

Evaluation of Lung Fibrosis in Post COVID-19 Patients in Tertiary Care Centre**Harshit Jain¹, Ravendra Singh², Shubham Mishra³**¹Senior Resident, School of Excellence in Pulmonary Medicine, NSCB Medical College, Jabalpur (MP)²Senior Resident, School of Excellence in Pulmonary Medicine, NSCB Medical College, Jabalpur (MP)³Assistant Professor, School of Excellence in Pulmonary Medicine, NSCB Medical College, Jabalpur (MP)

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Conflict of interest: Nil

Abstract:

Introduction: An outbreak of novel coronavirus was responsible for coronavirus disease-19(COVID-19) which was first reported in Hubei province, Wuhan, China, on November 17, 2019. It had rapidly spread all over the world with approximately 66.4 crore cases, 64.40 crore recoveries and 67.1 lakh deaths (200,000 deaths within first four month) till now. In India there were 4.46 crore cases of which 4.41 crore recovered and there were 5.30 lakh deaths till now (JHU CSSE COVID-19 Data).

Aims: Assessment of lung fibrosis in post COVID-19 follow up cases.

Materials and Method: The prospective observational study was carried out at R.D. Gardi Medical College, Ujjain in the Department of Respiratory Medicine. All post COVID-19 cases attending post covid clinic was included in the study with minimum 119 patients.

Result: In our study, out of total 119 post covid follow up cases, lung fibrosis was seen in 67(56.3%) patients of which only in 3 patients had residual lung fibrosis while other improved.

Conclusion: the patients who had lung fibrosis were fewer than expected (<5%). These sequelae were mostly occurring in the elderly patients with comorbidities, longer hospital stay, severity of covid infection and smoking are the other risk factors for its development. Post Covid patients had various symptoms like weakness, cough, breathlessness etc which required symptomatic management.

Keywords: COVID-19, Lung fibrosis, ARDS and Antifibrotic.

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Introduction

The World Health Organization (WHO) officially announced COVID-19 as a pandemic disease in March 2020 [1]. This disease is highly infectious and mainly spreads by coughing, talking with close contacts, or sneezing [2]. A large number of infected COVID-19 cases had very mild symptoms - such as loss of taste or smell, fever, fatigue, and dry cough - or are completely asymptomatic.

However, acute respiratory distress syndrome (ARDS) can develop in about 14% of the cases, which is a potentially fatal condition [3]. ARDS can especially develop in patients predisposed to certain risk factors, such as old age, diabetes mellitus, and hypertension etc [4]. COVID-19 is primarily considered a respiratory condition however it is a systemic disease as it can adversely affect multiple organs, including the cardiovascular, gastrointestinal, nervous and hematopoietic. This can be due to the angiotensin-converting enzyme 2 (ACE2)'s abundant presence in many organs of the body [5]. After the COVID-19 pandemic, increasing number of patients

worldwide who have survived COVID-19 continue to battle the symptoms of the illness, long after they have been clinically tested negative for the disease. They are called as long – haulers. As we battle through this pandemic, the most difficult part is how to manage this COVID-19 sequelae which may vary from mild in terms of fatigue and body aches to severe forms requiring long term oxygen therapy and even lung transplantation due to lung fibrosis or significant cardiac abnormalities and stroke leading to impairment in quality of health. [6,7]

The major lung involvement can lead to ARDS. The pathophysiological correlate of ARDS is the diffuse alveolar damage (DAD) which is characterized by an initial (acute inflammatory) exudative phase with edema, hyaline membranes, and interstitial acute inflammation, followed by an organizing phase with loose organizing fibrosis mostly within alveolar septa, and type 2 pneumocyte hyperplasia. A potent third stage of ARDS can be the fibrotic stage [8]. Abnormal

immune mechanism initiates and promotes pulmonary fibrosis, possibly because of a cytokine storm. Dysregulation release of matrix metalloproteinases during the inflammatory phase of ARDS causes epithelial and endothelial injury. VEGF and cytokines such as IL-6 and TNF alpha are also implicated in fibrosis process.

Our hospital during the pandemic became a dedicated Covid tertiary care centre (DCH) and patients who recovered were coming with various post covid symptoms so this study was carried out here to evaluate and manage these patients.

Methods

Study design- A prospective observational study was carried out in patient who is COVID cases (RTPCR positive/ RAT positive/CT scan of thorax suggestive of covid infection) and was recovered from COVID infection and come for follow up in post COVID care clinic of Respiratory Medicine at C.R. Gardi Hospital, Ujjain. Recruitment of the patient according to the inclusion and exclusion criteria. The patient and/or relatives had been explained about procedure and informed and written consent was taken from the patient and/or relatives.

Inclusion criteria: All COVID-19 cases (RTPCR positive/ RAT positive/CT scan of thorax suggestive of covid infection) and ready to give consent and to be a part of the study.

Exclusion criteria: Patient with known case of interstitial lung disease, pulmonary tuberculosis and previous illness that may cause lung fibrosis.

Method

According to the presence of ILD on follow-up CT after discharge, patients were reclassified into two groups and assigned as the “non-fibrotic group” (without evident fibrosis) and “fibrotic group” (with evident fibrosis). We compared between these two groups based on the recorded clinical data, patient demographic information (i.e., sex and age), length of stay (LOS) in the hospital, admission to the ICU, laboratory results (peak C-reactive protein [CRP] level, lowest lymphocyte level, D-dimer, administration of steroid), and CT features (CT severity score and CT consolidation/crazy-paving score). Significant statistical test had been applied.

Results

In our study of 119 patients, 29 (24.4%) were females and 90 (75.6%) were males of which, 15 (22.4%) females and 52 (77.6%) males in fibrotic group. Of total, 51(42.85%) patients were below 50yr of age and 68(57.1%) patients were above 50yr of age, while in fibrotic group, 20(29.85%) patients were below 50yr of age and 47(70.14%) patients were above 50yr of age ($p=0.0240$). Mean age of $54.9701(\pm 12.5493)$ years was higher in patient with post covid lung fibrosis compared to non-fibrotic group (45.7885 ± 14.5108) ($p=0.0003$). Out of total, only 6(5.0%) patients were in home isolation and 113(95.0%) patients had been admitted in hospital during Covid ($p=0.0043$). The duration of hospital stay (days) was significantly higher in fibrotic group [17.1045 ± 7.5741] compared tonon-fibrotic group [12.3913 ± 5.4792] ($p=0.0004$).

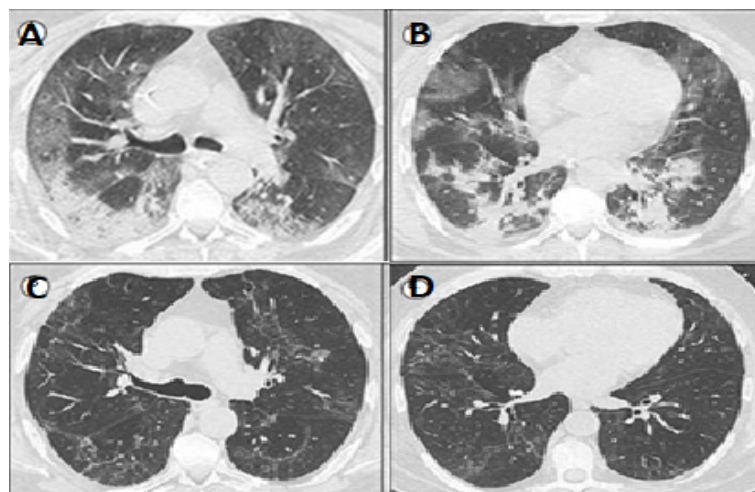


Figure 1: Chest CT scans, A and B done 15 days after discharge from covid showed consolidation, GGO and fibrosis. C and D are scan was done after 3 months of follow up that showed marked resolution.

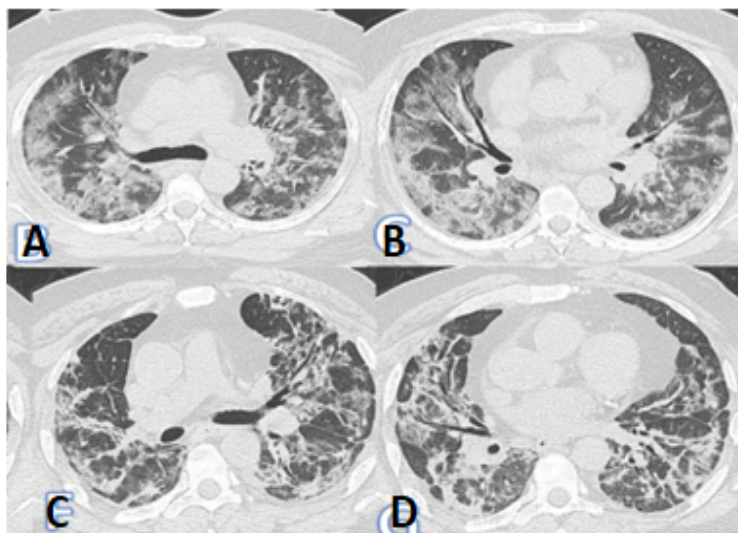


Figure 2: Chest CT scans, A and B done 15 days after discharge from covid showed consolidation, GGO and fibrosis. C and D CT scan was done 5 months after discharge that showed residual fibrosis.

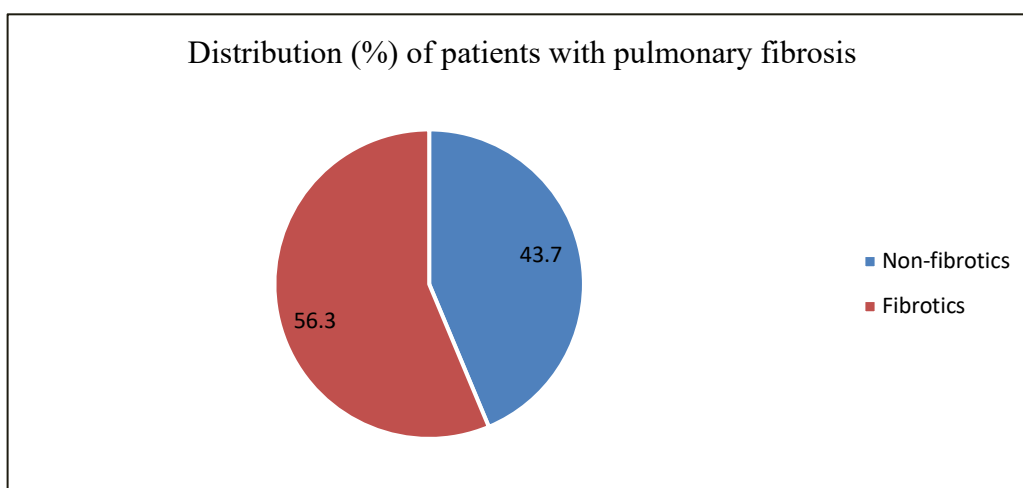


Figure 3 : Distribution (%) of patients with pulmonary fibrosis

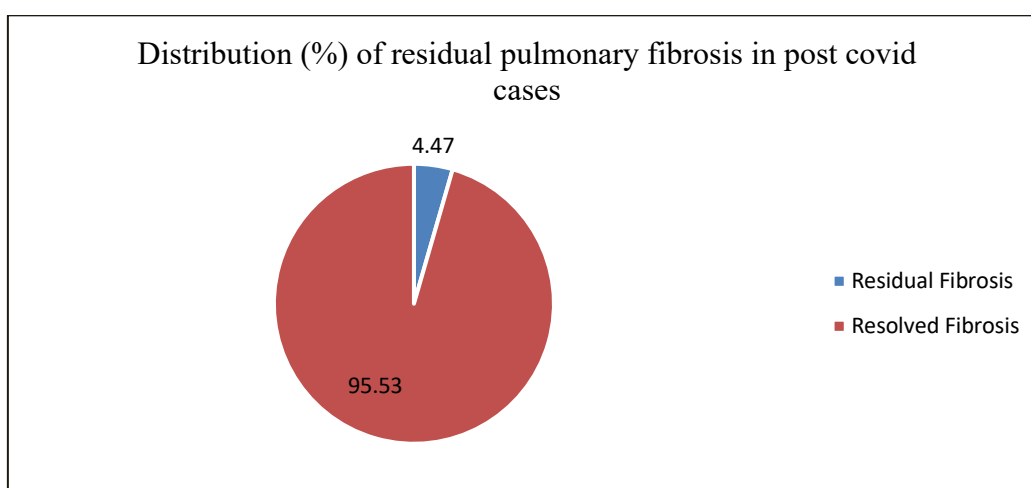


Figure 4: Distribution (%) of residual pulmonary fibrosis in post covid cases

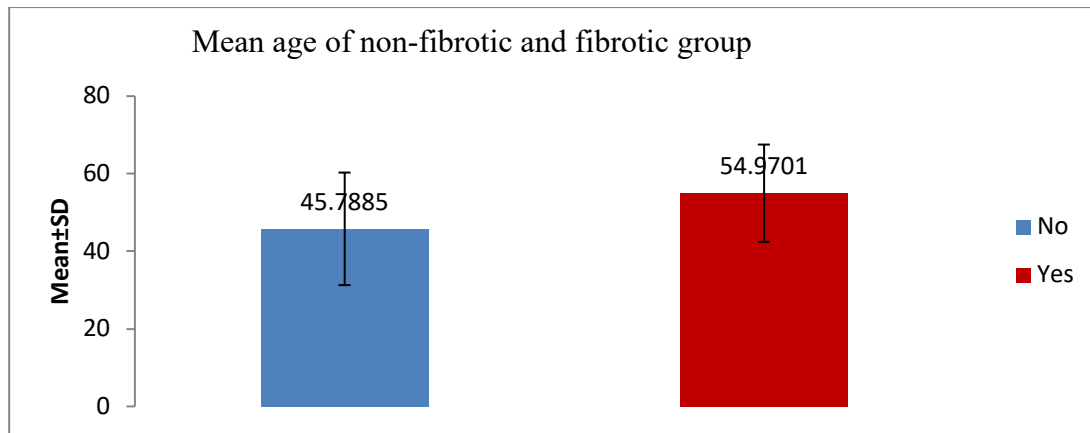


Figure 5: Mean age of non-fibrotic and fibrotic group

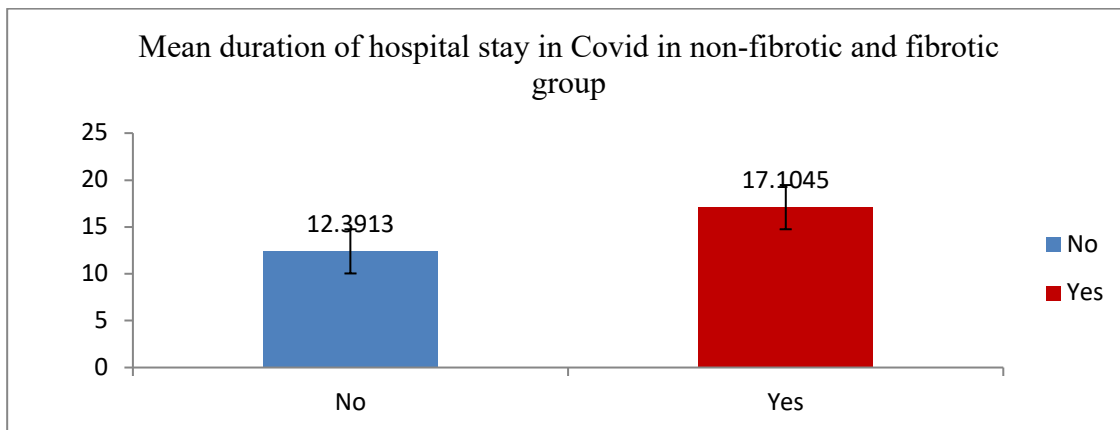


Figure 6: Mean duration of hospital stay in Covid in non-fibrotic and fibrotic group

In fibrotic group, only 1(1.49%) patient was having mild Covid infection, 18(26.86%) were patients of moderate Covid infection and 48(71.64%) patients had severe Covid infection. On the evaluation it was found that in fibrotic group, only 1(1.49%) patient was on room air, 6(8.95%) patients were on nasal prong, 11(16.41%) patients were on face mask, 16(23.88%) patients were on NRBM, 3 (4.47%) patients were on HFNC and 30 (44.77%) patients were on BiPAP/NIV.

Hence maximum patient in fibrotic group had received oxygen support during hospitalization. Out of total patients, 109 (91.6%) have received corticosteroids (p=0.0020), 48 (40.3%) had received Remdesivir (p<0.0001) and 5(4.2%) had also received Tocilizumab (p=0.0441) for their Covid management according to severity of lung damage.

In lung fibrotic group, 33(49.3%) patients had diabetes mellitus (p=0.0016), 29(43.3%) patients had hypertension (p=0.0011), 2(3.0%) patients had asthma and COPD (p=0.7139). 27 (40.3%) patients were smokers(p=0.0137) in fibrotic group. In our study 119 follow up cases, patients presented with various persisting symptoms such as 101(84.9%) weakness, 44 (37.0%) cough, 21 (17.6%) expectoration, 12(10.1%) fever, 64(53.8%)

breathlessness, 14(11.8%) chest pain, 12(10.1%) joint pain, 31 (26.3%) insomnia, 10(8.4%) sore throat, 1(7.1%) abdominal pain, 2(14.3%) constipation, 1(7.1%) dry mouth, 1(7.1%) gum weakness, 1(7.1%) headache, 3(21.4%) haemoptysis, 1(7.1%) neuropathy, 2(14.3%) running nose, 1(7.1%) skin rash and 1(7.1%) vertigo. These symptoms were more severe in fibrotic group compare to non-fibrotic group.

Out of 119 post covid-19 follow up patients, only 67(56.3%) patients had bilateral infiltrate and reticular shadows on chest X-ray (p<0.0001) and these patients also had interstitial fibrosis, intra and inter septal thickening on HRCT thorax (p<0.0001). On follow up of these, 67 patients of lung fibrosis, only 3(4.47%) patients had residual fibrosis and in rest the fibrosis resolved between 2-5 months.

We found that in our study, wCRP (<5) was significantly higher in [96.6418±242.1744] the lung fibrotic group compared to non-fibrotic group [25.2423±60.9711] (p=0.0403) also D-Dimer (<500) values were significantly higher in lung fibrotic group [1260.1940±992.9654] compared to non-fibrotic group [312.8846±695.9704] (p<0.0001).

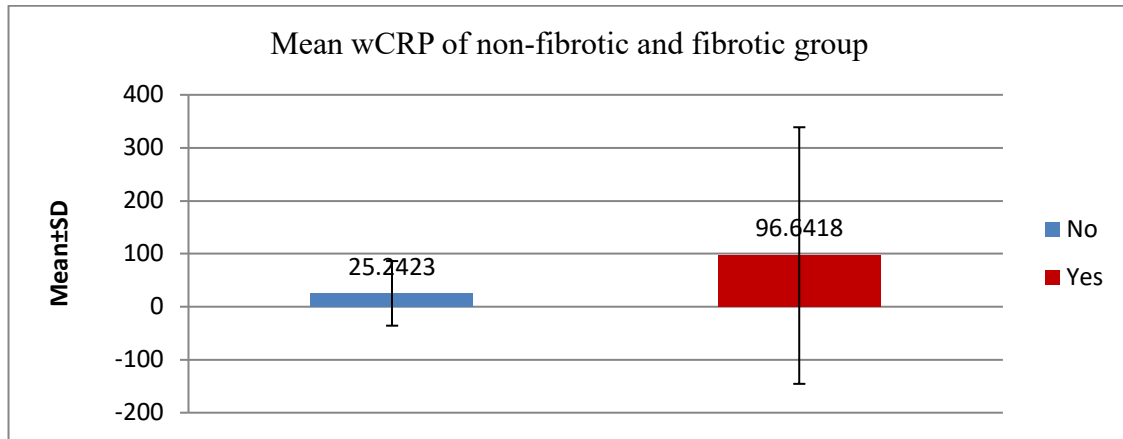


Figure 7: Mean wCRP of non-fibrotic and fibrotic group

In our study of 119 patient, 45 (37.8%) patients had been given anti-coagulants in post Covid follow up ($p < 0.0001$). In this study, out of the 119 patients, all of the 67(56.3%) patients who had developed post Covid lung fibrosis had also received Pirfenidone (anti-fibrotic) to prevent lung fibrosis. Out of these 67 patients of lung fibrosis, 51 patients had been given anti-fibrotic for 2 to 3 months, 13 patients had received it for 4 to 5 months and only 3 patients had developed residual fibrosis for which anti-fibrotic were continued($p < 0.0001$).

Discussion

The various clinical presentation of COVID-19 can range from mild symptoms to severe illness that lead to permanent lung damage or even mortality [9]. Most of the mild to moderate cases were completely recovered as seen in non-fibrotic group of our study but only few of severe cases with acute respiratory distress syndrome (ARDS) continued to remain hypoxemic despite receiving adequate medical treatment, developed post-COVID lung fibrosis was one of the important sequelae [10]. In Many theories, it was discussed as a potential cause of post-COVID pulmonary fibrosis; older age, severity of illness, prolonged ICU stay, mechanical ventilation, history of smoking, comorbidities are the risk factors for its developments [11]. But later, it was found to be in most cases to be bronchovascular bundle distortion, fibrotic strips, architectural distortion, sub pleural curvilinear atelectasis which resolved over time [12]. As in our study, out 67 patients of lung fibrosis, only 3 patients had developed residual fibrosis while other improved [13]. This may be due to as they had received anti-inflammatory drugs like steroids, Tocilizumab and anti-fibrotic in covid [14]. Also, patients presented with various symptoms in post-covid phase [15].

Conclusion

Covid-19 pandemic has gradually spread globally with lots of mortality. Based on limited data from

our study of 119 post covid follow up cases, the evaluation of long-term consequences of acute COVID-19 has shown that these had post covid sequelae like lung fibrosis were seen in 67(56.3%) patients of which only in 3(4.47%) patient residual lung fibrosis was developed. Post covid CT thorax showed interstitial fibrosis, intra and inter septal thickening which were later found to be actually bronchovascular bundle distortion, fibrotic strips, architectural distortion, sub pleural curvilinear atelectasis. So, the patients who had developed post covid lung fibrosis were fewer than expected ($< 5\%$) as this could be due to the use of anti-inflammatory medication and the use of anti-fibrotic. These sequelae were mostly occurring in the elderly patients with comorbidities, having longer duration of hospital stay, severity of covid infection and smoking are the other risk factors for its development. Post Covid-19 patients had various symptoms like weakness, cough, breathlessness, ghabarahat, joint pain, palpitation, and brain fogging etc which required symptomatic management.

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