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Pulmonary evaluation of post-COVID-19 patients: an Ecuadorian experience

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Pulmonary Evaluation of Post-COVID-19 Patients: An Ecuadorian Experience

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Abstract

Background: Despite the growing concerns related to the potential of long-term pulmonary sequelae due to COVID-19, data about intermediate and long-term changes in the respiratory function of patients who recover is relatively sparse, particularly in developing countries.

Objectives: To assess the characteristics and pulmonary function at follow-up in a sample of Ecuadorian patients that recovered from the virus.

Methods: We conducted a cross-sectional study that included 43 patients after symptomatic COVID infection, who were evaluated by spirometry, single breath DLCO, and 6MWT. For statistical analysis we performed point biserial correlations, and chi squared tests.

Results: Overall, 30.3% of patients (n = 13) reported persistent symptoms, with fatigue being the most common (23.3%, n = 10). Around 34.9% (n = 15) of the sample had a restrictive spirometry pattern, 18.6% (n = 8) had an abnormally decreased adjusted DLCO. A restrictive spirometry pattern was associated with an abnormally low adjusted DLCO ($\chi^2(2) = 11,979, p = 0.001$).

Conclusion: We found that a considerable proportion of patients presented with persistent symptoms and alterations in pulmonary function following COVID-19, mainly a restrictive respiratory pattern and abnormally low DLCO. Further studies are needed to determine which patients may benefit from the follow-up with specific pulmonary function tests.

Keywords: COVID-19, DLCO, Interstitial lung disease, Pulmonary function tests, South America

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1. Introduction

To date more than 169 million patients infected with COVID-19 have recovered, however there are growing concerns related to the potential of long-term pulmonary sequelae due to the virus.¹ Even after moderate COVID, there are reports of impaired diffusing capacity of the lungs for carbon monoxide (DLCO) and persistent lung damage in up to a third of patients after one year.² Some pathophysiologic mechanisms involved may be related to inflammation causing extensive injury to alveolar epithelial cells and endothelial cells, with secondary fibroproliferation as seen in cases of ARDS.³ These persistent respiratory complications have the potential for additional morbidity and long-term disability.²

Data about intermediate and long-term changes in the respiratory function of patients who recovered from COVID-19 is relatively sparse, particularly in developing countries. With this study, our aim is to contribute to the literature by assessing the characteristics and pulmonary function in a group of Ecuadorian patients who recovered from the virus.

2. Materials and methods

2.1. Design and participants

We conducted a cross-sectional study that included 43 patients who had survived a primary COVID-19 symptomatic infection regardless of whether they received ambulatory or in-hospital management. The data of each participant was recorded between May to December 2020 at Respiralab Research Center (Guayaquil-Ecuador), an outpatient clinic specialized in respiratory care. To be included, the patient must have had a past clinical diagnosis compatible with an acute SARS-CoV-2 pulmonary infection, further confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR), dating ≥ 90 days. During this initial acute infection, whose data was gathered through medical records, a clinical diagnosis could encompass but was not limited to a patient with dyspnea, respiratory rate >30 min or SpO₂ $\leq 93\%$ at room air under the context of positive radiological abnormalities characteristic of COVID-19 pneumonia such as ground-glass opacifications with/without mixed consolidation, adjacent pleural and/or interlobular thickening, air bronchograms and more.^{4,5} Demographic and clinical features were collected. Anthropometric measurements included body mass index (BMI). During the clinic visit, patients underwent a comprehensive evaluation, including a history and

physical examination and function tests such as spirometry, carbon monoxide diffusing capacity (DLCO) and 6-min walk test (6MWT).

2.2. Ethical considerations

This study was conducted according to the principles established by the Declaration of Helsinki and was approved by the Expedited Ethics Committee of the Ecuadorian Health Ministry (Approval N° 024–2020). With the information recollected in the survey, personal identification was not possible; as such, anonymity, and personal data protection was guaranteed.

2.3. Measurement

Patients were evaluated by spirometry and single breath DLCO (EasyOne Pro Lab® machine by NDD version 03.07.01.09). As a sensitive procedure to methodological changes, the 6MWT was carefully performed under the instructions and encouragement suggested by the official European Respiratory Society/American Thoracic Society technical standard.^{6,7} Walked distance in meters was recorded as the primary outcome, while the lowest arterial oxygen saturation was considered a marker of disease severity and prognosis. Enright's formula was used to estimate the percentage of test performance.⁸ Regarding the symptoms reported by the patient during the test such as subjective fatigue or dyspnea, the modified Medical Research Council scale (mMRC) was used, as it has shown to be a good indicator of disability in chronic respiratory diseases.^{9–11}

For analysis purposes, we classified patients into three main categories:

- 1) Restrictive spirometry pattern: if their results reported both a FEV₁ < 70 and a FEV₁/FVC ≥ 0.8 ¹²
- 2) Altered DLCO: if the DLCO value was $< 80\%$ than predicted according to the Global Lung Function Initiative (GLI).¹¹
- 3) Restriction with gas exchange abnormality: if patients had both a “restrictive respiratory pattern” and an “altered DLCO” per the previous definitions.

2.4. Statistical analysis

Categorical variables, whenever dichotomous or multinomial, were reported as frequencies and percentages. Descriptive statistics are reported as

mean (standard deviation [SD]). To ascertain if a correlation between dichotomic independent variables and quantitative dependent variables was present, a point–biserial correlation analysis was run. To meet the assumptions of such method, normality was assessed by the Shapiro–Wilk test, while homogeneity of variances was assessed through Levene's test of equality of variances. On the other hand, to determine associations between two nominal variables, the Chi-square test for associations was applied. Whenever assumptions were violated, a Fisher's exact test was used instead. Statistical significance was set at a p-value less than 0.05. Analyses were performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA; Version 24.0) software.

3. Results

3.1. Patient population

The study included 43 patients with a mean age of 55.7 (SD, 13.0) years and gender distribution of 55.8% (n = 24) males and 44.2% (n = 19) females. Regarding past medical history of COVID-19 pneumonia, 48.8% (n = 21) reported a severe course. However, only 25.6% (n = 11) were hospitalized due to medical service unavailability during the peak of the pandemic. In average, participants waited 159 (SD, 80.3) days after primary infection symptoms appeared to attend a follow-up appointment at the outpatient clinic; 30.3% (n = 13) reported persistent symptoms, with fatigue being the most common (23.3%, n = 10). Other characteristics of the study population are listed in [Table 1](#).

3.2. Spirometry, DLCO, and 6-min walk test

With respect to function tests, about a third (34.9%, n = 15) of the sample presented restrictive spirometry pattern, two out of ten (18.6%, n=8) patients had an abnormally decreased adjusted DLCO, and only 16.3% (n = 7) met the criteria for restriction with gas exchange abnormality. Specific spirometry and DLCO measurements are included in [Table 2](#). Regarding the 6MWT, 72.1% (n = 31) finished the full 6-min test. The mean 6MWD was 376.9 (SD, 108.4) meters; only 4.7% (n = 2) walked the ideal distance. Variations of other parameters such as SpO₂ and heart at baseline, during test and at rest are best described in [Table 2](#). A restrictive spirometry pattern was associated with an altered DLCO ($\chi^2(2) = 11,979$, $p = 0.001$), however no statistically significant associations between disease severity

Table 1. Demographic and clinical information of surveyed population (n = 43).

Characteristics	Value % (N)
Age, mean (SD)	55.7 (13.0)
Gender	
Male	55.8 (24)
Female	44.2 (19)
Comorbidities	51.2 (22)
Arterial hypertension	34.9 (15)
Diabetes mellitus	11.6 (5)
Chronic kidney disease	4.7 (2)
Allergic rhinitis	62.3 (1)
BMI, mean (SD)	1.26 (4.3)
Normal	18.6 (8)
Overweight	44.2 (19)
Obese class 1	32.6 (14)
Obese class 2	2.3 (1)
Obese class 3	2.3 (1)
Symptom persistence ^a	30.3 (13)
Fatigue	23.3 (10)
Dyspnea	2.3 (1)
Thoracic pain	2.3 (1)
Back pain	2.3 (1)
Past covid infection	
Severe disease	48.8 (21)
SpO ₂	90.8 (7.4)
Hospitalization required	25.6 (11)

Notes: BMI, body mass index.

^a Symptom persistence is considered when it lasts ≥ 90 days.

and any of the function tests measurements were found.

3.3. Restriction with gas exchange abnormalities

We found a negative correlation between restriction with gas exchange abnormality and time walked ($r_{pb} = -0.434$, n = 43, $p = 0.007$). As a matter of fact, these patients were less likely to finish the 6MWT ($\chi^2(2) = 6.016$, $p = 0.042$). Additionally, patients with restriction with gas exchange abnormality were more likely to have a higher mMRC dyspnea score ($\chi^2(2) = 10.674$, $p = 0.013$).

4. Discussion

According to a previous systematic review and metanalysis post infection COVID-19 patients show considerable impairment in lung function, 39% presented altered DLCO, while 15% had a restrictive pattern on spirometry.¹³ In our study, a similar proportion of patients were found to have a restrictive respiratory pattern, however the proportion of patients with abnormally low DLCO was considerably lower (39% vs 18.6%).¹³ This latter finding may be related to the timing at which follow-up pulmonary tests were performed. For instance in the studies by Mo and Huang, the DLCO

Table 2. Functional tests performed in the studied sample (n = 43).

Characteristics	Mean (SD)
Restrictive spirometry pattern^a, % (n)	34.9 (15)
FEV ₁	89.6 (17.5)
FVC	86.4 (17.5)
FEV ₁ /FVC	81.7 (5.0)
TLC	101.5 (23.8)
Abnormal DLCO^b, % (n)	18.6 (8)
Adj DLCO	90.0 (30.2)
Restriction with gas exchange abnormality^c, % (n)	16.3 (7)
6MWT ideal distance achieved^d, % (n)	4.7 (2)
Test finished, % (n)	72.1 (31)
Minutes achieved	5.6 (1.0)
6MWD	376.9 (108.4)
Expected percentage	69.0 (17.8)
SpO ₂	
Baseline	96.4 (3.2)
Minimal during test	94.2 (4.4)
Maximal during test	96.7 (3.9)
At rest after test	96.5 (3.9)
Heart rate	
Baseline	83.8 (12.1)
Minimal during test	92.5 (15.8)
Maximal during test	105.9 (13.6)
At rest after test	92.7 (12.9)
Maximal mMRC category reported during test	
Grade 0	34.9 (15)
Grade 1	27.9 (12)
Grade 2	4.7 (2)
Grade 3	11.6 (5)
Grade 4	9.3 (4)

Notes: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; DLCO, carbon monoxide diffusing capacity; adj DLCO, carbon monoxide diffusing capacity adjusted for age, sex and hemoglobin; 6MWT, 6-min walk test; 6MWD, 6-min walk distance; SpO₂, peripheral capillary oxygen saturation; mMRC, modified Medical Research Council.

^a Defined as FEV₁<70 plus FEV₁/FVC ≥0.8.

^b Defined as adj DLCO <80%.

^c Defined as patients who meet “a” and “b” definitions.

^d Defined as patients who achieved the expected percentage of walked distance in 6 min for healthy patients calculated according to Enright's formula.

was measured at one month follow-up time and showed a higher proportion of abnormalities (47.2% and 52.6% respectively).^{14,15} On the other hand, another study by Zhao and colleagues assessed patients at 3 months, with a similar proportion of abnormal DLCO(16%) compared to our study.¹⁶ An abnormally low DLCO in these types of patients may indicate potential pulmonary fibrosis, or an incomplete recovery, but it is still unclear whether they persist in the long-term due to limited data regarding follow-up.

In relation to specific predictors for potential pulmonary dysfunction after recovery, a recent meta-analysis found that severe COVID-19 is a risk factor for abnormalities in almost all PFT parameters including reduced lung volumes and DLCO,

however a reduced FEV₁/FVC which indicates airway obstruction, showed no difference between groups.¹⁷ In contrast, we did not find any statistically significant association between disease severity and pulmonary function tests, but it is worth noting this may be consequence of a reduced sample size. Apart from an increased risk to develop pulmonary sequelae, a higher COVID-19 severity has also been associated with other complications such as joint pain, dyspnea, palpitation, anxiety, and depression.¹⁷

In addition from spirometry and DLCO, the 6MWT is a simple, reproducible, and inexpensive method that may be useful to monitor changes in pulmonary function.¹⁸ A previous prospective study in patients after recovery from COVID-19 found that those with severe pneumonia tended to have a non-statistically significant shorter mean 6MWT.¹⁹ Even though we did not find an association between disease severity and walking distance, those with restrictive respiratory patterns had a shorter walking distance and were less likely to complete the test. While the exact role of the 6MWT in the follow-up of COVID patients has yet to be established, it can provide information on the impairment of daily activities and its correlation with peak oxygen uptake may indicate lung function.²⁰

4.1. Limitations

Although we included participants of different demographic characteristics, the sample size of 43 patients may not have been sufficient to generate statistically significant results for all comparisons, which might have led to type II errors. Also, due to the limited follow-up we cannot ascertain if the observed alterations in pulmonary function persist over time. To the best of our knowledge, this study is among the first to assess changes in pulmonary function of Latin American patients following COVID pneumonia.

5. Conclusions

In conclusion, we found that a considerable proportion of patients presented with persistent symptoms and alterations in pulmonary function following COVID-19, mainly a restrictive respiratory pattern and abnormally low DLCO. Further studies are needed to determine which patients may benefit from the follow-up with specific pulmonary function tests, 6MWT, and imaging. Assessing potential lung function changes after COVID-19 could help in earlier medical recognition, diagnosis, follow-up, and management.

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Declaration of competing interest

The authors report there are no competing interests to declare in relation to this work.

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