DOI: 10.7860/JCDR/2021/48871.15129

Original Article

Internal Medicine Section

Clinical and Radiological Outcomes of Recovered COVID-19 Patients- An Observational Study during the Early Phase of Pandemic

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ABSTRACT

Introduction: The pandemic caused by the Coronavirus Disease 2019 (COVID-19) has caused huge economic and health crisis. It is reported to have pulmonary sequelae which can overburden the healthcare systems. Survivors needing medical attention in the form of pulmonary rehabilitation should be prioritised.

Aim: To study the impact of COVID-19 infection in terms of the pulmonary and extrapulmonary sequelae.

Materials and Methods: This cross-sectional observational study was carried out at a tertiary hospital in India. Recovered COVID-19 patients who were admitted from April to July 2020 were enrolled. Participants with radiological evidence of pneumonia during hospitalisation were assessed two months post-discharge. They were evaluated for persistent symptomatology, chest radiography, Six-Minute Walk Test (6MWT). The relationship between the outcome parameters with the baseline epidemiology, laboratory and radiology were evaluated by using student t-test, Mann-Whitney U test and multivariate logistic regression analysis.

Results: Thirty participants were recruited. Their mean age was 47.93 years. Males were more than females. Persistent symptoms were reported by 17 (56.66%) and 4 (13.33%) developed pulmonary fibrosis on Chest X-Ray (CXR). Prolonged hospitalisation (mean >20 days) strongly correlated to the fibrosis (p=0.022). A fall in the finger oxygen saturation after the 6MWT was significant (p≤0.001). Higher serum levels of lactate dehydrogenase and D-dimer were associated with a more severe disease (p=0.02 and p≤0.001, respectively).

Conclusion: Convalescent phase of COVID-19 is characterised by persistent symptomatology in half of the recovered patients. Simple and inexpensive CXRs and the 6MWT can be used as the primary investigation to identify post COVID-19 patients requiring pulmonary rehabilitation in resource limited settings.

Keywords: Coronavirus disease 2019, Peak expiratory flow rate, Pulmonary fibrosis, Six-minute walk test

INTRODUCTION

The first cluster of cases of the COVID-19 pandemic was reported on 31st December 2019 in Wuhan, China [1]. Researchers from China have shown that the S-protein of the novel coronavirus responsible for COVID-19 is partially homologous to the S-protein of Severe Acute Respiratory Syndrome (SARS) coronavirus [2]. A study from China has shown that pulmonary function defects and reduced exercise capacity occurred in SARS survivors [3]. There are a number of studies describing the clinical and radiological features in symptomatic COVID-19 patients [4-6]. However, there are very few studies related to the short-term outcomes [7,8]. Hence, it has remained a concern whether similar sequelae exist for COVID-19.

The COVID-19 lung disease can be identified on conventional CXR as well as chest Computed Tomography (CT). Formal cardiopulmonary exercise testing helps in identifying integrative responses of pulmonary, cardiovascular, neuropsychological, and skeletal muscle systems [9]. A 6MWT is a functional exercise test [10]. Systematic overviews have shown that when used as a functional walk test, it is the investigation of choice for clinical and research purposes. It reflects cardiopulmonary function that requires daily living activities than any other tests [11]. As per the guidelines by the American Thoracic Society, a practice test prior to performing it is not mandatory [12].

The authors assessed the epidemiological and clinical profile at the time of COVID-19 infection with the clinical and radiological outcomes at two-month post-discharge. The hospital at which the study was done became a designated COVID-19 centre on the 14th April 2020 in the collaboration with the Pune Municipal Corporation. At the time of submission of this article, the numbers of active and cumulative cases were maximum in the state of Maharashtra [13]. Additionally, COVID-19 cases in the rural and urban areas are equal in the state of Maharashtra [14].

Hence, the study was conducted to see the impact of COVID-19 infection in terms of the pulmonary and extrapulmonary sequelae. The findings will help the regional health authorities for policy making decisions. Additionally, it will help the doctors in the follow-up of these patients in rural areas where there is lack of advanced diagnostic tests.

MATERIALS AND METHODS

This cross-sectional observational study was carried out at a tertiary care hospital in Pune, Maharashtra, India. The duration of the study was seven months from may 2020 to november 2020. It was carried out in an 850 bedded tertiary care hospital in Pune, Maharashtra, India. The study began after the institutional Ethical Committee approval (Letter no. BVDUCMC/IEC/11).

Inclusion criteria: Patients >12-year-old with a positive nasopharyngeal Real Time-Polymerase Chain Reaction (RT-PCR) swab for COVID-19 from Government approved centres and atleast one abnormal CXR during their hospital stay were recruited.

Exclusion criteria: Patients who were not reachable telephonically even after three successive attempts.

Study Procedure

The medical records of discharged COVID-19 patients from 14th April to 14th July 2020 were reviewed from the medical records section. Various laboratory investigations like, complete haemogram, inflammatory markers e.g., Lactate Dehydrogenase (LDH), D-dimer, C-Reactive Proteins (CRP) were recorded. Out of these, 82 patients with abnormal CXRs were contacted telephonically after two months of their discharge. Amongst them, six were not reachable and 46 patients denied participation. Hence, total 30 cases were enrolled were enrolled and evaluated at the time of final follow-up.

On the day of the follow-up, the participants were asked simple questions regarding their current health status based on a pre-tested and validated questionnaire in the language best understood by them (Hindi or Marathi). They then underwent a complete clinical examination, CXR, standardised 6MWT and the Peak Expiratory Flow Rate (PEFR) estimation. Among these 30 patients, the 6MWT was not done for two as they were non-ambulatory due to Grade III bed sores and one was denied cardiac fitness due to a co-existent cardiac pacemaker. Therefore, for these three, only PEFR and CXR were done.

CXR protocols: The first abnormal CXR during hospitalisation was considered as baseline. CXRs of all patients were done at the follow-up visit. The on-duty radiologist compared the baseline and follow-up CXRs. To avoid interpersonal variation, they were reviewed by a senior radiologist with over 25 years of experience who was blinded to the study and the clinical data.

Standardised 6MWT protocol: Twenty-seven patients were evaluated by the 6MWT on follow-up visits by graduate doctors undergoing training in pulmonary medicine who were blinded to the clinical data.

PEFR protocol: PEFR were recorded with standardised and calibrated disposable peak flowmeters by the same blinded doctors before the 6MWT. Individual patient reading of PEFR was compared with their Indian reference values [15].

Data Collection

Medical records of the participants were identified. Their basic epidemiological, clinical, laboratory and radiological parameters were noted. As per the clinical management protocol: COVID-19 (version 5, 3rd July 2020) by the Government of India, patients were categorised as mild, moderate or severe disease [16].

The case definitions were as follows: Mild- laboratory confirmed cases without evidence of breathlessness or hypoxia; Moderate- laboratory confirmed cases with pneumonia but no signs of severe disease, i.e., with presence of clinical features of dyspnoea and or hypoxia, fever, cough, including SpO_2 of range: 90% to 94% on room air, respiratory rate more or equal to 24/minute; Severe- laboratory confirmed cases with clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% on room air.

STATISTICAL ANALYSIS

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) software version 25.0. The continuous variable results were shown by descriptive statistics and the categorical variables by frequency and percentages. Group comparisons were done using the Chi-square test for categorical variables like severity and outcome categories. The student t-test was used for continuous variables with normal distribution and the Mann-Whitney U test for continuous variables with abnormal distribution. Multivariate logistic regression was applied for analysis of different dependent laboratory parameters with respect to the independent outcome variables. The Spearman's rho correlation was used to find out the correlation between different continuous laboratory parameters and ordinal variables. Results were shown with 95% confidence. The p-value <0.05 was considered significant.

RESULTS

A total of 30 participants were recruited with a mean age of 47.93 (±10.09) years (minimum 31, maximum 71). Amongst these, 20 (66.66%) were males. Total 22 (73.33%) required oxygen support. Initial symptoms, diseases severity, underlying co-morbidites and need of oxygen delivery devices during hospitalisation were summarised in [Table/Fig-1].

Baseline Radiological and Laboratory Findings

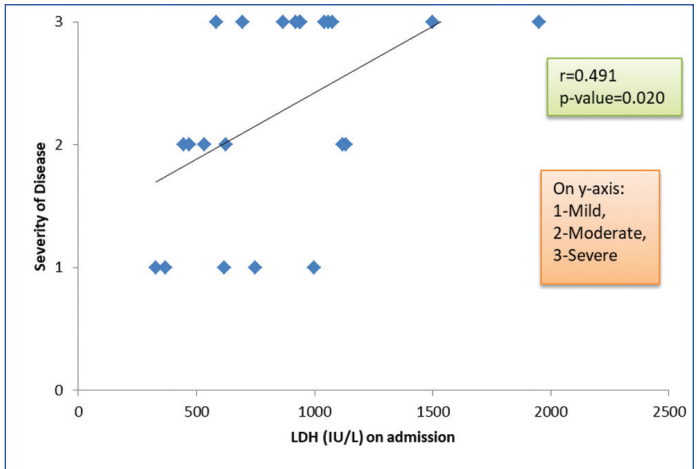
Peak findings on CXR during hospitalisation were noted. Baseline CXR characteristics were encapsulated in [Table/Fig-2]. LDH and D-dimer were done in 22 patients as per their disease severity. The mean of LDH was 861.82 (±383.23) IU/L and of D-dimer was 1420.18 (±2511.89) ng/mL. LDH and D-dimer levels had a positive correlation to the severity of disease [Table/Fig-3,4]. Abnormal value of CRP was not related to development of pulmonary fibrosis (p=0.9).

Patient characteristics during hospitalisation	Number of pateints (%)
Initial symptoms	
Fever	24 (80)
Dry cough	18 (60)
Dyspnoea	17 (56.66)
Weakness	6 (20)
Sore throat	4 (13.33)
Myalgia	4 (13.33)
Headache	2 (6.66)
Anosmia	1 (3.33)
Most frequent underlying co-morbidites	
Hypertension	10 (33.33)
Diabetes mellitus	6 (20)
Chronic respiratory disease	4 (13.33)
Disease severity	
Mild	9 (30)
Moderate	8 (26.66)
Severe	13 (43.33)
Oxygen delivery systems	
Hudson oxygen mask	10 (33.33)
Venturie	7 (23.33)
High flow nasal canula	2 (6.66)
Mechanical ventilation	3 (10)

[Table/Fig-1]: Patient characteristics during hospitalisation.

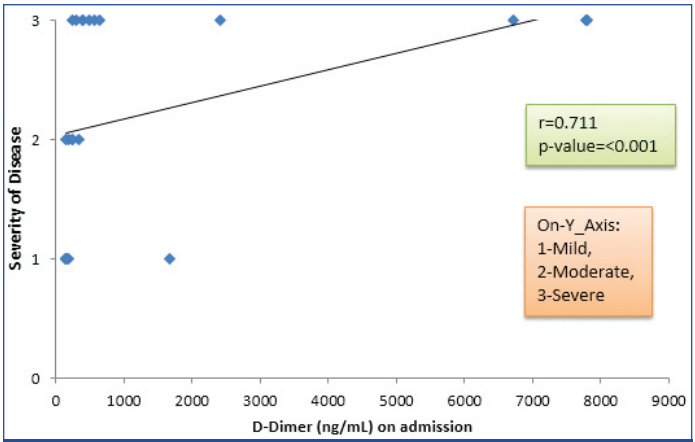
Baseline X-ray characteristics	Number of patients (%)
Consolidation	29 (96.66)
Pulmonary nodule	1 (3.33)
Pleural effusion	4 (13.33)
Bilateral lung involvement	24 (80)
Distribution of radiological finding	
Peripheral	18 (60)
Peripheral+Central	8 (26.66)
Central	4 (13.33)

[Table/Fig-2]: Baseline chest radiograph characteristics.



[Table/Fig-3]: Correlation of the disease severity to LDH on admission.
LDH: Lactate dehydrogenase

Clinical and radiological outcome on follow-up: On the follow-up visit, 17 (56.66%) volunteers were suffering from persistent symptom. The most common persistent symptom was dyspnoea on exertion which was present in 8 (26.66%) participants followed by dry cough (16.66%)



[Table/Fig-4]: Correlation of the disease severity to D-dimer on admission.

and generalised weakness (13.33%). Pulmonary fibrosis on CXR was present in 4 (13.33%) in the form of reticulonodular opacities. Amongst the 17 symptomatic volunteers, pulmonary fibrosis was present in three. Additionally, one asymptomatic volunteer also had similar findings. There was no correlation between the symptoms on follow-up and pulmonary fibrosis development. There was no association seen in persistence symptomatology and the epidemiological, haematological and biochemical parameters. In comparison with the volunteers with normal CXRs on follow-up, patients with pulmonary fibrosis had required a longer duration of hospitalisation (p=0.022) as shown in [Table/Fig-5].

Variables	Normal range	CXR, Mean (SD)		
		Fibrosis (n=4)	No fibrosis (n=26)	p-value
Age (Years)	-	54.25 (12.04)	46.96 (9.56)	0.31
Total leukocyte count (/mm^3)	4000-10,000	5950.00 (1823.00)	6323.08 (2965.71)	0.74
Neutrophils (%)	40-80	72.50 (7.33)	69.19 (10.42)	0.46
Lymphocyte (%)	20-40	17.25 (5.06)	22.04 (9.02)	0.168
Platelet (/mm^3)	1,50,000-4,50,000	189000.00 (191.165.94)	211038.47 (73280.00)	2.17
BMI (Kg/m^2)	-	24.22 (4.58)	27.39 (3.88)	0.076
Duration of hospitalisation (days)	-	20.50 (10.50)	13.54 (4.35)	**0.022**
N:L	1-3	4.05	3.24	0.3
C-Reactive protein (mg/L)	Up to 6	67.98	63.37	0.9

[Table/Fig-5]: Comparison of clinical and laboratory parameters in patients with and without pulmonary fibrosis.
Data are expressed as mean, SD and median; Student t-test was used for calcutating p-value for parameters: age, total leukocyte count, percentage of neutrophils and lymphocytes, platelet count, BMI and duration of hospitalisation and Mann-whitney U test; was used for calcution of p-value for parameters N:L and C-Reactive protein; BMI: Body mass index; N:L: Neutrophil: lymphocyte

Twenty-seven participants performed the 6MWT. Though there were no baseline values of the 6MWT available, there was a clinically significant drop in the SpO_2 before (98±1.71) and after (95.89±2.56) the test (p≤0.001). Six patients (22.22%) exhibited ≤95% fall in SpO_2 after the 6MWT. Amongst them, five had suffered from severe disease and one from moderate. This fall in SpO_2 was not related to the development of pulmonary fibrosis on CXR. Amongst the patients with normal CXR on follow-up, five showed a fall in SpO_2 post-test.

Amongst the 27 volunteers, only seven (25.92%) could perform the test satisfactorily. There was no correlation between the distance covered by the participants during the 6MWT and the symptomatology on follow-up. Amongst the patients with normal CXRs on follow-up, 17 had low results for the 6MWD than their expected lower limit. However, the difference in the distance walked by the participants with severe (348.2 m±149.77 m) and non-severe (383.35 m±83.79 m) disease groups was not found to be significant. The PEFR of 15 patients (50%) on follow-up was below the 10% of their expected value [Table/Fig-6].

Patient number	Oxygen saturation after 6MWT	6MWT distance expected for age and sex (Yes/No)	PEFR within 10% of normal range (Yes/No)
1	≥95%	No	Yes
2	≥95%	No	No
3	<95%	Yes	Yes
4	≥95%	No	Yes
5	≥95%	No	No
6	<95%	No	Yes
7	≥95%	No	No
8	Not done	Not done	Yes
9	≥95%	No	Yes
10	≥95%	No	No
11	≥95%	No	No
12	≥95%	No	Yes
13	≥95%	No	No
14	<95%	Yes	Yes
15	≥95%	No	Yes
16	≥95%	No	No
17	≥95%	Yes	Yes
18	≥95%	Yes	No
19	≥95%	No	Yes
20	≥95%	No	Yes
21	<95%	No	No
22	≥95%	No	No
23	Not done	Not done	No
24	<95%	No	No
25	≥95%	Yes	Yes
26	≥95%	No	No
27	≥95%	Yes	No
28	≥95%	Yes	Yes
29	Not done	Not done	No
30	<95%	No	Yes

[Table/Fig-6]: Interpretation of results of 6MWT and PEFT of individual patient.

DISCUSSION

The on-going COVID-19 pandemic has overburdened the healthcare system all over the globe. The recovery rate of COVID-19 in India as on 28th November 2020 is 93.68% [16]. It is reported that the survivors of SARS epidemic (2003) had decreased functional capacity on three and six-months follow-up evaluation [17]. Meo S et al., reported that the clinical manifestations of COVID-19, SARS and middle earth respiratory coronavirus are almost similar [18]. Therefore, it is necessary to follow these patients for their exercise capacity, radiological outcomes and pulmonary function. This is a single centre prospective observational study to know whether similar sequelae occur in COVID-19.

There are very few studies on COVID-19 survivors to look for pulmonary sequelae and exercise capacity [7,8]. In the study from Zhengzhou University, China, patients were evaluated for their Pulmonary Function Test (PFT) and the development of pulmonary fibrosis by CT scans [7]. In another study from Sun Yat-sen University, China, patients were followed with PFT, CT scans and 6MWT [8]. To the best of our knowledge, this is the first follow-up study from India assessing COVID-19 patients for their daily functional status and pulmonary sequelae.

In this study, it was observed that more than half of the participants suffered from at least one persistent symptom like dry cough, dyspnoea on exertion or fatigue. This finding is similar to a study from Italy where fatigue and dyspnoea were common persistent symptoms on follow-up after six weeks [19]. While Zhao Y et al.,

observed persistence of predominantly gastrointestinal symptoms on follow-up [7].

Due to infection control issues related to patient transport and CT room decontamination, portable CXRs were the baseline radiological investigation in our hospital during the active period of COVID-19 infection. Hence, to compare with the baseline CXRs, the authors evaluated the participants by X-rays. Though it is inferior to CT for diagnosing pulmonary fibrosis, in resource-limited situations, X-ray is the simplest and easily available investigation. All available research on follow-up studies has mainly focussed on CT scan abnormalities. This study is probably the first from India that has centred on X-ray findings of COVID-19 survivors on follow-up. It was observed that pulmonary fibrosis was present in four out of 30 participants after two months. Longer duration of hospitalisation (mean >20 days) is a risk factor for the pulmonary fibrosis development. Similarly, length of ICU stay was a risk factor in a study from Lombardy, Italy on 1300 patients [20]. Interestingly, a few participants with normal CXR also had a fall in SpO_2 after the 6MWT. There is also another study that has reported impaired lung function test results with normal CT imaging [8]. This may signify pathological processes other than fibrosis like microvascular changes in pulmonary circulation interfering with oxygenation. Autopsy findings of COVID-19 patients have vascular microthrombi in diffuse areas of alveolar damage which are associated with endothelial damage [21].

The 6MWT is useful to assess the cardiopulmonary function, muscle strength and nutritional status [12]. There is a decrease in the functional activity as authors observed that fall in SpO_2 after the 6MWT is significant. However, there was no significant drop in SpO_2 in the study from Germany on 33 patients [22]. For these controversial findings, more studies with larger sample size are needed. In the previous study from Sun Yat-sen University, there was a difference in the 6MWD in severe and non-severe disease groups [8]. Their finding was different from findings in this study. This difference might be due to the timing of follow-up and small sample size. Their study was done in the early convalescent phase in 57 patients while in this study 30 patients after 2 months were followed.

Patients who had a fall in SpO_2 after 6MWT and who were unable to walk the expected distance for their age, sex and BMI are candidates for further detailed assessments like PFT and cardiopulmonary stress tests.

Authors compared the values of individual PEFR with the Indian reference values [23]. The PEFR of 50% patients was below the expected values. Baseline values of individual PEFR were not available with us to compare. But this shows that some patients may develop pulmonary dysfunction. COVID-19 patients can develop restrictive, obstructive or combined pulmonary dysfunction [8]. Though PEFR do not differentiate types of pulmonary dysfunctions, it helps to identify those with abnormalities where detailed PFTs are not available.

Increased levels of serum LDH and D-dimer were associated with the severity of the disease which is consistent with previous studies [24-26]. There was no correlation between the increased D-dimer values during active infection and follow-up CXR abnormalities. This is unlike the findings from the study of Henan Province. This difference is due to the higher sensitivity of CT for diagnosing pulmonary fibrosis than CXR and their larger sample size [7].

Though the 6MWT is not ideal for testing exercise capacity, though it can be easily performed at an outpatient clinic without any sophisticated instruments by a clinician. As it is a subjective test, patients also get insight of their health status. In countries like India, where the healthcare system is already exhausted due to the on-going pandemic, such simple tests can specify individuals who require medical attention post discharge. Advanced imaging modalities like CTs are not available in the rural parts. Majority of the Indian population is from the rural areas, where CXR is cheap and easily available to identify pulmonary pathologies. In a study from Egypt, CXR has been a helpful modality on follow-up assessment [27]. The combined use of 6MWT and CXR will guide physicians while managing COVID-19 recovered patients in their follow-up visit. It was found that there were patients with normal CXR but their 6MWT result was unsatisfactory either in the terms of desaturation or unable to walk the expected distance. In such patients, pulmonary rehabilitation is needed subsequently even in the absence of pulmonary pathology on CXR. Therefore, it is important to follow all patients with COVID-19. This is because the asymptomatic ones might also have decreased functional capacity or pulmonary fibrosis. Such individuals may require further investigations and pulmonary rehabilitation.

Limitation(s)

First, the sample size was small. Secondly, there was missing data as LDH and D-dimer were done only in moderate and severe disease. Baseline values of these inflammatory markers were not available.

CONCLUSION(S)

This study demonstrated that persistent symptoms are experienced by COVID-19 patients even after 2 months. Even in the absence of persistent symptoms on follow-up, some patients were not able to maintain the SpO_2 after simple exercises like walking. The 6MWT and CXR can be easily and effectively used as a primary investigation for those who need pulmonary rehabilitation. This approach will short list the patients in need of detailed studies like pulmonary function and cardiopulmonary stress tests, decreasing the unnecessary workload on the healthcare.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 06, 2021
- Manual Googling: Apr 10, 2021
- iThenticate Software: May 26, 2021 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 05, 2021**
Date of Peer Review: **Mar 12, 2021**
Date of Acceptance: **May 11, 2021**
Date of Publishing: **Jul 01, 2021**