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Spectrum of Post-Covid-19 Syndrome – Post-Hospitalisation Covid-19 Study

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Abstract

Backgrounds: Covid-19 pandemic has affected large population across the globe. As the cases around the world rise, Covid-19 related complications are also reported from various areas of the world. Pulmonary complications are mostly reported all over the world. In this review, we emphasized the pulmonary functions in Covid-19 survivors.

Objectives: To determine the impact of Covid-19 on pulmonary functions and analysis of possible lung damage in long-term after covid recovery.

Methods: Study includes lab-confirmed RT-PCR positive, both discharged and home-isolated from Tertiary Care Centre New Medical College and attached Hospitals, Kota. All subjects were to undergo 6-min. walk test (6MWT) and included only those patients for Pulmonary Function Test who could perform 6MWT.

Results: 109 men and 57 women with age range, 21 to 77 years from the 166 subjects. Among these, 71 (42.77%) were discharged from hospitals and 95 (57.23%) were home-isolated. The predicted FVC% was 92.83 ± 12.42, predicted FEV1% 89.94 ± 12.71 and FEV1/FVC% predicted was 98.30 ± 14.13. 6MWT walked distance was 540.50 ± 2.40. 69 subjects (41.57%) faced fatigue during 6MWT. FEV value was significantly($p < 0.05$) higher for hospitalised patients compared to home-isolated patients. The mean FVC value was higher for home-isolated patients compared to hospitalised patients ($p < 0.05$). 23% of study subjects showed restrictive and 7.2% had obstructive pattern while 70.5% had normal PFT.

Conclusion: Covid-19 patients showed compromised respiratory functions, mainly restriction in close to 23% and obstruction in 7% of patients. PFTs explain the possible lung damage by Covid-19.

Keywords: Covid-19, pulmonary function test, 6-minute walk test (6MWT).

Introduction

People across the globe are facing the second wave of the pandemic declared by the World Health Organisation on 11 March 2020, as coronavirus disease 2019 (Covid-19)[1]. Approximately 105.4 million cases have been reported with around 2 million deaths worldwide[2]. India has faced 20.4 million cases overall with 2.62 lac deaths till now[3]. The rate of admission in hospitals due to COVID infection is around 20% which includes 6% in critical care units[4].

Cough, fever, fatigue are the most common presenting symptoms, but body aches, dyspnoea, nausea, vomiting, diarrhoea, headache were also observed in certain subsets – especially in the second wave of the pandemic. Involvement of lungs is in the form of bilateral diffuse lung lesions identified as Covid-19 pneumonia with consequent respiratory failure or acute respiratory distress syndrome (ARDS)[5].

Early studies of Covid-19 suggest that lungs are the organs that are most damaged by Covid-19 in the form of pulmonary consolidation, hyaline membrane formation, alveolar septal fibrous proliferation, and capillary damage. These changes in the lungs result in alveolar remodelling which leads to lung fibrosis and pulmonary hypertension[6].

These findings suggest that direct colonisation, as well as indirect involvement of lungs by Covid-19, may have long-term or permanent effects and this makes it necessary to objectively assess the magnitude and severity of long-term lung injury and its impact on the quality of life of recovered covid cases including those discharged after hospitalisation and those treated in home-isolation.

Methods

We conducted a cross-sectional observational study to assess the long-term impact of Covid on lung functions and capacity in patients. This study was approved by the institutional ethics committee of New Medical College and

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Our case series includes a total of 166 patients, both discharged and home-isolated from a tertiary care center – New Medical College and attached Hospitals, Kota, between September 1st, 2020, to February 10th, 2021. Contact information of subjects was obtained from the central registry. Subjects were contacted telephonically and those who showed willingness and consented to participate were invited to post-covid OPD. They were screened and those who fulfilled the inclusion criteria were included in the study. Written informed consent from the subjects was obtained.

Inclusion criteria were a lab-confirmed RT-PCR positive report from nasopharyngeal swab according to CDC criteria, age between 18 years to 70 years, history of hospitalisation or treatment in home-isolation 2 months ago or more.

Patients with any gross chest deformity, prior respiratory, cardiac, mental, or neurological illness, BMI > 28 kg/m^2, current or past smoking were excluded from the study.

All participants were subjected to a standard respiratory disease questionnaire administered by a single interviewer. Leading questions were avoided, and the response was recorded objectively.

All study subjects were to undergo 6-minute walk test (6MWT) which was done following the ATS guideline. We included only those patients for PFT who could perform 6MWT with moderate severity according to the modified Borg Dyspnoea Scale.

6-minute walk test

A classic 6-minute walk test (6MWT) as described in the American Thoracic Society statement was used to assess the one-time functional status of the patient. The principle of the 6-minute walk test in Covid-19 is to identify patients who are not hypoxic at rest but become hypoxic (silent hypoxia) on a 6-minute walk test. The 6MWT provides evidence of hypoxia defined as SpO2 less than 94% or an absolute drop in SpO2 by more than 3% from baseline during or at the end of the test. The test was done in all patients who were not hypoxic or short of breath at rest. The test was stopped if the subject became hypoxic at rest SpO2 < 94%, developed shortness of breath at rest, and was not able to walk unassisted. Walk test interpretations were done following ATS guidelines. The patient's performance was evaluated in terms of four parameters, i.e., distance walked in 6 minutes, development of dyspnoea and fatigue, heart rate response, and fall in oxygen saturation.

We took 20 healthy controls of different age and sex groups for 6MWT to serve as a reference population.

Pulmonary function test

Pulmonary function tests were performed using MIR (Medical International Research) 'Portable Spirolab 3' spirometer. The subject's age, sex, and height were recorded and entered into the spirometer to obtain predicted curves and values. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were included in the analysis. For each subject, lower limit of normality (LLN) values for FEV1, FVC, and upper limit of normality (ULN) values for FEV1/FVC were taken after the subject's best effort. The test was administered by single medical personnel who ensured correct performance of forced expiration. If any subject was on bronchodilator therapy, that was withheld for 12 hours before PFT. Subjects were made comfortable and preferably had recently emptied their bladder before the performance as the procedure could cause urinary incontinence. Ideally, they are seated for the procedure to avoid the small risk of syncope.

All possible precautions were observed to minimise any cross-infection via the spirometer. We used low resistance barrier filters and disposable mouthpieces to reduce the risk of infection and to protect the equipment from exhaled secretions. A new filter was used for each patient. To protect laboratory staff and health professionals, lung function tests were performed in a room with a negative pressure setting. Staff wore personal protective equipment, including N95 respirators, protective glasses, gloves, and gowns.

Statistical methodology

Statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 22.0. Quantitative Continuous variables data were expressed as mean ± standard deviation whereas Quantitative discrete variables data were expressed as frequencies are expressed as numbers (%). The qualitative data were expressed in Medians with interquartile ranges. The Student's t-test and x2-test were used to compare the difference for means between two or more than two groups or to compare categorical variables, while continuous variables were compared using the Mann- Whitney U test. All statistical tests were two-tailed. Statistical significance was taken as $p < 0.05$.

Results

Enrolled Covid-19 patients

This study involved a total of 166 patients for the study sample. Patients having respiratory and coronary artery disease were excluded. Twenty normal subjects were taken for 6 MWT as controls. The mean duration was 2 months and more (3.9 ±

1.22 months) after successful treatment of Covid-19 in both groups. There were 109 men and 57 women with a mean age of 41.27 ± 14.08 years (age range, 21 to 77 years). Among the 166 subjects, 71 (42.77%) had a history of hospitalisation and were discharged from various wards or intensive care units of the dedicated Covid-19 centre of Medical College, Kota, and 95 (57.23%) had been treated in home-isolation. 39 (23.49%) patients had pre-existing illnesses. These included hypertension (3 patients), diabetes (15 patients), hypothyroidism (20 patients), CVA (1 patient).

The predicted FVC% was 92.83 ± 12.42, predicted FEV1% 89.94 ± 12.71 and FEV1/FVC% predicted was 98.30 ± 14.13. 6MWT walked distance was 540.50 ± 2.40. 69 subjects (41.57%) faced fatigue during 6MWT.

Table I: Baseline characteristics of Covid-19 patients.

Clinicopathologic factors		total (N=166)
Gender	Male	109 (88%)
	Female	57 (12%)
Age, yr.	Mean ± SD	41.27 ± 14.68
	Range	(21 - 77)
Hospitalised	Yes	71 (42.77%)
Home-isolation	Yes	95 (57.23%)
Duration after disease	Mean in months	3.9 ± 1.22
Co-morbidity	CVA	1 (0.6%)
	Hypothyroidism (HT)	20 (12.04%)
	T2DM	15 (9.04%)
	HTN	3 (1.8%)
	No	127 (76.50%)
FVC% predicted	Mean SD	92.83 ± 12.42
	Range	(66 - 122)
FEV1% predicted	Mean SD	89.94 ± 12.71
	Range	(60 - 139)
FEV1/FVC% predicted	Mean ± SD	98.30 ± 14.13
	Range	(55 - 122)
6MWD	Mean ± SD	540.50 ± 2.40
	Range	(450 - 600)
Fatigue	Yes	69 (41.57%)

Table II: Age wise distribution of Covid-19 patients.

Age	Case crequency (N = 166)	Percentage
< 20	0	0.0%
21 - 30	54	32.5%
31 - 40	42	25.3%
41 - 50	16	9.6%
51 - 60	33	19.9%
61 - 70	15	9%%
71 - 80	6	3.6%
Total	166	100.00%

The table indicates that a maximum (32.5%) of subjects are in the age group 21 - 30 years.

Pulmonary function test

The mean Forced Expiratory Volume (FEV) value is higher for hospitalised patients compared to home-isolated patients. The mean difference in FEV value was found statistically significant as the p-value is less than 0.05. The mean Forced Vital Capacity (FVC) value is higher for home-isolated patients compared to hospitalised patients. The mean difference in FVC value was found statistically significant as the p-value is less than 0.05.

The table shows a comparison between hospitalised and home-isolated patients PFT.

Table IIIA: Comparison between hospitalised and home-isolation patients.

Variable	Hospitalised 71 (42.77%)	Home-isolation 95 (57.23%)	t-Test value	Chi-square test/U test	p value
Age (Years)	46.87 ± 13.80	37.08 ± 13.97	3.545		< 0.0001
Sex, Male	48 (67.60%)	61 (64.21%)		0.2077	0.6485
Co-morbidity	22 (30.98%)	11 (11.57%)		9.6082	0.0019
FVC% predicted	88.46 ± 11.65	96.09 ± 12.02	4.098		0.0000
FEV1% predicted	97.53 ± 9.45	91.75 ± 14.47	2.13		0.0171
FEV1/FVC% predicted	100.4 ± 13.59	96.74 ± 14.39	1.646		0.1015

Table IIIB: Comparison between hospitalised and home-isolation patients.

Hospital duration among hospitalised subjects	Total subjects	Restrictive pattern in PFT	Obstructive pattern in PFT	Total (compro-mised lungs)	Chi-square Test	p value
< 5 days	15	3	1	4 (26.6%)	1.3471	0.245777
5 - 10 days	21	7	3	10 (47.6%)	31.0495	< 0.00001
> 10 days	35	16	5	21 (60%)	26.6338	< 0.00001
Home-isolated	95	11	3	14 (14.7%)		
Total	166	37	12	49 (29.51%)		

Table IV: Distribution of lung pathology in the subjects.

Severity remark	Case frequency (N = 166)			Percentage %
	Male	Female	Total	
Normal	75	42	117	70.5%
Restrictive	25	12	37	22.3%
Obstructive	9	3	12	7.2%

Pulmonary function tests of 23% of study subjects showed restrictive pattern whereas 7.2% of subjects had

obstructive pattern. 70.5% of subjects had normal pulmonary function tests.

Table VA: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N = 166)	Number of patient with restrictive lungs	Chi square value	P value
Male	109	25	0.077	0.781
Female	57	12		
Total	166	37		

Table VB: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N = 166)	Number of patient with obstructive lungs	Chi square value	P value
Male	109	9	0.5	0.479
Female	57	3		
Total	166	12		

Table VC: Sex-wise distribution of compromised lungs.

Gender	Case frequency (N=166)	Number of patient with compromised lungs (Restrictive + Obstructive)	Chi square value	P value
Male	109	34	0.428	0.512
Female	57	15		
Total	166	49		

Out of total 166 subjects, 49 subjects had compromised lung function parameters. 34 males and 15 females had compromised pulmonary function tests. Among affected males, 25 had restrictive and 9 had obstructive pattern whereas among affected females 12 females had restrictive and 3 females had an obstructive pattern in PFT.

Table VIA: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with restrictive lungs	T value	P value
21 - 30	54	5	22.756	0.0003
31 - 40	42	5		
41 - 50	16	4		
51 - 60	33	12		
61-70	15	8		
71 - 80	6	3		
Total	166	37		

Table VIB: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with obstructive lungs	T value	P value
21 - 30	54	0	32.922	0.000
31 - 40	42	1		
41 - 50	16	0		
51 - 60	33	4		
61 - 70	15	4		
71 - 80	6	3		
Total	166	12		

Table VIC: Age-wise distribution of lung function tests.

Age	Case frequency (N = 166)	Number of patient with compromised lungs (restrictive + obstructive)	T value	P value
21 - 30	54	5	53.9	0.000
31 - 40	42	6		
41 - 50	16	4		
51 - 60	33	16		
61 - 70	15	12		
71 - 80	6	6		
Total	166	49		

Subjects from all age groups had altered pulmonary function tests. However, those in the 51 to 60 years age group were the most affected showing both types of lung compromise. Younger age group subjects had a significant compromise. When further explored across various age categories this pattern of pulmonary compromise achieved statistical significance.

Table VII: Mean FVC% predicted in subjects.

Age	Case frequency (N = 166)	Mean FVC% predicted	F Value	P Value
21 - 30	54	96.16 ± 11.65	2.4710	0.034
31 - 40	42	94.83 ± 12.17		
41 - 50	16	89.12 ± 8.85		
51 - 60	33	98.42 ± 12.27		
61 - 70	15	87.46 ± 14.97		
71 - 80	6	90.83 ± 15.60		
Total	166			

There is a significant difference in the mean FVC% predicted value concerning different age groups.

Similarly, there was a significant decline in the mean FEV1% from predicted value across different age groups.

Table VIII: Mean FEV1% predicted in subjects.

Age	Case frequency (N=166)	Mean FEV1% predicted	F Value	P Value
21 - 30	54	96.51 ± 12.43	15.5883	0.0000
31 - 40	42	94.78 ± 10.90		
41 - 50	16	87.62 ± 4.52		
51 - 60	33	82.18 ± 8.44		
61 - 70	15	77.60 ± 10.32		
71 - 80	6	76.66 ± 12.50		
Total	166			

Table IX: Mean FEV1/FVC% predicted in subjects.

Age	Case frequency (N = 166)	Mean FEV1/FVC% predicted	F value	P value
21 - 30	54	101.350 ± 8.22	2.6684	0.024
31 - 40	42	100.97 ± 10.58		
41 - 50	16	98.68 ± 11.56		
51 - 60	33	94.06 ± 16.52		
61 - 70	15	92.26 ± 23.12		
71 - 80	6	88.00 ± 28.92		
Total	166			

Mean FEV/FVC as % of predicted value followed the same trend irrespective of age group.

6 Minute walk rest

Table X: 6MWT in subjects.

		Case n = 166	Reference n = 20
6MWD	Mean ± SD	540.50 ± 2.40	542.65 ± 42.19
	Range	(450 - 600)	(480 - 600)
SPO2%	Mean ± SD	97.51 ± 1.42	98.2 ± 0.83
	Range	(88 - 99)	(96 - 99)
Pulse rate	Mean ± SD	83.76 ± 9.0	83.2 ± 8.88
	Range	(67 - 100)	(67 - 98)
Fatigue	Yes	69 (41.57%)	2 (10%)

Table XI: Borg scale grading (up to moderate) for dyspnoea.

Grade of dyspnoea	Case frequency (N = 166)			Percentage %
	Male	Female	Total	
0	82	37	119	71.69%
1	12	10	22	13.25%
2	7	7	14	8.43%
3	8	3	11	6.63%

Table XII: Distribution of mean 6-minute walk distance predicted among subjects.

Age	Case frequency (N = 166)	Mean 6MWD predicted	F value	P value
21 - 30	54	543.70 ± 44.31	1.766	0.123
31 - 40	42	552.47 ± 42.85		
41 - 50	16	536.06 ± 36.45		
51 - 60	33	531.36 ± 35.48		
61 - 70	15	523.73 ± 27.91		
71 - 80	6	532 ± 41.26		
Total	166			

There is no significant difference in mean 6MWD value concerning different age group

Table XIII: Fatigue faced by subjects among various age groups.

Age	Case frequency (N = 166)	Number of subjects with fatigue	T value	P value
21 - 30	54	13	5.295	0.003
31 - 40	42	9		
41 - 50	16	8		
51 - 60	33	21		
61 - 70	15	12		
71 - 80	6	6		
Total	166	69		

A significant number of subjects in different age categories faced fatigue.

Further subgroup analysis revealed that the degree of initial clinical insult reflected in terms of length of hospital stay, the requirement of oxygen therapy, and the need for mechanical ventilation showed a positive correlation with findings of pulmonary spirometry. Among this duration of hospital stay could be subjected to statistical analysis as the size of the sample proved small for other subgroup analyses. Duration of hospital stay had a linear correlation with the long-term impact of Covid on lung volume and capacities.

Discussion

This can be very well concluded from the study observations that Covid-19 does have a long-term impact on the lungs, which is reflected by changes in pulmonary function tests in the form of both restrictive and obstructive patterns. Importantly these changes persisted even after 4 months of a hospital or domiciliary treatment in home-isolation. Previous studies suggest that pulmonary functions improved after 6 weeks, but some degree of restrictive

and obstructive alterations persisted even after 4 months. In our study, 37 (22.3%) patients had restrictive and 12 (7.2%) patients had an obstructive pattern in the pulmonary function test.

Even among patients who survived severe influenza A (H1N1) pneumonia, pulmonary function tests were found to improve significantly after 3 months but further significant improvement was not seen from 3 to 6 months after discharge[8] and some of them faced permanently altered pulmonary function[9].

Various degrees of destruction in alveolar structure and pulmonary interstitial fibrosis were observed in autopsies of Covid-19 patients[10]. These findings, confirmed by CT[11] further boost the desire to know the long-term deleterious effect in Covid-19 patients. Because restrictive and obstructive spirometry patterns after lung disease have been found to be associated with an increased risk of life-threatening comorbidities[7].

Starting of lung injury by acute inflammation finally terminates into a cascade process for recovery by the host's immune system[12]. This cascade can result in full recovery or can lead to fibrosis of the affected area of the lung. This recovery is by native stem cells and connective tissue deposition at the damaged site[14]. For this process, Alveolar macrophages play an important role by phagocytising alveolar debris and release of cytokines and growth factors[15]. Angiogenesis, fibroblast activation, and collagen deposition come into role[16]. Alveolar exudates are followed by the fibroblastic invasion of the alveoli and its transformation into myofibroblasts results in the deposition of fibroblastic extracellular matrix (ECM)[16]. Epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) enhances stem cells for the replacement of damaged alveolar epithelium[17]. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) boost pulmonary capillary angiogenesis[18]. If the basement membranes are intact, this process results in full recovery[13,19]. If there is continuous damage or greater impact of the pathogen on the lungs, it can lead to damage to the basement membranes, in such case fibroblastic activity will persist, and this will convert into a fixed and/or progressive fibroblastic tissue[13,20]. The resulting scar tissue distorts alveolar architecture[21]. Deposition of the extracellular matrix is a part of the pathway leading to lung fibrosis. This leads to interlobular septal thickening and traction bronchiectasis[22].

The linear correlation observed between the severity of initial Covid infection and subsequent long-term sequelae of compromised lung functions can be very well explained by the magnitude of the initial inflammatory response. Clinical severity usually parallels the inflammatory response generated. The inflammatory response can be roughly gauged in terms of cytokine levels. However, the observation that subgroups requiring hospitalisation, having a longer duration of hospital stay, and requiring oxygen and assisted ventilation demonstrated deranged late pulmonary function test results.

In Covid-19 infection, chemokines as IL-8 bring more leukocytes to damaged areas of lungs[23] which damage alveolar-capillary with chemical mediators such as histamine, bradykinin, and leukotrienes, and increase endothelial permeability. This results in leakage of fluid into the interstitium and alveolar spaces[12]. Fluid, fibrin, and cellular debris-filled alveolar spaces all lead to respiratory distress. These exudates in the airway, alveolar collapse, and interstitial oedema show as ground-glass opacity, consolidation, and septal thickening in chest imaging[21].

Inflammatory marker CRP, cytokine factor IL-6, and generated series of immune responses by these markers in Covid-19 are found similar to the immunopathogenesis observed in SARS[24]. This is responsible for fibrosis of lung parenchyma during recovery. High inflammatory indicators, interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal bands, are contributory factors in the process of developing lung pathology[25].

In hospitalised patients, ventilator-induced lung injury and oxygen toxicity both are important causes for the generation of fibrosis in severe Covid-19 pneumonia. Because patients with extensive lung involvement due to pneumonia need more oxygen for a prolonged time. Due to this prolonged delivery of oxygen, there is excessive production of oxygen-derived free radicals. These radicals damage the epithelium of the lungs[26]. Patients who are very sick due to acute respiratory distress syndrome (ARDS) due to Covid-19 pneumonia need prolonged mechanical ventilation. High plateau pressures by these ventilators, are also a contributory factor for the generation of lung fibrosis[27].

Thus Covid-19 infection has shown a significant long-term impact on lung volumes and capacities. This very fact highlights the importance of understanding the gravity of Covid-19 infection both for an individual and for the community at large, and emphasizes the importance of following all possible precautionary measures to cut down transmission of the virus. This fact also compels the treating physicians to adopt a more cautious and aggressive approach in handling Covid cases as timing and appropriateness of the therapeutic intervention would not only decide the immediate outcome but also has the potential to limit the long-term morbidity.

Limitations in this study were a small sample size which was stratified and analysed. That was reduced due to the inability of some subjects to perform 6MWT because of the Covid-19 sequelae. Only subjects with up to moderate

severity on the Borg scale were included. Further, a reservation on part of some patients about visiting the hospital and sharing the equipment set also restricted the number of participants. Secondly, we did not perform a follow-up study on subjects. One more limitation was that pre-Covid-19 PFT was not available for these patients, although we had already excluded those patients whose previous illness might confound results.

Conclusion

Post-infection Covid-19 patients showed compromised respiratory function. The most important of the PFT changes was the restriction in close to 23% and obstruction in 7% of patients. The conclusion of PFTs must be analysed carefully and considering the possible damage by Covid-19, further studies in post-Covid-19 infection patients, quantitatively assessing the relation of infection severity and pulmonary function are needed.

Study in the future should be focused on the short and long-term lung damage and sequelae of Covid-19 for the decision-making in the management of this pandemic and better clinical practices. Early aggressive therapy for the acute phase should be started to halt the disease process with suitable antivirals, immunomodulators, immunosuppressants, and plasma therapy so that the process of fibrosis can be prevented or minimised right from the beginning of the disease. After the acute phase is over, management strategies should focus on sequential spirometry. This sequential spirometry should be done every 4 weekly so that early intervention can be initiated in the form of antifibrotic, antioxidant, anti-inflammatory, and tyrosine kinase inhibitor agents, to overcome the symptoms and to attain long-term survival benefits.

Patients should be educated before discharge about the consequences of Covid-19 and the adverse effects of environmental factors such as air pollution and smoking, as these can reduce the efficacy of pulmonary functions. The data collected in this analysis could be useful for further studies.

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