



# Lung function of patients hospitalized with COVID-19 at 45 days after hospital discharge: first report of a prospective multicenter study in Brazil

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## ABSTRACT

**Objective:** Because SARS-CoV-2 infection can severely affect the lungs and persistent functional changes can occur after severe disease, we aimed to determine lung function parameters of COVID-19 patients at 45 days after hospital discharge and compare changes according to the severity of the disease. **Methods:** This was a prospective descriptive analytical multicenter study. The participants were allocated into three groups: ward admission (WA) group; ICU admission not on mechanical ventilation (ICU/MV-) group; and ICU admission on MV (ICU/MV+) group. Lung volumes, DL<sub>CO</sub>, MIP, MEP, and six-minute walk distance (6MWD) were measured 45 days after discharge.

**Results:** The sample comprised 242 patients (mean age = 59.4 ± 14.8 years; 52.1% of males), and 232 (96%) had altered lung function. In the total cohort, restrictive disorder was observed in 96%, as well as reductions in DL<sub>CO</sub> (in 21.2% of the patients), FEV<sub>1</sub>/FVC (in 39.7%), and PE<sub>max</sub> (in 95.8%), with no differences between the groups. Comparing the groups, the ICU/MV+ group had reduced DL<sub>CO</sub> in 50% of the patients (p < 0.001) and a lower mean 6MWD % of the predicted value (p = 0.013). Oxygen desaturation in the six-minute walk test was observed in 32.3% of the cohort and was less frequent in the IE group. **Conclusions:** This is the first South American study involving severe COVID-19 survivors whose lung function was assessed 45 days after hospital discharge. Changes were frequent, especially in those on MV, which highlights the importance of lung function evaluation after severe COVID-19.

**Keywords:** COVID-19; Respiratory function tests; Pulmonary diffusing capacity; Virus disease; SARS-CoV-2.

## INTRODUCTION

In March of 2020, the SARS-CoV-2 infection, a highly contagious viral respiratory disease first described in December of 2019 and later designated COVID-19, was declared a pandemic by the WHO. About 5% of cases require ICU admission, and 2.3% require mechanical ventilation (MV).<sup>(1)</sup> Similarly to SARS and Middle East respiratory syndrome, other coronavirus infections, COVID-19 can severely affect the lungs, and hypoxemic acute respiratory failure and death can occur.<sup>(2)</sup> In addition, histopathological studies of severe forms of the disease showed alveolar damage, causing progressive respiratory failure.<sup>(3)</sup>

One early study assessing the lung function of patients hospitalized for COVID-19 immediately after discharge found that impaired DL<sub>CO</sub> was the most common change, followed by restrictive ventilatory disorder, both associated with disease severity.<sup>(4)</sup> A 3-month follow-up

study including 39 patients with changes on CT in the acute phase of the disease found a 16% reduction in DL<sub>CO</sub> and an 11% reduction in FVC.<sup>(5)</sup>

Reduced exercise capacity in the follow-up period after COVID-19 has been described. In a cohort of 225 patients who performed the six-minute walk test (6MWT) 2 months after disease onset, patients with moderate or severe disease had shorter walking distance (6MWD) when compared with those with mild disease.<sup>(6)</sup> Among 186 patients undergoing the 6MWT 30-90 days after the onset of symptoms of COVID-19, those with persistent dyspnea had a lower 6MWD in percentage of predicted values (%pred) than did those without dyspnea.<sup>(7)</sup>

Respiratory muscle strength after COVID-19 has been poorly described to date. In a study of SARS survivors during the 2003 epidemic, a reduction in MIP and MEP was observed in a significant proportion of patients at 12 months of follow-up.<sup>(8)</sup>

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Clinical and functional follow-up assessment may detect persistent lung dysfunction and guide strategies to improve the outcomes of hospitalized patients with COVID-19.<sup>(9)</sup> The objectives of the present study were to describe the lung function of patients hospitalized for confirmed SARS-CoV-2 infection and SARS at 45 days after hospital discharge, and to compare the results between groups according to the severity of the acute disease. The hypothesis was that patients who required MV would have worse performance at follow-up than would those who did not.

## METHODS

This was a prospective descriptive analytical multicenter study that evaluated for inclusion adult patients admitted to three public referral hospitals for COVID-19 in the city of Belo Horizonte, Minas Gerais, Brazil, with a confirmed diagnosis of COVID-19 (positive RT-PCR result from nasal or oropharyngeal swabs) and SARS between June 16 and November 11 of 2020. The Brazilian Ministry of Health definition of SARS was adopted<sup>(10)</sup>: a hospitalized individual with fever and cough or sore throat, associated with dyspnea, feeling of tightness in the chest, or  $SpO_2 < 95\%$ . Patients with indication for palliative care were considered ineligible. Patients who were too weak to perform the tests and those who withdrew consent were not included in the analysis.

This study was approved by the *Comitê Nacional de Ética em Pesquisa* (CONEP, Brazilian national research ethics committee), protocol number 4.044.191. Consent of the local ethics committees of the three hospitals was obtained. All participants gave written informed consent.

Of a sample of 551 patients who were considered eligible, a total of 294 (53.4%) were initially included. However, 49 were lost to follow-up (9 died, 7 withdrew consent, and 33 failed to attend follow-up), and 3 were too weak to perform the tests. Therefore, the final sample comprised 242 patients (43.9%).

Patients were stratified into three groups: ward admission (WA) group; ICU admission not on MV (ICU/MV-) group; and ICU admission on MV (ICU/MV+) group.

Demographics, clinical manifestations, comorbidities, continuous medications, smoking, date of onset of respiratory symptoms, date of hospital admission, length of hospital stay, length of ICU stay, length of MV, and complications during hospitalization were recorded. Laboratory tests and chest imaging at admission were performed at the discretion of the attending clinicians. Arterial blood gases, complete blood workup, C-reactive protein (CRP), LDH, serum albumin, prothrombin time/international normalized ratio (INR), D-dimer, creatinine, ALT, and AST results were recorded when available. Gas exchange was evaluated by the  $PaO_2/FiO_2$  ratio. The proportion of pulmonary impairment on CT scans was recorded

as informed in the reports provided by the radiology services of the hospitals.

The major outcomes studied were lung function (spirometry, lung volumes, and  $DL_{CO}$ ), exercise capacity (6MWD), and respiratory muscle strength (MIP and MEP).

In accordance with the study design, assessment for eligibility and inclusion took place within 24 h of admission, and follow-up assessment was scheduled for 45 days after admission, with a tolerance of  $\pm 15$  days. This planning considered an expected average duration of hospital stay of 15 days and a transmission period of up to 30 days after the onset of symptoms. The assessment of patients with prolonged hospital stays was scheduled and carried out as soon as possible after discharge.

In the follow-up visit, the presence of cough and dyspnea (in accordance with the modified Medical Research Council scale),<sup>(11)</sup> as well as vital data, weight, and height, were recorded. Lung function tests were performed in the Pulmonary Function Laboratory of the University Hospital of the Federal University of Minas Gerais. A Collins CPL system (Ferraris Respiratory, Louisville, CO, USA) was used for the determination of absolute lung volumes, spirometry parameters, and  $DL_{CO}$ , in accordance with international criteria.<sup>(12,13)</sup> The helium dilution method in a constant volume system was used in order to measure lung volumes. The following variables were studied: TLC, slow vital capacity (SVC), FVC,  $FEV_{1,}$  and  $FEV_{1}/FVC$  ratio. Measurements were reported as absolute values and %pred for the Brazilian population.<sup>(14,15)</sup> The single breath method was used for the determination of  $DL_{CO}$ , considering the values suggested by Guimarães et al.<sup>(16)</sup>

The 6MWT was performed in a 30-m corridor using a portable oximeter (Nonin Medical Inc., Plymouth, MN, USA) in accordance with international standards.<sup>(17)</sup> The following variables were recorded:  $SpO_2$ , HR, RR, Borg dyspnea scale score at the beginning and end of the test, HR in %pred in relation to the maximum HR in %pred for adults, HR at the end of 6MWT, HR 1 min after recovery time, and 6MWD. Oxygen desaturation  $\geq 4\%$  or a change in HR 1 min after recovery time  $< 12$  bpm were considered altered results.<sup>(18)</sup> The 6MWD was expressed in absolute values and in %pred for the Brazilian population.<sup>(19)</sup>

MIP and MEP were measured with an analog manometer (Makil, Londrina, Brazil), as described by Laveneziana et al.<sup>(20)</sup> The maneuver was repeated five to eight times, respecting a 10% reproducibility. The highest value obtained was recorded. Predicted values were calculated in accordance with Neder et al.<sup>(21)</sup> The lower limit of normal (LLN) for each variable was calculated from prediction equations.<sup>(13)</sup>

Diagnosis of COVID-19, lung function measurements, and selection bias were considered possible sources of bias. Diagnosis was defined by the gold standard test RT-PCR; the equipment used was calibrated according

to the recommendations of the manufacturers, and clinical evaluation followed standardized questionnaires applied by trained personnel. Selection bias was minimized by the multicenter design.

### Data analysis

Data were collected using the REDCap platform (Vanderbilt University, Nashville, TN, USA) and analyzed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as frequencies and proportions. Continuous variables with normal distribution were described as means and standard deviations, whereas those with non-normal distribution were described as medians and interquartile ranges. Predicted values and LLN were used as risk to categorize continuous variables. Proportions were compared using Pearson's chi-square or Fisher's exact tests. The Kruskal-Wallis test or ANOVA was used for those with measures of central tendency. To verify differences between the groups, post hoc multiple comparisons, using parametric Student's t-test or

nonparametric Mann-Whitney U test, were carried out. Hypothesis testing was two-sided, and the level of significance was set at  $p < 0.05$ .

### RESULTS

The analysis included 242 patients discharged from hospital during the study period. The WA, ICU/MV- and ICU/MV+ groups comprised 141 (58.3%), 70 (28.9%), and 31 (12.8%) of the participants, respectively. The groups were homogeneous regarding age ( $59.4 \pm 14.8$  years), sex (52.1% were male), level of education, family income, self-reported skin color, marital status, and comorbidities (Table 1).

The majority of the participants (86.4%) had at least one comorbidity. Asthma and COPD occurred in 11.1% and in 7.2%, respectively, and 62 patients (26.1%) were smokers (Table 1). The most common symptoms on admission were dyspnea (in 80.2%) and cough (in 68.6%), which were more frequent in the ICU/MV- group. Anosmia, dysgeusia, and diarrhea were more frequent in the WA group (Table 2).

**Table 1.** Sociodemographic characteristics and pre-existing conditions in the sample studied.<sup>a</sup>

Variable	Total	Group			p
	(N = 242)	WA (n = 141)	ICU/MV- (n = 70)	ICU/MV+ (n = 31)	
Male	126 (52.1)	71 (50.4)	36 (51.4)	19 (61.3)	0.540
Age, years	59.4 ± 14.8	61.0 ± 14.3	57.8 ± 14.9	56.2 ± 16.4	0.146
Level of education, years of schooling <sup>b</sup>					
> 12	20 (8.9)	11 (8.3)	8 (12.1)	1 (3.7)	
9-12	102 (45.3)	64 (48.5)	28 (42.4)	10 (37.0)	0.444
< 9	103 (45.8)	57 (43.2)	30 (45.5)	16 (59.3)	
Family income, MW <sup>b</sup>					
> 3	36 (16.5)	17 (13.4)	16 (24.6)	3 (11.5)	0.107
≤ 3	182 (83.5)	110 (86.6)	49 (75.4)	23 (88.5)	
Self-reported skin color <sup>b</sup>					
White	63 (26.1)	39 (27.9)	17 (24.3)	7 (22.6)	
Brown	128 (53.1)	71 (50.7)	38 (54.3)	19 (61.3)	0.915
Black	50 (20.8)	30 (21.4)	15 (21.4)	5 (16.1)	
Marital status <sup>b</sup>					
Not married	108 (46.8)	68 (49.6)	31 (46.3)	9 (33.3)	0.299
Married	123 (53.2)	69 (50.4)	36 (53.7)	18 (66.7)	
<b>Pre-existing conditions</b>					
Comorbidities	209 (86.4)	122 (86.5)	61 (87.1)	26 (83.9)	0.904
Hypertension <sup>c</sup>	143 (68.8)	79 (65.3)	46 (75.4)	18 (69.2)	0.380
Obesity <sup>c</sup>	75 (38.7)	40 (34.8)	26 (46.4)	9 (39.1)	0.340
Diabetes mellitus <sup>c</sup>	71 (34.0)	38 (71.1)	23 (37.7)	10 (38.5)	0.593
Other CVD <sup>c</sup>	37 (17.8)	19 (15.7)	12 (19.7)	6 (23.1)	0.605
Asthma <sup>c</sup>	23 (11.1)	15 (12.4)	5 (8.2)	15 (12.4)	0.693
COPD <sup>c</sup>	15 (7.2)	10 (8.3)	3 (5.0)	2 (7.7)	0.724
Smoking <sup>b</sup>	62 (26.1)	40 (29.0)	15 (21.4)	7 (23.3)	0.470
Use of immunosuppressive medication <sup>c,d</sup>	11 (5.4)	6 (5.1)	3 (5.0)	2 (7.7)	0.860
Other <sup>b,e</sup>	108 (51.7)	66 (54.1)	28 (45.8)	14 (53.8)	0.563

WA: ward admission; ICU/MV-: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; MW: minimum wage; and CVD: cardiovascular disease. <sup>a</sup>Values expressed as n (%) or mean ± SD. <sup>b</sup>Missing data ≤ 10%. <sup>c</sup>Missing data = 11-20%. <sup>d</sup>Prednisone > 20 mg/day for more than two weeks; cyclosporine; cyclophosphamide; mycophenolate; rituximab; azathioprine; chemotherapy within the past 30 days. <sup>e</sup>Active solid organ or blood cancer, chronic kidney disease, solid organ or bone marrow transplant, and other comorbidities.

Complications during hospitalization were more frequent in the ICU/MV+ group. Acute kidney injury occurred in 14 (5.9%) of the patients, 7 of whom required hemodialysis. Vascular thrombosis occurred in 27 (11.4%), being more frequent in the ICU/MV+ group (Table 2). Duration of MV was  $11.5 \pm 10.8$  days. Tracheostomy was performed in 20 patients (66.7%) in the ICU/MV+ group.

Regarding laboratory screening and severity scores at admission, inflammation and acute phase markers—CRP, LDH, serum albumin, total leukocytes, neutrophils, and D-dimer—showed the greatest changes in the two ICU groups. Mean  $\text{PaO}_2/\text{FiO}_2$  was

significantly higher in the WA group than in the ICU groups. In contrast, SOFA scores were higher in ICU patients.

At admission, CT was performed in 164 (67.8%) of the patients, and pulmonary involvement  $> 50\%$  was identified in 53 (32.3%), more commonly among the ICU patients.

The length of hospital stay was longer in the most severely ill patients and in those undergoing MV (Table 2). The mean time to follow-up assessment was  $60.1 \pm 21.7$  days (range: 31-152 days) after admission and  $46.4 \pm 22.5$  days (range: 4-136 days) after discharge. Intervals were shorter in the ICU/MV+ group.

**Table 2.** Clinical and laboratory characteristics at hospital admission and during the acute phase of COVID-19.<sup>a</sup>

Variable	Total	Group			p
	(N = 242)	WA (n = 141)	ICU/MV – (n = 70)	ICU/MV + (n = 31)	
<b>Symptoms</b>					
Time from symptom onset to hospitalization, days	7.8 ± 10.0	8.2 ± 12.4	7.3 ± 5.8	7.2 ± 3.9	0.785
Dyspnea	194 (80.2)	103 (73.0)*	64 (91.4) <sup>††</sup>	27 (87.1)* <sup>‡</sup>	0.004
Cough (dry or productive)	166 (68.6)	90 (63.8)*	58 (82.9) <sup>†</sup>	18 (58.1)*	0.008
Fever	141 (58.5)	84 (59.6)	41 (59.4)	16 (51.6)	0.706
Myalgia	119 (49.2)	72 (51.1)	31 (44.3)	16 (51.6)	0.624
Alterations in taste	103 (42.6)	73 (51.8)*	26 (37.1) <sup>†</sup>	4 (12.9) <sup>‡</sup>	< 0.0001
Alterations in olfaction	94 (38.8)	64 (45.4)*	23 (32.9) <sup>††</sup>	7 (22.6) <sup>†‡</sup>	0.029
Diarrhea	63 (26.0)	45 (31.9)*	16 (22.9)*	2 (6.5) <sup>†</sup>	0.011
Rhinorrhea	46 (19.0)	32 (22.7)	11 (15.7)	3 (9.7)	0.175
Sore throat	43 (17.8)	25 (17.7)	14 (20.0)	4 (12.9)	0.690
Abdominal pain	26 (10.7)	15 (10.6)	8 (11.4)	3 (9.7)	0.964
<b>Complications during hospitalization</b>					
Vascular thrombosis	27 (11.4)	11 (7.9)*	8 (11.8) <sup>††</sup>	8 (26.7) <sup>††</sup>	0.014
Acute kidney injury	14 (5.9)	1 (0.7)*	5 (7.4) <sup>†</sup>	8 (26.7) <sup>†</sup>	< 0.0001
Antibiotic use	223 (94.1)	129 (92.8)	64 (94.1)	30 (100.0)	0.317
<b>Laboratory tests</b>					
$\text{PaO}_2/\text{FiO}_2$ <sup>b</sup>	279.1 ± 122.3	322.7 ± 119.1*	227.81 ± 104.5 <sup>†</sup>	203.7 ± 90.1 <sup>†</sup>	< 0.0001
SOFA score within the first 24 h <sup>b</sup>	2.3 ± 2.1	1.6 ± 1.3*	2.3 ± 1.3 <sup>†</sup>	5.6 ± 3.5 <sup>‡</sup>	< 0.0001
Total leukocytes/mm <sup>3b</sup>	8,367 ± 4,137	7,875 ± 3,893*	8,519 ± 4,138 <sup>††</sup>	10,277 ± 4,752 <sup>††</sup>	0.014
Lymphocytes/mm <sup>3b</sup>	1,208 ± 815	1,275 ± 905	1,180 ± 720	970 ± 494	0.170
C-reactive protein, mg/L <sup>b</sup>	97.9 ± 74.3	80.3 ± 59.4*	117.1 ± 82.8 <sup>†</sup>	134.1 ± 91.5 <sup>†</sup>	< 0.0001
LDH, U/L <sup>b</sup>	384.2 ± 159.9	336.5 ± 109.4*	422.5 ± 157.3 <sup>†</sup>	521.8 ± 245.5 <sup>‡</sup>	< 0.0001
Creatinine, mg/dL <sup>b</sup>	0.9 ± 0.6	0.8 ± 0.4*	0.9 ± 0.4*	1.4 ± 1.4 <sup>†</sup>	< 0.0001
AST, U/L <sup>c</sup>	45.0 [34.0-64.0]	43.0 [33.0-61.7]	46.0 [37.0-65.1]	37.0 [46.0-78.3]	0.131 <sup>§</sup>
ALT, U/L <sup>c</sup>	35.0 [25.0-62.7]	34.0 [23.0-62.0]	36.5 [27.0-61.7]	30.0 [36.0-65.0]	0.249 <sup>§</sup>
D-dimer, µg/mL <sup>d</sup>	1,000 [579-1,647]	945 [579-1,514]*	1,120 [551-1,667]*	1,566 [774-6,164] <sup>†</sup>	0.039 <sup>§</sup>
<b>Lung involvement on chest CT scan<sup>c</sup></b>					
< 50%	111 (67.7)	79 (79.0)*	24 (51.1) <sup>†</sup>	8 (47.1) <sup>†</sup>	0.001
≥ 50%	53 (32.3)	21 (21.0)*	23 (48.9) <sup>†</sup>	9 (52.9) <sup>†</sup>	
<b>Time outcomes</b>					
Length of hospital stay, days	13.7 ± 11.9	8.7 ± 4.4*	15.8 ± 9.6 <sup>†</sup>	31.4 ± 19.5 <sup>‡</sup>	< 0.0001
Length of ICU stay, days	9.6 ± 14.5	-	6.6 ± 12.6	16.4 ± 16.3	0.002
Interval between discharge and follow-up evaluation, days <sup>b</sup>	46.4 ± 22.5	48.8 ± 19.9	45.1 ± 26.7	38.7 ± 22.4	0.069

WA: ward admission; ICU/MV–: ICU admission not on mechanical ventilation; and ICU/MV+: ICU admission on mechanical ventilation. <sup>a</sup>Values expressed as n (%), mean ± SD, or median [IQR]. <sup>b</sup>Missing data ≤ 10%. <sup>c</sup>Missing data = 11-16%. <sup>d</sup>Missing data = 21%. <sup>†,††</sup>Equal symbols indicate similar means (Student's t-test with post hoc analysis) medians (Mann-Whitney U test), or proportions (Pearson's chi-square test). <sup>§</sup>Nonparametric test.

A TLC below the LLN was the most frequent alteration in lung function, detected in 96.8% of the cohort. However, the mean TLC %pred was above 80% in 87.9%. Only the ICU/MV+ group had a mean TLC %pred below 80% (79.5%), which was significantly lower than in the other groups.

The FEV<sub>1</sub>/FVC ratio was below the LLN in 39.7% of the study cohort, but no difference was detected between the groups. The ICU/MV+ group had lower SVC %pred and FVC %pred, as well as a higher frequency of SVC, FVC, and FEV<sub>1</sub> below the LLN.

DL<sub>co</sub> was below the LLN in 21% of the cohort, but in 50% of the patients in the ICU/MV+ group. DL<sub>co</sub> %pred was significantly lower in this group.

A MEP below the LLN was observed in 95.8% of the cohort. Accordingly, the mean MEP %pred was 53.5%. The MIP below the LLN was found in 59.3% of the patients in the ICU/MV+ group. The mean MIP %pred in this group was 72.1%.

The 6MWD was similar between the groups. However, the 6MWD %pred was significantly shorter in the ICU/MV+ group. Oxygen desaturation was observed in 32.3% of the cohort and was less frequent in the WA group (Table 3). Table 4 presents other variables studied.

## DISCUSSION

To the best of our knowledge, this is the first study reporting lung function parameters in survivors of severe COVID-19 in South America. The main results of this prospective study of 242 patients followed up at 45 days after discharge showed that 96% of those had some change in lung function, and functional impairment was greater and more common in patients on MV. The changes were characterized mainly by restrictive disorder, reduced DL<sub>co</sub>, and reduced 6MWD in association with oxygen desaturation.

Information on persistent symptoms and late changes in lung function after COVID-19 is widely available.<sup>(1,22-26)</sup> In our results, the ICU/MV+ group had a higher frequency of cough, but not of dyspnea, at follow-up assessment. A dyspnea score  $\geq 2$  was present in 18% of the patients after discharge. Huang et al.<sup>(26)</sup> evaluated 1,773 patients 6 months after hospital discharge and reported that 26% of those had a dyspnea score  $> 1$ , with a higher risk in the groups that had required high-flow oxygen and MV.

Although most patients in the present cohort had some abnormality in lung function, the changes were mild. Restrictive ventilatory disorder was the most prevalent one. This is in agreement with studies that included patients with moderate to severe COVID-19.<sup>(2,4,22,23)</sup> All subjects in the ICU/MV+ group had reduced TLC 45 days after discharge, but restrictive disorder was mild (TLC %pred =  $79.5 \pm 15.6\%$ ). Huang et al.<sup>(2)</sup> reported altered TLC in 12.6% of 30 patients evaluated 30 days after discharge; however, only 17 had severe disease. Another study reported that 35% of patients with a history of ICU admission still had TLC  $< 80\%$  6 months after hospitalization.<sup>(27)</sup>

Lung involvement  $> 50\%$  was present in 32% of those who underwent CT at admission. This proportion was higher in the ICU/MV+ group (52.9%). Autopsy studies showed different degrees of alveolar structure destruction and interstitial fibrotic changes in patients who died of COVID-19, suggesting that this could be the mechanism of restriction.<sup>(26)</sup> In addition, ventilator-induced lung injury is a well-described post-SARS sequel, which may impact lung function recovery after severe illness.<sup>(28)</sup>

Reduced DL<sub>co</sub> is the most frequently described change after COVID-19, either in mild or in severe forms.<sup>(26,29-31)</sup> Reduced DL<sub>co</sub> was observed in 21% of the patients in our cohort and in 50% of those in the ICU/MV+ group. Other studies have shown similar results. Smet et al.<sup>(23)</sup> reported reduced DL<sub>co</sub> in 21% of 220 patients at 10 weeks of follow-up. An association between reduced DL<sub>co</sub> and severe COVID-19 has been described.<sup>(1,26,31)</sup> Guler et al.<sup>(24)</sup> reported reduced DL<sub>co</sub> in severe COVID-19 patients after adjusting the analysis for age, sex, and BMI. It has been suggested that decreased DL<sub>co</sub> after COVID-19 is not secondary to residual interstitial lung or vascular abnormalities, but rather a consequence of reduced alveolar volume.<sup>(30,31)</sup> Others have argued that reduced DL<sub>co</sub> could be associated with small vessel abnormalities and microthrombus formation.<sup>(26)</sup>

Obstructive ventilatory disorder was observed in 40% of the present cohort, which could not be explained by the reported frequencies of asthma and COPD in the study population; it is important to consider that predicted values were calculated according to national recommendations.<sup>(14)</sup> Smokers represented 26% of the cohort, and the frequency of obstructive pattern was higher in smokers than in nonsmokers (42% vs. 23%;  $p = 0.008$ ; data not shown). A 9-year follow-up study of COPD in Brazil showed that this disease can be underdiagnosed in up to 70% of cases.<sup>(32)</sup> This could explain the finding of obstruction in patients with previously undiagnosed smoking-related COPD. However, information on previous respiratory symptoms or worsening wheezing after COVID-19 was not collected. Finally, the study cohort was selected from two referral hospitals for respiratory diseases and one referral hospital for infectious diseases. This may have introduced a selection bias for respiratory disease.

Obstruction could also be explained by the emphysematous abnormalities present in areas showing the "vacuole" sign on baseline imaging, as well as in areas with no lung infiltration. The former finding can be explained by direct parenchymal destruction caused by the infection, and the latter, as a manifestation of ventilator-induced lung injury.<sup>(22)</sup>

Impairment of expiratory muscle strength was similar in all groups, but reduced inspiratory muscle strength was mainly observed in the ICU/MV+ group. This could be consequent to transient changes in mechanical properties of the chest wall and respiratory muscles after critical illness and be attributed to the post-intensive care syndrome, which is characterized

**Table 3.** Cough, dyspnea, BMI, lung function results, and six-minute walk test results 45 days after hospital discharge.

Variable	Total (N = 242)	Group			p
		WA (n = 141)	ICU/MV – (n = 70)	ICU/MV + (n = 31)	
Dyspnea <sup>b</sup>	126 (52.3)	71 (50.7)	39 (55.7)	16 (51.6)	0.789
Dyspnea, mMRC ≥ 2	74 (59.2)	40 (56.3)	23 (59)	11 (73.3)	0.477
Cough <sup>b</sup>	60 (25.0)	25 (18.0) <sup>*</sup>	21 (30.0) <sup>†</sup>	14 (45.2) <sup>†</sup>	0.004
BMI	30.8 ± 6.9	30.6 ± 6.9	31.4 ± 6.5	30.2 ± 7.9	0.639
<b>Spirometry<sup>b</sup></b>					
SVC, %pred	83.7 ± 15.7	86.4 ± 14.6 <sup>*</sup>	82.1 ± 17.0 <sup>*</sup>	74.9 ± 14.0 <sup>†</sup>	0.001
SVC < LLN	80 (35.4)	33 (25.0) <sup>*</sup>	28 (42.4) <sup>††</sup>	19 (67.9) <sup>†</sup>	< 0.0001
FVC, %pred	80.3 ± 15.1	82.7 ± 14.0 <sup>*</sup>	79.0 ± 16.3 <sup>†</sup>	72.7 ± 14.8 <sup>†</sup>	0.003
FVC < LLN	93 (40.6)	42 (31.1) <sup>*</sup>	30 (46.2) <sup>†</sup>	21 (72.4) <sup>†</sup>	< 0.0001
FEV <sub>1</sub> , %pred	78.2 ± 15.9	79.4 ± 16.1	77.8 ± 15.6	73.7 ± 14.7	0.192
FEV <sub>1</sub> < LLN	96 (41.9)	48 (35.6) <sup>*</sup>	29 (44.6) <sup>†</sup>	19 (65.5) <sup>†</sup>	0.011
FEV <sub>1</sub> /FVC, %pred	78.3 ± 8.9	77.0 ± 9.9 <sup>*</sup>	79.3 ± 6.7 <sup>†</sup>	82.0 ± 6.6 <sup>†</sup>	0.009
FEV <sub>1</sub> /FVC < LLN	91 (39.7)	58 (43.0)	24 (36.9)	9 (31.0)	0.423
<b>Lung volumes<sup>b</sup></b>					
TLC, %pred	87.9 ± 15.8	91.2 ± 14.9 <sup>*</sup>	85.0 ± 16.2 <sup>†c</sup>	79.5 ± 15.6 <sup>†</sup>	< 0.0001
TLC < LLN	211 (96.8)	123 (96.9)	63 (95.5)	25 (100.0)	0.546
RV, %pred	89.6 ± 27.2	90.9 ± 26.2	89.6 ± 29.4	83.4 ± 26.6	0.430
RV/TLC, %pred	36.7 ± 9.9	37.1 ± 9.8	36.4 ± 10.0	35.6 ± 9.9	0.720
<b>DL<sub>co</sub><sup>c</sup></b>					
DL <sub>co</sub> , %pred	100.8 ± 26.0	107.1 ± 23.3 <sup>*</sup>	96.3 ± 27.0 <sup>†</sup>	81.9 ± 25.7 <sup>†</sup>	< 0.0001
DL <sub>co</sub> < LLN	46 (21.2)	14 (11.1) <sup>*</sup>	19 (29.2) <sup>†</sup>	13 (50.0) <sup>†</sup>	< 0.0001
<b>Respiratory muscle strength<sup>c</sup></b>					
MIP, %pred	86.7 ± 30.5	86.6 ± 30.6 <sup>*</sup>	93.0 ± 28.7 <sup>*</sup>	72.1 ± 30.2 <sup>†</sup>	0.011
MIP < LLN	88 (40.9)	52 (41.9) <sup>*,b</sup>	20 (31.3) <sup>*</sup>	16 (59.3) <sup>†</sup>	0.043
MEP, %pred	53.6 ± 18.1	53.8 ± 18.0	54.7 ± 18.2	50.4 ± 18.8	0.579
MEP < LLN	204 (95.8)	119 (96.7)	59 (93.7)	26 (96.3)	0.604
<b>Six-minute walk test<sup>b</sup></b>					
Distance, m	437.1 ± 111.7	439.1 ± 114.5	449.4 ± 104.3	396.3 ± 110.4	0.107
Distance, %pred	83.8 ± 20.1	84.7 ± 19.6 <sup>*</sup>	86.2 ± 20.9 <sup>*</sup>	73.2 ± 18.3 <sup>†</sup>	0.013
Oxygen desaturation during the test ≥ 4%	75 (32.3)	33 (24.1) <sup>*</sup>	30 (44.1) <sup>†</sup>	12 (44.4) <sup>†</sup>	0.006

WA: ward admission; ICU/MV–: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; mMRC: modified Medical Research Council dyspnea scale; SVC: slow vital capacity; %pred: % of predicted values; and LLN: lower limit of normality. <sup>a</sup>Values expressed as n (%). <sup>b</sup>Missing data ≤ 10%. <sup>c</sup>Missing data = 11-12%. <sup>\*</sup>,<sup>†</sup>,<sup>††</sup>Equal symbols indicate similar means (Student's t-test with post hoc analysis) or proportions (Pearson's chi-square test).

by the presence of physical, cognitive, or mental impairment in patients undergoing prolonged ICU stay,<sup>(33)</sup> including those with COVID-19.<sup>(31,34)</sup> Another possible explanation for respiratory weakness could be the occurrence of interstitial lung disease after COVID-19, which we cannot confirm due to the lack of lung imaging exams concomitant with functional assessment.<sup>(35)</sup> MEP was low in almost all patients (95.8%), whereas only 40.9% had reduced MIP. This discrepancy should not be expected when evaluating respiratory muscle strength. Indeed, volitional assessment of muscle strength is dependent on patient cooperation and coordination with the examiner.<sup>(36)</sup> Thus, our finding may be subject to false-positive results due to inadequate performance of the technique, such as incomplete seal of the mouthpiece.

Mean 6MWD %pred was significantly lower in the ICU/MV+ group. Similar results were reported in

cohorts that included patients who required MV.<sup>(6,33)</sup> In contrast, Daher et al.<sup>(25)</sup> found even lower values in a sample of patients not on MV. However, those patients met the criteria for severe COVID-19 and had a mean of 64 years of age, which can reduce exercise capacity.<sup>(25)</sup> Another study with COVID-19 patients (mean age = 46.7 years) reported a mean 6MWD of 562 ± 45.3 m, and only 30% of their sample had severe COVID-19.<sup>(2)</sup> The worse performance of the patients who required MV in the 6MWT may be a consequence of critical illness polyneuropathy.<sup>(37)</sup> In addition, this fact may be associated with fatigue, the most common manifestation of the post-COVID syndrome.<sup>(37)</sup> More than 50 manifestations of the disease have been described and have been tentatively referred to as "late COVID-19," "post-acute COVID-19," or "post-COVID-19 syndrome." Fatigue was the most common symptom in a meta-analysis of post-COVID-19 patients, and its similarities

**Table 4.** Clinical and laboratory characteristics at hospital admission and during the acute phase of COVID-19, as well as lung function and six-minute walk test results 45 days after hospital discharge.

Variable	Total		Group		p
	(N = 242)	WA (n = 141)	ICU/MV – (n = 70)	ICU/MV + (N = 242)	
<b>Laboratory tests</b>					
Neutrophils/mm <sup>3b</sup>	6,550 ± 3,695	6,056 ± 3,471*	6,717 ± 3,752*	8,441 ± 4,030†	0.005
Platelets, ×1,000/mm <sup>3b</sup>	248 ± 93	248 ± 99	258 ± 86	225 ± 87	0.279
Bilirubin, mg/dL <sup>c</sup>	0.5 ± 0.3	0.5 ± 0.3	0.6 ± 0.4	0.5 ± 0.2	0.234
INR <sup>b</sup>	1.05 [1.0-1.11]	1.03 [1.0-1.09]†	1.06 [1.0-1.13]†	1.07 [1.02-1.14]†	0.011
<b>Spirometry<sup>b</sup></b>					
SVC, L	3.1 ± 0.9	3.1 ± 0.9	3.0 ± 0.8	3.0 ± 0.9	0.831
FVC, L	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 0.9	0.921
FEV <sub>1</sub> , L	2.3 ± 0.7	2.2 ± 0.7	2.3 ± 0.6	2.3 ± 0.6	0.782
<b>Lung volumes<sup>b</sup></b>					
TLC, L	4.8 ± 1.2	4.9 ± 1.2	4.7 ± 1.2	4.6 ± 1.2	0.435
RV, L	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	1.6 ± 0.6	0.323
<b>DL<sub>CO</sub><sup>b</sup></b>					
DL <sub>CO</sub> , mL.min <sup>-1</sup> .mmHg <sup>-1</sup>	22.1 ± 7.4	22.9 ± 7.0	21.6 ± 8.3	19.4 ± 6.9	0.077
<b>Respiratory muscle strength<sup>d</sup></b>					
MIP, cmH <sub>2</sub> O	78.7 ± 29.9	77.4 ± 30.3	85.0 ± 28.0	69.6 ± 30.0	0.061
MEP, cmH <sub>2</sub> O	93.1 ± 34.6	93.0 ± 36.7	94.4 ± 32.7	90.9 ± 29.8	0.910
<b>Six-minute walk test<sup>b</sup></b>					
HRR <sub>1</sub> , bpm	95.6 ± 16.8	95.7 ± 16.1	94.5 ± 19.2	97.6 ± 13.9	0.715
ΔFinal HR – HRR <sub>1</sub> , bpm	17.2 ± 14.7	16.6 ± 13.5	19.5 ± 16.9	15.07 ± 15.21	0.309
HRmax, %	70.0 ± 12.1	70.2 ± 12.5	70.3 ± 10.8	68.5 ± 13.4	0.773
Final Borg ± 4	92 (39.7)	61 (44.5)	24 (35.5)	27 (25.9)	0.134

WA: ward admission; ICU/MV–: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; INR: international normalized ratio; SVC: slow vital capacity; HRR<sub>1</sub>: recovery HR in the first minute; HRmax: maximum HR achieved; and Final Borg: Borg dyspnea scale score at the end of the test. <sup>a</sup>Values expressed as n (%), mean ± SD, or median [IQR]. <sup>b</sup>Missing data ≤ 10%. <sup>c</sup>Missing data = 25%. <sup>d</sup>Missing data = 11-16%. \*†Equal symbols indicate similar means (Student’s t-test with post hoc analysis) or medians (Mann-Whitney U test).

with the chronic fatigue syndrome/encephalomyelitis syndrome (CFS/EMS) were described.<sup>(38)</sup> CFS/EMS can be associated with viral infections, such as Epstein-Barr virus, cytomegalovirus, enterovirus, and herpesvirus. Thus, SARS-CoV-2 could also cause CFS/EMS.

The strengths of the present study are the number of participants (N = 242), the inclusion of patients at different levels of disease severity, the assessment of different aspects of lung function, and the multicenter design. However, there are some limitations. First, there is a lack of information on previous respiratory symptoms and lung function, particularly in smokers. The obstructive disorders were more common in smokers, suggesting that some of them could have previous undiagnosed disease. The lack of chest imaging exams at follow-up also limited the correlation of ventilatory disorders with morphological changes. Second, appropriate investigation of respiratory muscle weakness as a cause of MIP and MEP reduction shall include nonvolitional techniques, such as diaphragm ultrasound and measurement of transdiaphragmatic pressure, which were not available. Third, there were variations in the interval between hospital discharge and follow-up assessment. Patients admitted to the ICU remained hospitalized for a longer time (Table 3) and were possibly evaluated later. One could

speculate that the results would have been skewed by the longer time interval between admission and follow-up. To verify this possibility, we compared the outcomes in two groups according to the time to follow-up assessment after discharge: ≤ 60 days and > 60 days. Since no associations with that time were found for any of the demographic, clinical, or outcome variables, this possibility was not confirmed.

In conclusion, we found a high frequency of lung function alterations in patients hospitalized for COVID-19 after a 45-day follow-up, especially in those who underwent MV. The major changes were restrictive disorder, reduced DL<sub>CO</sub>, reduced muscle strength, reduced 6MWD, and oxygen desaturation. These findings highlight the importance of long-term follow-up assessment of lung function parameters in severe COVID-19 survivors.

#### AUTHOR CONTRIBUTIONS

EVM: study conception and design; data collection, analysis, and interpretation; drafting and revision of the manuscript; and approval of the final version. CCM and GLLMC: study conception and design; data collection and analysis; drafting and revision of the manuscript for important intellectual content; and approval of

the final version. ABP: study conception and design; statistical analysis and tables; and approval of the final version. JGFO, BHA, ALTB, ASML, PCF, and JRCR: data collection, analysis, and interpretation; revision of the manuscript; and approval of the final version. ASL: study conception and design; data collection,

analysis, and interpretation; database organization; revision of the manuscript; and approval of the final version. VMA: study conception and design; data analysis and interpretation; revision of the manuscript for important intellectual content; approval of the final version; and guarantor of the article.

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