão manual, teste senta e levanta de 30 segundos (TSL30) e atividade física na vida diária.* ***Resultados:*** *Sessenta e cinco participantes (54,8 ±12,5 anos, 54% homens) foram avaliados aos 15, 90 e 180 dias após a alta hospitalar, apresentando, respectivamente: capacidade vital forçada (CVF): 67,6 ± 25,4%, 76,7 ± 20,5% e 70,1 ± 22,6% do previsto; PIM: 77,4 ± 49,8%, 76,5 ± 48,8% e 84,0 ± 54,1% do previsto; mMRC: 2,0 (0,0 – 3,0), 1,0 (0,0 – 2,5) e 1,0 (0,0 – 3,0) pontos; TD6: 70,7 ± 25,9%, 80,2 ± 29,8% e 84,8 ± 31,3% do previsto; TSL30: 61,3 ± 23,8%, 65,6 ± 19,5% e 71,7 ± 20,0% do previsto; força de preensão manual: 101,3 ± 40,1%, 99,8 ± 35,5% e 101,7 ± 31,2% do previsto; nível de atividade física: 23,1%, 10,8% e 23,1% dos participantes eram sedentários.* **Conclusão:** *Indivíduos pós-hospitalização por COVID-19 apresentam dispneia persistente, reduções na CVF, PIM, capacidade funcional, força muscular periférica e baixos níveis de atividade física. Cento e oitenta dias após a alta hospitalar, ainda foram observados dispneia, redução da CVF, força muscular periférica e baixos níveis de atividade física.*

Palavras-chave: *COVID-19. Teste de esforço. Síndrome pós-COVID-19 aguda. Testes de função respiratória.*

Introduction

The post-acute COVID-19 syndrome, also known as long COVID, is defined as a collection of manifestations that affect individuals following SARS-CoV-2 infection. These manifestations typically occur three months after the onset of COVID-19, with symptoms persisting for at least two months and not explained by an alternative diagnosis.[1]

The prevalence of long COVID is 43%, suggesting that approximately 200 million individuals have experienced or are experiencing long-term health consequences related to COVID-19. Among individuals hospitalized for COVID-19, the prevalence is 54%, which is higher compared to non-hospitalized patients, where it stands at 34%.[2]

Long COVID is characterized by a heterogeneous array of long-term sequelae, encompassing respiratory, cardiovascular, thrombotic, and cerebrovascular manifestations, as well as sequelae like type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome, and dysautonomia. These sequelae can persist for years, and in some cases, may become permanent.[3,4] Changes in the respiratory system, such as reduced gas diffusion capacity, altered ventilation-perfusion relationships, hypoxemia, hypercapnia, and dyspnea, may occur in the short- and medium-term. In terms of functional capacity, individuals may experience fatigue, reduced exercise tolerance, decreased physical activity levels, diminished muscle mass, endurance, strength, and a lower quality of life.[5-7] In addition, corticosteroid use and bed rest during hospitalization may exacerbate these manifestations.[8,9]

Nevertheless, the respiratory and functional repercussions of COVID-19 still need to be studied longitudinally to allow a better understanding of their prevalence, severity, and evolution. These results can guide clinicians in establishing adequate preventive and rehabilitative strategies, as well as in selecting appropriate evaluation tests for this population. Therefore, the aim of this study was to assess the respiratory and functional repercussions in the short- and long-term in individuals after COVID-19 hospitalization.

Methods

An observational, longitudinal, multicenter study was conducted with individuals post-hospitalization for COVID-19 from June to October 2021 in three tertiary care hospitals, following the STROBE statement. Participants were recruited during hospitalization and invited to participate after discharge. The study was approved by the research ethics committees (protocol numbers: 4.002.358, May 1st, 2020; 4.056.210, May 28, 2020; and 4.013.533, May 7, 2020) and all participants provided informed consent.

Participants

This study enrolled a convenience sample of patients aged ≥ 18 years with confirmed COVID-19 by RT-PCR. Exclusion criteria included physical limitations due to neurological, musculoskeletal, or osteoarticular diseases affecting tests execution; unstable cardiovascular disease; cognitive disorders; and participation in a post-hospitalization physical rehabilitation program. To conduct an analysis comparing individuals at different severity levels, participants were categorized into two groups: those hospitalized in the ward (ward group) and those admitted to the intensive care unit (ICU group).

Procedure

Assessments were conducted at participants' homes by trained researchers to ensure standardized administration of tests and questionnaires. The same assessor performed evaluations for each participant consistently over time.

Anthropometric, demographic, and clinical data were collected, including the level of consciousness (Glasgow Coma Scale), Charlson Comorbidity Index, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score 3 (SAPS 3) upon hospital admission. Additionally, the length of hospital and ICU stays were recorded.

Forced vital capacity (FVC), assessed via spirometry, and the number of steps in the 6-minute step test (6MST) were designated as primary outcomes. Lung function measurements were conducted using a portable spirometer following established guidelines for pulmonary function testing.[10] FVC, forced expiratory volume in the first second (FEV_1), and the FEV_1/FVC ratio were recorded and compared with reference values.[11]

Functional capacity was assessed using the 6MST. The protocol involved ascending and descending a single 20 cm step as quickly as possible for six minutes.[12] The number of steps climbed was recorded and compared with reference values.[13]

Respiratory muscle strength was assessed by measuring the maximum inspiratory (MIP) and expiratory pressures (MEP) and comparing with reference values.[14,15] Dyspnea was assessed using the modified Medical Research Council scale.[16] Peripheral muscle strength was assessed by the handgrip test using a manual hydraulic dynamometer; data were expressed in absolute and percentage of predicted values.[17,18] Physical performance and lower limb strength were assessed using the 30-second sit-to-stand test (30sSTS); the number of complete repetitions was compared with reference values.[19] Physical activity level was assessed using the International Physical Activity Questionnaire, classifying individuals as very active, active, insufficiently active (A or B), or sedentary.[20]

Statistical analysis

The sample size was calculated using G*Power software (Heinrich-Heine-Universität Düsseldorf), based on changes in lung function and functional capacity observed in previous studies conducted with individuals after COVID-19. A sample of 26 individuals was considered adequate, considering an effect size of 0.74 for the evolution of FVC, an α error of 0.05, and a power of 0.90.21 Similarly, a sample of 14 individuals was considered adequate, considering an effect size of 1.05 for the change in performance in the step test.7 Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp, Chicago, Illinois). Shapiro-Wilk test verified data normality.

Continuous variables with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution were described as median and 25% - 75% interquartile range. Categorical variables were described as absolute and relative fre-quencies. Predicted values and lower limits of normality (LLN) were used to categorize continuous variables. Comparisons between groups were performed using the analysis of variance (ANOVA) 3-way repeated measures test with Bonferroni post hoc. Pearson's chi-square or Fisher's exact test compared categorical variables. The analysis of individuals who reached or not the LLN of the FVC and 6MST was performed using Student's t test for parametric variables, Mann-Whitney test for non-parametric variables and Chi-square test for categorical variables. The variables associated with the FVC and 6MST at 15, 90 and 180 days after hospital discharge were analyzed using the multivariate regression analysis, inserting in the model the variables that presented $p < 0.10$ in the univariate regression analysis. A p-value < 0.05 was considered significant.

Results

A total of 226 potentially eligible individuals were selected for the study. Of these, 161 were excluded, resulting in an initial sample of 65 individuals assessed 15 days after hospital discharge (first assessment). For the second assessment, there was a sample loss of 28 participants, resulting in 37 individuals. In the third assessment, there was a sample loss of 11 participants, leaving a final sample of 26 individuals (Figure 1).

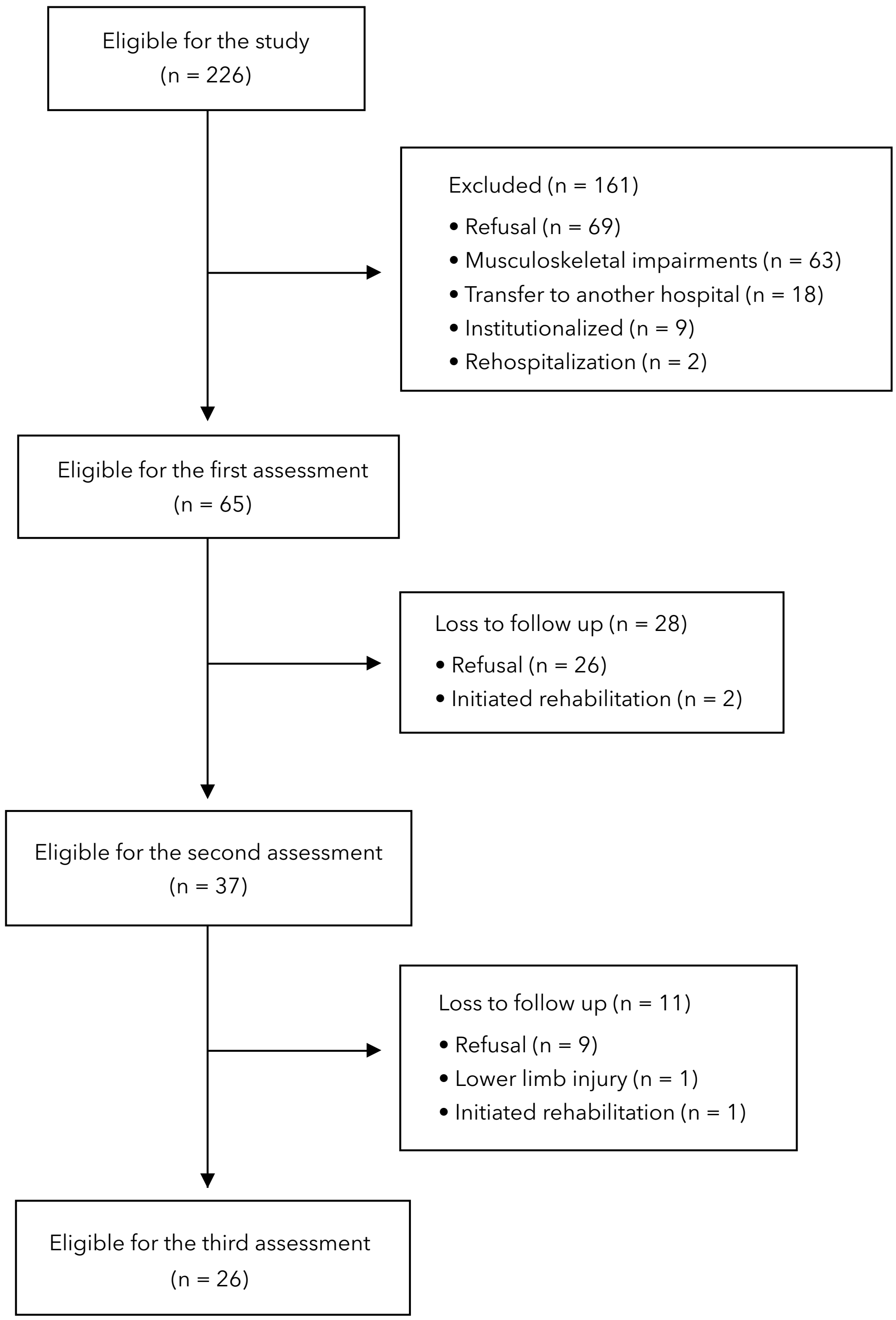

Figure 1 - Flowchart of the study.

The patients had a mean age of 54.8 ± 12.5 years (54% male). Thirty-seven individuals were hospitalized in wards, while 28 were in the ICU. Those in the ICU had a longer length of hospital stay. No other significant differences between the groups were observed, as shown in Table 1.

Table 1 - Sample characteristics

	Total (n = 65)	Ward group (n = 37)	ICU group (n = 28)
Age, years	54.8 ± 12.5	54.6 ± 13.9	55.6 ± 10.5
Gender, M/F	35/30	19/18	16/12
Body mass index, kg/m^2	29.2 ± 6.8	29.5 ± 7.8	28.8 ± 5.4
Glasgow, admission	15	15	15
Comorbidity index	1.0 [0.0 – 2.5]	1.0 [0.0 – 3.0]	1.0 [0.0 – 2.0]
Length of hospital stay, days	13.9 ± 13.9	8.1 ± 5.6	21.5 ± 17.6*
Length of ICU stay (n = 28), days	-	-	15.6 ± 14.3
Mehanical ventilation use,n (%)	11 (16.9)	-	11 (39)
Duration of MV (n = 11), days	-	-	16.6 ± 13.2
Tracheostomy, n (%)	3 (4.6)	-	3 (10.7)
SOFA score	-	-	2.0 [2.0 – 3.0]
SAPS 3 score	-	-	38.9 ± 11.2

Note: ICU = intensive care unit; M = male; F = female; MV = mechanical ventilation; SOFA = sequential organ failure; SAPS 3 = Simplified Acute Physiology Score 3. Values are expressed in mean ± standard deviation, median [interquartile range] and frequency (%). *p < 0.05 compared with ward group.

Assessing the total sample, FVC showed a reduction 15, 90, and 180 days after hospital discharge, with no improvement during this period. FEV_1 was within the normal range and improved significantly between the first and second assessments. MIP was reduced in the first and second assessments. Although it presented a normal average in the third period, 61.5% of participants had a value below the LLN. MEP was within normal ranges in all assessments. Dyspnea was reported in all assessments. The number of steps climbed in the 6MST was below the LLN in the first assessment and within the LLN in the following assessments. Lower limb strength and performance were reduced in all assessments, while handgrip strength was within the LLN. The number of active individuals remained reduced throughout the study period. Except for the improvement in FEV_1 between the first and second assessments, no other variable showed a significant change among the three evaluations (Tables 2 and 3).

When comparing patients categorized into two groups (ward and ICU), we observed that in all three assessments, the ICU group had poorer performance in the 6MST compared to the ward group. This trend was also observed in the 30sSTS test during the third assessment (Table 2). The results of the evaluation 15 days after hospital discharge, categorizing individuals into groups that who reached or not the LLN of the FVC and 6MST, demonstrated that those below the LLN in the 6MST stayed more time in MV. No other differences were found between groups (Table 4). FVC in the first assessment was associated with male sex ($p = 0.021$) and comorbidity index ($p = 0.033$); $r^2 = 0.315$. In the second assessment, FVC was associated with male sex ($p < 0.0001$) and age ($p = 0.011$); $r^2 = 0.413$. In the third assessment, FVC was associated with male sex ($p = 0.026$) and age ($p = 0.002$); $r^2 = 0.398$.

The number of steps climbed in the 6MST in the first assessment was associated with length of hospital stay ($p < 0.0001$), male sex ($p = 0.007$), and BMI ($p = 0.006$); $r^2 = 0.394$. In the second assessment, 6MST was associated with length of hospital stay ($p = 0.002$), male sex ($p = 0.035$), and BMI ($p = 0.009$); $r^2 = 0.442$. In the third assessment, 6MST was associated with length of hospital stay ($p = 0.008$) and BMI ($p = 0.016$); $r^2 = 0.376$.

Table 2 - Results at 15 days (first assessment), 90 days (second assessment), and 180 days after hospital discharge (third assessment) for the total sample, intensive care unit (ICU) and ward groups

	Assessment 1 (n = 65)			Assessment 2 (n = 37)			Assessment 3 (n = 26)		
	Total (n = 54)	Ward (n = 37)	ICU (n = 28)	Total (n = 37)	Ward (n = 21)	ICU (n = 16)	Total (n = 26)	Ward (n = 14)	ICU (n = 12)
LF									
FVC, % pred.	67.6 ± 25.4	70.7 ± 28.7	63.5 ± 20.1	76.7 ± 20.5	78.4 ± 20.3	74.4 ± 21.3	70.1 ± 22.6	68.8 ± 21.8	71.7 ± 24.3
FVC < LLN, n (%)	47 (72.3)	26 (70.3)	21 (75.0)	21 (56.7)	10 (47.6)	10 (62.5)	17 (65.3)	10 (71.4)	7 (58.3)
FEV_1, % pred.	81.4 ± 23.4	83.6 ± 26.2	78.6 ± 19.1	93.6 ± 15.9*	95.9 ± 16.9	90.7 ± 14.4	89.8 ± 21.4	89.5 ± 25.7	90.0 ± 14.4
FEV_1 < LLN, n (%)	30 (46.1)	19 (51.4)	11 (39.3)	8 (21.6)*	4 (19.0)	4 (25.0)	6 (23.0)	4 (28.6)	2 (16.7)
FEV_1/FVC	82.5 ± 12.7	83.1 ± 14.1	81.8 ± 10.8	80.5 ± 9.9	81.0 ± 9.9	79.9 ± 10.2	82.8 ± 10.5	83.6 ± 13.7	81.9 ± 5.1
FEV_1/FVC < LLN, n (%)	6 (9.2)	4 (10.8)	2 (7.1)	4 (10.5)	2 (9.5)	2 (12.5)	1 (3.8)	1 (7.1)	0 (0.0)
RMS									
MIP, cmH_2O	69.7 ± 37.9	69.2 ± 37.8	69.8 ± 38.6	61.6 ± 30.3	57.1 ± 28.4	67.5 ± 32.6	71.6 ± 34.6	67.9 ± 32.9	76.0 ± 37.4
MIP, % pred.	77.4 ± 49.8	69.4 ± 33.7	67.8 ± 29.7	76.5 ± 48.8	62.4 ± 29.4	67.7 ± 28.4	84.0 ± 54.1	71.7 ± 32.0	76.0 ± 31,1
MIP < LLN, n (%)	44 (67.7)	24 (64.9)	20 (71.4)	26 (70.2)	14 (66.7)	12 (75.0)	16 (61.5)	9 (64.3)	7 (58.3)
MEP, cmH_2O	84.9 ± 34.7	85.0 ± 35.5	84.71 ± 34.1	82.8 ± 34.8	74.0 ± 34.3	94.4 ± 33.0	96.4 ± 38.9	88.2 ± 33.9	106.0 ± 43.6
MEP, % pred.	85.4 ± 32.8	82.9 ± 32.3	80.0 ± 28.3	87.0 ± 32.2	76.1 ± 29.0	91.1 ± 26.7	100.4 ± 34.4	90.1 ± 25.2	98.7 ± 35.7
MEP < LLN, n (%)	33 (50.8)	18 (48.6)	15 (53.6)	15 (40.5)	11 (52.4)	4 (25.0)	8 (30.8)	5 (35.7)	3 (25.0)
Dyspnea									
mMRC	2.0 [0.0 – 3.0]	1.0 [0.0 – 3.0]	2.0 [1.0 – 3.0]	1.0 [0.0 – 2.5]	1.0 [0.3 – 3.0]	1.0 [0.3 – 3.0]	1.0 [0.0 – 3.0]	0.0 [0.0 – 2.3]	1.0 [1.0 – 3.0]
Grade 0#	17 (26.2)	13 (35.1)	4 (14.3)	16 (43.2)	12 (57.1)	4 (25.0)	10 (38.5)	8 (57.1)	2 (16.7)
Grade 1#	13 (20.0)	6 (16.2)	7 (25.0)	10 (27.0)	5 (23.8)	5 (31.3)	7 (26.9)	2 (14.3)	5 (41.7)
Grade 2#	15 (23.1)	8 (21.6)	7 (25.0)	2 (5.4)	1 (4.8)	1 (6.3)	1 (3.8)	1 (7.1)	0 (0.0)
Grade 3#	16 (24.6)	10 (27.0)	6 (21.4)	8 (21.6)	3 (14.3)	5 (31.3)	8 (30.8)	3 (21.4)	5 (41.7)
Grade 4#	4 (6.1)	0 (0.0)	4 (14.3)	1 (2.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
FC									
Steps, n	93.8 ± 34.7	102.3 ± 29.3	82.6 ± 38.5ǂ	103.5 ± 40.2	118.5 ± 38.0	83.8 ± 34.9ǂ	109.4 ± 41.4	125.6 ± 35.6	90.6 ± 40.9ǂ
Steps, % pred	70.7 ± 25.9	76.8 ± 21.1	62.7 ± 29.7ǂ	80.2 ± 29.8	94.0 ± 26.7	62.2 ± 24.0ǂ	84.8 ± 31.3	98.2 ± 22.6	69.2 ± 33.6ǂ
Steps < LLN, n (%)	39 (60.0)	20 (54.1)	19 (67.9)	21 (56.8)	7 (33.3)	14 (87.5)	10 (38.5)	4 (28.6)	6 (50.0)
LLS/P									
30sSTS, repetitions	10.0 ± 3.6	10.4 ± 3.1	9.4 ± 4.1	10.5 ± 3.2	10.9 ± 3.4	9.9 ± 2.8	11.4 ± 3.2	12.8 ± 2.9	9.8 ± 2.9ǂ
30sSTS, % pred	61.3 ± 23.8	62.0 ± 20.7	60.5 ± 27.7	65.6 ± 19.5	67.4 ± 19.6	63.2 ± 19.8	71.7 ± 20.0	79.0 ± 15.9	63.0 ± 21.3ǂ
30sSTS < LLN, n (%)	55 (84.6)	32 (86.5)	23 (82.1)	28 (75.6)	15 (71.4)	13 (81.3)	18 (69.2)	8 (57.1)	10 (83.3)

Note: LF = lung function; FVC = forced vital capacity; LLN = lower limits of normality; FEV_1 = forced expiratory volume in the first second; RMS = respiratory muscle strength; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; FC = functional capacity; LLS/P = lower limb strength/performance. Values are expressed in mean ± standard deviation, median [interquartile range] and frequency (%). *p < 0.05 in comparison to assessment 1. ǂp < 0.05 in comparison to ward group. #Grades: n (%).

Table 3 - Results at 15 days (first assessment), 90 days (second assessment), and 180 days after hospital discharge (third assessment) for the total sample, intensive care unit (ICU) and ward groups

	Assessment 1 (n = 65)			Assessment 2 (n = 37)			Assessment 3 (n = 26)		
	Total (n = 54)	Ward (n = 37)	ICU (n = 28)	Total (n = 37)	Ward (n = 21)	ICU (n = 16)	Total (n = 26)	Ward (n = 14)	ICU (n = 12)
PMS									
Handgrip strength, kgf	34.6 ± 15.0	37.0 ± 17.5	31.5 ± 10.5	32.9 ± 10.1	31.3 ± 9.4	34.9 ± 10.9	34.4 ± 11.6	34.8 ± 12.1	34.0 ± 11.4
Handgrip strength, % pred	101.3 ± 40.1	107.3 ± 41.2	93.3 ± 37.8	99.8 ± 35.5	95.2 ± 28.0	105.7 ± 43.6	101.7 ± 31.2	103.2 ± 19.9	99.9 ± 41.6
Handgrip strength < LLN, n (%)	18 (27.7)	9 (24.3)	9 (32.1)	9 (24.3)	6 (28.6)	3 (18.8)	4 (15.4)	1 (7.1)	3 (25.0)
PAL, n (%)									
Very active	3 (4.6)	2 (5.4)	1 (3.6)	1 (2.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Active	18 (27.7)	12 (32.4)	6 (21.4)	14 (37.8)	9 (42.9)	5 (31.3)	15 (57.7)	8 (57.1)	7 (58.3)
Insufficiently active A	9 (13.8)	5 (13.5)	4 (14.3)	9 (24.3)	3 (14.3)	6 (37.5)	3 (11.5)	2 (14.3)	1 (8.3)
Insufficiently active B	20 (30.8)	9 (24.3)	11 (39.3)	9 (24.3)	7 (33.3)	2 (12.5)	2 (7.7)	2 (14.3)	0 (0.0)
Sedentary	15 (23.1)	9 (24.3)	6 (21.4)	4 (10.8)	2 (9.5)	2 (12.5)	6 (23.1)	2 (14.3)	4 (33.3)

Note: PMS = peripheral muscle strength; LLN = lower limits of normality; PAL = physical activity level. Values are expressed in mean ± standard deviation, median [interquartile range] and frequency (%).

Table 4 - Sample characteristics categorized by groups according to lung function (forced vital capacity) and functional capacity (6MST) 15 days after hospital discharge

	FVC < LLN (n = 47)	FVC > LLN (n = 18)	6MST < LLN (n = 39)	6MST > LLN (n = 26)
Age, years	56.5 ± 11.5	50.9 ± 14.2	54.2 ± 12.8	56.1 ± 12.2
Gender, M/F	31 / 16	4 / 14	23 / 16	12 / 14
Body mass index, kg/m^2	28.5 ± 7.1	31.1 ± 5.7	30.4 ± 7.5	27.5 ± 5.4
Length of hospital stay, days	14.5 ± 15.0	12.2 ± 10.7	15.7 ± 16.2	11.1 ± 9.1
ICU hospitalization (n = 28), n (%)	21 (44.7)	7 (38.9)	19 (48.7)	9 (34.6)
Length of ICU stay (n = 28), days	6.7 ± 12.5	6.6 ±11.6	7.6 ± 13.5	5.4 ± 9.9
MV use (n = 11), n (%)	8 (17.0)	3 (16.7)	8 (20.5)	3 (11.5)
Duration of MV (n = 11), days	17.5 ± 14.9	14.0 ± 9.5	20.1 ± 13.9	7.0 ± 4.0*
Comorbidity index	1.0 [1.0 – 3.0]	1.0 [0.0 – 3.0]	1.0 [0.0 – 2.0]	1.5 [0.0 – 3.0]
SOFA score (n = 28)	2.0 [2.0 – 3.0]	2.0 [0.6 – 3.0]	2.0 [1.6 – 3.0]	2.0 [2.0 – 4.0]
SAPS 3 score (n = 28)	39.7 ± 12.0	36.2 ± 7.8	37.9 ± 7.1	40.9 ± 17.1
SAPS 3 score	-	-	38.9 ± 11.2	38.9 ± 11.2

Note: FVC = forced vital capacity; LLN = lower limit of normality; 6MST = six-minute step test; M = male; F = female; ICU = intensive care unit; MV = mechanical ventilation; SOFA = Sequential Organ Failure; SAPS 3 = Simplified Acute Physiology Score 3. Values are expressed in mean ± standard deviation, median [interquartile range] and frequency (%). *p < 0.05 compared with 6MST < LLN group.

Discussion

This study assessed the respiratory and functional repercussions of individuals hospitalized with COVID-19 at 15, 90, and 180 days post-discharge. Upon discharge, individuals exhibited dyspnea, reduced FVC, inspiratory muscle strength, functional capacity, physical performance, lower limb strength, and physical activity levels. At the 180-day follow-up, dyspnea persisted along with reduced FVC, physical performance, lower limb strength, and physical activity levels.

Despite significant advancements in our understanding of COVID-19, numerous questions remain unanswered. Notably, even prior to the emergence of SARS-CoV-2, various viral and bacterial infections were recognized to cause post-infectious complications. Emerging evidence suggests that COVID-19 may share similar characteristics, potentially leading to long-term sequelae.[3,4] It is plausible that there are multiple, potentially overlapping causes for long COVID. Several hypotheses regarding its pathogenesis have been proposed, including the presence of persistent reservoirs of SARS-CoV-2 in tissues; immune dysregulation, with or without reactivation of underlying pathogens, including herpes viruses such as Epstein-Barr virus and human herpesvirus 6 (HHV-6); impacts of SARS-CoV-2 on the microbiota, including the virome; autoimmunity and pre-conditioning of the immune system by molecular mimicry; microvascular blood clotting with endothelial dysfunction; and dysfunctional signaling in the brainstem and/or vagus nerve.[3,4]

Lung function indicated a restrictive disorder, as previously demonstrated in other studies.[22,23] Although FEV_1 improved 90 days after the disease, no improvement in FVC was observed. A restrictive disorder occurs because the inflammatory process and lung injury stimulate areas of consolidation and pulmonary fibrosis with an interstitial pattern. The fibrous tissue appears during the resolution of respiratory infection (i.e., between 5 and 6 months after disease onset) and gradually changes lung function, ventilation, and gas diffusion.[24]

Dyspnea is one of the most prevalent symptoms in long COVID, affecting 31% of individuals one year after the disease.[25] Our study demonstrated that 61.5% of individuals had dyspnea 180 days after hospitalization; 30.8% of these presented severe dyspnea. This result was probably due to the inclusion of individuals after hospitalization, which may justify the disease severity. Dyspnea is a multicausal symptom and may result from several pathophysiological phenomena caused by COVID-19, such as damage to the lung parenchyma, cardiovascular dysfunction, and changes in lung function and gas exchange.[26,27]

Dyspnea can also be related to the reduced inspiratory muscle strength. In our study, 68% and 62% of individuals presented reduced inspiratory muscle strength 15 and 180 days, respectively, after hospital discharge. Decreased inspiratory muscle strength is common in post-COVID-19 individuals. For example, previous studies demonstrated a prevalence of 49% of individuals 30 days after hospital discharge, 40.9% after 45 days,[28] and 31.8% after 270 days of hospital discharge.[29]

Functional capacity was assessed using the 6MST, demonstrating its feasibility in post-COVID-19 individuals, even hospitalized.[30] The 6MST test can be an alternative to the barriers for performing cardiopulmonary exercise and walking-based tests because it is a simple and low-cost test that requires little space and can be performed at home. In our study, individuals showed a mean functional capacity below the LLN after hospital discharge and above the LLN at 90 and 180 days after hospital discharge. However, when evaluating proportions, a considerable number of individuals were below the LLN. Although functional capacity in post-COVID-19 individuals has been mostly assessed using the six-minute walk test, most individuals submitted to this test do not present an altered functional capacity.[28] The difference between our study and others using the six-minute walk test can be explained by the fact that climbing stairs requires greater peripheral muscle strength and cardiac and metabolic demands than walking on flat ground, mainly because of the effort needed to lift the body against gravity.[31] Physical performance and lower limb strength were below predicted values during the follow-up; mean handgrip strength values were within the normality. A previous study showed that individuals presented normal handgrip strength within one year after hospital discharge;[32] in contrast, a reduced strength has been demonstrated in 52.2% of individuals up to twelve months after hospital discharge.[31] This variability may be attributed to the broad spectrum of disease severity among individuals.[33]

Changes observed in functional capacity, lower limb performance, and inspiratory and peripheral muscle strength can be explained by the effects of the virus on muscle cells and the inflammatory process on muscle tissue. These phenomena induce muscle fiber proteolysis, fibroblast activation, fibrosis, and blockage of progenitor cells of new muscle fibers, which explains why physical recovery is problematic after COVID-19.[7] Muscle tissue is also affected by immobilization and corticosteroids used to control the inflammatory process.[8,9]

A less active lifestyle is present in individuals after COVID-19 in our study. Despite the increased number of active individuals observed 90 days after hospital discharge, 42.3% were classified as sedentary or insufficiently active. A previous study showed that individuals spent about 10 hours per day in a sedentary lifestyle six months after hospitalization.[33]

The longitudinal follow-up of this study provides a detailed analysis of the prevalence, severity, and persistence of respiratory and functional repercussions following COVID-19. Our findings offer valuable insights to aid clinicians in developing appropriate rehabilitative therapeutic strategies for this population. This information can also guide professionals involved in clinical practice to implement a preventive strategy, aiming to prevent complications or mitigate their severity. The substantial number of individuals experiencing long COVID necessitates specialized attention from rehabilitation teams with knowledge about the sequelae of the disease.

This study has some limitations. The low adherence of individuals resulted in a significant sample loss. Although sample losses are common in longitudinal studies, factors such as social isolation and fear of reinfection may have influenced the number of refusals, despite reaching the calculated sample size. Different researchers conducted the assessments; however, all were previously trained, and tests were performed following standardized guidelines. Due to the routine of the participating hospitals, only the SAPS 3 and SOFA scores of patients hospitalized in the ICU were recorded. Further investigations are needed to explore the findings of this study over a longer follow-up period.

Conclusion

Individuals after COVID-19 hospitalization showed significant respiratory and functional consequences. Following hospital discharge, there was a high degree of dyspnea, reduction in FVC, inspiratory muscle strength, functional capacity, lower limb strength, and performance, as well as a decrease in physical activity level. At 180 days after hospital discharge, dyspnea, reductions in FVC, lower limb strength and performance, and physical activity level persisted.

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Authors' contributions

CVA, MMR, CM and AJ were responsible for the study conception and design. CVA, YASM and AJ, for data curation. CVA, CCO, YASM, LFC, MMR, CM and AJ, for formal analysis and investigation. CCO, CM, AJ, LFC, CM and AJ, for the methodology. CVA, CCO, LFC, MMR, CM and AJ, for validation, and CVA, CCO, YASM, LFC, MMR, CM and AJ, for visualization. CVA and AJ wrote the original draft, while CCO, YASM, LFC, MMR and CM reviewed it. AJ was also responsible for the project administration and supervision. All authors approved the final version.

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