Post-Covid-19 Pulmonary Fibrosis: Pathogenesis, Risk Factors, Diagnosis, And Emerging Therapeutic Strategies

D. Suresh[1*], C. Pavithra[1], R. Pravalika[1], P. Sravya[1], Dr K. Thirumala Naik[2]

1* Pharm D Intern, Department of Pharmacy Practice, Krishna Teja Pharmacy College, Tirupati

Pharm D Interns, Department of Pharmacy Practice, Krishna Teja Pharmacy College, Tirupati

Associate Professor & Head Clinical Preceptor, Krishna Teja Pharmacy College, Tirupati

Abstract:
Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant global morbidity and mortality. While many patients recover, a subset experiences persistent pulmonary complications, including post-COVID-19 pulmonary fibrosis (PCPF), a condition characterized by irreversible lung scarring and impaired gas exchange. Several risk factors, such as advanced age, male sex, pre-existing lung disease, and severe COVID-19 requiring mechanical ventilation, contribute to its development. Radiological assessments, particularly high-resolution computed tomography, reveal hallmark features such as reticular opacities, traction bronchiectasis, and parenchymal bands, aiding in diagnosis. Current therapeutic strategies include corticosteroids, antifibrotic agents (pirfenidone, Nintedanib), and immunosuppressants, though no standardized treatment exists. Pulmonary rehabilitation and supplemental oxygen therapy offer symptomatic relief and improved functional outcomes. Future research explores novel agents, including buloxibutid, saracatinib, sirolimus, and resveratrol, as potential antifibrotic therapies. This review provides an overview of the pathogenesis, clinical manifestations, diagnostic approaches, and evolving treatment strategies for PCPF, emphasizing the need for continued research to optimize patient outcomes.

Key words: SARS-CoV-2, ARDS, Pulmonary Fibrosis, fibroblasts, Pirfenidone, Nintedanib

Introduction:

Coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in December 2019. As this disease is highly contagious, it quickly spread across the globe, becoming the massive pandemic of the 20th century[1]. By June 25, 2021, about 180 million cases have been confirmed with this disease worldwide, including about 4 million deaths[2]. The World Health Organization proclaimed a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020 . As of 13 December 2023, over 772 million confirmed cases and almost 7 million deaths were reported globally. [3]

Patients infected with COVID-19 often experience range of symptoms, specifically respiratory issues that can progress to severe pneumonia and Acute Respiratory Distress Syndrome[ARDS]. Additionally, it has been reported that some individuals who recovered from the disease with negative laboratory tests for the virus still experience persistent symptoms, ranging from mild discomfort to severe respiratory distress which may require long-term oxygen therapy due to residual effects such as pulmonary fibrosis. SARS-CoV2 has the potential to impact multiple organs, causing acute damage and long-term complications [2&4]. Pulmonary fibrosis following SARS-CoV-2 respiratory viral infection occurs as a sequela of severe lung damage in which

a significant fraction of patients hospitalized with acute respiratory distress syndrome develop progressive pulmonary fibrosis.[5]

The term Pulmonary Fibrosis refers to a pathological condition in which the lung parenchyma undergoes an irreversible process of over growth, hardening, and scarring due to excess deposition of extracellular matrix components including collagen. Interstitial lung diseases(ILDs) encompass a diverse group of disorders with varying clinical, radiological, and pathological features that extensively involve lung parenchyma. Pulmonary fibrosis is a key characteristic of several ILDs, all of which involve chronic inflammation and or collagen deposition within the interalveolar space. This process disrupts gas exchange by impairing the movement of oxygen and carbon dioxide across the alveolar epithelium [6]. The clinical manifestations of Post Covid Pulmonary Fibrosis(PCPF)have various symptoms, including dyspnoea, dry cough, fatigue, chest pain, and weight loss, which are related to decreased quality of life. The complications of PCPF that increase the risk of death are respiratory failure, sepsis, and acute kidney injury.[4]

Pathogenesis of PCPF:

Although pulmonary fibrosis has been observed in varying extents in patients with SARS CoV-2 infection, its underlying mechanism remain insufficiently studied and elucidated. Several potential causes have been suggested, including chronic inflammation, as well as idiopathic, genetic, and age related fibroproliferative processes[4]. Pulmonary fibrosis can develop when the lung's healing process becomes overactive or does not resolve properly after injury. Although different pulmonary and extra pulmonary related factors can lead to acute respiratory distress syndrome (ARDS), they may share a common pathway that results in fibrosis. This process can be exacerbated by production of cytokines from lung epithelial cells and immune cells or by damage caused by mechanical ventilation.

One key pathway in fibrosis is the fibroblast, a cell that helps repair lung tissue. When the alveoli are injured, fibroblasts move to the damaged areas, produce and regulate the supportive tissue (extracellular matrix), and can transform into myofibroblasts, which contribute to scarring. These cells respond to inflammatory signals such as interleukin (IL)-1β, IL-6, and transforming growth factor (TGF)-β1—some of which can be upregulated in severe COVID-19 cases[7]. Finally, reactive oxygen species, when produced in excess from the innate inflammatory system, induce epithelial apoptosis and the secretion of profibrotic cytokines, and stimulate the differentiation of fibroblasts in myofibroblasts [8]

Another important pathway in fibrosis is a type of immune cell called monocyte-derived alveolar macrophages (MoAMs). These macrophages interact with fibroblasts to promote tissue repair. Macrophages release platelet-derived growth factor A (PDGFA) to activate fibroblasts, while fibroblasts produce macrophage colony-stimulating factor (M-CSF) to attract more macrophages. If this repair process does not shut down properly, the continued cycle of fibroblast and macrophage activity leads to excessive scarring, and making breathing difficult.[7]

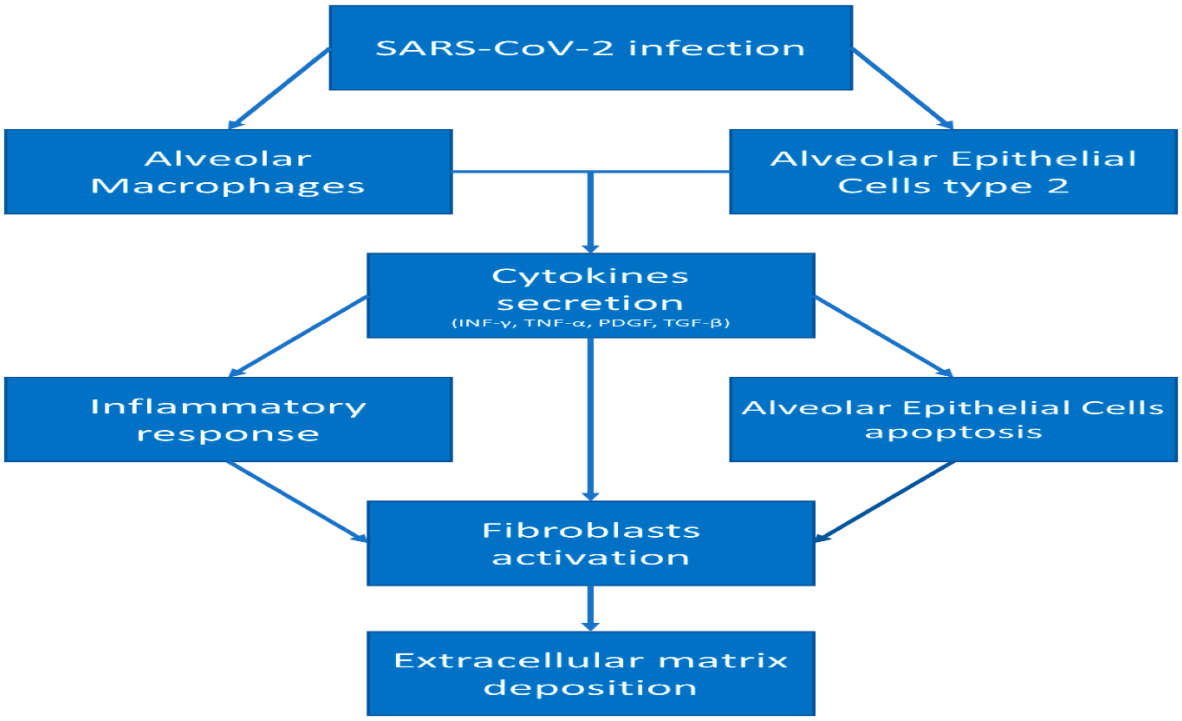

Figure 1.1: Describes the Pathogenesis of PCPF (Post Covid Pulmonary Fibrosis)

Chronic persistent inflammation is a hallmark of SARS-CoV-2, particularly in severe cases with Pulmonary fibrosis. However, transcriptomic analysis of circulating monocytes has shown reduced responsiveness to interferon (IFN) signalling, contributing to delayed resolution of acute respiratory distress syndrome (ARDS) in severe COVID-19. An impaired or dysregulated IFN response during early infection appears to initiate significant downstream effects, leading to hyperimmune activation and cytokine storm. Specifically, in SARS-CoV-2-induced PF, lower levels of circulating IFN-γ (type II IFN) may increase the risk of persistent fibrosis. Additionally, another study linked PF development in post-COVID-19 patients to reduced circulating IFN-β and elevated IL-1α and TGF-β levels. [9]

Risk factors:

Several risk factors may contribute the development of pulmonary fibrosis in COVID-19 patients, including older ageing, male sex, comorbidities such as diabetes and hypertension, preexisting lung conditions and the need for ventilatory support. However, it is also possible that certain medications could also contribute to the development or worsening of pulmonary fibrosis in patients with COVID-19. Prolonged use of amiodarone or cancer chemotherapies such as bleomycin has been associated with fibrosis development. [5&10]

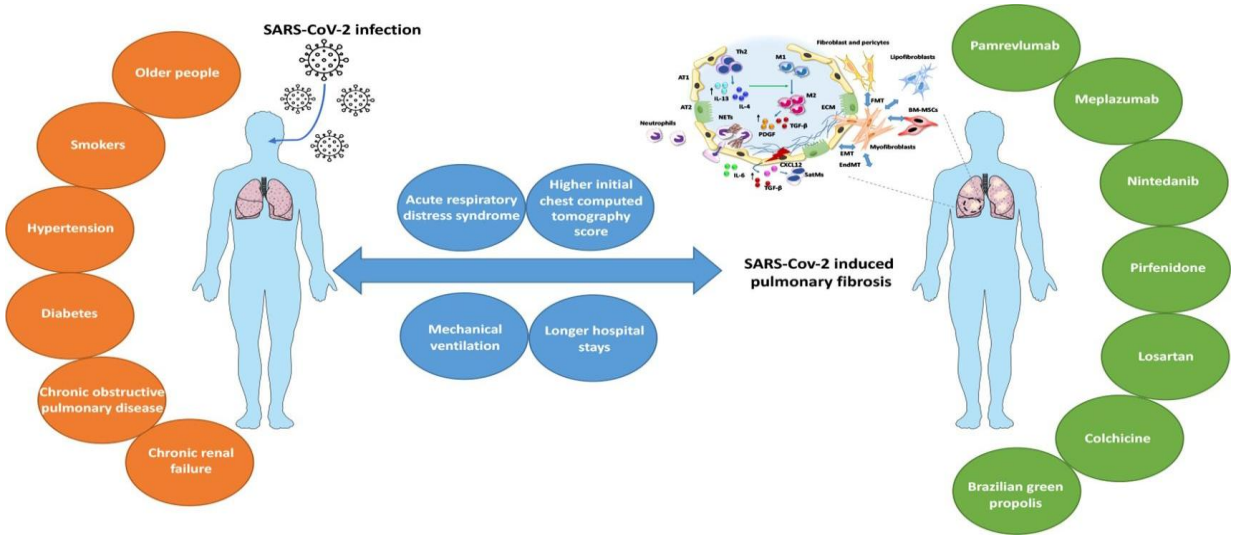

Figure 1.2; shows various Risk Factors of PCPF (Post Covid Pulmonary Fibrosis)

Radiological findings:

Different types of functional respiratory evaluations can be performed objectively, commonly used are Pulmonary Function Tests(PFTs) such as spirometry, diffusion capacity, and lung volume measurements. Additionally, tests that assess respiratory muscle strength and airway resistance helps to improve the study of lung properties and allowing for the objective determination of the impacts of acute or chronic respiratory diseases.[11]

Post-COVID-19 Pulmonary Fibrosis (PCPF) can be detected through radiological evaluations, particularly on follow-up CT scans. Previous studies have reported that post-COVID-19 sequelae may present fibrosis-like features, including a honeycomb pattern, reticular opacities, traction bronchiectasis, and parenchymal bands. Additionally, non-fibrotic manifestations such as ground-glass opacities (GGOs), consolidation, and nodules may also be observed. However, the presence of a honeycomb pattern, a definitive marker of fibrosis, rarely seen in COVID-19 cases [12].

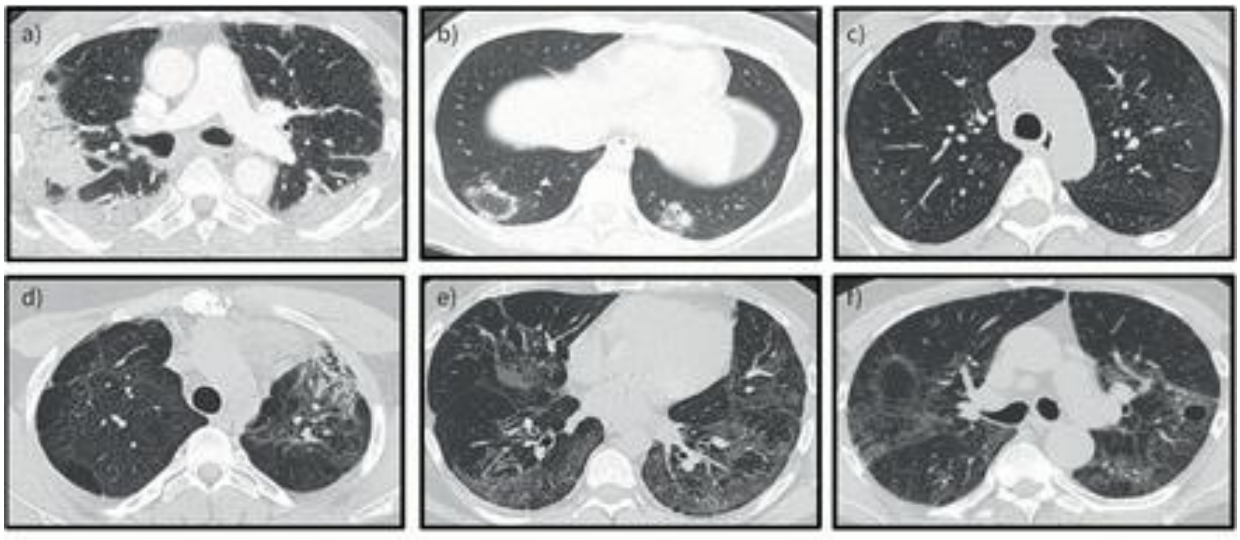

Figure1.3: Representative CT scan findings (a) dense consolidations, (b) patchy consolidation and ground-glass opacities with an atoll sign, (c) diffuse ground-glass opacities, (d) fibrosis with honeycomb

changes in the left upper lobe, (e) ground-glass opacities with reticular changes, and (f) ground-glass opacities, reticulation, and a pneumatocele.

Pharmacological approaches for post COVID-19 pulmonary fibrosis:

To our knowledge, there is currently no clear consensus regarding the treatment of a patient with interstitial pulmonary involvement due to COVID-19. Immunosuppressive therapy is the primary treatment approach, while antifibrotic agents are recommended for progressive fibrotic forms that do not respond to immunosuppressants. Corticosteroids became the cornerstone pharmacological treatment for patients with severe lung disease in the course of SARS-CoV-2 infection [1&13]. Pirfenidone (PFN) is an antifibrotic drug with a considerable anti -inflammatory role in treating idiopathic pulmonary fibrosis (IPF). PFN suppresses the accumulation and recruitment of inflammatory cells, fibroblast proliferation, and extracellular matrix deposition. Nintedanib is another antifibrotic drug approved by the FDA for treating pulmonary fibrosis which is a tyrosine kinase inhibitor that inhibits fibroblast and myofibroblast cascades [14]. Immunosuppressants can help regulate an exaggerated immune response. Medications such as tacrolimus, cyclosporine are calcineurin inhibitors which suppress the activity of T cells. Mycophenolate mofetil, inhibits the proliferation of both T and B cells, further modulating immune activity in post covid conditions. Corticosteroids suppress inflammation by reducing pro-inflammatory cytokine release. In post COVID-19 fibrosis, an overactive immune response can lead to tissue damage, and corticosteroids help mitigate this effect. They inhibit fibroblast activation and collagen synthesis, slowing fibrosis progression. By interfering with collagen deposition and other fibrotic components, corticosteroids can help prevent or reduce the severity of fibrotic changes in affected tissues.[3]

Rehabilitation and Nonpharmacological Management

Non-pharmacological therapy and rehabilitation play a crucial role in alleviating severe symptoms of post-COVID-19 pulmonary fibrosis (PC19-PF) and enhancing patients' quality of life. Recent clinical guidelines highlight the benefits of pulmonary rehabilitation, which incorporates exercise training, patient education, and behavioural modifications to improve both physical and psychological well-being. Patients experiencing resting hypoxemia or severe oxygen desaturation during exercise may benefit from supplemental oxygen therapy, which can help alleviate symptoms and enhance overall quality of life.[14]

Future directions:

In the ever-evolving field of medical research, the quest for innovative therapeutic approaches has identified four promising molecules: buloxibutid, saracatinib, sirolimus, and resveratrol. Recent studies have explored the role of buloxibutid, an angiotensin II type-2 receptor (AT2R) agonist, in pulmonary fibrosis patients, particularly in relation to the AT2R pathway and the activation of the renin–angiotensin system—two key mechanisms involved in SARS-CoV-2 entry and the host's immune response. [3]

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