

POST COVID PULMONARY FIBROSIS

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ABSTRACT

Patients with coronavirus disease 2019 (COVID-19) usually suffer from post-acute sequelae of coronavirus disease 2019 (PASC). Pulmonary fibrosis (PF) has the most significant long-term impact on patients' respiratory health, called post-COVID-19 pulmonary fibrosis (PC19-PF). PC19- PF can be caused by acute respiratory distress syndrome (ARDS) or pneumonia due to COVID-19. The risk factors of PC19-PF, such as older age, chronic comorbidities, the use of mechanical ventilation during the acute phase, and female sex, should be considered. Individuals with COVID-19 pneumonia symptoms lasting at least 12 weeks following diagnosis, including cough, dyspnea, exertional dyspnea, and poor saturation, accounted for nearly all disease occurrences. PC19-PF is characterized by persistent fibrotic tomographic sequelae associated with functional impairment throughout follow-up. Thus, clinical examination, radiology, pulmonary function tests, and pathological findings should be done to diagnose PC19-PF patients. PFT indicated persistent limitations in diffusion capacity and restrictive physiology, despite the absence of previous testing and inconsistency in the timeliness of assessments following acute illness. It has been hypothesized that PC19-PF patients may benefit from idiopathic pulmonary fibrosis treatment to prevent continued infection-related disorders, enhance the healing phase, and manage fibroproliferative processes. Immunomodulatory agents might reduce inflammation and the length of mechanical ventilation during the acute phase of COVID-19 infection, and the risk of the PC19-PF stage. Pulmonary rehabilitation, incorporating exercise training, physical education, and behavioral modifications, can improve the physical and psychological conditions of patients with PC19-PF.

KEYWORDS

COVID-19, Post-acute sequelae of coronavirus disease 2019 (PASC), Pulmonary fibrosis (PF), Post-COVID-19 pulmonary fibrosis (PC19-PF), Antifibrotic treatment.

1.INTRODUCTION

In the space of 7 short months, the SARS-COV-2 virus has acutely infected more than 50 million people and killed over 1.2 million. It has left in its wake, in severely affected survivors, a trail of devastating pulmonary fibrosis which physicians will need to urgently address and manage. While fibrosis is a physiologic response to any pulmonary infection, chest physicians across the globe are encountering vast number of patients who have recovered from their acute COVID-19 pneumonia only to be left with severe residual lung fibrosis and oxygen dependence. This review attempts to draw attention to the problem of post-COVID-19 interstitial lung disease (PC-ILD), a condition likely to be ever-more frequently encountered as this virus continues its relentless march across the globe(1).

2. DEFINITION

Post-COVID pulmonary fibrosis (PCPF) is a condition characterized by the development of persistent fibrotic changes and scarring in the lung tissue following SARS-CoV-2 infection, particularly after severe COVID-19 pneumonia. It may result from prolonged inflammation, alveolar epithelial injury, abnormal wound healing, and excessive deposition of extracellular matrix proteins such as collagen. These changes can lead to reduced lung

compliance, impaired gas exchange, and persistent respiratory symptoms, including breathlessness, cough, and reduced exercise tolerance(2).

3. EPIDEMIOLOGY

ILA and pulmonary fibrosis have been described in both short-term and long-term follow-up studies. For short-term pulmonary fibrosis complicating acute COVID-19, many studies reported this complication in the course of acute COVID-19 and some cases even required immediate lung transplantation. For instance, pulmonary fibrosis described as collagen deposition and loss of lung aeration was the main pathological finding of the lung cryobiopsy performed for patients while on mechanical ventilation and after their death, which correlated with the HRCT signs of lung fibrosis conducted few days before the cryobiopsy(3). Furthermore, pulmonary fibrosis causing refractory hypoxia accounted for 19% of ICU deaths in a single-center study. In a multicentre trial, the explanted lungs of 12 COVID-19 patients worldwide, who underwent lung transplantation, were reviewed. As expected, diffuse alveolar damage (DAD) was the main pathological finding of the explanted lungs of all patients (4). As the time from the diagnosis to transplant increases, DAD becomes more organized into lung fibrosis with bronchiolization of the alveoli associated with microscopic honeycombing, which are some of the classical features of lung fibrosis. Gulati and Lakhani studied the CT changes in the lung parenchyma during acute COVID-19 infection and shortly after it. The average time between the initial CT and the follow-up was a month, excluding patients with previous diagnosis of ILD. The study confirmed the evolution of acute changes, highlighted by the presence of GGO, into lung fibrosis manifested as reticular abnormalities, traction bronchiectasis, and architectural distortion. Moreover, almost half of the patients developed honeycombing or nonemphysematous cysts, which are the hallmark radiological features of advanced-stage lung fibrosis. Although this was observed only in a few patients, it definitely signifies the short-term sequelae of COVID-19 (5).

Pulmonary fibrosis as a long-term complication of COVID-19 has been reported by many centres. One of the noteworthy studies is that by Huang *et al.* on long-term pulmonary complications among COVID-19 survivors(6). In their study, the patients were categorized into three groups according to the respiratory support requirement as follows: Scale 3, patients not requiring oxygen therapy; Scale 4, requiring oxygen supplementation; and Scale 5–6, requiring intensive medical support with a high-flow nasal cannula, noninvasive ventilation (NIV), or invasive mechanical ventilation (IMV). Their results showed that 52.6% of the study population had radiological abnormalities on HRCT, mostly GGO, 6 months post-COVID-19. These abnormalities decreased significantly on follow-up HRCT 1-year post-COVID-19; however, they were more likely to persist among patients with severe disease(7).

These patients particularly had a higher percentage of reticulation at follow-up 6 months post-COVID-19 than that at the baseline, which speculates the progression of the disease to irreversible fibrosis. This chronic and mostly irreversible radiological abnormality coincided with functional abnormalities, where almost 39% and 57% of survivors of severe COVID-19 (Scale 5–6) had reduced total lung capacity (TLC) of <80% and reduced diffusion capacity of carbon monoxide (DLCO) of <80%, respectively(8). This functional reduction persisted during the 12-month follow-up period. Furthermore, post-COVID-19 pulmonary fibrosis was confirmed by surgical lung biopsy in a study by Konopka *et al.* In their study, surgical lung biopsies were performed for 18 patients with persistent symptoms and/or radiological abnormalities after recovery from acute COVID-19 infection to characterize the abnormalities further. The average time between COVID-19 diagnosis and surgical

lung biopsy was almost 5 months. The study showed that usual interstitial pneumonia (UIP) was the most common pathological finding reported in 7 out of 12 patients(9).

4. PATHOGENESIS

The pathogenesis of early and late pulmonary fibrosis complicating COVID-19 has not been elucidated. Here, we propose the following two theories: two-hit hypothesis and direct SARS-CoV-2 stimulation profibrotic cascade. Figure 1 summarize the pathogenesis of COVID-19-induced lung fibrosis(10).

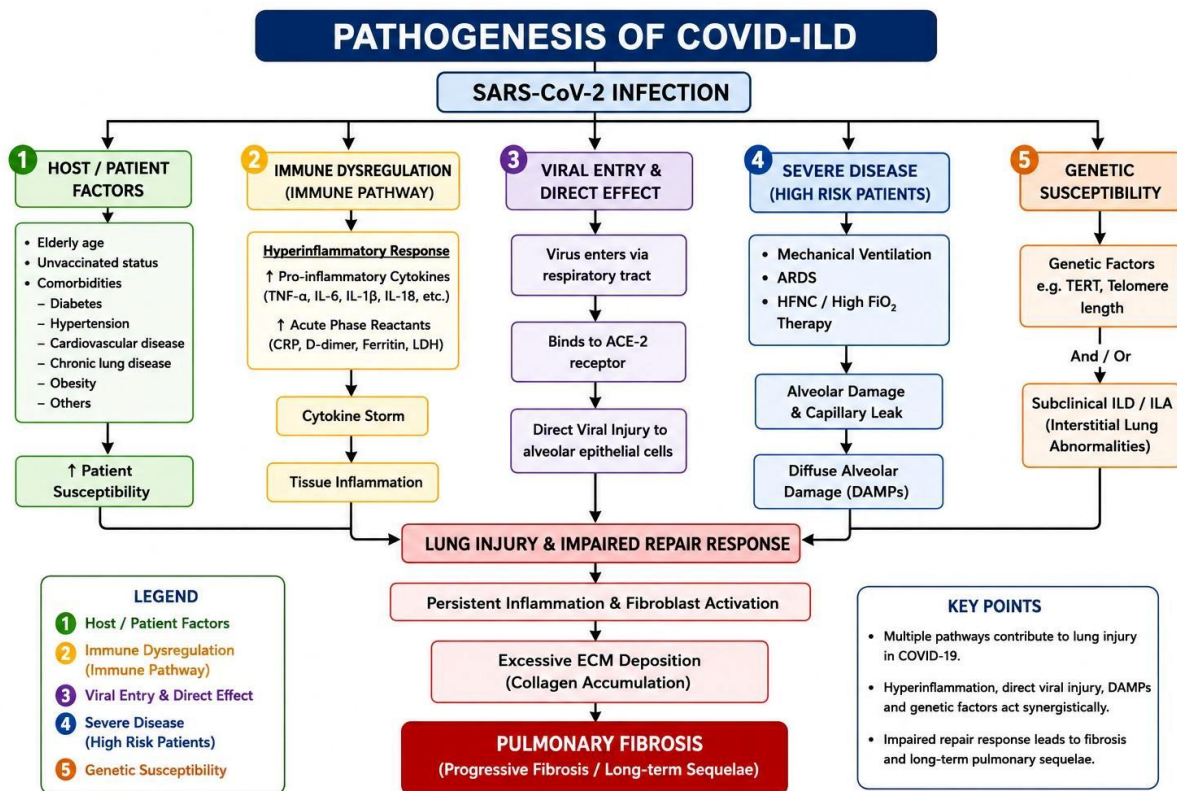


Fig 1 : Pathogenesis of COVID- ILD

5. PATHOPHYSIOLOGY

The development of pulmonary fibrosis following COVID-19 involves a series of complex and interconnected molecular and cellular mechanisms. This cascade of events contributes to progressive scarring, reduced lung compliance, and impaired gas exchange capacity.

1. Alveolar epithelial injury:

SARS-CoV-2 predominantly enters the host through respiratory droplets, targeting type II alveolar epithelial cells in the lungs via the angiotensin-converting enzyme 2 (ACE2) receptor. These cells play a critical role in surfactant production and alveolar repair. Once the virus invades these cells, it exerts direct cytopathic effects, resulting in widespread cell damage and apoptosis. The breakdown of the epithelial barrier facilitates the entry of inflammatory cells and pathogens, further intensifying local injury. This initial injury is considered the primary event triggering the fibrotic response. The loss of alveolar epithelial integrity also disturbs the delicate alveolar-capillary membrane, impairing oxygen exchange and predisposing to long-term structural changes.

2. Cytokine storm and inflammation:

In patients with severe COVID-19, the immune response becomes dysregulated, leading to a hyper inflammatory state commonly referred to as a “cytokine storm.” This involves the release of large quantities of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and transforming growth factor-beta (TGF- β). These cytokines play a pivotal role in recruiting immune cells such as neutrophils and macrophages to the site of infection. However, persistent and excessive inflammation leads to tissue damage rather than repair. TGF- β in particular is a potent pro-fibrotic mediator that activates fibroblasts and promotes their differentiation into myofibroblasts, which are responsible for excessive collagen production and extracellular matrix deposition. The prolonged presence of these cytokines sustains inflammation, delays resolution, and promotes fibrosis(11).

3. Aberrant tissue repair:

Normally, following injury and inflammation, the lung initiates a tightly regulated repair process aimed at restoring structure and function. However, in a subset of post-COVID patients, this process becomes aberrant. Instead of epithelial regeneration, fibroblasts proliferate and secrete large quantities of collagen and fibronectin, leading to the formation of fibrotic foci. Myofibroblasts, characterized by their contractile properties and resistance to apoptosis, accumulate in the interstitium, further disrupting alveolar architecture. This maladaptive repair is exacerbated by persistent inflammation and hypoxia, resulting in the formation of irreversible fibrotic tissue that impairs gas exchange and lung compliance. Over time, this can culminate in progressive fibrosing Interstitial Lung Disease (ILD).

4. Microvascular damage:

In addition to epithelial injury, SARS-CoV-2 also causes significant endothelial damage, contributing to vascular dysfunction. The endothelium expresses ACE2 receptors, making it a direct target for viral invasion. This results in endothelial activation, increased vascular permeability, and a pro-thrombotic state. Microvascular thrombosis is frequently observed in severe COVID-19 and has been implicated in worsening hypoxia and lung damage. Capillary dropout and rarefaction reduce perfusion and oxygen delivery, perpetuating a cycle of ischemic injury and fibrotic remodeling. The interplay between vascular injury and immune activation also contributes to the fibrotic cascade, as activated endothelial cells release cytokines and growth factors that further stimulate fibroblast(12)..

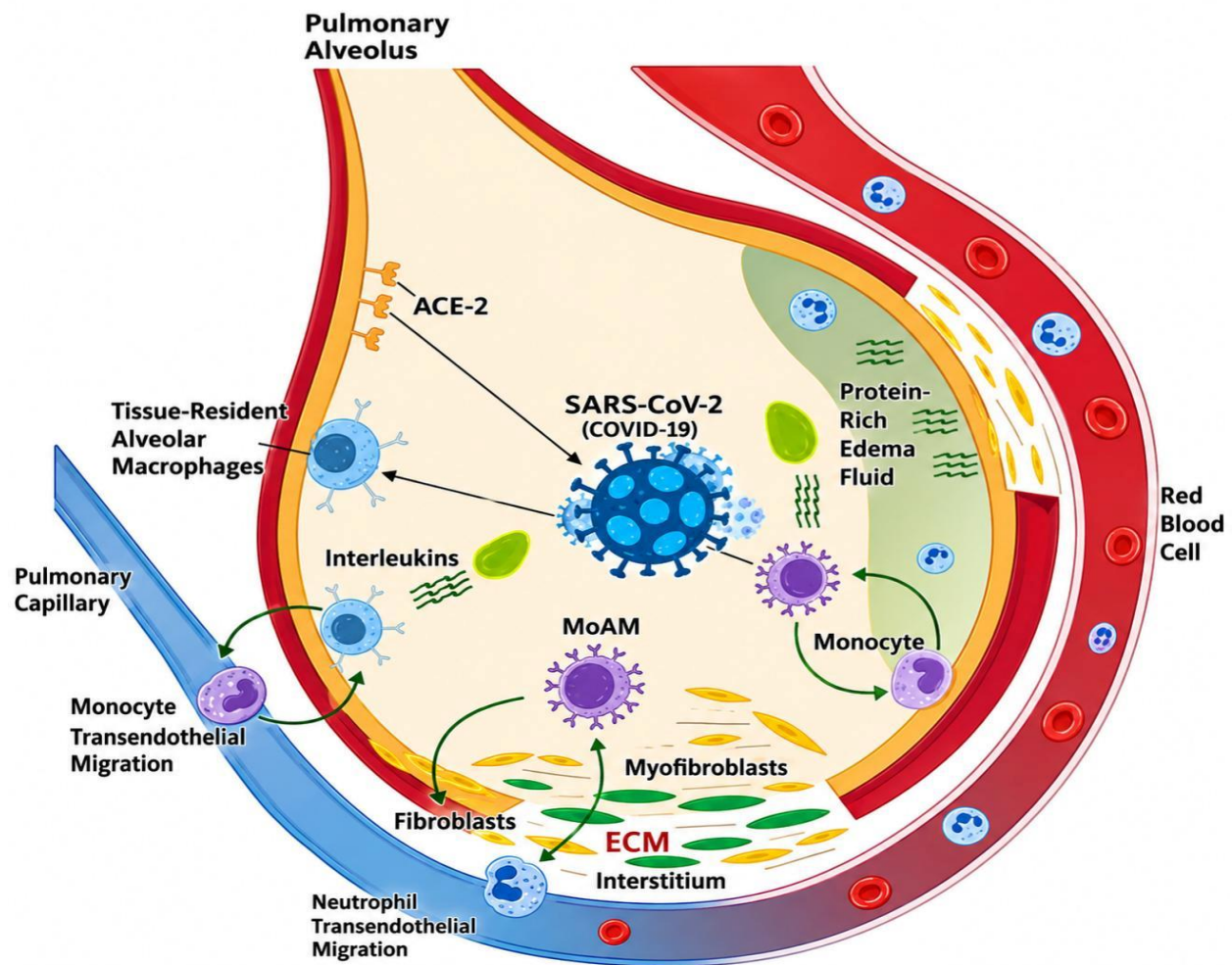


Fig 2: Pathophysiological mechanisms of post covid pulmonary fibrosis

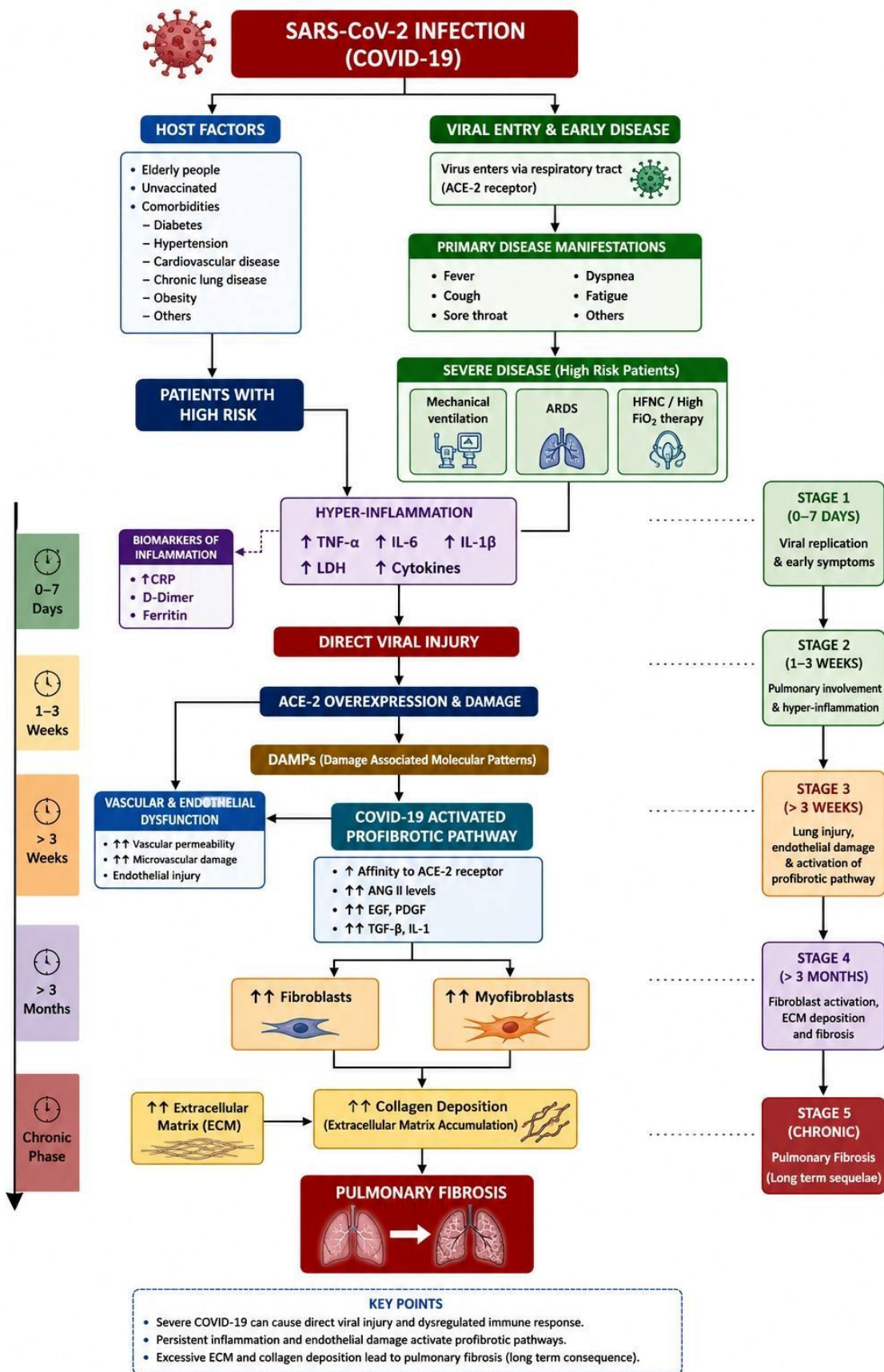


Fig 3: Process of post covid pulmonary fibrosis and risk factors

7. DIAGNOSIS

Clinical presentation

PC-ILD is a complex clinical syndrome for which, to date, no official diagnostic criteria exist. It is usually suspected in patients who, several weeks to months after clinical recovery from acute COVID-19, have chronic or ongoing respiratory symptoms such as exertional breathlessness, cough, chest tightness or discomfort, and fatigue. PC-ILD is also identified in asymptomatic patients on follow-up in select instances, especially where there are ongoing or worsening PFTs or imaging evidence of ILAs.

The diagnosis of PC-ILD is usually made based on an integrated assessment involving clinical evaluation, imaging of the chest and PFTs, after ruling out other explanations for ongoing symptoms. In cases where symptoms persist in the absence of radiological or functional impairment, alternative diagnoses, such as cardiovascular disease or deconditioning, should be considered(13).

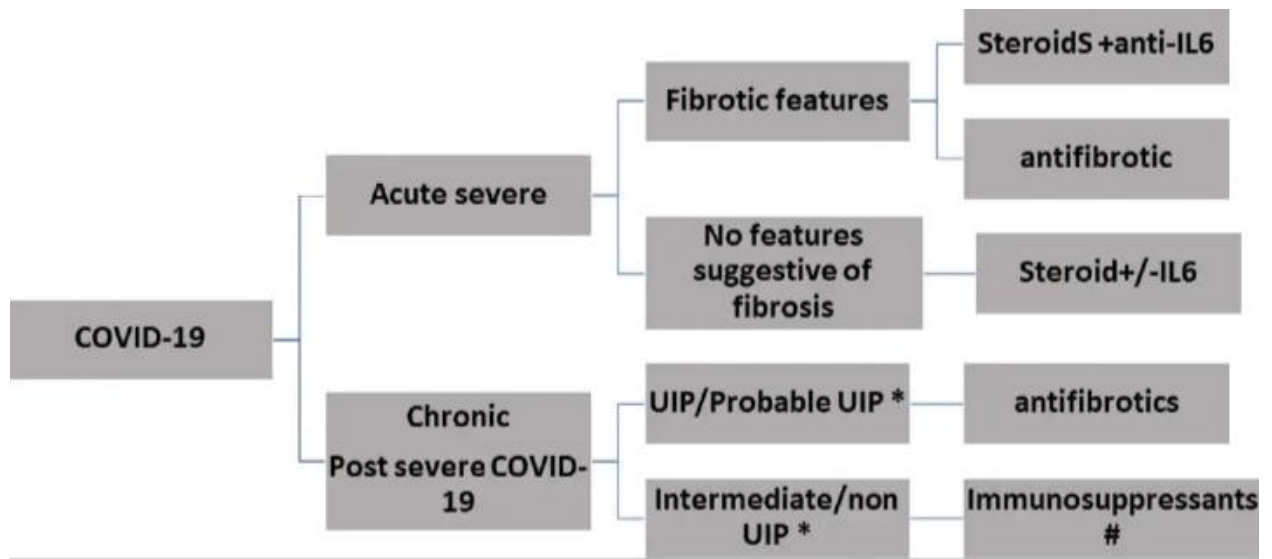
Radiographic findings in PC-ILD

Acute COVID-19 infection typically manifests on imaging as organising viral pneumonia with a broad spectrum of radiographic features. The most commonly reported chest CT findings include GGOs in 50–95% of cases and consolidations in 30–40%, both with a bilateral and peripheral distribution (figure 6). Less typical findings, such as reticulations (27%), nodules (3–15%) and the crazy-paving pattern (5–36%), may also be observed. Radiographic abnormalities frequently correlate with the same anatomical regions affected during the acute phase, supporting the hypothesis of resolving viral pneumonia or residual fibrosis following localised injury. Notably, fibrotic changes can appear as early as 2–3 weeks after symptom onset, particularly in patients with severe acute illness(14)

8. TREATMENT

Long-term treatment of post-COVID-19 ILDs depends on many factors but largely on the pattern of ILD involvement as well as the significance of the radiological abnormalities, i.e., ILA versus ILD. The most common pattern of post-COVID-19 ILD is OP, followed by NSIP. In both patterns, immunosuppressant therapy is the main treatment option, and antifibrotics are indicated for progressive fibrotic type not responding to immunosuppressants. On the other hand, antifibrotic can be the initial therapy of choice in those with UIP pattern. summarises the treatment approach for managing post-COVID-19 pulmonary fibrosis(15).

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- Pirfenidone, an antifibrotic agent, works by inhibiting the recruitment and accumulation of inflammatory cells, impeding fibroblast proliferation, reducing extracellular matrix deposition, and disrupting SARS-CoV-2 pathogenesis by inhibiting furin, a critical protein required for viral entry. Furthermore, it regulates signaling pathways associated with PC19-PF. These dual anti-inflammatory and antifibrotic properties suggest a potential therapeutic approach to slowing the progression of PC19-PF..
- Nintedanib, an alternative therapeutic option, is a tyrosine kinase inhibitor that targets the fibroblast and myofibroblast cascades, potentially affecting pulmonary angiogenesis. Notably, clinical trials such as INPULSIS have demonstrated its capacity to attenuate the decline in forced vital capacity (FVC) observed in IPF patients, thus impeding disease progression over a brief period of 4–6 weeks.. Antifibrotic therapies show promise in slowing the progression of fibrosis in patients with confirmed radiological evidence of fibrosis and an increased risk of disease progression.
- Steroids: Most patients who develop PC-ILD are hypoxic, and after the results of the RECOVERY trial[35] were announced on June 16, steroids became the standard of care in hypoxic patients in ICUs across the world. We would like to stress that the doses of steroids recommended in COVID-19, in the acute stage, were modest doses of 4–6 mg dexamethasone for no more than 10 days. Despite most patients currently receiving steroids in equivalent or higher doses, steroids alone do not seem to be sufficient to prevent the development of fibrosis. There are initial reports of patients with COVID-19 pneumonia going on to develop well-marked PC-ILD and fibrosis despite being on moderately high doses of steroids through their illness. Steroids should, in our opinion, be continued on discharge if the CT scan prior to discharge continues to show significant GGOs and the patient remains hypoxic. At this stage again, we would caution against the use of large doses of oral steroids as they could worsen hyperglycemia and contribute to proximal myopathy which in turn would retard the patients' mobility and rehabilitation. We recommend using no more than 20–30 mg of prednisolone at discharge and tapering it on follow-up depending on the patient's response
- A biomarker to identify which of these patients will proceed to develop fibrosis would indeed be invaluable, but till one emerges, CT scan evidence of fibrosis with traction bronchiectasis and/or honeycombing would be useful to identify which patients would potentially benefit from antifibrotics. We would also argue that antifibrotics should be reserved for those post-COVID patients who demonstrate evidence of progression. Giving these drugs to those who are spontaneously improving over time or whose fibrosis is static is unlikely to be useful. Of course, progression is difficult to ascertain when the patient is first seen and is only apparent over time, making

the correct identification of the subset of patients most likely to benefit from antifibrotic therapy a difficult task(16).

- Pulmonary rehabilitation, in our opinion, is also of vital importance and must be commenced as soon as the patient is shifted out of the ICU and continued at home.
- Anticoagulation: Patients with PC-ILD continue to be at high risk for clotting complications after discharge. Even a minor pulmonary embolism at this stage in a hypoxic patient would be a major setback. They are not yet fully mobile because of muscle wasting and breathlessness and should be continued on anticoagulants for a few weeks or months post discharge until their mobility improves.
- Lung transplantation: There are already reports of lung transplantation being successfully offered to patients with severe PC-ILD though this is not practical, and at present can only be offered to very select numbers of patients with COVID-19-related ARDS(17).

PREVENTION STRATEGIES TO MITIGATE PC19-PF

Given the lack of definitive treatments for PC19-PF, prevention is crucial in reducing the risk of PC19-PF. Since severe COVID-19 is the main driver of fibrotic lung damage, minimizing disease severity is key. Vaccination remains the most effective tool, significantly lowering mortality and hospitalization across all major variant waves (Pre-Alpha to Omicron), as shown in a large South Carolina cohort study of over 860,000 adults. By reducing severe illness, vaccination helps prevent lung injury and fibrotic sequelae(18).

Additional preventive strategies such as mask-wearing, hand hygiene, physical distancing, and improved ventilation in diagnosed individuals remain important for curbing viral spread and associated complications. Emerging evidence also shows that newer SARS-CoV-2 variants like Omicron cause milder lung disease, especially in vaccinated populations. Booster doses further reduce pneumonia severity. Moreover, early use of antivirals like nirmatrelvir/ritonavir has been linked to a reduced risk of post-COVID lung complications, regardless of prior vaccination or infection, likely by limiting viral replication and inflammation(19).

Preventive efforts should also extend into the acute and post-acute phases of illness. During acute infection, corticosteroids, antivirals, and lung-protective ventilation strategies can reduce lung damage. Following recovery, early pulmonary rehabilitation, regular lung function and imaging follow-up, and healthy lifestyle changes support lung healing. Patient education, adherence to care, and accessible follow-up are also key components of long-term prevention and recovery(20).

CONCLUSION:

Post-COVID-19 pulmonary fibrosis is an important long-term respiratory complication, particularly in patients who experienced severe COVID-19 pneumonia, acute respiratory distress syndrome, prolonged hospitalization, or mechanical ventilation. Persistent inflammation, epithelial injury, abnormal tissue repair, and profibrotic pathways may contribute to structural lung changes and impaired pulmonary function. Early identification through clinical assessment, pulmonary function testing, and appropriate chest imaging is important for monitoring patients with persistent respiratory symptoms. However, not all post-COVID fibrotic-appearing changes are necessarily permanent, as some abnormalities may gradually improve during follow-up. At present, there is no universally established, disease-specific treatment for post-COVID-19 pulmonary fibrosis, and evidence for antifibrotic therapies remains an area of ongoing research. Therefore, long-term follow-up, pulmonary rehabilitation, appropriate supportive care, and further research into biomarkers and targeted antifibrotic strategies are essential. Better understanding of the mechanisms and natural history of this condition may help develop effective approaches to prevent progression and improve the quality of life of COVID-19 survivors.

Reference

- [1]. Muhammad A, Balan I, Yadav S, et al. Post-COVID-19 pulmonars fibrosis.Cureus.2022;14(3).
- [2]. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in discharged from hospital: a cohort study. Lancet. 2021;397:220–32.
- [3]. Mylvaganam RJ, Bailey JI, Sznajder JI, et al. Recovering from a pandemic: pulmonary fibrosis after SARS-CoV-2 infection. Eur Respir Rev. 2021;30: 210194.
- [4]. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601–15.
- [5]. Tang YW, Johnson J, Cruz-Gervis R, Graham B, Brigham K, Oates J, et al. Increased detection of herpesvirus DNA in idiopathic pulmonary fibrosis. Chest. 2001;120:74S–5S.
- [6]. Tang YW, Johnson JE, Browning PJ, Cruz-Gervis RA, Davis A, Graham BS, et al. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol. 2003;41:2633–40.
- [7]. Tang YW, Johnson JE, Browning PJ, Cruz-Gervis RA, Davis A, Graham BS, et al. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol. 2003;41:2633–40.
- [8]. Ball L, Barisione E, Mastracci L, Campora M, Costa D, Robba C, et al. Extension of collagen deposition in COVID-19 post mortem lung samples and computed tomography analysis findings. Int J Mol Sci. 2021;22:7498.
- [9]. De Roquetaillade C, Bredin S, Lascarrou JB, Soumagne T, Cojocaru M, Chousterman BG, et al. Timing and causes of death in severe COVID-19 patients. Crit Care. 2021;25:224.
- [10]. Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon R, Jr., Kim S, et al. Early outcomes after lung transplantation for severe COVID-19: A series of the first consecutive cases from four countries. Lancet Respir Med. 2021;9:487–97.
- [11]. Gulati A, Lakhani P. Interstitial lung abnormalities and pulmonary fibrosis in COVID-19 patients: A short-term follow-up case series. Clin Imaging. 2021;77:180–6.
- [12]. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: A longitudinal cohort study. Lancet. 2021;398:747–58.
- [13]. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month follow- up chest CT findings after severe COVID-19 pneumonia. Radiology. 2021;299(1).
- [14]. Alarcón-Rodríguez J, Fernández-Velilla M, Ureña-Vacas A, et al. Radiological management and follow-up of post-COVID-19 patients. Radiologia. 2021;63:258.
- [15]. Inoue Y, Kaner RJ, Guiot J, et al. Diagnostic and prognostic biomarkers for chronic fibrosing interstitial lung diseases with a progressive phenotype. Chest. 2020;158:646–659.

- [16] D'Ettorre G, Gentilini Cacciola E, Santinelli L, et al. Covid-19 sequelae in working age patients: a systematic review. *J Med Virol.* 2022;94(3):858–68. .
- [17]. Mongelli A, Barbi V, Gottardi Zamperla M, et al. Evidence for Biological Age Acceleration and Telomere Shortening in COVID-19 Survivors. *Int J Mol Sci.* 2021;22(11):6151.
- [18] Rai DK, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis. Is it real threat? *Indian J Tuberc.* 2021;68(3):330–3. .
- [19]. Wu C, Chen X, Cai Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. China *JAMA Intern Med.* 2020;180(7):934–43.
- [20] Liu X, Zhou H, Zhou Y. Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. *J Infect.* 2020;81(1).



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