Study to Identify the Prevalence and Predictive Factors of Post COVID Lung Fibrosis in COVID-19

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: SARS CoV-2 has affected more than 494 millions of people all over across the globe till date. Most lethal infection of SARS-CoV-2 is highly representative of patients suffering with idiopathic pulmonary fibrosis (IPF) [1]. Interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal bands manifesting in the course of the disease might be predictors of pulmonary fibrosis in these patients [2].

Objectives and Methods: Objective of the study is to identify the prevalence and predictive factors of post covid lung fibrosis in covid-19 patients. The study was conducted in a retrospective manner and included 100 patients in our tertiary care center. HRCT thorax conducted in all patients were evaluated on admission, one month, 3 month and 6 months whereever indicated.

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Results: The prevalence of post covid lung fibrosis was 2 % at 6 months , with CT severity score more for elderly male population. In our study we found a significant corelation between clinical severity and post covid fibrosis.

Conclusion: From our study, the post COVID lung changes are reversible, with only 2 % developing the post covid lung fibrosis.

1. INTRODUCTION

SARS CoV-2 has affected more than 494 millions of people all over across the globe till date. Most lethal infection of SARS-CoV-2 is highly representative of patients suffering with idiopathic pulmonary fibrosis (IPF) [1]. Previous studies inferred that substantial proportion (about 25%) of patients who developed ARDS in the pre-COVID era, irrespective of aetiology, experienced residual and long-term impairment of their pulmonary function, with radiographic evidence of pulmonary fibrosis on computed tomography (CT). Interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal bands manifesting in the course of the disease might be predictors of pulmonary fibrosis in these patients [2]. A study by Chang et al. in patients with SARS showed that when a second CT scan was repeated 4–6 months after the initial scan in patients with these two viral pneumonias, the parenchymal bands,traction bronchiectasis, and even honeycombing had regressed in significant numbers [3].

The severity of the lung injury and the inflammatory response are known to correlate with the extent of fibroblastic response required to repair the injury [4]. Higher levels of inflammatory markers like CRP, IL-6, LDH etc. during illness might lead to the formation of fibrosis during recovery and were also found to significantly correlate with the risk of pulmonary fibrosis following other coronavirus infections like MERS-CoV infection [5,6] and SARS.

COVID - 19 is a disease caused by SARS CoV – 2, a virus of the coronavirus family. The strain originated in Wuhan, China in November of 2019 and spread across the globe causing the worst pandemic known to mankind and claiming 6,152,898 lives [7]. The transmission of the virus is from human-to-human via respiratory route but alternative routes have been suggested - zoonotic spread [8,9,10].

Symptoms of COVID – 19 show a great diversity, that range from a mild illness to respiratory failure and death [11,12]. Common symptoms are headache, loss of smell and taste, nasal congestion and runny nose, cough, muscle pain, sore throat, fever, diarrhoea and breathlessness [13]. People with the same infection may have different symptoms, and their symptoms may change over time. Three common clusters of symptoms have been identified: one respiratory symptom cluster with cough, sputum, shortness of breath, and fever; a musculoskeletal symptom cluster with muscle and joint pain, headache, and fatigue; a cluster of digestive symptoms with abdominal pain, vomiting, and diarrhoea [14] In people without prior ear, nose, and throat disorders, loss of taste, combined with loss of smell is associated with COVID-19 and is reported in as many as 88% of cases [15-17].

COVID – 19 is a systemic disease and has many sequelae. Of these, one is post-COVID lung fibrosis. Following an initial phase of lung injury causing acute inflammation, repair mechanisms can elicit the restoration of normal pulmonary architecture or they may lead to pulmonary fibrosis with architectural distortion and irreversible lung dysfunction. The nature of the inflammatory response may influence the resident tissue cells and the ensuing inflammatory cells, since the latter additionally exacerbate inflammation by secreting chemokines, cytokines, and growth factors [18]. Many cytokines are involved throughout the wound-healing response, with specific groups of genes activated in different conditions. Interleukin (IL)-4 (IL-4), IL-13, and transforming growth factor-beta (TGF-β) are cytokines that have received attention with regard to various pulmonary fibrotic conditions since each can exhibit pro-fibrotic activity by promoting the recruitment, activation and proliferation of fibroblasts, macrophages, and myofibroblasts [19]. Various biological and radiological markers have been postulated to predict the sequalae of COVID – 19. The biomarkers for acute phase of COVID-19 that predict fibrosis are – CRP, Lymphocyte count, LDH, IFN- gamma, MMP-9, sST2 [20,21,22,23]. Those of the follow-up

period are – TNF–alpha, IL-17A, IL-17D, VCAM-1, ICAM-1, PIGF, KL-6 [24,25,26].

Chest CT plays a vital role in the diagnosis and follow-up of patients with COVID-19 pneumonia. Xiaoyu Han et.al. in their study concluded that follow-up CT scans within 6 months of disease onset showed fibrotic-like changes in the lung in more than one-third of patients who survived severe COVID-19 pneumonia and also found that patients were older and had more severe disease during the acute phase [27]. MehrdadNabahati et.al. in their study revealed that patients with severe COVID-19 pneumonia, consolidation, older age, acute respiratory distress syndrome, longer hospital stays, tachycardia, non-invasive mechanical ventilation, and higher initial chest CT score in the initial chest CT scan, was associated with increased risk of post-COVID-19 lung fibrosis [28].

Determining the predictive factors for the post-COVID-19 lung fibrosis can possibly help in management of morbid complication through controlling of the risk factors and/or administrating the anti-fibrotic drugs in high-risk cases. In the current study, we aimed to prospectively assess the prevalence, clinical, radiological characteristics like lung fibrotic-like changesas well as to explore their predictive factors, in the patients who survived COVID-19 infection.

2. METHODOLOGY

Retrospective evaluation of 100 patientsRT- PCR positive for SARS CoV – 2, from the time period of April 2021 to June 2021 and collected their data on development of post-COVID fibrosis, and post-COVIDsequelae. The study has been conducted after ethics committee approval. The study centre is Ruby Hall Clinic, Pune, India.

2.1 Inclusion Criteria

a. Age between – 20-80 years
b. Male and Female patients.
c. RT-PCR positive disease
d. Rapid antigen positive disease

2.2 Exclusion Criteria

a. Pre-existing ILD
b. Pre-existing lung metastasis.
c. Age greater than 80 years
d. Pre-existing Interstitial Lung abnormalities

126 cases were initially taken for study, out of which 26 patients were excluded based on exclusion criteria.

3. METHODS

After taking approval from institutional ethical committee,HRCT thorax of all patients were done in MDCT scanner with 64 channels.The tube voltage used was 120 Kvp, low dose CT-scan of Thorax was taken, and slice thickness were 1.0 mm with a reconstruction interval of 1-3mm. CT images were taken in supine position with full inspiration without a contrast medium. The different CT patterns like ground glass opacities, reticulations, consolidation, cavitation, septal thickening, architectural distortion, traction bronchiectasis, honeycombing were evaluated.Honeycombing with or without traction bronchiectasis, presence of irregular thickening of interlobular septa irrespective of timeperiod are considered as features of lung fibrosis.Other parameters studied were - peripheral or central shadows, unilateral or bilateral distribution. The HRCT thorax were done initially at the time of admission, or when patients developed breathlessness and desaturation, at one month, 3 monthsand 6 months. All the above-mentioned patterns were evaluated on HRCT Thorax.

3.1 CT Severity Score

It is a score for degree of lung affection based on dividing the lung into five lung lobes; each lobe affection was visually scored on a scale of 0–5, with 0 indicating no involvement, 1 indicating less than 5% involvement, 2 indicating 5–25% involvement, 3 indicating 26–49% involvement, 4 indicating 50–75% involvement, and 5 indicating more than 75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) [29].

3.2 Clinical Severity [30]

- Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.
- Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

- Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.
- Severe Illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

4. RESULTS

The table shows that means age of males in study is 44.26 and females is 48. Females are more affected. The CT severity index was more in females. 20 patients required ICU admission, and 9 patients among them got discharged from ICU. The prevalence of post covid fibrosis at 3 and 6 months are 2% each.

Table 2: Table 2 shows the HRCT thorax features at admission, one month, 3 month and 6 month where GGO, consolidation, reticulations, septal thickening, traction bronchiectasis, honeycombing and cavity evaluated.

Table 1. Demographic result

Demographic data	
Mean age: Male	44.26 years
Female	48 years
GENDER Male	26 %
Female	74 %
CT severity index Male	5.46
Female	7.97
Need of ICU admission	20 %
Discharged from ICU	9 %
Prevalence of post COVID fibrosis 3 months	2%
6months	2%

**Table 2. HRCT features at admission, one month, 3 month, 6 months**

CT Features	Initial CT	1 Month	3 Months CT	6 Months CT
GGO	100	10	4	1
Consolidation	4	3	1	1
Reticulations	3	3	1	2
Septal thickening	3	6	2	2
Traction Bronchiectasis	0	2	2	2
Honey combing	0	0	2	2
Cavity	0	2	2	1

Table 3. Association of clinical severity and death

	Mean	SD	P value
Died	12.45	4.03	
Discharged	6.68	4.96	<0.001**

Table 4. Prevalence of post COVID lung fibrosis

	n	%
1 month	6	6
3 month	2	2
6 month	2	2
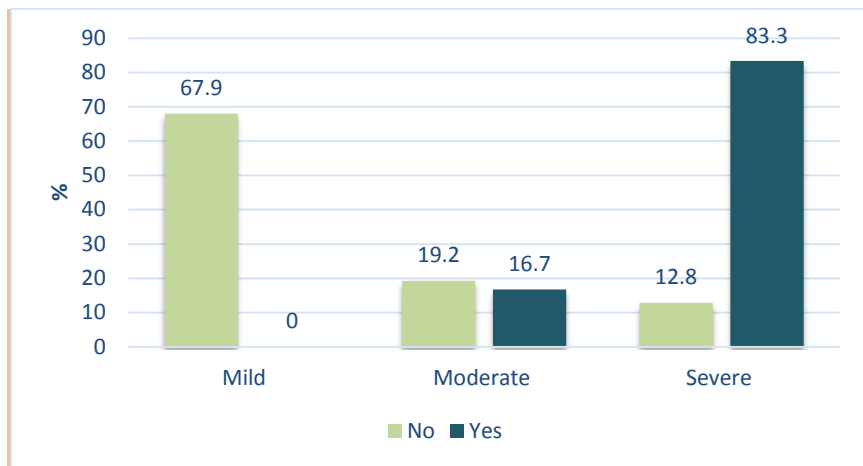
Graph 1. Association of clinical severity and fibrosis at one month

Table 5. Association of clinical severity and fibrosis at 3 month

3 month	No LF	LF	P value
Mild	53(68.8)	0	
Moderate	12(15.6)	2(100)	
Severe	12(15.6)	0	<0.001**

Table 6. Association of CT severity index and Post covid lung fibrosis at one month

1month	Mean	SD	P value
No	5.82	4.09	
Yes	15.83	5.67	<0.001**

Table 7. Association of CT severity index and Post covid lung fibrosis at 3 month

3 month	Mean	SD	P value
No	6.05	4.58	
Yes	11.0	9.89	<0.001**

Chart 1 : chart shows the significant association of CT severity index and post covid lung fibrosis at 3 months with a p value of < 0.001.

Chart 1. Association of CT severity index and Post covid lung fibrosis at 3 month

3 month	Mean	SD	P value
NO	6.05	4.58	<0.001
YES	11.0	9.89	

Fig. 1. The CT thorax of patient showing predominant ground glass opacities at the admision, predominant seotal thickening and reticulations at one month post covid, with septal thickening and traction bronchiectasis at 3 months post covid
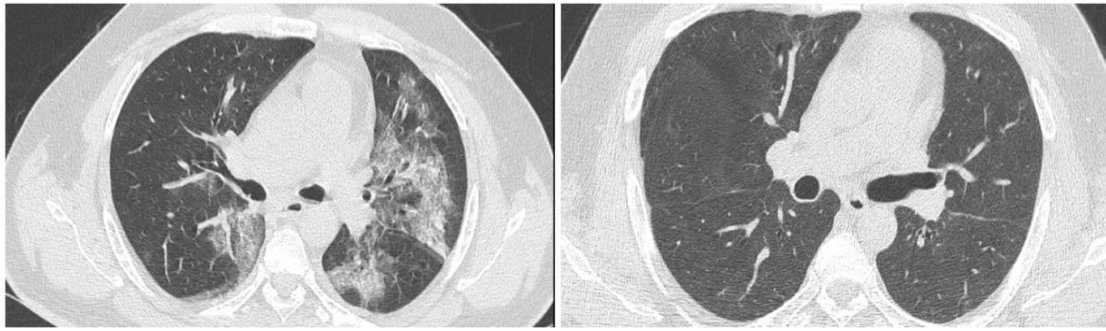
Fig. 2. The CT thorax of the patient showing predominant ground glass opacities at the admision, with total resolution at 3 months post covid

5. DISCUSSION

The mean age of the patients enrolled in our study is 44 (36 for females and 48.27 for males). There were 26 % females and 74% males in our study. 30 % of the patients were from 31-40 years followed by 23 % patients who were 51-60 years. 53 % of the patients in our study were having mild clinical severity where as 20 % were moderate and 27 % belongs to severe clinical severity class. 2% of patients developed fibrosis after 3 to 6 months and there is significant correlation of fibrosis with age, comorbidities and clinical severity.

CT severity index was maximum for 61-70 years followed by 51-60 years and 41-50 years. CT severity index was more for male patients. This is in correlation with study done byAmmar Mosa Al-Mosawe et al. [31] which showed strong positive correlation between higher CT severity score and male gender. In this study, there was significant correlation of CT severity score and increasing age. Zhichao Feng et al. [32] in 2020 also identified positive correlation of CT severity score with increasing age.

CT severity index is maximum for age > 60 years in a study conducted by Ammarmosa Al-mosawe et al. [31] Liu et al. [33] which is correlating with our study. This relation can be mostly attributed to the aging of lung in older age group and presence of co-morbidities [31].

The initial CT scan was done within 10 days of onset of symptoms or when patient developed breathlessness. All patients had ground glass opacities in their first scan, where as 4 % patients had consolidation. This study enrolled patients during the second wave of COVID-19 in India where hospitalisation was more for patients with co-morbidities, and HRCT showing pneumonia. In the study by Ammar Mosa Al-Mosawe et al. [31] ground glass opacities were the most common encountered pattern of pulmonary changes and were seen in (79%). Zhichao Feng et al. [34] reported that initial CT severity score is an independent predictor of short term disease progression. The study conducted by Omar et al. [35] and Adnan et al. [36] also predicts that ground glass opacities were the most common radiological pattern in COVID-19 pneumonia.

The CT scan done at one month was showing ground glass opacities in 10 % patients, septal thickening in 6 % patients, consolidation and reticulations in 3 % patients each. The CT scan after 3 months showed ground glass opacities in 4 % patients, where as 2 % patients had septal thickening and traction bronchiectasis (Fig. 1) and 1 % patients had either reticulations or consolidation. 2 % patients at 6 months had septal thickening, reticulations, traction bronchiectasis and honeycombing. Most of the patients showed significant resolution at 3 months post covid (Fig. 2).

The prevalence of post COVID fibrosis after3 and 6 months is 2 % each.20 % of the patients were requiring intensive care, and 11 % patients died due to COVID or post COVID sequelae. The mean duration of stay in hospital were 10.22 days. This is similar to many studies that reported mean duration of hospital stay between 8 to 14 days.

There was significant correlation between clinical severity and death, fibrosis at 3 and 6 months. GhufranArefSaeed et al. [37] in their study concluded that the oxygen requirements and length of hospital stay were increasing with the increase in scan severity. MehrdadNabahati et al. [38] observed Post-COVID19 lung fibrosis in

about half of the survivors in their study. They also found that patients with severe COVID-19 pneumonia were at a higher risk of pulmonary fibrosis. Moreover, consolidation, as well as a higher CSS, in the initial chest CT scan, was associated with increased risk of post-COVID-19 lung fibrosis.

There was significant correlation between CT severity and fibrosis Jia-Ni Zou et al. [39] reported thatground-glass opacities, linear opacities, interlobular septal thickening, reticulation, honeycombing, bronchiectasis and the extent of the affected area were significantly improved 30, 60 and 90 days after discharge compared with at discharge. The more severe the clinical severity of COVID-19, the more severe the residual pulmonary fibrosis was; however, in most patients, pulmonary fibrosis improved or even resolved within 90 days after discharge.

Rasha Mostafa Mohamed Ali et al. [40] noted that although there was no specific cause for post-COVID19 lung fibrosis, there were some predicting factors such as old age, cigarette smoking, high CT severity score, and long-term mechanical ventilation.

Mehrdad Nabahati et al. [39] observed Post-COVID-19 lung fibrosis in about half of the survivors. Also, patients with severe COVID-19 pneumonia were at a higher risk of pulmonary fibrosis. Moreover, consolidation, as well as a higher CSS, in the initial chest CT scan, was associated with increased risk of post-COVID-19 lung fibrosis. In their study, repeat CT was done after 6 months and in 61% people fibrotic changes remained unchanged. This is in contrast to our study.

6. CONCLUSION

From our study, the post COVID lung changes are reversible, with only 2 % developing the post covid lung fibrosis.

The article focusses on post covid lung fibrosis prevalence and the predictive factors which include patient's age, sex, comorbidities, clinical and CT severity. Burden of post covid lung fibrosis may increase as a huge number of patients affected during all the covid waves. Further researches are needed to evaluate the effect of antifibrotics on these lung fibrosis and to know whether antifibrotics can be used as prophylactic agents for preventing post covid lung fibrosis. It will shed more light into the effective management of morbidity and mortality in future pandemics.

7. LIMITATIONS

The main limitations are the study being retrospective, there is bias in timing of HRCT thorax (in some patients HRCT was done at the time of admission vs HRCT thorax done at first episode of desaturation or breathlessness).

The study being conducted in a single tertiary centre which includes patients with more of moderate to severe lung involvement.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

DATA AND MATERIAL AVAILABILITY

The data and material for the case report has been obtained from hospital records.

CONSENT

It is not applicable.

ETHICS APPROVAL

Ethical committe approval is taken before conducting the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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