

## Review Article

# Facing the Challenge of Post COVID-19 Pulmonary fibrosis: What is so unique about it?

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*COVID-19 pandemic is the highlight of the 21st century that took drastic effects on humanity. Over 23 million confirm infected with the majority with mild infection. However, over 62,000 cases are in critical condition with varying degrees of ARDS. A potential complication of severe ARDS could be Post COVID-19 Pulmonary fibrosis. Possible use of biomarkers to detect progression to fibrosis, along with prompt treatment of acute lung injury caused by COVID-19 and administration anti-fibrotic therapies, could be the next best method to treat this permanent and devastating sequela of COVID-19.*

**Introduction:**

Since the first report of Coronavirus 2019 in Wuhan, China, in December 2019, Coronavirus disease 2019 (COVID-19) has emerged as a pandemic, with 18,043,836 infected cases and 689,187 deaths worldwide<sup>1</sup>. Almost all symptomatic COVID-19 patients have features of pneumonia. In the first large case series in Wuhan, China, all patients were found to have bilateral ground-glass opacities, a classic feature of COVID-19 disease. About 61% of patients developed Acute Respiratory Distress Syndrome (ARDS), and 26% required intensive care<sup>2</sup>. The Hallmark of ARDS is Diffuse alveolar damage can be divided into 3 phases: 1) Acute phase: which characterized by edema, hyaline membranes, and interstitial acute inflammation, followed by 2) Subacute Phase: characterized by loose organizing fibrosis mostly within the alveolar septa, and type II pneumocyte hyperplasia<sup>3</sup>. It can be caused by a myriad of contributors, most significant of which is believed to be CRS that is triggered by viral antigen, drug-induced pulmonary toxicity, mechanical ventilation-induced high airway pressure, and hyperoxia causing acute lung injury. Dysregulated immune response initiated by the cytokine syndrome in COVID-19 leading to ARDS, could possibly result in long term complications such as pulmonary fibrosis<sup>4</sup>.

**POST COVID-19 FIBROSIS:**

Progressive, fibrotic irreversible interstitial lung disease is defined by declining lung function, increasing the extent of fibrosis on CT, worsening symptoms and quality of life, and early mortality<sup>5</sup>. Viruses can play a crucial role in developing interstitial lung disease, not by itself, but as an aftermath of

the lung damage caused by the organism itself. In the older population, viruses pose a more significant threat, as even a relatively small residual, but non-progressive fibrosis could result in significant morbidity and mortality. COVID-19 had been notoriously known for affecting the older population, many of whom has pre-existing pulmonary conditions. In a recent retrospective study in China, 108 discharged COVID cases without a history of chronic pulmonary disease were recruited to measure the diffusing capacity of the lung for carbon monoxide (DLCO) by the single-breath method. The study showed that about 51(47%) of the patients had impaired diffusion capacity, and 27(25%) had reduced total lung capacity (TLC)<sup>6</sup>. Those with severe pneumonia undergoing mechanical ventilation showed a reduction in both DLCO and TLC, pointing towards restrictive fibrosis<sup>7</sup>. A number of biomarkers have been identified from a study in Wuhan, that can be used as indicators for COVID-19 prognostic prediction, namely LDH, hs-CRP and lymphocytes. Along with them, previous studies have detected fibrogenesis biomarkers to be present in the bronchoalveolar fluid 24 hours after onset of ARDS. These include N-terminal pro-peptide of type III collagen, C-terminal pro-peptide of type I collagen, TGF- $\beta$ , and alveolar fibroblasts and fibrocytes. Among these, fibrocytes have been associated with poor outcome in ARDS patients. Recent study has shown expansion of fibrocytes in bone marrow, lung and especially blood that could be used to predict fibrotic outcomes in patients with acute lung injury<sup>8</sup>.

**PATHOGENESIS:**

Lung fibrosis usually occurs secondary to acute and chronic interstitial lung diseases. It is characterized by alveolar re-epithelialization failure, persistence, and proliferation of fibroblast and excessive deposition of ECM components, including collagen and others<sup>9</sup>. Progression of lung fibrosis results in increased interstitial matrix widening, eventual compression, and destruction of lung parenchyma and capillaries, leading to ventilatory insufficiency<sup>10</sup>. Many etiologies have been pointed out to cause lung fibrosis. However, chronic inflammation secondary to the disease process is considered as the primary contributor to lung fibrosis. According to studies, alveolar epithelial damage and

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formation and proliferation of active myofibroblast foci are the pathological mechanism responsible for most lung fibrotic processes<sup>11-14</sup>. Any damage to the lung tissues causes the production of a set of growth factors and cytokines, such as monocyte chemoattractant protein-1 (MCP-1), transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin- $1\beta$  (IL- $1\beta$ ), and interleukin-6 (IL-6), etc. These factors stimulate the hyperproliferation of Type II alveolar cells, one of the major sources of fibrogenic factors responsible for the regeneration of lung parenchyma. The Type II epithelial cells, in turn, secrete growth factors to recruit fibroblasts and activate them into myofibroblasts. These myofibroblasts result in increased synthesis or decreased degradation of ECM or both, which leads to excessive accumulation of ECM such as type I, type III, type VI collagen. Among the factors involved in ECM degradation, the plasminogen activator/plasmin system plays the most crucial role, regulated through the plasminogen activator inhibitor 1 (PAI-1). In fibrotic lung patients, PAI-1 is increased<sup>11,15</sup>. Another cytokine that plays a key role in developing lung fibrosis is TGF- $\beta$ . It belongs to the superfamily of structure-related growth factors like TGF- $\beta$ , activin, bone morphogenetic proteins (BMPs), and others. These cytokines play a complex regulatory role in cell growth, differentiation, death and migration, and matrix remodeling<sup>16-18</sup>.

In addition to TGF- $\beta$ , Angiotensin converting enzyme (ACE-2) plays a significant role in the development of fibrotic lung SARS-CoV-2. According to several studies, high-affinity interaction of viral spike protein 2 with ACE2 receptors on various cell surfaces, especially lungs, results in the internalization of the virus and the formation of multinucleated giant cells, with subsequent reduction in ACE2 expression. Reduced ACE2 expression leads to increased Angiotensin-II (Ang- II) levels, which results in lung fibrosis with consequent lung failure<sup>19</sup>.

Another mechanism, well established in previous literature to cause pulmonary fibrosis, is hyperoxia. Severe COVID-19 patients requiring high levels of oxygen supplementation develop hyperoxia, characterized by  $FiO_2 > 60\%$  and  $PaO_2 > 40.0$  kPa. At the core of this condition, the researchers described a complex mechanism involving reactive oxygen species (ROS), causing inflammation. ROS, generated from activated macrophages, platelets, and neutrophils due to hyperoxia, can trigger a secondary inflammatory response. Hyperoxia can affect different kinds of epithelium, namely, alveolar epithelium, macrophages, and vascular endothelium in different pathways<sup>20</sup>. However, pulmonary epithelium is more susceptible to hyperoxia-induced injury due to the passage of numerous vasoactive and fibrinolytic substances such as serotonin, norepinephrine, and bradykinin, angiotensin, prostaglandins, tissue plasminogen activator. Moreover, studies have shown that higher  $FiO_2$  of about .8-.9 can produce high stretch mechanical ventilation, which can cause endothelial hypermetabolism, leading to pulmonary injury<sup>21</sup>

Recent studies also demonstrated that hyperoxia could

increase the Renin-Angiotensin-Aldosterone system (RAAS), leading to increased Ang-II levels. This effect is mediated by increased Ang II type 1 receptor (AT1R) expression, inducing molecular profibrotic pathway characterized by increased expression of phosphorylated extracellular signal-regulated kinase (ERK),  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), and collagen type I expression. The cumulative effect of RAAS on collagen production in human lung fibroblasts can lead to pulmonary fibrosis<sup>22</sup>.

#### IMAGING FINDINGS:

COVID-19 patients were found to have bilateral and peripheral ground glass opacities, sometimes with consolidation in Chest X-ray in acute setting. Studies have also found crazy-paving pattern, air-bronchogram, linear opacities, bronchial wall thickening and distortion in CT scan of COVID-19 patients<sup>23</sup>. However, these are considered non-specific findings. Moreover, in earlier stage of the disease, there are reported inconsistencies clinical finding and imaging appearances, including high proportion of normal chest CT scan in infected asymptomatic patients<sup>24,25</sup>. Patients diagnosed with Chest X-ray showed similar trend in disease extent and progression to the patients who underwent CT scan. Based on the overwhelming number of patients and limited number of resources, American College of Radiology recommended to use CT scan only in patients with worsening respiratory status and moderate-severe clinical features with high pretest probability of disease.<sup>26</sup>

Fig 1 shows an anteroposterior chest radiograph with multiple peripheral consolidation opacities in both lungs;



**Figure-1:** (Reprinted from Extension of Coronavirus Disease 2019 (COVID-19) on Chest CT and Implications for Chest Radiograph Interpretation Choi H, Qi X, Yoon SH, et al Radiol. Cardiothorac Imaging. 2020;2(2):e200107. Published 2020 Mar 30. doi:10.1148/ryct.202020010)

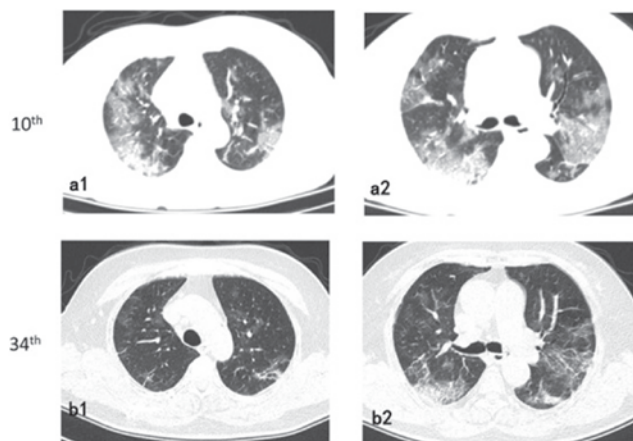
Figure-2 shows Ground glass opacity (GGO) in a 68-year-old female with confirmed COVID-19. Axial CT images shows multiple round morphology of GGOs in the bilateral upper lobes. Lesions are located in peripheral lung fields. Persistence of lung abnormalities were noted nearly two months after the onset.



**Figure-2:** (Reprinted from A systematic review of chest imaging findings in COVID-19 by Sun Z, Zhang N, Li Y, Xu X. *Quant Imaging Med Surg.* 2020;10(5):1058-1079. doi:10.21037/qims-20-564)

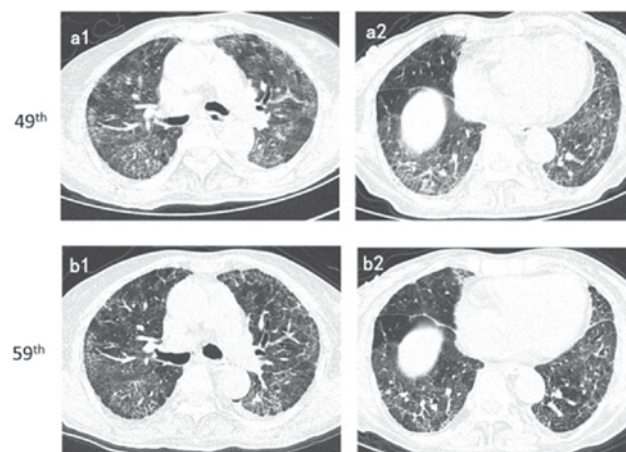
A retrospective study conducted at a single center between January 12, 2020, and March 16, 2020, on 12 COVID-19 infected ICU patients, showed a decrease in acute Ground glass opacity finding. Interestingly, a reduction in ground-glass opacities and consolidation was depicted early on by the CT. However, most patients depicted a gradual increase in fibrosis about  $56.1 \pm 7.7$  days from illness onset. Fibrosis was depicted by fibrous shadows (such as fibrous stripes, subpleural line, and traction bronchiectasis) involving diffuse lung lobes changes<sup>27</sup>.

Figure-3 shows follow-up axial chest CT images (34th day from onset) (b1-b2) showed a decrease in the extent of ground-glass opacities than the 10th day CT images and an increase in fibrotic lesions (a1-a2) in 72 year/old female;



**Figure-3:** (Reprinted from Pulmonary fibrosis in critical ill patients recovered from COVID-19 pneumonia: Preliminary experience by . Fang Y, Zhou J, Ding X, Ling G, Yu S., 2020 Jul 19, *Am J Emerg Med.* 2020; doi:10.1016/j.ajem.2020.05.120)

Figure-4 shows follow-up axial chest CT images (59th day from onset) (b1-b2) showed slight decrease in the extent of ground-glass opacities than the 49th day CT images, with negligible changes in fibrotic lesions (a1-a2) in 72 year/old female;



**Figure-4:** (Reprinted from Pulmonary fibrosis in critical ill patients recovered from COVID-19 pneumonia: Preliminary experience by . Fang Y, Zhou J, Ding X, Ling G, Yu S., 2020 Jul 19, *Am J Emerg Med.* 2020; doi:10.1016/j.ajem.2020.05.120)

**MANAGEMENT:**

**STEROIDS:**

At present, corticosteroids are among the few drugs used worldwide to treat COVID-19 induced acute respiratory failure. The biggest randomized controlled, open-labeled, adaptive, platform trial was conducted at 176 hospitals in the United Kingdom, with 6425 hospitalized and clinically suspected or lab-confirmed COVID-19 patients. This study, namely the RECOVERY trial, showed that the use of 6 mg of dexamethasone once daily for up to 10 days resulted in reduced 28-day mortality in COVID patients receiving respiratory support due to acute lung injury. However, steroids did not change the outcome among patients who did not require oxygen. These findings led researchers to hypothesize that COVID-19 could be responsible for immunological dysregulation besides active viral replication causing characteristic clinical features. Use of Corticosteroids could result in mitigation of short and long-term effects of pneumonia and ARDS caused by COVID-19<sup>28,29</sup>.

**ANTI-FIBROTIC THERAPIES:**

Several lung diseases are attributed to be due to COVID-19, including anything from organizing pneumonia to severe acute lung injury, which ultimately led to extensive fibrotic changes. The pro-fibrotic changes in COVID patients is considered to be due to a combination of immunologically mediated damage and classic acute lung injury. A comparative study done in 2020 by Chinese researchers shows that both SARS and COVID-19 have similar post-mortem pathological features indicating severe fibrotic organizing pneumonia, which could be a sequelae of cytokine syndrome, in addition

to diffuse alveolar damage and microvascular thrombosis<sup>30</sup>. As the chances of developing lung disease following SARS Cov-2 are deemed very high, new treatment options, namely novel anti-fibrotic drugs, are being considered to address these long-term effects of COVID-19.

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) and Nintedanib (tyrosine kinase inhibitor) are two anti-fibrotic drugs that showed a promising outcome in diminishing the rate of lung function decline by 50% with Idiopathic pulmonary fibrosis (IPF) without COVID-19<sup>31,32</sup>. Observed similarities in risk factors of COVID-19 and IPF and compelling resemblance between post-SARS ARDS fibrosis and post COVID-19 fibrosis, contributed to the therapeutic rationale of using Pirfenidone and Nintedanib as potential treatment options for COVID-19 induced fibrotic lung disease<sup>33,34</sup>. However, it is essential to mention that these drugs do not play a role in attenuating either the immune dysregulation or the prothrombic aspects of SARS-CoV-2 infection. They have only been exclusively studied IPF and progressive fibrotic lung disease in disorders other than IPF<sup>34</sup>. Therefore, the use of anti-fibrotic therapy in COVID-19 can be justified only by inferring the data from studies done on chronic lung diseases. The data regarding the use of anti-fibrotic agents must be taken into account in case acute lung injury superimposed on fibrotic lung diseases are inconclusive. Randomized phase 3 clinical trials done on anti-fibrotic agents like Pirfenidone and Nintedanib (INPULSIS and ASCEND trials) showed significant early separation (4-6 weeks) in FVC trends in case of Nintedanib therapy, but not in Pirfenidone therapy (evaluated in 1 year follow up<sup>32,33</sup>). Moreover, when pooled INPULSIS-1 and INPULSIS-2 study was analyzed, there was no significant difference in the frequency of acute exacerbations between Nintedanib and placebo<sup>30</sup>. However, in a small number of events, the significance increased when an expert panel only considered the episodes defined as genuine acute exacerbations in the pooled adjudicated analysis. When these considerations are taken into account, it can be stated that theoretically, early use of anti-fibrotic therapy could be beneficial in COVID-19. Nevertheless, a randomized placebo-controlled clinical trial is warranted to estimate the beneficial effects of these therapy in post-COVID-19 fibrosis patients. Considering the caveats mentioned above, a combination regimen approach (including traditional treatment of corticosteroids and mycophenolic acid with the anti-fibrotic agents) should be adopted to reduce the fibrotic consequences while addressing the immediate pro-inflammatory and pro-fibrotic pathways<sup>35</sup>.

#### NOVEL THERAPIES:

Some of the newer therapies targeting the TGF- $\beta$  pathway are  $\alpha\beta 6$  integrin blockers (BG00011 [Biogen, Cambridge, MA, USA]; PLN-74809 [Pliant Therapeutics, San Francisco, CA, USA]) and Gal-3 inhibitors. (TD139 [Galacto Biotech, Copenhagen, Denmark]) can be useful in mitigating viral-induced lung injury. SARS-CoV-2 spike protein contains the integrin-binding site, and other different strains of coronaviruses contain galectin folds, which makes these drugs

beneficial to treat COVID-19<sup>36</sup>. Moreover, IL-1, a key player in COVID-19 induced cytokine storm, is thought to convey inflammatory effects through integrins<sup>37</sup>.

Another drug is, OATD-01, which is a chitotriosidase 1 (CHIT1) inhibitor. Some current studies show that the virus may increase CHIT1 expression, causing fibrosis in lung tissues<sup>38,39</sup>. However, extensive studies need to be conducted to consider these drugs effective and safe concerning COVID-19 treatment.

Another potential anti-SARS-CoV-2 target could be mTOR. mTOR pathway has been shown to play a role in the development of IPF by a large-scale genome-wide association study<sup>40,41</sup>. Hence, mTOR inhibitor rapamycin and PI3K inhibitors could be useful in post-COVID fibrosis treatment<sup>42,43</sup>. Rapamycin has shown promising results in reducing viral replication and NLRP3 inflammasome when combined with oseltamivir<sup>44</sup>.

A novel drug, C21 (an agonist of Angiotensin 2 receptor, AT2R), has been approved for phase 2 study in COVID-19 (EudraCT 2017-004923-63)<sup>45</sup>. Angiotensin 1 receptor (AT1R) leads to increased Angiotensin-II levels, which results in lung fibrosis with consequent lung failure. AT2R usually has an antagonistic effect on AT1R (Angiotensin 1 receptor) signaling<sup>46</sup>. It has shown anti-inflammatory properties. However, its effect on viral pathogenesis is not known.

A recent trial of Mesenchymal stem cell therapy has also shown potential improvement in mitigating the long-term effects of lung injury by COVID-19. Previously, studies have shown that mesenchymal stem cells can be a potential treatment option to reduce the progression of COVID-19 from severe to critical illness and 28-day mortality rate<sup>47</sup>. Reducing the extent of lung injury by using mesenchymal stem cells like fibroblasts could reduce post-COVID fibrosis incidence.

Hyperbaric oxygen therapy (HBOT) has also been proposed as a treatment option to prevent the development of post-COVID fibrosis. This is hypothesized on the observation that HBOT can induce the production of two powerful transcription factors, namely Nrf-2 and heat shock transcription factor 1, that stimulates numerous anti-inflammatory cell defense proteins. HBOT also plays a crucial role in improving mitochondrial function by altering the balance between glycolysis and mitochondrial respiration, taking into account the translocation sHSPs (Small Heat Shock Protein) when in stress<sup>48</sup>.

#### CONCLUSION

At the moment, no prospective study is being conducted to recognize the long-term pulmonary consequences of COVID-19. Nevertheless, given the enormous population across the globe affected by COVID-19, even rare complications, like lung fibrosis, will have a significant health effect at the population level. Whether the COVID-19 itself or the physician prescribed treatment directed towards improving the patients' health is causing a hazardous effect like fibrosis, is still unknown to humanity. Proper diagnostic tools and method needs to be developed to promptly identify

the complications of COVID-19, including the development of pulmonary fibrosis in the survivor population. Knowledge of previous epidemics can be a useful tool in determining the rapidity and extent of fibrosis development. Regardless of the small amount of research done on the effects of anti-fibrotic drugs on respiratory virus-induced IPF, the study strongly suggests that these novel drugs could hypothetically assist in curbing the long-term effects of COVID-19. However, the need for well-designed studies to evaluate these drugs' effects and side effects cannot be denied. Only then can we adequately address the lasting implications of COVID-19 on the lungs.

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