Original Article

Assessment of Pulmonary Functions in COVID-19 Survivors and their Clinical Correlation at 6-month Follow-up: A Prospective Observational Study

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Abstract

Background: Long term impact of COVID-19 on pulmonary functions is still an area of active research. **Objective:** To assess pulmonary functions and their relationship with clinical severity of disease among COVID-19 survivors at six-month follow-up after being discharged from the hospital. **Methods:** It was a hospital based prospective observational six-month follow-up study. After fulfillment of all inclusion and exclusion criteria, subjects underwent spirometry and diffusion capacity of lung for carbon monoxide (DLco). Ninety-six subjects had completed the tests and were enrolled for the study. Categorization of subjects was made based on their clinical disease severity profile according to Government of India guidelines. Test results were correlated with clinical severity of disease. **Results:** Of 96 subjects, 46 were mild, 28 were moderate, 18 were severe and 4 were critical cases. Majority of subjects had normal spirometry (65.6 %) and DLco (66.6 %). Among abnormal lung functions, the commonest was reduced DLco (33.3%) followed by restrictive (18.7%), small airway disease (10.4 %), obstructive (3.1 %) and mixed (2%) spirometry patterns. With the advancement of clinical disease severity, the frequency of restrictive pattern ($P<0.01$) and reduced DLco increases significantly ($P<0.05$). **Conclusion:** After six months, few COVID-19 survivors had residual lung function impairment in terms of reduced DLco and restrictive spirometry pattern. Hence, we recommend regular lung function assessment with various methods such as spirometry and DLco in COVID-19 survivors and advocate more large scale - long term follow-up studies to investigate the further progression or resolution in these abnormalities over the time.

Keywords: *COVID-19 survivors, diffusion capacity of lung for carbon monoxide, pulmonary function test, spirometry*

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Introduction

The COVID-19 pandemic, which was brought on by the new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is linked to high morbidity and mortality and it continues to pose unheard-of difficulties for the world's health-care systems. Lungs are the most affected organ in acute phase of COVID-19 that can undergo different pathophysiological alterations[1] going from pulmonary consolidation and alveolar epithelium destruction to hyaline membrane formation, capillary damage and bleeding, and alveolar septal fibrous proliferation.

It has been observed that many patients presented with persistent respiratory symptoms even after recovering from the acute phase of disease. Few patients require

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oxygen therapy for long time even after discharge from the hospital. The results of the autopsy[2] on the lung tissue showed inflammatory cell infiltration, fluid buildup inside the alveoli, alveolar wall disintegration, lung fibrosis, and microthrombi formation in the pulmonary capillaries. It was assumed that this residual fibrosis may be responsible for post-COVID-19 respiratory symptoms.

Spirometry and diffusion capacity of lung for carbon monoxide (DLco) are the common tools used for assessing lung functions, particularly in COVID-19 survivors. Few studies have been done to assess pulmonary functions in COVID-19 survivors in early phase after being discharged. Based on these studies, it was witnessed that COVID-19 has an impact on lung functions in terms of reduction in DLco and restrictive pattern on spirometry. While the available studies regarding the pulmonary functions in COVID-19 survivors were limited to early convalescence phase only, long-term follow-up studies were still lacking. It was also observed that with advancement of clinical severity of disease, there was a reduction in lung functions. These findings raise a concern regarding potential long-term pulmonary sequelae. As a result, it is important to screen for any changes in lung function in COVID-19 survivors. Hence, we did this study to investigate the pulmonary functions and their clinical correlation in COVID-19 survivors at 6-month follow-up after discharge from the hospital.

Objectives:

- To study the spirometry pattern in COVID-19 survivors at 6-month follow-up after discharge
- To study the diffusion lung capacity for carbon monoxide (DLco) in COVID-19 survivors at 6-month follow-up after discharge
- To study the correlation between pulmonary functions and clinical profile of COVID-19 survivors at 6-month follow-up after discharge.

Materials and Methods

It was a prospective observational study, done in Pacific Medical College and Hospital, Udaipur, Rajasthan, India. The study was approved by the Institutional Ethical Committee with protocol no. IEC/PG/2020/49. The objective of this study was to investigate spirometry patterns and DLco in COVID-19 survivors and to establish their correlation with clinical severity of the disease at 6 months after being discharge from the hospital.

Sample selection

The patients above 18 years of age of either sex with a positive nasopharyngeal and/or throat swab for SARS-CoV-2, with or without pneumonia, admitted to our institute during February 2021 to April 2021 were screened for the study. Patients below 18 years of age, history of any chronic lung disease, refusal to participate in the study, pregnancy, smoking history, unable to perform pulmonary function tests (PFTs) at 6-month follow-up, and contraindications of PFTs were the exclusions.

Study protocol

The study protocol was explained in detail, and informed and written consent was taken for each patient. The selected candidates underwent a detailed clinical history, especially regarding any previous history of chronic lung disease, smoking, and any comorbid conditions that may affect the lung functions. At the time of hospitalization, the patients were graded for clinical severity according to the Government of India clinical management guidelines for COVID-19.[3]

The treatment protocol and discharge criteria were according to the national guidelines. The clinically mild patient received only symptomatic treatment while the moderate patient received low-flow oxygen therapy and steroids along with the symptomatic treatment. The patients with severe diseases received high-flow oxygen therapy, positive pressure ventilation, steroid, anticoagulant, and remdesivir while critically ill patients received the same treatment as severe diseases with additional mechanical ventilation. On discharge, mild patients were advised for symptomatic treatment (dextromethorphan, pantoprazole, zinc, Vitamin C, paracetamol, and chlorpheniramine) in need while moderate, severe, and critical patients were advised symptomatic treatment, anticoagulants, bronchodilators, and oxygen therapy if required. On subsequent follow-ups, the need for these medicines was assessed and stopped in case of no need.

We screened 168 participants for eligibility criteria and enrolled 139 patients after exclusions. Out of these 139, only 5 patients were discharged on oxygen therapy. These patients were kept on regular telephonic and voluntary physical follow-ups on a regular basis. The patients with severe and critical illness underwent a mandatory regular physical follow-up for any further need of medications. The need for oxygen therapy was assessed at each visit. Three patients at 2-month follow-up and two patients at 3-month follow-up showed no need of supplemental oxygen.

An appointment date (6 months after discharge) had been allocated to each of these patients.

At 6 months, the detailed history was taken again for any residual symptoms followed by systemic examination. Patients underwent the following PFTs: spirometry and

DLco. A chest CT was performed in case of persistent cough and dyspnea. A total of 96 subjects were taken for final analysis. After completion of tests, results were correlated with clinical severity of disease. Data were analyzed, results were finalized, and conclusion was made.

Pulmonary function tests

All PFTs were carried out by a trained respiratory technician at the Department of Respiratory Medicine, Pacific Medical College, and Hospital. Tests were performed and interpreted as per the ATS-ERS guidelines.[4,5]

Spirometry

The test was conducted using RMS Helios 401 spirometer. The following parameters were measured in our study with the help of spirometry: forced vital capacity (FVC), forced expiratory volume in the 1st s (FEV1), FEV1/FVC, and forced expiratory flow (FEF) 25%–75%.

The interpretation was done as follows:

- Normal: If both FVC and the FEV1/FVC ratio are in the normal range
- Obstructive pattern: If FEV1/FVC ratio was <70% of the normal predicted value and FEV1 <80% of predicted. In case of obstruction, a repeat spirometry was also done, 15 min after inhalation of 400 µg of salbutamol by pMDI with spacer for reversibility testing
- Restrictive pattern: If FEV1/FVC ratio was ≥70% of the normal predicted value, and the total lung capacity (TLC) <80% of the predicted value. In case of unavailability of TLC, a reduction in the FVC <80% of predicted was considered
- Mixed pattern: If FEV1/FVC <70% and FVC <80% of predicted value
- Small airway diseases: If FEF 25%–75% was <65% of normal predicted value.

If obstruction present, the spirometry measurements were repeated after 15 min for reversibility after administration of a bronchodilator (400 µg of salbutamol by pMDI with spacer).

DLco

The test was conducted using EasyOne Pro with software and measured by means of the single breath test. The hemoglobin value was also taken for correcting DLco. Interpretation of DLco was made as following:

- Normal DLco: >75% of predicted
- Reduced DLco: <75% of predicted.

Table 1: Demographic and clinical characteristics of study subjects (*n*=96)

Variable	Data, *n* (%)
Age (years), mean±SD	40.5±12.2
Gender	
Male	54 (56.2)
Female	42 (43.7)
BMI (kg/m^2), mean±SD	24.9±2.4
Comorbidities	
HTN	16 (16.6)
DM2	8 (8.3)
Hypothyroidism	3 (3.1)
Symptoms	
Fever	50 (52.0)
Dry cough	27 (28.1)
Fatigue	29 (30.2)
Myalgia	18 (18.7)
SOB	22 (22.9)
Sore throat	16 (16.6)
Loss of taste	17 (17.7)
Loss of smell	17 (17.7)
Back pain	6 (6.2)
Nausea	9 (9.3)
Productive cough	2 (2.0)
Headache	3 (3.1)
GI upset	6 (6.2)
CT chest findings	
GGO	56 (58.3)
Consolidation	21 (21.8)
Crazy paving	7 (7.2)
Reticular pattern	41 (42.7)
Interlobular septal thickening	10 (10.4)
Length of hospital stay (days), mean±SD	14.9±5.5
Type of oxygen support required in 3.1%, mixed airway disease in 2% and small airway disease in 10.4% of subjects.	
Room air	46 (47.9)
LF	28 (29.1)
HF	11 (11.4)
NIV	7 (7.2)
MV	4 (4.1)
COVID-19 clinical severity	
Mild	46 (47.9)
Moderate	28 (29.1)
Severe	18 (18.7)
Critical	4 (4.1)

BMI: Body mass index, SD: Standard deviation, HTN: Hypertension, DM2: Diabetes mellitus type 2, CT: Computed tomography, MV: Mechanical ventilation, GGO: Ground-glass opacity, SOB: Shortness of breath, NIV: Noninvasive ventilation, GI: Gastrointestinal, LF: Low flow, HF: High flow

Statistical analysis

The collected data were tabulated in Microsoft Excel sheet and then transferred to the SPSS version 22, (Armonk, New York, United states of America for

analysis. In addition, the Excel environment is used to draw graphs. Continuous data were presented as mean and standard deviation while the categorical variables were presented as frequency and percentages. We applied Chi-square test for categorical data. Test of significance was done for *P* value calculation, and $P < 0.05$ was considered statistically significant [Figure 1].

Results

Demographic and clinical characteristics of study subjects

The demographic and clinical characteristics of study subjects are presented in Table 1. It was a male predominant study including 54 (56.2%) males and 42 (43.7%) females. The mean age of study subjects was 40.5 ± 12.2 years. The most common comorbid condition was hypertension followed by diabetes. At the time of hospital admission, the most common presenting symptoms were fever (52%), fatigue (30.2%), dry cough (28.1%), and dyspnea (22.9%). Loss of taste and smell were observed in 17.7% of subjects while 6.2% of subjects had GI symptoms. As per the protocol, all admitted patients underwent a chest computed tomography (CT) preferably on the 6th day of their symptoms. The most common chest CT findings at the time of hospital admission were ground-glass opacity (58.3%), reticular pattern (42.7%), and consolidation (21.8%). A crazy-paving appearance was found in 7.2% of subjects. The mean duration of hospital stay in study subjects was 14.9 ± 5.5 days. Based on clinical severity criteria, 47.9% (46) of study subjects were labeled as mild cases while 29.1% (28) and 18.7% (18) of subjects were labeled as moderate and severe cases, respectively. The critical illness was present in 4.1% of subjects.

Pulmonary function test results at 6-month follow-up

The PFT results at 6-month follow-up are presented in Table 2.

The spirometry findings were normal in 65.6% of subjects. The abnormal spirometry patterns were restriction in 18.7%, obstruction in 3.1%, mixed airway disease in 2% and small airway disease in 10.4% of subjects. The normal DLco was observed in 66.6% while the remaining 33.3% of subjects had reduced DLco.

Clinical correlation with pulmonary function test results

The correlation of PFT results with clinical severity of disease is presented in Table 3.

Table 2: Pulmonary function test results at 6-month follow-up (*n*=96)

PFT	Data, *n* (%)
Spirometry interpretation	
Normal	63 (65.6)
Obstructive	3 (3.1)
Restrictive	18 (18.7)
Mixed	2 (2.0)
Small airway disease	10 (10.4)
DLco interpretation	
Normal	64 (66.6)
Reduced	32 (33.3)

PFT: Pulmonary function tests, DLco: Diffusion capacity of lung for carbon monoxide

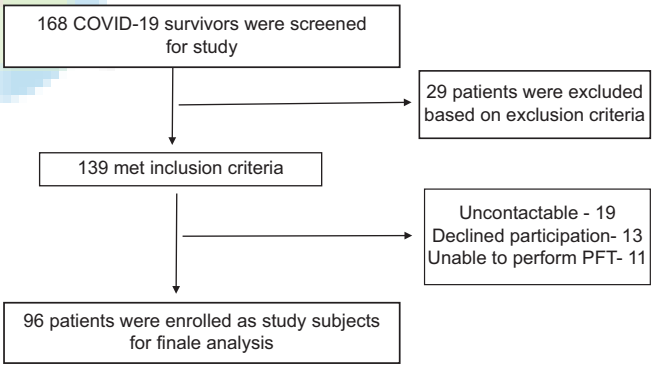

Figure 1: Study subjects' selection flowchart

Table 3: Clinical correlation with pulmonary function test results

PFT	COVID-19 clinical severity				*P* (χ^2)
	Mild (*n*=46), *n* (%)	Moderate (*n*=28), *n* (%)	Severe (*n*=18), *n* (%)	Critical (*n*=4), *n* (%)	
Spirometry interpretation					
Normal	36 (78.2)	18 (64.2)	8 (44.4)	1 (25.0)	*P*<0.01
Obstructive	0	1 (3.5)	2 (11.1)	0	
Restrictive	3 (6.5)	6 (21.4)	7 (38.8)	2 (50.0)	
Mixed	1 (2.1)	0	0	1 (25.0)	
Small airway disease	6 (13.0)	3 (10.7)	1 (5.5)	0	
DLco interpretation					
Normal	37 (80.4)	17 (60.7)	9 (50.0)	1 (25.0)	*P*<0.05
Reduced	9 (19.5)	11 (39.2)	9 (50.0)	3 (75.0)	

PFT: Pulmonary function tests, DLco: Diffusion capacity of lung for carbon monoxide

Discussion

The COVID-19 pandemic raised several questions regarding long-term pulmonary sequelae. This study emphasized pulmonary functions and their correlation with clinical severity of the disease among COVID-19 survivors at 6-month follow-up.

In this study, majority of subjects had normal spirometry (65.6%) and DLco (66.6%) indicating the absence of residual functional abnormality in majority of COVID-19 survivors. Our findings were in line with a previous study done by Ora *et al*.,[6] in which majority of COVID-19 survivors had normal pulmonary functions at 6-month follow-up after being discharge from the hospital. Our results were at odds with the earlier hypothesis based on radiology and autopsy studies, which suggested that COVID-19 survivors may experience long-term restrictive lung impairment due to involvement of the lung interstitium and vasculature. Few earlier studies done at 12-week follow-up have documented predominant restrictive lung impairment among COVID-19 survivors.[7,8] The restrictive impairment in these studies may be because of an early phase of lung recovery or a possible residual neuromuscular effect of COVID-19. As we are in the learning phase of this novel disease, it may be possible that the disease has a long duration of its course.

The most common pulmonary function abnormality in our study was reduced DLco (33.3%) followed by restrictive lung disease (18.7%), indicating a residual effect on lung parenchyma in around 1/3 of COVID-19 survivors. A 1-month follow-up study done by Mo *et al*.[9] has also reported reduced DLco as the most common pulmonary function abnormality among COVID-19 survivors which also support the involvement of lung parenchyma as a residual COVID-19 lung effect. The prevalence of impaired DLco and restrictive spirometry pattern according to a meta-analysis[10] was 39% and 15%, respectively. In few early convalescent phase studies, the frequency of DLco abnormality ranged from 42% to 53% while restrictive impairment ranged from 9% to 28%.[9,11,12] This frequency of residual functional abnormalities may not represent the actual picture of the disease as earlier follow-up studies showed a predominant restrictive pattern while predominant normal lung functions in our study were done at 24 weeks. From these observations, it seems that the disease has a longer duration of its course and currently is in recovery phase among these patients who showed a restrictive pattern.

Prior coronavirus outbreaks brought on by the Middle East respiratory syndrome coronavirus (MERS-CoV) and the SARS-CoV were also linked to persistent pulmonary function impairment that lasted up to 6 months after recovery from acute illness. In a meta-analysis of 28 studies on the long-term effects of the MERS-CoV and SARS-CoV on lung function, it was discovered that DLco, FVC, and TLC continued to be impaired 6 months after recovery. However, the impairment in DLco persisted even after 6 months.[13]

We found a significant increment in frequency of restrictive spirometry and reduced DLco with the advancement of clinical disease severity. This observation indicates that the baseline clinical severity is an important predictor of lung functions among COVID-19 survivors. There was almost complete recovery in lung functions in milder diseases, while in severe and critical diseases, still recovery was going on. Although we found abnormal lung functions in around 50% of severe and critically ill patients, it will be hasty to say that COVID-19 left a permanent lung function impairment.

One more point to emphasize here is the presence of small airway disease in milder form of COVID-19 only. These observations were similar to a study done by Mo *et al*.[9] at 1 month follow-up. From this observation, it can be assumed that milder form of disease remains limited to the small airways, while in severe disease, there is an involvement of lung interstitium and capillaries.

The precise mechanism through which COVID-19 damages the lungs is still an unresolved issue. In studies that included autopsies of COVID-19 patients, diffuse alveolar damage and fibrotic alterations were documented together with microthrombi in the pulmonary vasculature as part of an acute lung injury.[14-16] The most likely explanation of the restrictive limitation of lung function is fibrotic alterations in the lung after an acute COVID-19 infection. COVID-19 lung injury results in fibroblast recruitment and activation, and post-COVID-19 patients were found to have a greater chance of developing pulmonary fibrosis.[17] The fatigue of the respiratory muscles is another factor that may contribute to the decline in pulmonary function. In post-COVID-19 survivors, a significant improvement in PFT was seen after 6 weeks of respiratory rehabilitation,[18] though this rehabilitation did not result in a full recovery, which may indicate the persistence of lung damage. As seen in autopsy and CT findings, the extensive inflammation that resulted in interstitial fibrosis and alveolar degradation could be the fundamental mechanism that may explain the diffusion limitation in severe instances.[19,20] We recommend longer-duration follow-up studies, especially in severely and critically ill patients.

Limitations of study

With relation to the cohort of COVID-19 survivors, the sample size in our study seems to be smaller. Second, we do not have the data of prior pulmonary functions for the comparison. A significant number of dropouts was also the limitation of this study as we were able to analyze only 96 patients out of 139 enrollments.

Conclusion

Majority of COVID-19 survivors had normal pulmonary functions at 6-month follow-up. Reduction in DLco was the most common abnormality observed followed by restrictive spirometry pattern. There is an increment in frequency of restrictive spirometry pattern and reduced DLco with the advancement of clinical disease severity. Hence, we recommend postrecovery regular follow-up for lung function assessment with various methods such as spirometry and DLco and advocate more large-scale-long-term follow-up studies to investigate the further progression or resolution in these abnormalities over the time.

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Conflicts of interest

There are no conflicts of interest.

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