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ORIGINAL ARTICLE

# Characterization of Pulmonary Function in Colombian COVID-19 Survivors

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## ARTICLE INFORMATION

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## ABSTRACT

**Introduction:** SARS-CoV-2 acutely affects human pulmonary function, and respiratory alterations may persist after overcoming the infection.

**Objectives:** To characterize the pulmonary function among Colombian survivors of COVID-19.

**Methods:** A pilot study was conducted where pulmonary function was assessed using a MiniBox™ device, aerobic fitness with a six-minute walk test, and fatigue perception with the Multidimensional Fatigue Inventory (MFI-20).

**Results:** Out of an initial group of 70 participants, only 39 completed the study, with a disease course ranging from mild to moderate. Women comprised the majority (51%) of the participants, and no abnormal values were found in pulmonary function. The total fatigue score was 39 ± 9.2; for general fatigue, it was 5 ± 0, the same as for physical fatigue (5 ± 0); for mental fatigue, the score was 8.56 ± 3.5; for reduced activity, it was 11.2 ± 2.96, and for reduced motivation, it was 9.38 ± 4.4. Additionally, the peak oxygen co sumption ($VO_2$ peak) was 19.51 ml/kg/min ± 2.8 ml/kg/min.

**Conclusions:** Pulmonary function and fatigue levels in Colombian COVID-19 survivors residing in Bogotá who did not require ventilatory support were normal according to the tests performed, while cardiopulmonary fitness was low.

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ARTÍCULO ORIGINAL

# Caracterización de la función pulmonar en los sobrevivientes colombianos de la COVID-19

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**INFORMACIÓN ARTÍCULO**

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## RESUMEN

**Introducción:** el SARS-CoV-2 afecta agudamente la función pulmonar de los seres humanos y las alteraciones respiratorias pueden persistir después de superada la infección.

**Objetivos:** caracterizar la función pulmonar de los sobrevivientes colombianos de la COVID-19.

**Métodos:** estudio piloto en el cual se evaluó la función pulmonar con un dispositivo MiniBox™, la aptitud aeróbica con una caminata de seis minutos, y la percepción de la fatiga con el inventario multidimensional de la fatiga (MFI-20).

**Resultados:** de un grupo inicial de 70 participantes, únicamente 39 lograron completaron el estudio, con un curso de enfermedad que osciló entre leve y moderado. Las mujeres constituyeron la mayoría (51%) de los participantes y no se hallaron valores anormales en la función pulmonar. El puntaje para la fatiga total fue de 39 ± 9,2; para la fatiga general fue de 5 ± 0, al igual que para la fatiga física (5 ± 0); para la fatiga mental el puntaje fue de 8,56 ± 3,5, para la actividad reducida fue de 11,2 ± 2,96, y para la motivación reducida fue de 9,38 ± 4,4. Asimismo, el consumo de oxígeno pico ($VO_2$ pico) fue de 19,51 ml/kg/min ± 2,8 ml/kg/min.

**Conclusiones:** la función pulmonar y la fatiga en colombianos sobrevivientes del COVID-19 residentes en Bogotá y que no recibieron soporte ventilatorio fueron normales de acuerdo con las pruebas realizadas, mientras que la aptitud cardiorrespiratoria fue baja.

## INTRODUCTION

Since the World Health Organization (1) declared COVID-19 as the sixth public health emergency on January 30, 2020, and subsequently declared it a pandemic on March 11 of the same year (2), an international effort was initiated to control the spread of the disease and prevent the collapse of health systems. Among the reported paraclinical findings, the presence of nonspecific pulmonary changes including evidence of alveolar or mixed opacities suggestive of diffuse pulmonary lesions has been mentioned, as observed in computed axial tomography (CAT). These pulmonary changes have corresponded to pulmonary consolidation in 59% of the cases and to the presence of ground-glass opacities in 41% (3), findings also documented in some moderate and even asymptomatic cases (4). The progression of these lesions can lead to acute respiratory distress syndrome, which is responsible for 28.8% of deaths (5). In this regard, histopathological studies of post-mortem lung biopsies have shown the presence of reactive hyperplasia of type II pneumocytes, intra-alveolar fibrinous exudates, loose interstitial fibrosis, and chronic inflammatory infiltrates (6), all suggestive of interstitial lung disease.

The previously described lesions, resulting from the inflammatory response typical of such an aggressive infectious process, can trigger long-term effects on pulmonary function. These effects may include a decrease in the diffusion capacity of carbon monoxide, alterations in parameters indicative of an airflow obstruction, among others (7). These conditions lead to the appearance of limiting symptoms such as dyspnea, which restrict the individuals' ability to engage in physical activity, including daily tasks. Consequently, the affected individuals present a significant compromise in their quality of life for an extended period of time. A comprehensive study involving 124 patients diagnosed with mild to moderate and severe to critical COVID-19 described a correlation between disease severity and decreased DLCO (diffusing capacity of the lungs for carbon monoxide). Additionally, a correlation was observed between the 99% reduction in areas of parenchymal damage on the pulmonary CT reports and the 93% return to normalcy in the X-rays three months after clinical discharge. Only 22% of patients had low exercise capacity, and overall health status was poor, with 64% experiencing functional impairment, 69% reporting fatigue and 72% noting diminished quality of life (8).

For post-COVID-19 patients who have recovered from mild to moderate or severe pneumonia and exhibit clinical recovery but persistent chest X-ray changes at 12 weeks after discharge, periodic pulmonary function testing is recommended (9). Spirometry is considered by some authors as the best practice for measuring pulmonary function and as a biomarker of health since it allows the identification of individuals at risk and prediction of premature mortality. However, spirometry may require other complementary tests to determine a diagnosis. Therefore, the measurement of lung volumes and DLCO has been used in the evaluation of this type of patients and has turned out to be heterogeneous. While DLCO allows determining the damage in the alveolocapillary membrane, it does not always correlate with parenchymal damage nor the histological changes that occur in interstitial pneumopathies (10).

The immunoregulation that usually occurs after an infectious process, and that is apparently responsible for these pulmonary changes, has also been linked to persistent fatigue in various clinical scenarios. An explanation for this phenomenon is the secondary response to an anomalous hyperexcitability of the central nervous system, which generates different perceptions of pain intensity, even at a cognitive and affective level (11).

Related to this issue, the presence of chronic fatigue has been reported as a persistent clinical manifestation of COVID-19, either alongside other atypical manifestations like anosmia and ageusia,



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or as the only reported symptom (12). These immunomodulated changes, which produce modifications in pulmonary function and trigger fatigue, also result in lower aerobic fitness. Therefore, the present investigation sought to characterize pulmonary function, aerobic fitness and perceived fatigue levels in Colombian survivors of COVID-19 residing in Bogotá.

## METHODS

In a pilot study, variables such as pulmonary function, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), ratio between forced expiratory volume in the first second and forced vital capacity (FEV1/FVC), maximum inspiratory flow (MIF), peak expiratory flow (PEF) and flows from 25% to 75%, as well as lung volumes, total lung capacity (TLC), forced expiratory flow (FEF), peak expiratory flow (PEF), residual volume (RV) and oxygen volume ($VO_2$) were assessed using the MiniBox™ equipment, as it is a reliable method for measuring lung volumes (13). The assessment of aerobic fitness was carried out through a six-minute walking test using the formula peak $VO_2$ = (0.03* distance in meters + 3.98) (14), and the assessment of fatigue perception was achieved by applying the multidimensional fatigue inventory (MFI-20) developed in 1995 by Smets et al. (15), as it shows high internal consistency and validity. Since aerobic fitness could be affected by physical activity levels, all participants were required to fill out the international physical activity questionnaire IPAQ.

The study population consisted of Colombian adult survivors of COVID-19. A probabilistic sampling was performed based on a probability of 0.05 of finding pulmonary function sequelae, and a confidence level of 0.95. Accordingly, the sample size of 45 subjects was determined by the equation (16). The inclusion criteria required to be of legal age, have a diagnosis of COVID-19 (self-report of positive CRP and not diagnosed in the last month) and have lived in Bogota for over five years. Exclusion criteria encompassed spirometry that did not meet acceptability and reproducibility criteria according to the American Thoracic Society (17): active smokers; electronic cigarette users; subjects with acute or chronic respiratory, cardiac or musculoskeletal disease; individuals with a history of exposure to materials causing occupational lung diseases; subjects with respiratory symptoms or presenting symptoms suggestive of reinfection by SARS-CoV-2; and pregnant women. The criterion for withdrawal encompassed subjects who did not complete all the assessments, for which a questionnaire was applied to corroborate any of these situations. The study subjects were recruited from March to July 2021 using the snowball sampling technique via WhatsApp (Figure 1).

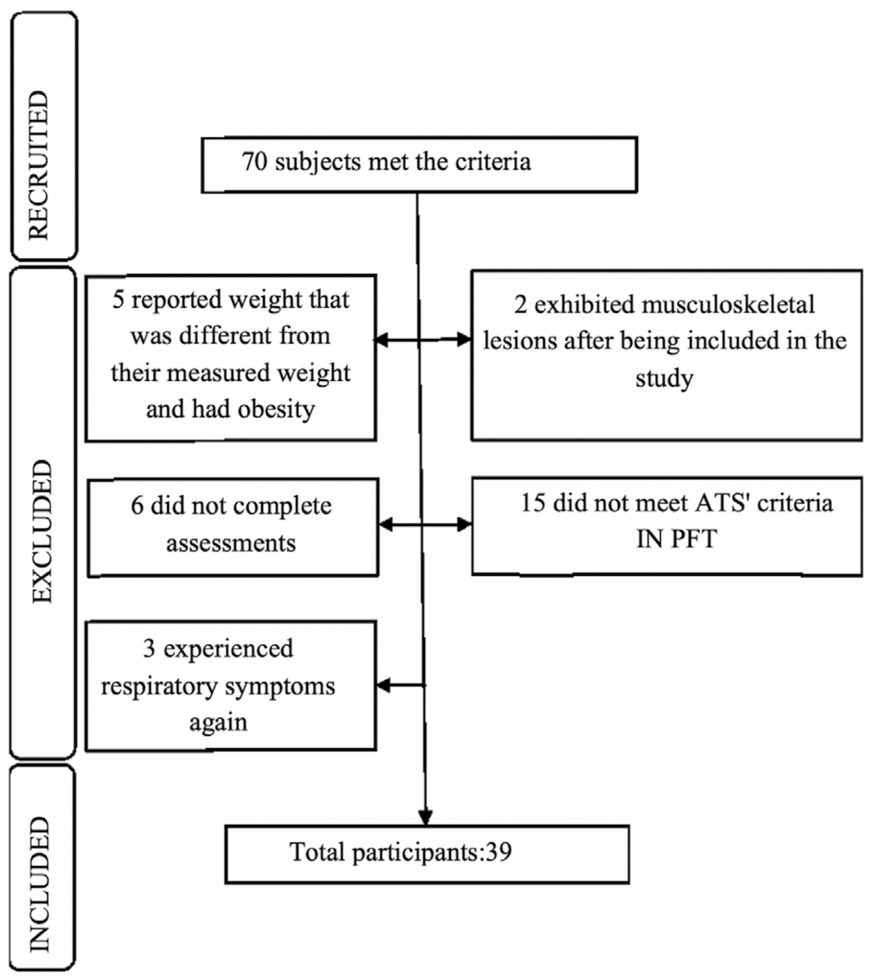


**Figure 1. Flowchart of Participants Involved in the Study**

ATS: American Thoracic Society; PFT: Pulmonary Function Tests
Source: own elaboration

The protocol was communicated to the participants virtually via Google Meet platform and they were briefed on the benefits and risks. They signed the informed consent form on the assessment day, which took place between the last week of August and September 2021. All subjects were evaluated at the Clinical Simulation Laboratory of Fundación Universitaria del Area Andina, where their weight was measured using the Omron Premium HN-289 silky grey digital scale, and height was measured with the InBody InLab measuring device. On the day of the test, the participants' hemodynamic stability was confirmed by taking vital signs and oxygen saturation with a Nonin oximeter, while adhering to all biosafety protocols.

Additionally, participants were asked if they required intensive care unit management and invasive ventilatory support; 100% of the sample responded that they did not.

The data from the subjects under study were analyzed using the SPSS version 25.0 statistical package. This way, a descriptive analysis of the variables was performed through measures of variance and central tendency. Additionally, the Shapiro-Wilk normality test was applied, an inferential analysis of unrelated groups was conducted to compare quantitative variables, and an analysis of association between variables was carried out using Pearson's correlation test. The research adhered to the Helsinki principles and resolution N°008430 of 1993, which regulates health research in Colombia. The subjects signed the informed consent form approved by the Ethics Committee of the National Research Directorate of the Fundación Universitaria del Area Andina.

## RESULTS

Out of a total of 70 subjects selected to participate in the study, only 39 COVID-19 survivors completed all study procedures (see Figure 1). Among these participants, 54% were female (n = 21) and 46% male (n =18). Their average age was 36 years ±13 years, weight 64 kg ± 9 kg, height 164 cm ± 9 cm, with a BMI of 24 kg/m$^2$ ± 3 kg/m$^2$. Also, there was a 5.3 months ± 3.8 months interval between diagnosis and test completion. Aerobic fitness expressed as peak $VO_2$ was 19.5 ml/kg/min ± 3 ml/kg/min and reached an average distance of 518 meters ± 94 meters. This represented a percentage of 71.7 ± 14.1 in relation to the predicted value according to Troosters' formula (refer to Table 1 and Table 2).

**Table 1. Pulmonary Function Results in Colombian Covid-19 Survivors Residing in Bogotá in 2021**

| Variable | Mean ± S.D. |
|---|---|
| FVC (L) | 4.37 ± 0.9 |
| FVC (%) | 109 ± 18 |
| VEF 1 (L) | 3.52 ±0.69 |
| FEV 1 (%) | 105.3 ± 12 |
| FEV 1/FVC | 82.2 ± 7 |
| FEF 25-75 (L/s) | 3.6 ± 1 |
| TLC (L) | 5.59 ± 1 |
| TLC (%) | 99.5 ± 11 |
| RV (L) | 1.21 ±0.5 |
| RV (%) | 88.5 ± 26.9 |
| RV/TLC | 88.59 ± 22.3 |
| IC/TLC (L) | 2.88 ± 0.6 |
| IC/TLC (%) | 103.49 ± 13 |
| TGV (L) | 2.6 ± 0.6 |
| TGV (%) | 98.26 ± 20 |
| ERV (L) | 1.46 ± 0.6 |
| ERV (%) | 114 ± 33 |
| CV(L) | 4.37 ± 1 |
| VC (%) | 103 ± 12 |
| SVC (L) | 4.15 ± 1 |
| SVC (%) | 102 ± 14 |

Abbreviations: S.D: standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEF: forced expiratory flow; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; TGV: thoracic gas volume; ERV: expiratory reserve volume; VC: vital capacity; SVC: soft vital capacity.

Source: own elaboration

**Table 2. Comparative Analysis by Gender Among Colombian COVID-19 Survivors Residing in Bogotá in 2021**

| Variables | Men Mean ± S.D. | Women Mean ± S.D. | Significance (*p < 0.05) |
|---|---|---|---|
| Age (years) | 35.67 ± 12.98 | 36.52 ± 13.81 | 0.54 |
| Weight (kg) | 69.11 ± 7.92 | 58.95 ± 7.44 | 0.83 |
| Height (cm) | 170.11 ± 5.97 | 158.57 ± 6.67 | 0.28 |
| BMI (kg/m2) | 23.87 ± 2.28 | 23.60 ± 3.78 | 0.04* |
| Total meters (m) | 492.22 ± 95.76 | 539.29 ± 89.61 | 0.48 |
| In relation to Walteros reference value (%) | 77.53 ± 16.53 | 90.86 ± 13.91 | 0.27 |
| Maximum HR(%) | 46.75 ± 15.53 | 51.81 ± 11.28 | 0.33 |
| FVC (L) | 5.03 ± 0.77 | 3.79 ± 0.71 | 0.71 |
| FVC (%) | 112.5 ± 21.27 | 106.1 ± 14.53 | 0.17 |
| FEV 1 (L) | 4.04 ± 0.60 | 3.14 ± 0.58 | 0.90 |
| FEV 1 (%) | 106.06 ± 9.58 | 104.71 ± 13.96 | 0.32 |
| FVE 1/FVC ratio | 81.39 ± 6.59 | 82.78 ± 7.43 | 0.36 |
| FEF 25-75 (L/s) | 3.80 ± 1.23 | 2.85 ± 1.53 | 0.08 |
| PEF (L/s) | 101.33 ± 14.76 | 111.38 ± 19.13 | 0.30 |
| TLC (L) | 6.25 ± 0.86 | 4.69 ± 1.22 | 0.53 |
| TLC (%) | 100.28 ± 10.89 | 98.95 ± 12.39 | 0.60 |
| RV (L) | 1.21 ± 0.38 | 1.18 ± 0.60 | 0.23 |
| RV (%) | 84.72 ± 29.62 | 51.81 ± 11.28 | 0.61 |
| RV/TLC ratio | 83.44 ±21.16 | 93 ±22.89 | 0.74 |
| OV; (ml/kg/min) | 18.74 ±2.87 | 20.15 ±2.68 | 0.27 |

Abbreviations: S.D: standard deviation; BMI: body mass index; HM: maximum heart rate; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEF: forced expiratory flow; PEF: peak expiratory flow; TLC, total lung capacity; RV: residual volume; $VO_2$: volume of oxygen.

Source: own elaboration

Both FVC and FEV1 were higher in men compared to women, and a correlation was found between these variables and gender, as follows: r = 0.593 with p: 0.00 and r = 0.699 with p: 0.00, in each case. The FEV1/FVC ratio was higher than the Lower Limit of Normality (LNL) in both cases, and the forced expiratory flow (FEF 25 - 75%) showed no significant changes. The distance achieved in the six-minute walk test was higher in women (539 m ± 90 m) compared to men (492 m ± 95 m), with a significant difference ($p < 0.05$), and was moderately correlated to the perception of fatigue (r = 0.401; p = 0.01). The total fatigue score was 39 ± 9.2, with specific scores of 5 ± 0 for both general and physical fatigue; for reduced activity the score was 11.2 ± 2.96; for reduced motivation 9.38 ± 4.4; and for mental fatigue 8.56 ± 3.5.

## DISCUSSION

Early studies on pulmonary function in COVID-19 survivors reported that patients, regardless of the clinical severity, had restrictive disorders and mild airway dysfunctions that could be persistent over prolonged periods of time (18). In this study, it was evidenced that pulmonary function assessed by measuring lung volumes and spirometry, including the 25-75 flow that would reflect peripheral airway injury (19), remained within normal ranges in the evaluated subjects who had mild to moderate disease between four to six months and up to one year after diagnosis. Conversely, in 2021, Huang et al. (20), in a cohort study with a six-month follow-up after acute infection, found that the subjects mainly manifested fatigue or muscle weakness, alongside anxiety, depression and sleep difficulties. Patients with progressive deterioration during their hospital stay showed more significant changes in their pulmonary function in this regard; the authors recommend the implementation of comprehensive intervention plans that facilitate their long-term recovery.

Similarly, a study involving apparently healthy adults from different Spanish hospitals with SARS-CoV-2 infection revealed that lung function was adequately preserved 45 days after symptom onset. In contrast, Xiaoneng Mo et al. (21) in 2020 documented in subjects with different levels of disease severity between 20 and 41 days after hospital discharge, disturbances in lung function which consisted of disturbances in diffusion, total lung capacity (TLC), forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV 1 / FVC ratio and small airway function. However, their participants had previous comorbidities, unlike those in our study.

Lewis et al. (22) conducted a multicenter cohort study aiming to compare pulmonary function tests before and after infection in patients diagnosed with COVID-19. The authors conducted a retrospective search of electronic medical records which revealed a significant deterioration in lung function among patients who were older or had pre-disease tests showing a history of interstitial lung disease or cystic fibrosis.

These variations in lung function behavior suggest that pulmonary sequelae may largely reflect the individual response developed by the immune system and pre-existing comorbidities.

In a group of 87 patients comprised of Thai men and women, Eksombatchai et al. (23) observed both restrictive and obstructive abnormalities in spirometry among individuals who had developed mainly severe pneumonia, as well as those with non-severe pneumonia and mild symptoms. In the latter two groups, the mean six-minute walking distance was 538 m ± 56.8 m and 527.5 m ± 53.5 m, respectively, with normal lung function observed 60 days after hospital discharge. In our study, an overall distance of 517.56 m ± 94.3 m was observed. Women covered 539 m ± 90 m and men covered 492 m± 95 m, respectively. These values are lower compared to the distances reported by Walteros et al. (24): 658.9 m for men and 592.75 m for women, and by Viola et al. (25): 602.7 m for women and 672.4 m for men. Both studies were conducted in Bogotá. Similarly, Guler et al. (26) reported in the Swiss COVID-19 lung study that patients with mild/moderate classification showed normal lung function during the four-month follow-up. In contrast, those classified as severe/critical exhibited lower lung volumes that remained within the normal range. Conversely, the severe/critical illness group showed a 120-meter reduction in the six-minute walk distance, with an average SpO2 decrease of 5.6% ± 3.8% among those requiring mechanical ventilation, compared to 2.6% ± 3.1% in the mild/moderate illness group (p = 0.02). These differences suggest that having mild to moderate COVID-19 may condition the distance traveled in this submaximal test and thus $VO_2$ (26).

Furthermore, peak $VO_2$, which reflects cardiorespiratory fitness and determines the subject's ability to endure varying intensities of physical activity for prolonged periods of time, reached a value of 19.51 ml/kg/min ± 2.8 ml/kg/min, placing this physical quality below the mean (27). However, it is important to note that the six-minute walk is an indirect and submaximal test (28) that may limit the categorization of the population. This cardiorespiratory fitness measure was directly related to fatigue perception at the conclusion of the test (r = 0.403; p : 0.01) and to FVC (r = 0.335; p : 0.03). In this regard, it has been determined that the improvements in FVC are correlated with positive effects on $VO_2$, thereby enhancing both functional capacity (29) and survival (30). An indication of this relationship can be found in the study by Vásquez et al. (28), which illustrates moderate correlations between the distance achieved with this test and aerobic capacity among individuals with cardiorespiratory disorders ($r = 0.51$ and $0.88$) and stroke patients ($r = 0.4$ to $0.8$ $p < 0.05$).

Similarly, Cortés et al. (31) assessed functional capacity using six-minute walk test in 186 COVID-19 survivors and, according to this, categorized them into three groups: the mild disease group, without hypoxemia and managed at home, achieved a distance of 493 m ± 74 m; the moderate disease group, managed at home with oxygen supplementation, walked 428 m ± 97 m; and the severe disease group, hospitalized without receiving invasive mechanical ventilation, recorded 439 m ± 111 m. The data found in this study are lower than those observed in the mild level category of our study. However, it should be noted that cardiorespiratory fitness can be influenced by natural processes of altitude adaptation, a situation that occurs in a city like Bogotá.

Regarding pulmonary responses to exercise in patients recovering from COVID-19, it has been reported that these have a direct relationship with the persistent symptoms reported by patients recovered from the disease. Szekely et al. (32) observed among 71 patients who were prospectively evaluated by stress echocardiography combined with cardiopulmonary stress testing, that the most common symptoms included fatigue (in 34%), muscle weakness or pain (in 27%), dyspnea (in 22%) and a lower $VO_2$. Similarly, Aparisi et al. (33) conducted a prospective study involving COVID-19 patients (with and without referred dyspnea during mid-term follow-up), undergoing various assessments including a cardiopulmonary exercise test, a six-minute walk, among others. Some important findings were related to dyspnea ($n = 41$; 58.6%), noting a higher prevalence among women (73.2% vs. 51.7%; $p = 0.065$) and without a significant difference in pulmonary function tests results. In general, patients who referred persistent dyspnea showed a significant decrease in predicted $VO_2$ max consumption (77.8% [64 - 92.5] vs. 99% [88 - 105]; $p < 0.00$; $p < 0.001$), in total distance covered in the six-minute walk test (535 [467-600] vs. 611 [550-650] meters; $p=0.001$), and in quality of life measured by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ), as the score was 60.1 ± 18.6 vs. 82.8 ± 11.3; $p < 0.001$. These findings align with those reported in our study.

According to the Borg scale, the perception of effort in the six-minute walk, categorized as very light, correlated to the distance achieved. In this regard, dyspnea has been mentioned as a symptom that persists beyond three months, and in some cases, it is associated with affected pulmonary function in individuals who presented non-critical illness (34). However, this relationship of perceived exertion with walking was not found with any of the spirometric variables or lung volumes, despite the fact that lung function is reported as normal with low perceived exertion.

Based on the results obtained in the assessment of fatigue levels using the multidimensional scale (MFI-20), and the values reached, according to the study by Jin-Mann et al. (35) general fatigue and physical fatigue scores are below the mean, while reduced activity, reduced motivation and mental fatigue fell within mean ranges for the population. Morin et al. (36) measured fatigue levels using the MFI-20 in COVID-19 survivors four months after hospital discharge; the researchers described a median score of 4.5 for reduced motivation and of 3.7 for mental fatigue. These results are markedly lower compared to the current study, possibly due to the significantly larger sample size (478 survivors) and the evidence of manifest pulmonary alterations in fibrotic lesions in 19.3% of the subjects. It is important to consider that the stay in the intensive care unit may complicate the patient's evolution.

Although this study has limitations in terms of the number of participants, the selection criteria were strict in order to avoid confusion in the interpretation of the tests, so that any anomaly observed can be attributed specifically to COVID-19 and not to pre-existing comorbidities. Therefore, it can be affirmed that the findings in this population reflect the reality of the survivors, since they were previously healthy individuals. For future studies, in addition to increasing the number of participants, it is recommended that pulmonary function be monitored using an ambispective approach to analyze its evolution.

## CONCLUSIONS

The results of this research allowed us to identify two main findings: firstly, the subjects who did not require ventilatory support and participated in the pilot study did not show any pulmonary function disorders; secondly, the perception of fatigue and dyspnea were low between 5 months and 9 months after the diagnosis of the disease.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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