Clinical Predictors of Lung Function In Patients Recovering From Mild COVID-19

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Abstract

Background: There are few studies have assessed lung function in Hispanic subjects recovering from mild COVID-19. Therefore, we examined the prevalence of impaired pulmonary diffusing capacity for carbon monoxide (DLCO) as defined by values below the lower limit of normal ($< \text{LLN}$, $< 5^{\text{th}}$ percentile) in Hispanics recovering from mild COVID-19. We also examined the prevalence of a restrictive spirometric pattern as defined by the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) being $\geq \text{LLN}$ with the FVC being $< \text{LLN}$. Finally, we wanted to examine factors that cause the prevalence of an impaired DLCO to vary between studies.

Methods: In this observational study, adult patients ($n = 146$) with mild COVID-19 were recruited from a Long-term follow-up COVID-19 clinic in Yucatan, Mexico between March, and August 2021. Spirometry, DLCO, and self-reported signs/symptoms were recorded 34 ± 4 days after diagnosis.

Results: At post-evaluation, 20% and 30% patients recovering from COVID-19 were classified as having a restrictive spirometric pattern and impaired DLCO, respectively; 13% had both. The most prevalent reported symptoms were fatigue (73%), persistent cough (43%), shortness of breath (42%) and a blocked/runny nose (36%). Increased age, a blocked/runny nose, excessive night sweats, and a restrictive spirometric pattern increased probability of having an impaired DLCO. The proportion of patients with previous mild COVID-19 who had impaired DLCO increased by 12% when the definition of impaired DLCO was $< 80\%$ predicted instead of $< \text{LLN}$. Having severe (compared to mild) COVID-19 increased the percentage of those with impaired DLCO by 20%.

Conclusions: One-third of patients with mild COVID-19 have impaired DLCO thirty-four days post-diagnosis. One-fifth of patients have a restrictive spirometric pattern. The criteria that define impaired DLCO and the severity of COVID-19 disease affects the proportion of those with impaired DLCO at follow-up.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a virus that originated in Wuhan City, China, in December of 2019, and is responsible for the coronavirus disease (COVID-19) [1]. Between December 29th, 2019, and February 16th, 2020, the number of deaths increased from 1 to 1666 in China.¹ By October 1st, 2021, over 4.79 million people worldwide has died from COVID-19 [2]. As such, COVID-19 has become one of the most fatal pandemics ever recorded in human history.

COVID-19 is a heterogenous disease, with several long-term sequelae [3]. Patients recovering from the acute phase may report long-term multi-system symptoms including various pulmonary function abnormalities [3–22], psychological sequelae [3], and reduced physical functioning [10, 23, 24]. Specifically, pulmonary diffusing capacity for carbon monoxide (DLCO) has been shown to be significantly impaired 30 to 180 days after the onset of onset of (SARS-CoV-2) (**Table S1**). However, most of these studies evaluated lung function in patients that were hospitalised due to the severity of their

condition; very few studies focused on patients recovering from mild COVID-19 [4, 7, 10, 20]. Furthermore, there are even fewer studies focusing on the effects of COVID-19 in Latino populations [6, 25]. As the number of patients recovering from COVID-19 increases around the world, there is an urgent need to keep analysing pulmonary sequelae to facilitate optimal clinical treatments.

Recent reports indicate the presence of racial and ethnic disparities with disproportionate burden of COVID-19-related severity infections and mortality [26, 27]. These disparities may be at least partly attributable to the higher rates of comorbidities that worsen COVID-19 outcomes [28]. Mexico has a high prevalence of chronic non-communicable diseases such as obesity, hypertension, and diabetes; also, pandemic data after acute COVID-19 about Latinos has been severely limited due to categorizations, language and other research barriers, therefore, very few descriptions have analyzed physiological explanations on persistent symptoms and lung function in the Latino community [28].

Our main objective was to determine factors associated with an impaired DLCO in Hispanic patients with mild COVID-19. Impaired DLCO was defined as below the lower limit of normal ($< \text{LLN}$, $< 5\text{th percentile}$). Another objective was to examine data from previous studies to determine which factors predicted the proportion of patients who had both previous COVID-19 disease and impaired DLCO at follow-up.

Materials And Methods

Study design

This is an observational cross-sectional study from the Long-term follow-up COVID-19 clinic at the High Specialty Regional Hospital of Yucatan, Mexico from March 2021 to August 2021. We consecutively enrolled one hundred and fifty patients during the period. Inclusion criteria were adults over 18 years old recovering from mild COVID-19 according to current WHO diagnostic criteria [29]. All patients were scheduled after 4-6 weeks (34.4 ± 3.8 days) of baseline symptoms to perform pulmonary function test and were evaluated for persistent symptoms at the clinic. Ethics approval was obtained from the Ethics Committee of the High Specialty Regional Hospital in Yucatan, Mexico (Protocol number 2020-024). A written informed consent to participate was signed by all patients at the scheduled visit in compliance with the Helsinki declaration. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Methods

Patients received a comprehensive medical assessment with a detailed medical history. Data including demographics, persistent symptoms from surveys, and pulmonary function test results were collected during the follow-up visit. Demographic data included age, sex, body mass index (BMI), and previous cardiovascular disease risk factors for which regular pharmacological treatment was incorporated including systemic hypertension, cardiac disease, diabetes mellitus, Tobacco use (current or former smoker vs. never smoker), obesity (defined as body mass index $> 30 \text{ kg/m}^2$). Patients were asked if they received oral corticosteroids and/or anticoagulants during the disease and to recount presence or

absence of symptoms at the time of the visit including: fatigue, shortness of breath on effort, cough, chest tightness, chest pain, sore throat, blocked and/or runny nose, loss of smell, loss of taste, diarrhea, abdominal pain, muscle or joint pain, headache, tachycardia, sore or red eyes, excessive sweating (over a 24hr period, including night sweats), hair loss, and weight loss [30, 31].

Spirometry and measurements of DLCO, were performed approximately four weeks following baseline symptoms through standard equipment (Easy One Pro[®], NDD Medical Technologies, Switzerland). Spirometry reference equations were obtained from Hankinson (1999) [32]. The technical quality of spirometry was adhered to per 2019 spirometry standards [33]. The reference equations for pulmonary diffusing capacity for carbon monoxide (DLCO) was obtained from Vazquez-Garcia and colleagues [32]. The 2017 Technical standards for DLCO were followed for technical quality [34].

Analysis

A Fisher's exact test compared the number males versus females being below the LLN for DLCO. A Fisher's exact test also compared the number males versus females with a restrictive spirometric pattern as defined by the ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) being $\geq$ LLN with the FVC being less than the LLN. The Fisher's Exact Test would allow an examination of a sex differences in the proportion of males versus females that had abnormally low lung function. Several N-1 Chi-Squared Tests were used to determine whether the percentage of several signs and symptoms that were present post-COVID-19 were different between those with a DLCO < LLN and those with a DLCO $\geq$ LLN [35]. A Benjamini-Hochberg procedure was used to control the false discovery rate [36], which we set to 0.05.

Binary logistic regression was performed using the Forward: Likelihood ratio method (enters independent variables one at a time) to determine the factors associated with an impaired DLCO (DLCO < LLN) in the mild post-COVID-19 patients. Cardiovascular disease (CVD) risk factors [smoking status (yes, no), high blood pressure (yes, no), cardiac arrhythmia (yes, no), obesity (yes, no)], true cardiac disease (yes, no), fatigue, dyspnoea, cough, headache, chest tightness, sore throat, persistent loss of smell (yes, no), dysfunction in the sense of taste (yes, no), conjunctivitis, blocked and/or runny nose, use of oral corticosteroids during the disease (yes, no), use of anticoagulant medications (yes, no), sex (male, female), age in z scores, height in z scores, weight in z scores, body mass index (BMI) in z scores, a restrictive spirometric pattern (forced vital capacity or FVC below the lower limit of normal, LLN, and FEV₁/FVC $\geq$ LLN), forced expiratory volume in 1 s (FEV₁) (y = yes, 0 = no), forced expiratory flow rate over the middle half of expiration (FEF₂₅₋₇₅) in z scores and peak expiratory flow (PEF) in z scores.

Using mean data from 22 previous studies (including the current study), multiple linear regression analysis using forward selection was used to identify which of the five following factors would predict the proportion of patients who had previous COVID-19 and impaired DLCO at follow-up. The mean age (years), mean body mass index (kg/m²), mean number of days between receiving the COVID-19 diagnosis and follow-up, history of mild vs severe COVID-19 disease (i.e. patients that were either hospitalized, intubated, presented with fibrotic CT changes in the lung were labelled as 1, compared to

those that were not labelled as 0), and the criteria used to define impaired DLCO (DLCO < 80% predicted labelled as 1, vs DLCO < LLN labelled as 0) were predictors used in the model.

All data were analysed by a statistical software package (IBM SPSS Statistics, Version 27, Chicago IL). A p-value of < 0.05 was used to signify statistical significance. Any case with a studentized residual ≥ 3.0 were removed from any model.

Results

One hundred and fifty subjects were recruited from the Long-term follow-up COVID-19 clinic. Four patients were removed due to the reference equations not fitting the age range of the subjects, leaving 146 patients for the analysis. The anthropometric characteristics are presented in Table 1. Approximately, 50% of the subjects were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). The gas exchange parameter, DLCO, was significantly reduced compared to predicted values (Table 2). In fact, 30% of the sample had a DLCO value that was below the LLN, and the percentages were similar between males and females (Table 3). Twenty-one percent of the sample had a restrictive spirometric pattern ($\text{FVC} < \text{LLN}$ and an $\text{FEV}_1/\text{FVC} \geq \text{LLN}$) (Table 3) and when coupled with an $\text{DLCO} < \text{LLN}$, about 13% of the patients had both impaired DLCO and lung restriction.

Table 1
Anthropometric and lung function data post mild COVID-19.

	Males (n = 59)	Females (n = 87)
Age (yrs)	50 (13) [28-82]	50 (14) [25-83]
Weight (kg)	84.6 (15.0) [61.0-133.0]	70.0 (15.3) [42.0-118.0]
Height (cm)	168 (8) [150-182]	153 (8) [137-169]
Body mass index (kg/m ²)	29.9 (4.0) [22.2-42.0]	30.0 (6.2) [16.6-44.1]
FVC (L)	3.97 (1.00) [1.20-6.73]	2.16 (0.66) [1.18-4.51]
FEV ₁ (L)	3.26 (0.81) [1.06-5.18]	2.14 (0.59) [0.88-3.75]
FEV ₁ /FVC	0.82 (0.05) [0.64-0.91]	0.82 (0.06) [0.61-0.95]
PEF (L/s)	9.26 (2.15) [3.29-14.91]	5.75 (1.73) [2.07-9.70]
DLCO (mL•min ⁻¹ •mmHg ⁻¹)	26.6 (7.7) [7.6-53.6]	18.7 (4.8) [7.3-30.8]
VA (L)	6.03 (1.43) [1.88-9.53]	4.36 (0.89) [1.92-6.25]
KCO mL•min ⁻¹ •mmHg ⁻¹ •L ⁻¹	4.44 (0.91) [2.46-6.84]	4.31 (0.84) [1.71-7.04]
Altitude of testing (m)	7	7
Data are showed as mean (SD). Brackets represent ranges.		

Table 2
Percent predicted for several lung function indices.

	Males (n = 59)	Females (n = 87)
% predicted FVC	91 (16) [31-127]	93 (14) [61-131]
% predicted FEV ₁	95 (17) [34-124]	90 (14) [56-120]
% predicted FEV ₁ /FVC	104 (6) [83-116]	101 (6) [78-116]
% predicted PEF	107 (24) [49-158]	105 (28) [53-180]
% predicted DLCO	81 (19) [25-136]	78 (17) [39-153]
Data are showed as mean (SD). Brackets represent ranges.		

Table 3
The number and percentage of males and females below the lower limit of normal

	Males (n = 59)	Females (n = 87)	Total (n = 146)
FVC	15 (25%)	18 (21%)	33 (23%)
FEV ₁	11 (19%)	14 (16%)	25 (17%)
FEV ₁ /FVC	1 (2%)	3 (3%)	4 (3%)
PEF	6 (10%)	9 (10%)	15 (10%)
DLCO	16 (27%)	28 (32%)	44 (30%)
A Fisher's Exact test was used to compare frequencies between males and females. No statistically significant differences were noted between males and females			

For the regression analysis, two subjects had missing data, so 144 subjects were used. The binary logistic regression revealed an overall model of four predictors that was statistically reliable in distinguishing between those with a DLCO below the LLN and those with normal DLCO [-2 Log Likelihood = 131.7, Cox & Snell R^2 = 0.26, Nagelkerke R^2 = 0.38; Omnibus tests of model coefficients χ^2 = 43.9, df = 4, p = 0.000]. Increased age, a blocked/ runny nose, excessive sweating, and a restrictive spirometric pattern increased the probability of having an impaired DLCO. The model was a good fit [Hosmer and Lemeshow Test, χ^2 = 2.44, df = 8, p = 0.96], correctly identifying 77% of the cases (Table 4).

Table 4
Variables in the equation to predict impaired DLCO in mild COVID-19 patients (n = 144).

Variables	B	S.E.	Wald	df	Sig.	Odds ratio	95% CI for odds ratio
							lower-upper
Age (Z scores)	0.945	0.24	15.3	1	0.000	2.57	1.60 to 4.13
Excessive sweating (yes = 1, no = 0)	1.322	0.66	4.0	1	0.045	3.75	1.03 to 13.64
Blocked nose (yes = 1, no = 0)	1.184	0.51	5.5	1	0.019	3.27	1.21 to 8.80
Restriction (1 = yes, 0 = no)	1.914	0.50	14.6	1	0.000	6.78	2.52 to 18.17
Constant	-2.494	0.77	10.6	1	0.01	0.08	

Using mean data from 22 previous studies (including the current study, see **Table S1**), multiple linear regression analysis was used to identify which factors would predict the proportion of previously infected SARS-CoV-2 patients with impaired DLCO at follow-up. Regression results indicate an overall model of three predictors (previous history of severe COVID-19, criteria used to define impaired DLCO, and mean age of the group) that significantly determined the percentage of previously infected COVID-19 patients with an impaired DLCO at follow-up [$R^2_{adj} = 0.37$, $F(3,34) = 8.24$, $p = 0.0003$]. The model accounted for 37% of the variance defining those with DLCO impairment. A summary of the regression model is presented in Table 5. Having a previous severe case of COVID-19 increases the proportion of those with impaired DLCO by 20% at follow-up. As well, when using the more liberal definition of impaired DLCO (< 80% of predicted), the proportion of those with impaired DLCO increased by 12% in a given study. Finally, when the mean age for each study increased by 1 year in age (from 41 to 69 years), the proportion of those with impaired DLCO increased by about 4%. Interestingly, the time of follow-up (20 to 180 days) did not seem to affect the percentage of those with impaired DLCO in a particular study.

Table 5

Variables that predict the proportion of patients who had previous COVID-19 disease with an impaired DLCO at follow-up.

Variables	Unstandardized Coefficients		Standardized coefficients		Sig.	95% CI for odds ratio	
	B	S.E.	B	t		Lower bound	Upper bound
History of previous mild vs severe COVID-19	19.9	5.8	0.45	2.78	0.002	8.1	31.7
Mean age (yrs.)	1.04	0.4	0.39	2.59	0.014	0.2	1.9
Criteria to define impaired DLCO	11.5	5.7	0.26	2.01	0.053	-0.2	23.1
Constant	-34.6	22.3		-1.55	0.13	-80.0	10.8
Where mild COVID-19 = 0; Severe COVID-19 = 1; impaired DLCO defined by DLCO < LLN = 0; DLCO defined by being less than 80% of predicted = 1. Standard error of the estimate = 17.6%.							

Discussion

A main purpose of this study was to identify possible predictors of impaired DLCO in patients that had mild COVID-19 within the first 4 to 6 weeks. We found that patients who are recovering from mild COVID-19 also have persistent symptoms (**Table S2**) as well as pulmonary function abnormalities (Table 3). For each one standard deviation unit increase in age (which approximates 13 years), the odds of having an impaired DLCO increased by nearly 3-fold, while having a restrictive spirometric pattern increased the risk of having an impaired DLCO by almost 7-fold (Table 4). Regarding symptoms, having reported a blocked/runny nose and excessive sweating at follow up also increased the odds of having an impaired DLCO by about 3 to 4-fold, each (Table 4). When using the logistic model, using a mean age of 50.6 years (z score = 0), having no lung restriction (0), no blocked nose (0) and no excessive night sweats (0), the probability of an impaired DLCO in this population is 8%. The probability increases to 36% when a restrictive spirometric pattern is evident (Table 4). Thus, having a restrictive spirometric pattern increases the odds of having impaired DLCO at follow-up. While 20% percent of the patients had a restrictive spirometric pattern, only 3% of patients showed an obstructive pattern (as defined by a FEV₁/FVC below LLN), which demonstrates that the after-effects COVID-19 are likely to result in lung restriction and poor pulmonary diffusion.

Another purpose of this study was to determine the variables that predict the percentage of previously infected SARS-CoV-2 patients who had a DLCO impairment during follow-up. Having severe COVID-19 disease at diagnosis, increased the percentage of those with impaired DLCO by nearly 20%. If the study used the usual cutoff < 80% of predicted to define DLCO impairment, then 12% more patients would be classified as having abnormal gas exchange. Thus, if using the stricter definition of DLCO impairment as being below the LLN (i.e., below the 5th percentile) for height, age, sex, and ethnicity, then 12% few

patients would be classified as having a reduced DLCO. The definition of a low DLCO being < 80% of predicted is not correct and may misclassify patients, as the percent of the predicted value at the LLN (5th percentile) decreases beginning at about 40 years of age.[37, 38] Patients who have the same height, sex, and ethnicity have a DLCO that is about 79% of predicted at 40 years of age at the LLN (5th percentile) compared to about 73% of predicted at 85 years of age at the LLN [38]. Therefore, using z-scores are more correct to use instead of using absolute cutoff < 80% predicted to define a clinically low DLCO.

We were not able to measure total lung capacity (TLC) using a body plethysmograph to verify lung restriction, thus a restrictive spirometric pattern ($FEV_1/FVC \geq LLN$ and $FVC < LLN$, pre-bronchodilator) was used instead as a surrogate of true lung restriction. The sensitivity to identify true pulmonary restriction ($TLC < LLN$) with a restrictive spirometric pattern is about 34% but the specificity is nearly 98% [39]. The negative predictive value (NPV), meaning that the percentage of patients who do not have a restrictive spirometric pattern and whom do not have restrictive lung disease is 97% [39]. The prevalence of a restrictive spirometric pattern ($FEV_1/FVC \geq LLN$ and $FVC < LLN$, pre-bronchodilator) in populations is about 3 to 9% [39, 40]. In this group of patients that had mild COVID-19, we found that the restrictive spirometric pattern to be about 20% which is more than double the population average.

Among persistent symptoms, fatigue, shortness of breath on effort are the most prevalent descriptors included in Long COVID-19 and these were not different in ambulatory patients recovering from mild COVID-19 [30]. About 74% of the patients experienced undue fatigue and nearly half experienced shortness of breath on effort and / or a significant cough.

Limitations

Our study has some limitations. In addition to not having measured lung volumes with plethysmography, we do not have any baseline lung function data in these patients prior to SARS-CoV-2 infection as well as a control group, due to the pandemic, to perform further analysis. However, mostly all studies involving lung function analysis among COVID-19 survivors were done with the same limitation. Indeed, it is difficult to determine with certainty that these patients with poor diffusing capacity and/or a restrictive spirometric pattern is due to them having mild COVID-19. Nonetheless, these patients are compared against established reference norms and the prevalence of an impaired DLCO in our sample was five-times more than expected in a normal population and at least two-fold more than expected for a restrictive spirometric pattern. To reduce this bias, we analysed all risk factors related with lung function abnormalities including published studies. Also, there is gap in implementing regular lung function assessment in case of suspected obstructive lung disease, instead chest x-ray studies are more frequently requested, especially in countries with limited-resource settings, therefore it is expected that patients were not subjected to pulmonary function tests prior to SARS-CoV-2 infection.

Conclusions

Nearly one-third of patients with mild COVID-19 have impaired DLCO 34 days post-diagnosis and one-fifth of patients have lung restriction. The odds of having an impaired DLCO at follow-up increased nearly 7-fold if a restrictive spirometric pattern was evident. Increased age, having excessive night sweats, and a blocked/runny nose also increased the probability of an impaired DLCO at follow-up. In a summary of 22 studies, having severe COVID-19 disease at diagnosis increased the percentage of those with impaired DLCO by nearly 20%. And, if the study used < 80% of predicted to define DLCO impairment, then 12% more patients would be classified as having poor gas exchange.

List Of Abbreviations

SARS-CoV2: Severe acute respiratory syndrome coronavirus 2

COVID-19: coronavirus disease 2019

DLCO: pulmonary diffusing capacity for carbon monoxide

LLN: lower limit of normality

WHO: world health organization

BMI: body mass index

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

FEF₂₅₋₇₅: forced expiratory flow rate over the middle half of expiration

PEF: peak expiratory flow

TLC: total lung capacity

CVD: cardiovascular disease

Declarations

• Ethics approval and consent to participate

-Ethics approval was obtained from the Ethics Committee of the High Specialty Regional Hospital in Yucatan, Mexico (No. CONBIOETICA- 31-CEI-002-20170731)

-The Ethics Committee assigned the Protocol number 2020-024.

-A written informed consent to participate was signed by all patients at the scheduled visit in compliance with the Helsinki declaration.

- **Consent for publication**

-Not applicable.

- **Availability of data and material**

-All data generated or analysed during this study are included in this article and/or its supplementary material files. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

-The authors declare that they have no competing interests.

- **Funding**

-None.

- **Authors' contributions**

- ACT, EFH, DLOF, GSZ designed the study.

- ACT, EFH, DLOF collected the data and interpreted the patient data regarding lung function.

- ACT and GSZ analyzed the data and prepared the manuscript.

- All authors made critical revisions to the manuscript and approved the final version.

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-Not applicable.

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