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Post COVID Pulmonary Fibrosis: Is it Reversible?

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged viral pathogen that leads to coronavirus disease-2019 (COVID-19) [1]. Post-COVID lung fibrosis is a consequence of SARS-CoV-2 infection following the acute phase of the disease. Post-COVID status commences after 30 days of acute COVID-19 infection. This is otherwise termed as Long COVID. Post-COVID Pulmonary fibrosis (PCPF) is one of the manifestations of Long COVID. These can have varying effects on individuals, and the long-term consequences may differ from person to person. As per the present understanding, post-COVID fibrosis can be transient fibrosis which will resolve over time or permanent fibrosis which will have long-term impact. The development of pulmonary fibrosis is considered one of the key concerns regarding COVID-19 pulmonary sequelae as it is associated with architectural distortion of the lung parenchyma and overall impairment of lung function resulting in decreased quality of life [2]. The impact of lung fibrosis will depend on several factors, including the severity of the initial COVID-19 infection, the presence of any underlying health conditions, and the effectiveness of medical interventions and management.

COVID-19 and the Lungs

Among the COVID-19 patients, less severe illness (Category A) does not have much involvement in the respiratory system, except, upper respiratory symptoms and cough. All these symptoms resolve by 7-14 days. At the same time Category B and Category C disease have involvement in the form of pneumonia, acute respiratory distress syndrome (ARDS) and respiratory failure. Category C disease is often presented with pneumonia requiring hospitalization and this is manifested as ARDS causing diffuse alveolar damage (DAD). ARDS takes longer time to resolve and needs intensive care admission and ventilator support. Usually it takes 12 weeks to resolve and when it resolves, residual fibrosis sets in. In COVID-19, lung fibrosis may be transient which resolves over time or it can lead to permanent fibrosis with residual damage to the lungs. About 44.9% of COVID-19 survivors developed pulmonary fibrosis [3,4,5]. Long COVID symptoms can persist for weeks, months, or even years, after the initial COVID-19 infection. It is not uncommon for individuals to experience symptoms for several months or more. The fact that why some individuals develop Long COVID, while others recover completely from COVID-19 is not well understood.

The fate of the lung fibrosis can be categorized in to 4 pathways:

1) *Resolution:* In some cases, lung fibrosis may improve or resolve over time with proper medical care, including medications and rehabilitation. Lung tissue can regenerate, and scarring may decrease, leading to improved lung function.

2) *Stable Condition:* Some individuals may experience stable lung fibrosis, where their lung function remains relatively constant over the years. With ongoing management and lifestyle modifications, they can maintain a reasonable quality of life.

3) *Progression:* Lung fibrosis may progress despite treatment in some individuals. This can lead to increasing symptoms in the form of dyspnoea, exercise intolerance, hypoxemia, and a decreased quality of life. In some cases, lung transplantation may be considered as a last resort.

4) *Fluctuating Symptoms:* Lung fibrosis may result in periods of stability followed by exacerbations. During exacerbations, individuals may experience worsening of symptoms and require more intensive medical intervention.

Risk Factors for development of PCPF

Main risk factors to predict long COVID or PCPF are [3]:

1) Computed tomography score of ≥18.

2) Intensive Care Unit (ICU) admission.

3) Invasive/non-invasive mechanical ventilation.

4) Longer hospitalization period.

5) Steroid, antibiotic and immunoglobulin treatments.

Clinical Impact

According to studies by Han et al. and Aul et al., recovered COVID-19 patients who have developed pulmonary fibrosis, suffer more frequently from persistent symptoms, including dyspnea, cough, chest pain, fatigue, and myalgia when compared to non-fibrotic patients [6,7]. Zou and colleagues after, 30 day, 60 day, and 90-day follow-up of PCPF patients have confirmed that pulmonary fibrosis in some patients will resolve over time; however, fibrosis in the majority of the patients will not resolve8.

We have followed up 30 cases of COVID-19 victims admitted in ICU and treated with ventilator support and oxygen (Category C disease). All these patients developed Post COVID pulmonary fibrosis (proved by HRCT Thorax). They were under regular follow up with symptom score, pulmonary function assessment and HRCT thorax. HRCT thorax was repeated once a year to study temporal changes (**Figures 1, 2, 3,**and **4**). The HRCT findings during the evaluation recorded parenchymal bands, reticulations, ground-glass opacities, honeycombing, traction bronchiectasis, irregular interfaces, interlobular septal thickening, lung distortion, parenchymal meshwork, crazy paving and organizing pneumonia, as reported by Yasin et al., and Zhang et al. [9,10].

These patients were managed with medications to alleviate specific symptoms and therapies such as pulmonary rehabilitation, physical therapy, and cognitive-behavioral therapy. Those patients having predominant ground glass opacities were treated with low dose oral steroids and immunomodulators like mycophenolate mofetil for a varying period of 6 months to one year along with supportive therapies like symptomatic drugs, noninvasive ventilation or home oxygen. It has been suggested that steroid therapy prevents irreversible lung injury [11]. But this remains a matter of debate even

now. Those patients having reticulations, honey combing and traction bronchiectasis were treated with antifibrotic drug (Nintedanib) for a varying period.

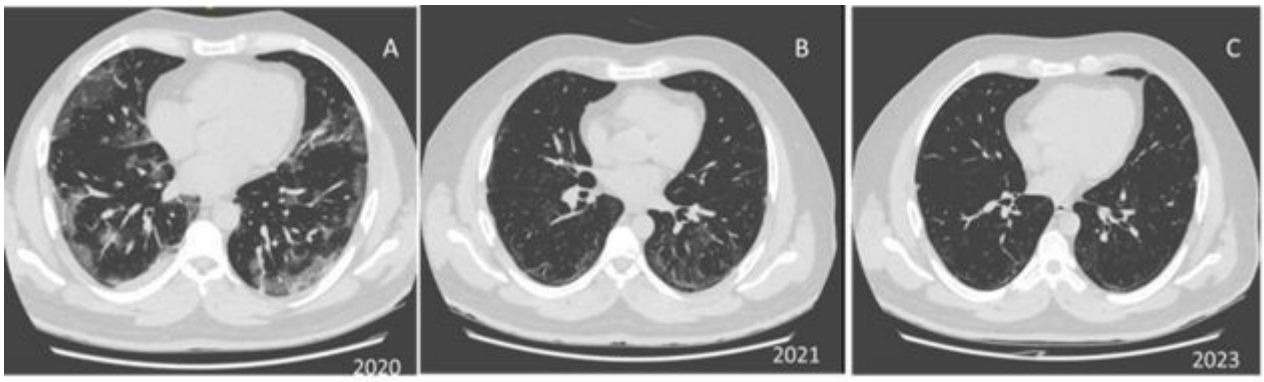

Figure 1: HRCT Thorax axial cut (A) showed multiple areas of ground glass shadows and reticular shadows. HRCT after one year (B) showed resolution of ground glass opacities and persistence of reticulations which after 2 years have almost completely resolved (C).

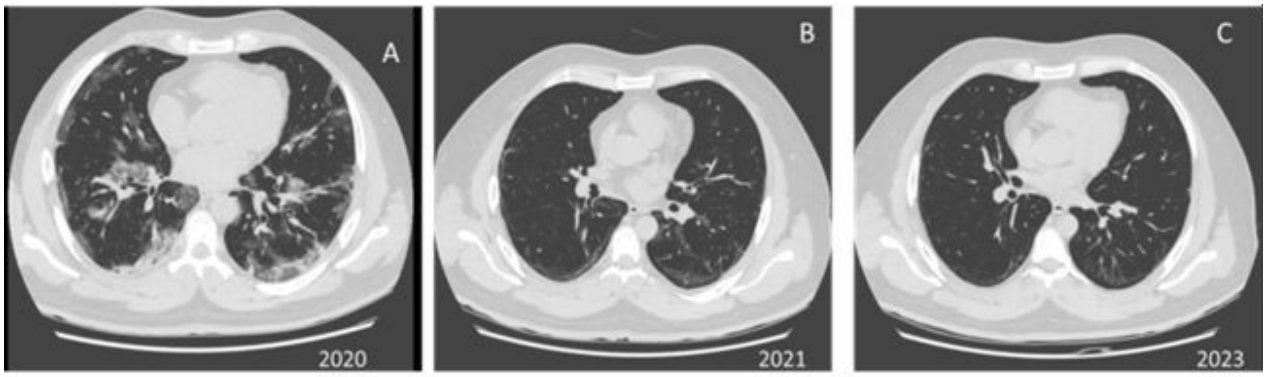

Figure 2: HRCT axial cut in 2020 showing bilateral interstitial involvement (A) which gradually resolved by 2021 (B) and minimal fibrosis persists in 2023 (C).

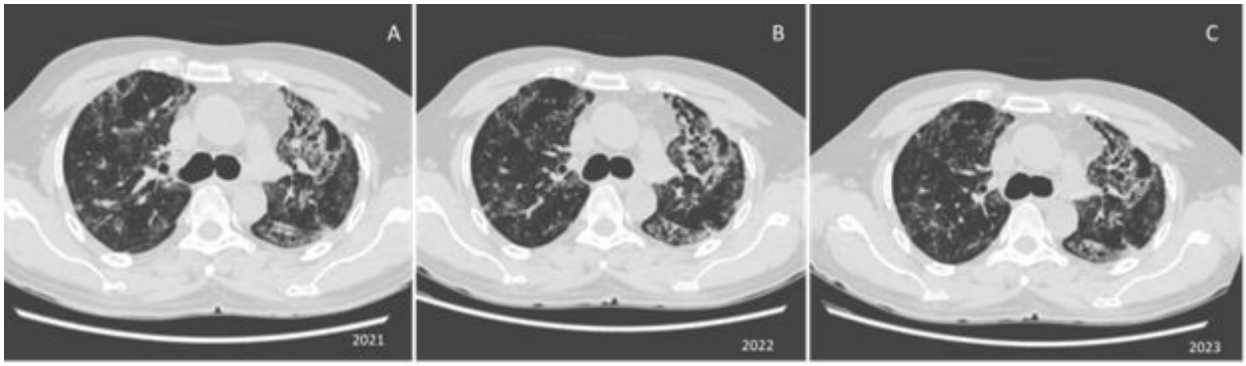

Figure 3: HRCT axial cut in 2021 showed severe interstitial involvement in the form of ground glass shadows, consolidation and reticulations (A). After 1 year only minimal reduction in shadows (B) and in 2023 shadows persist even though there is considerable reduction (C).

From our observation it was evident that 28 out of 30 patients showed reduction in the CT score compared to the first HRCT. But the level of resolution varies between patients. Two patients had stable HRCT findings. All of them were off oxygen and ventilator support at home. Their symptoms scores and exercise capacity have improved considerably.

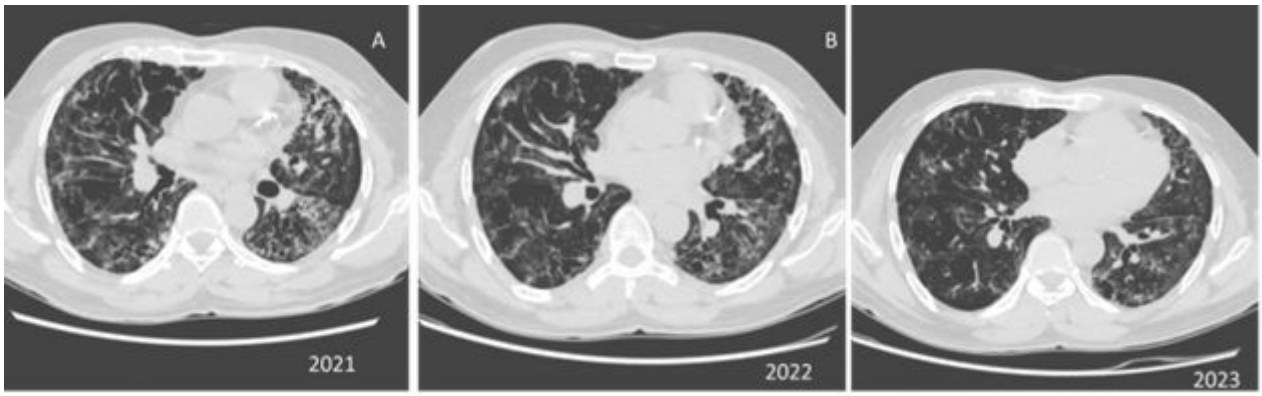

Figure 4: HRCT axial cut showing bilateral nodular shadows, reticulations and ground glass opacities (A) which showed partial resolution after one year (B) and considerable reduction in shadows after 2 years (C) even though residual fibrosis still present.

It is reported that those receiving invasive mechanical ventilation and having neutrophil-lymphocytic ratio (NLR) >3.13 at admission were strong risk factors for persistent parenchymal lung changes [12]. Neither the clinical severity of the acute illness nor the radiological change is found to predict the outcome. None of the medications received during the acute illness were found to alter the risk for this post-COVID-19 infection sequelae [12]. We found that early institution of treatment, especially when ground glass opacities and nodular lesions appear, gave a good clinical response compared to patients with honey comb lesions and traction bronchiectasis. Those patients who presented with predominant reticular and band like shadows responded well. Given the evolving nature of our understanding of Long COVID, it should be postulated that unlike other interstitial lung diseases such as UIP, most of the post COVID pulmonary fibrosis will recover to a satisfactory level by 2-3 years.

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