Original Article

Evaluation of the long-term effects of COVID-19 on pulmonary functions in recovered patients

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Abstract

Background: It is documented that COVID-19 survivors have prolonged morbidity and functional impairment for many years. Data regarding post-COVID-19 lung functions is lacking from the Indian population. We aim to evaluate the lung functions in such patients after 3–6 months of hospital discharge. **Methods:** In this prospective observational study, patients were assessed 3 to 6 months post-discharge and underwent standardized pulmonary function tests (PFTs) and CT Thorax if required. The following parameters were measured and correlated with the disease severity: Forced Vital Capacity (FVC), Forced Expiratory Volume in the First Second (FEV1), Forced Expiratory Flows at 25 and 75% of FVC (FEF25%-75%), Peak Expiratory Flow (PEF) and FEV1/FVC. **Results:** A total of 52 post-COVID-19 patients were enrolled in the study, with a median age of 43 years (78.8% males). 44.2% of patients had mild disease, 26.9% had moderate disease and 23.1% had severe disease at hospital admission. A restrictive pattern was seen in 20.8% of patients. The mean value of FEV1 and FVC decreased as the disease severity increased. FEV1: mild-3.21 ± 0.71, moderate-2.62 ± 0.61 and severe- 2.51 ± 0.72, $P = 0.02$; FVC: mild-3.69 ± 0.81, moderate-3.04 ± 0.71 and severe- 2.93 ± 0.87, $P = 0.02$. After adjusting the confounding factors, the mean pulmonary function values were lower in the patients who required oxygen support, with a significant difference in FEV1, FVC, PEF and FEF 25–75% with P values of 0.025, 0.046, 0.028 and 0.007, respectively. 66.67% had abnormal HRCT findings. Age and high LDH were correlated with HRCT abnormality with P values of 0.015 and 0.024. Age >50 years was found to be an independent predictor of the subsequent development of abnormality on the HRCT thorax. **Conclusions:** Patients with COVID-19 pneumonia, which required oxygen, especially severe disease at the time of hospitalization, had a higher rate of abnormal spirometry than patients with mild symptoms. Follow-up CT scans obtained within six months of disease onset showed abnormalities in more than half of patients, particularly elderly patients.

Keywords: COVID-19, lung function test, PFT, pneumonia, spirometry

Introduction

As of February 19, reported cases of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) have crossed 700 million.[1] Of the 44 million cases in India, approximately 5 lakh people have lost their lives.[1] The clinical spectrum of the disease is variable and ranges from asymptomatic infection to

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severe pneumonia requiring mechanical ventilation.[2-4] The term 'Long COVID' was first used by Elisa Perego in 2020, describing the persistent symptoms for weeks or months after initial recovery.[5,6] In post-COVID-19 syndrome, these symptoms could be persisting or relapsing-remitting in nature. The commonly reported symptoms were fatigue (53.1%), poor quality of life (44.1%), dyspnoea (43.4%), arthralgia (27.3%) and chest pain (21.7%).[7] Since the lungs are the primary site of involvement in COVID-19, persistent dyspnoea is a greater concern and also a significant cause of poor quality of life in such patients.

SARS-CoV-2 can produce a sustained inflammatory response at the alveolar epithelium months after initial infection. It ensues fibrotic changes in the lung tissue caused by fibroblast activation and collagen and fibronectin deposition.[8,9] The pulmonary function test (PFT) is a vital tool to assess these residual pulmonary symptoms in post-COVID-19 recovered patients, along with radio imaging. New data is emerging regarding abnormal lung function post-COVID-19 period. However, there is a lack of data from the Indian subcontinent. Moreover, due to a large population, many of these post-COVID patients couldn't reach out to the specialist clinic for persistent symptoms, the role of primary care physicians is prudent in such settings. We aim to highlight the usual pattern of post-COVID pulmonary symptoms that can be helpful for family physicians in the identification and assessment of the severity of pulmonary function. We aim to assess the pulmonary function in patients who recover from COVID-19 (within 3–6 months) and the relation between the initial severity of the disease and residual deficit in lung function.

Material and Methods

This prospective observational cohort study was conducted in a post-COVID-19 OPD clinic at All India Institute of Medical Sciences, Jodhpur, India. The study included all patients >18 years of age who presented for clinical follow-up after 3–6 months after recovering from either mild or moderate-severe COVID-19 illness. All patients were diagnosed with COVID-19 based on reverse transcriptase-polymerase chain reaction (RT-PCR) reports of the nasopharyngeal swab. Patients with a history of chronic lung diseases diagnosed with pulmonary embolism during hospitalization, connective tissue disease, active malignancy and age <18 years were excluded from the study.

Patients were divided into two groups based on oxygen requirement during hospitalization to determine the correlation of initial disease severity with long-term lung functions post-recovery. All patients provided written informed consent before enrolment. Institutional Ethics approval (Ref No-AIIMS/IEC/2021/3376) was obtained prior to the start of the study. Eligible patients underwent baseline laboratory investigations, including complete hemogram, liver function, renal function, D-dimer, coagulation parameters, anti-nuclear antigen (ANA), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK MB), spirometry and CT thorax. All PFT measurements were performed in the pulmonary function room, Department of Pulmonary Medicine, according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.[10,11] A qualified pulmonary function technologist ensured the correct performance of PFT measurements. The following parameters were measured: Forced Vital Capacity (FVC), Forced Expiratory Volume in the First Second (FEV1), FEV1/FVC, Forced Expiratory Flows at 25 and 75% of FVC (FEF25%-75%) and Peak Expiratory Flow (PEF). The severity of acute COVID-19 was defined as mild, moderate or severe as per the national guidelines for COVID-19.[12] The patients were categorized into mild, moderate and severe disease based on oxygen saturation (SpO2, ≥94%, 90% to 93% and <90%, respectively).

Statistical analysis

Continuous variables were described using mean with standard deviation (SD) or median with interquartile range (IQR). Group comparisons were made using an unpaired *t*-test for mean and Mann–Whitney test for median values. ANOVA test was performed to compare the mean between three or more groups. The Chi-square test was used to compare the categorical variables. Pearson's correlation was used to test any association between variables. Independent predictors for impaired pulmonary functions were investigated using logistic regression analysis. *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Version 20.0.

Results

Baseline characteristics

A total of 200 patients were screened in the post-COVID-19 clinic, and 52 patients were enrolled in this study following 3–6 months of acute COVID-19. The median age was 40 years, and most of the patients were male (78.8%). The median time from COVID-19 positivity to OPD follow-up visit was 49 days. Most patients belonged to the 25–45 years' age group, followed by 46–65 years [Table 1].

The mean age of patients with mild and moderate-severe COVID was 37 years (SD 14.84) and 49.5 years (SD 14.05), respectively. Most patients had mild COVID-19 at admission (44.2%), Table 1. Half of the study population required oxygen support during admission [Table 1]. All patients in the oxygenated group received steroids (dexamethasone) for seven days as per the institutional protocol. During the post-COVID-19 follow-up, fatigue was the most common symptom, followed by vague chest pain and dry cough [Table 1]. The laboratory and inflammatory markers are given in Table 2. 14% of the patients had raised inflammatory markers (ferritin, LDH and D-dimer) during a follow-up visit to the COVID-19 clinic.

Pulmonary function test characteristics

PFTs were performed in 52 participants at 3–6-month follow-up. Table 3 depicts the different PFT values in

Table 1: Demographical profile of study population (*n*=52)

Variable	*n*=52, (%)
Gender	
Female	11 (21.2)
Male	41 (78.8%)
Age, Median (IQR)	43 (31–58)
<25 years	4 (7.7%)
25–45 years	27 (51.9)
46–65 years	16 (30.8)
>65 years	5 (9.6)
Disease severity	
Asymptomatic	3 (5.8)
Mild	23 (44.2)
Moderate	14 (26.9)
Severe	12 (23.1)
Oxygen requirement during hospitalization	
Yes	26 (50)
No	26 (50)
Symptoms	
Cough	12 (23.1)
SOB	5 (9.6)
Fatigue	21 (40.4)
Chest pain	14 (26.9)

Table 2: Laboratory parameters at 3–6 months visit post-COVID-19 recovery (*n*=52)

Variables (Mean)	At 3–6 months
Haemoglobin (gm/dl)	13.50±1.78
Total leukocyte counts (10^3/μL)	7.09±2.44
Platelets (10^3/μL)	298.84±87.98
Alanine aminotransferase (IU/L)	25.3±11.4
Aspartate transaminase (IU/L)	25.9±14
Bilirubin (mg/dL)	0.54±0.24
Albumin (gm/dL)	4.41±0.33
Creatinine (mg/dL)	0.83±0.13
INR	0.94±0.06
APTT (seconds)	22.2±6.7
D-dimer (μg/ml), Median (IQR)	0.27 (0.06–1.48)
LDH (IU/L), Median (IQR)	200 (128–285)
Ferritin (ng/ml), Median (IQR)	84 (4.25–176.4)
CK-MB (IU/L), Median (IQR)	12 (7–29)
NT-proBNP (pg/ml), Median (IQR)	88.5 (35–162)

INR=International normalized ratio, APTT=Activated partial thromboplastin time, LDH=Lactate dehydrogenase

post-COVID-19 patients. Of 52 participants, 13.5% had abnormal FEV1, 23.1% had abnormal FVC and 28.8% had abnormal PEF [Figure 1]. In this study, 75.5% of participants had normal spirometry patterns, while a restrictive pattern was present in 20.8% and an obstructive pattern in 1.9% of participants. We also assessed the PFT in different age groups, which is depicted in Table 4. In post-COVID-19 period, FEV1 showed a decreasing trend as age increased and was significant (P = 0.019). FVC also showed a significant decreasing trend with an increase in age (P = 0.028). FEV and FVC were found to be lowest in the age group 56–65 years. PEF and FEF 25–75% also showed decreasing trend but with no significance (P = 0.351, P = 0.158, respectively).

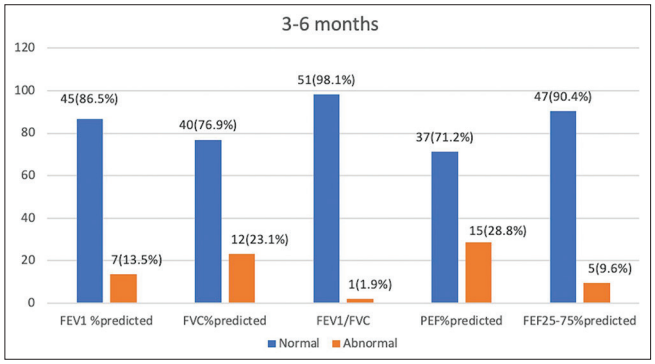

Figure 1: Spirometry abnormalities in post-COVID-19 patients at 3–6 months follow-up (N = 52)

Pulmonary function test and COVID-19 severity

COVID-19 disease severity is divided into asymptomatic, mild, moderate and severe based on ICMR guidelines. At a 3–6 months follow-up, there was a trend in decline in FEV1 and FVC with an increase in disease severity. However, it was insignificant when adjusted for age and other confounding factors [Table 5]. We also compared the different PFT parameters in post-COVID-19 patients depending on the oxygen requirement on admission. There was a significant difference in FEV1 (P = 0.002), FVC (P = 0.003), PEF (P = 0.013) and FEF 25–75% (P = 0.006) between the two groups at 3–6 months follow-up. This trend of PFT was also maintained after adjusting for age and other confounding factors [Table 6]. No correlation between PFT and inflammatory markers (ferritin, LDH and d-dimer) was noted in the post-recovery phase of COVID-19.

Out of 52, HRCT thorax was done in 21 patients. 33% of patients had normal CT thorax findings, and 66.7% had abnormal findings. Among CT thorax abnormalities, ground glass opacity was the most common finding (54%). Fibrosis (16%) and reticular opacities (10%) were the other abnormalities in the CT thorax. The correlation of HRCT abnormalities with age and other inflammatory markers was assessed using the Pearson correlation coefficient. We found a positive correlation between age and HRCT abnormality (correlation coefficient = 0.522, P = 0.015). Similarly, there was a positive correlation between LDH and HRCT abnormality (correlation coefficient = 0.515, P = 0.024. Univariable linear regression analysis was done to study the association between age and HRCT abnormalities and LDH and HRCT abnormalities. We found age >50 years (Odds ratio = 2.3; 95% CI = 0.15-0.92; P = .009) as an independent predictor of the subsequent development of abnormalities on HRCT thorax after 3–6 months follow-up.

Discussion

Long COVID (post-acute sequelae of COVID-19) is a persistent and debilitating condition which can have >200 symptoms with multiorgan impact.[13] More than 65 million patients still perceive these symptoms, with an incidence of around 10%, which is gradually rising.[13] Respiratory symptoms are one of the common

presentations of long COVID. Shortness of breath and persistent dry cough are the common symptoms in the post-COVID-19 period (40% and 20%).[14] However, there is a great heterogenicity in long COVID presentation, which remains a challenge for primary care physicians.[15] Many times there is an overlap in symptoms, some patients present with asthenia, extreme fatigue and breathlessness despite normal lung function. There is also a lack of correlation between the severity of COVID-19 symptoms and long COVID manifestation,[16] which makes the overall management challenging for primary care clinicians. We aim to assess the persistent respiratory symptoms by performing PFTs and radio imaging in 3–6 months after recovery from COVID-19. This study revealed abnormalities in nearly one-fourth of the study population with a restrictive pattern. The basis of residual deficit in lung functions was derived from previous studies conducted in patients who recovered from severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[17,18] These patients had significantly lower FVC and total lung capacity at six months of recovery.[17]

Table 3: Pulmonary function test values at follow-up visit of COVID-19 patients

Parameter	Mean±SD At 3–6 months (*n*=52)
FEV1 pre	2.76±0.72
FEV1 post	2.90±0.74
FEV1% predicted pre	92±15.22
FEV1% predicted post	93±29
FVC pre	3.26±0.87
FVC post	3.35±0.86
FVC % predicted pre	85.08±15.26
FVC % predicted post	89±27
FEV1/FVC pre	84.76±4.46
FEV1/FVC post	86.45±8
PEF pre	6.79±2.16
PEF post	88.33±19.75
PEF % predicted pre	81.22±20.35
PEF % predicted post	88.33±19.75
FEF 25–75% pre	3.30±0.98
FEF 25–75% post	3.66±1.06
FEF 25–75% predicted pre	76±26
FEF 25–75% predicted post	90.27±24.20

FEV1=Forced expiratory volume in the first second, FVC=Forced expiratory volume, PEF=Peak expiratory flow, FEF=forced mid-expiratory flow

There are reports on the aftermath of COVID-19 during short-term follow-ups with conflicting evidence regarding the state of pulmonary functions. After an average follow-up of 3–6 months after COVID-19, our cohort reveals that in patients without prior chronic lung diseases, COVID-19 had a definite impact on lung functions, especially in patients who recovered from moderate to severe COVID-19. The restrictive pattern (21%) in this study was less compared to previous studies (up to 50%).[19] This could be explained by reasons. Firstly, our study included all spectrums of COVID-19 patients, including mild and moderate-severe cases. Secondly, lung volumes and diffusion capacity of the lungs for carbon monoxide (DLCO) were not performed in our study. DLCO is a sensitive marker for poor residual lung functions in post-COVID-19, with some of the studies showing a significant reduction in DLCO.[20-22] In a meta-analysis by Castro *et al.*,[21] the prevalence of low DLCO was significantly high (39%) compared to restrictive (15%) and obstructive patterns (7%) in post-COVID-19 recovery. Guler *et al.*[20] discussed the role of DLCO %-predicted as an independent factor associated with previous severe COVID-19.

Table 4: Pulmonary function test values at 3–6 months follow-up among different age categories (*n*=52)

	<25 years	26–35 years	36–45 years	46–55 years	>55 years	*P*
FEV1 post	3.06±0.86	3.27±0.70	3.01±0.79	2.62±0.67	2.15±0.38	0.019
FVC post	3.44±0.93	3.78±0.80	3.57±0.98	3.03±0.81	2.56±0.43	0.028
FEV1/FVC post	90±4.6	86.1±4.5	83.8±3.6	88.2±5.1	86±9.3	0.282
PEF post	8.45±2.55	7.89±2.11	7.36±2.32	6.69±2.31	5.91±1.97	0.351
FEF 25–75% post	3.88±1.08	4.00±1.612	3.47±1.17	3.38±0.90	2.74±0.79	0.158

Table 5: Pulmonary function test values at 3–6 months follow-up in different COVID-19 severity categories (*n*=52)

	Asymptomatic	Mild	Moderate	Severe	Unadjusted *P**	Adjusted *P*
FEV1 post	3.51±0.83	3.21±0.71	2.62±0.61	2.51±0.72	0.02	0.34
FVC post	4.11±0.83	3.69±0.81	3.04±0.71	2.93±0.87	0.02	0.37
PEF post	9.80±1.68	8.04±1.96	5.93±1.75	7.58±2.25	0.19	0.37
FEF 25–75% post	3.86±1.32	4.09±1.14	3.13±0.74	3.38±0.92	0.05	0.12

Table 6: Pulmonary function test values at 3–6 months follow-up based on oxygen requirement (*n*=52)

	No oxygen requirement	Oxygen requirement	Unadjusted *P*	Adjusted *P*
FEV1	3.16±0.15	2.66±0.13	0.002	0.025
FVC	3.63±0.17	3.11±0.16	0.003	0.046
PEF	8.16±0.48	6.60±0.44	0.013	0.028
FEF 25%-75%	4.20±0.23	3.25±0.21	0.006	0.007

In contrast to the data, as mentioned earlier, a study by Lewis *et al.*[23] described no changes in PFT 3–4 months post-COVID-19 recovery. This result could be interpreted with caution as most of the study population had mild disease and did not require hospitalization or oxygen support. The role of acute inflammatory markers in predicting pulmonary function is already debated in acute COVID-19.[24] Similarly, we do not find any association between inflammatory markers (e.g., LDH, D-dimer and ferritin on admission) and prediction of PFT in the recovery phase. However, previous reports describe the role of TNF-α, interleukin (IL-2R, IL-8) and blood urea nitrogen in predicting abnormal PFT findings.[25,26] Santus *et al.*[27] reported a strong association between D-dimer and DLCO during the follow-up period. Results should be interpreted cautiously owing to different study population characteristics and follow-up time. Increasing age was the independent risk factor for poor lung functions in our report. Previous reports again failed to reach a consensus regarding this.[19,23] with some studies describing no effect of age in predicting the PFT in post-COVID-19.[19]

This study has a number of limitations. This study population did not have the baseline PFT. So comparison could not be made from baseline lung functions, which leads to the question of how much of the decline in PFT is attributable to COVID-19. However, we have tried to exclude the patient with evidence of chronic lung diseases that may impair lung functions. As reported by previous studies, the DLCO was not analysed in this study, which is considered one of the most sensitive indicators of post-COVID-19 lung fibrosis. The follow-up period is also relatively short; the more considerable period would have been helpful to delineate the course of residual lung disease and the overall time taken to recover from COVID-19. Finally, the number of patients in this study was relatively small, which can limit the inference in the general population.

Conclusions

The residual pulmonary function abnormalities are common in the COVID-19 recovery phase, even in mildly symptomatic patients. The severity of COVID-19 can predict persistent pulmonary function abnormalities months later. Long-term follow-up after COVID-19 recovery is essential for identifying and treating residual respiratory sequelae.

Authors' contributions

Author NK, DSM, DK and MKG conceived the study; NK, DK and GKB, MB, ND, MKG and SM designed the study protocol; DSM, NK, DK, GKB, RG and GKB drafted the manuscript; DSM, MKG, DK, MB, GKB and SM critically revised the manuscript for critical content. All authors read and approved the final manuscript.

Ethical standards

This work was approved by the Institutional Ethical Committee (AIIMS, Jodhpur, reference no- AIIMS/IEC/2021/3376).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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