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JPRR JOURNAL OF PULMONOLOGY AND RESPIRATORY RESEARCH
ISSN 2639-9954

Commentary

Post-COVID Pulmonary Fibrosis: Pathophysiological Mechanisms, Diagnostic Tools, and Emerging Therapies

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Abstract

Post-COVID pulmonary fibrosis has emerged as a significant long-term complication among survivors of severe SARS-CoV-2 infection. This review highlights the underlying pathophysiology, diagnostic modalities, and recent advances in the diagnosis and management of post-COVID pulmonary fibrosis. As global cases of COVID-19 continue to evolve, understanding and addressing this emerging chronic respiratory condition is critical for long-term patient care.

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Submitted: April 23, 2025
Approved: May 08, 2025
Published: May 09, 2025

How to cite this article: Sabu ST. Post-COVID Pulmonary Fibrosis: Pathophysiological Mechanisms, Diagnostic Tools, and Emerging Therapies. J Pulmonol Respir Res. 2025; 9(1): 009-013. Available from: https://dx.doi.org/10.29328/journal.jprr.1001067

Keywords: COVID-19; Pulmonary fibrosis; Antifibrotics; Lung injury; rehabilitation; Post-acute sequelae

Introduction

The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has left an indelible mark on global health. While the acute phase of the illness, characterized by respiratory and systemic symptoms, has been extensively studied and managed, there is a growing recognition of the long-term complications that persist in a substantial subset of survivors. Among the various post-acute sequelae of SARS-CoV-2 infection, pulmonary fibrosis has emerged as a particularly concerning condition due to its potential for progressive respiratory decline and permanent lung damage.

Pulmonary fibrosis refers to a pathological process marked by the thickening and scarring (fibrosis) of lung tissue, leading to a decline in respiratory function. It involves an aberrant wound healing response to lung injury, culminating in excessive deposition of collagen and extracellular matrix, and architectural distortion of the lungs. Post-COVID pulmonary fibrosis, while not a new disease entity, represents a novel clinical challenge due to the scale of the pandemic, the heterogeneous clinical presentations and the evolving insights into its pathogenesis.

Emerging evidence suggests that approximately 20% to 30% of patients recovering from moderate to severe COVID-19 pneumonia develop radiographic or physiologic evidence of fibrotic lung changes within three to six months of recovery. This prevalence is especially pronounced in individuals who required mechanical ventilation or experienced Acute Respiratory Distress Syndrome (ARDS). High-Resolution Computed Tomography (HRCT) scans of such patients frequently reveal ground-glass opacities, interstitial thickening, and, in some cases, honeycombing—hallmarks of fibrotic Interstitial Lung Disease (ILD).

The burden of COVID-related pulmonary fibrosis is not merely clinical but also socioeconomic. Affected individuals often face reduced exercise tolerance, persistent dyspnea, impaired quality of life, and a prolonged need for supplemental oxygen. This can result in significant healthcare utilization, loss of productivity, and psychological distress. Furthermore, the long-term implications of COVID-related pulmonary fibrosis are yet to be fully understood, raising concerns about the development of chronic progressive fibrotic diseases in previously healthy individuals.

Pathophysiologically, the development of fibrosis after COVID-19 is believed to be multifactorial, involving TGF-β, IL-6, fibroblast activation, alveolar epithelial damage, microvascular dysfunction, and transition from inflammation to fibrosis. These processes culminate in the activation of fibroblasts and myofibroblasts, leading to irreversible remodeling of the lung parenchyma. The overlap between the immunological mechanisms seen in COVID-19 and those observed in Idiopathic Pulmonary Fibrosis (IPF) and other

fibrosing interstitial lung diseases has prompted clinicians and researchers to explore common pathways and therapeutic interventions.

From a diagnostic standpoint, the identification and monitoring of post-COVID pulmonary fibrosis require a multidisciplinary approach. Imaging techniques, primarily HRCT, Pulmonary Function Tests (PFTs), and clinical assessments are pivotal in evaluating the extent and progression of fibrotic changes. Additionally, Biomarkers such as KL-6, SP-D, and TGF-β are being explored and should be correlated with imaging and PFTs for their potential role in early detection and prognostication.

Therapeutically, there is no consensus yet on a standardized treatment protocol for COVID-related pulmonary fibrosis. However, treatment strategies are largely extrapolated from established therapies for idiopathic pulmonary fibrosis and other ILDs. Antifibrotic agents like pirfenidone and nintedanib, which have shown efficacy in slowing disease progression in IPF, are currently being evaluated in clinical trials for their utility in post-COVID settings. Pulmonary rehabilitation, corticosteroids in selected cases, and supportive therapies such as oxygen supplementation also form integral components of management.

In conclusion, post-COVID pulmonary fibrosis represents a pressing healthcare concern with implications for long-term patient outcomes and health system preparedness. As the global medical community continues to navigate the challenges posed by COVID-19, it is imperative to focus attention on post-acute sequelae, particularly fibrotic lung disease. A comprehensive understanding of the pathophysiology, timely diagnosis, and evidence-based management of post-COVID pulmonary fibrosis will be crucial in mitigating its impact and improving quality of life for survivors. This review aims to summarize current knowledge regarding the pathophysiology, diagnosis, and emerging therapeutic strategies for post-COVID pulmonary fibrosis.

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 hyperinflammatory 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.

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 fibroblasts.

Together, these pathophysiological mechanisms create a self-perpetuating cycle of injury, inflammation, and fibrosis.

Understanding these interconnected pathways is essential for identifying potential therapeutic targets and optimizing management strategies for affected patients.

Diagnostic approaches

Timely and accurate diagnosis of post-COVID pulmonary fibrosis is essential for early intervention and optimized management. Given the complexity and variability in post-COVID lung disease presentation, a multimodal approach that integrates imaging, physiological testing, biomarkers, and functional assessment is required. Below is an in-depth discussion of the current diagnostic modalities.

1. High-Resolution Computed Tomography (HRCT): HRCT is considered the cornerstone for diagnosing and monitoring post-COVID fibrotic lung disease. It offers detailed imaging of the lung parenchyma, enabling the identification of subtle fibrotic changes that are not visible on conventional chest X-rays. Key radiographic findings in COVID-related pulmonary fibrosis include:

- **Ground-glass opacities (GGOs):** Often represent areas of active inflammation or early fibrosis.
- **Interlobular septal thickening and reticulations:** Indicative of interstitial involvement.
- **Traction bronchiectasis:** Reflects architectural distortion due to fibrosis.
- **Honeycombing:** Suggestive of established fibrosis and poor prognosis.

Serial HRCT scans are essential for monitoring disease progression or resolution over time. Imaging findings should be correlated with clinical symptoms and functional measures to guide therapy. The use of standardized scoring systems such as the CT severity index or visual fibrosis scores may aid in consistent reporting.

2. Pulmonary Function Tests (PFTs): PFTs are essential in quantifying the physiological impairment associated with pulmonary fibrosis. Common abnormalities observed in post-COVID fibrotic patients include:

- **Reduced Forced Vital Capacity (FVC):** Reflecting restrictive ventilatory defect.
- **Decreased Total Lung Capacity (TLC):** Due to scarring and reduced lung compliance.
- **Impaired Diffusing Capacity for Carbon Monoxide (DLCO):** Often the earliest and most sensitive indicator of interstitial involvement. A A DLCO value less than 80% of predicted is commonly observed in COVID-related pulmonary fibrosis.

Serial PFTs allow for objective monitoring of disease progression or improvement and are invaluable in assessing treatment response. DLCO trends, in particular, can provide early insight into fibrotic activity before clinical deterioration.

3. Biomarkers: The search for non-invasive biomarkers for early diagnosis and prognostication of pulmonary fibrosis is an area of active research. While no biomarker has yet been validated for routine clinical use, several candidates are under investigation:

- **Krebs von den Lungen-6 (KL-6):** A mucin-like glycoprotein produced by regenerating alveolar type II cells. Elevated levels correlate with disease activity and extent of fibrosis.
- **Surfactant protein-D (SP-D):** A lung-specific marker of alveolar epithelial cell injury. It has been associated with both acute and chronic lung damage.
- **Transforming Growth Factor-beta (TGF-β),** a central mediator of fibrosis, is involved in fibroblast activation and extracellular matrix deposition.
- **Matrix metalloproteinases (MMPs):** Reflect matrix remodeling and have been implicated in both injury and repair phases of lung injury.

These biomarkers are currently limited to research settings but may, in the future, complement imaging and functional tests in the early identification and stratification of patients at risk for progressive fibrosis.

4. 6-Minute Walk Test (6MWT): The 6MWT is a simple, cost-effective tool to assess functional status in patients with chronic lung disease, including COVID-related pulmonary fibrosis. It provides insight into the patient's exercise tolerance and cardiopulmonary reserve.

Key parameters assessed during the 6MWT include:

- **Distance walked in 6 minutes:** A decline in walking distance may reflect disease severity.
- **Oxygen desaturation during exertion:** A drop in SpO2 by more than 4% or to below 88% is significant.
- **Heart rate recovery and dyspnea score (Borg scale):** Provide additional information about cardiovascular fitness and perceived exertion.

The test is especially useful for assessing the need for supplemental oxygen during activities of daily living and can help evaluate the impact of pulmonary rehabilitation.

Integrated assessment

No single diagnostic test is sufficient to diagnose or monitor post-COVID pulmonary fibrosis. Instead, a combination of clinical history, imaging, lung function testing, and, when feasible, biomarker evaluation offers the most comprehensive assessment.

Periodic reassessment is necessary, particularly in patients with persistent symptoms beyond 12 weeks of recovery, unexplained dyspnea, or declining functional status. Clinicians should also be vigilant for signs of progressive fibrosing ILD, such as worsening PFTs, increasing fibrosis on imaging, and functional decline, which may necessitate escalation of therapy.

In conclusion, a structured diagnostic pathway incorporating HRCT, PFTs, 6MWT, and emerging biomarkers offers the best approach to identifying and managing post-COVID pulmonary fibrosis in clinical practice.

Emerging therapeutic strategies

The management of post-COVID pulmonary fibrosis is currently a developing field, largely informed by treatment paradigms from Idiopathic Pulmonary Fibrosis (IPF) and other Interstitial Lung Diseases (ILDs). With no established treatment guidelines specific to COVID-related pulmonary fibrosis, clinicians rely on a multidisciplinary approach tailored to individual patient needs. Emerging strategies span pharmacologic, supportive, rehabilitative, and regenerative domains.

1. Antifibrotic therapy: Antifibrotic medications such as pirfenidone and nintedanib, both approved for the treatment of IPF, are being actively evaluated for their efficacy in managing post-COVID fibrotic lung disease.

- **Pirfenidone** exerts antifibrotic and anti-inflammatory actions by inhibiting transforming growth factor-beta (TGF-β) and other pro-fibrotic cytokines. It has demonstrated a slowing in lung function decline in IPF and is being studied for similar utility in post-COVID patients with progressive fibrosis.
- **Nintedanib** is a tyrosine kinase inhibitor that targets multiple growth factor receptors involved in fibrosis, including Fibroblast Growth Factor (FGF), Platelet-Derived Growth Factor (PDGF), and Vascular Endothelial Growth Factor (VEGF). It has been shown to reduce the rate of forced vital capacity (FVC) decline and may benefit patients exhibiting a fibrosing post-COVID phenotype.

Preliminary observational studies and early-phase trials have reported encouraging outcomes. Clinical trials such as NCT04607928 are exploring the safety and efficacy of these antifibrotic agents in COVID-related ILD. While data is still emerging, antifibrotics may be considered in patients with radiological and functional evidence of progressive fibrosis, especially when inflammation is minimal.

2. Corticosteroids: Corticosteroids play a controversial yet significant role in the treatment of post-COVID pulmonary fibrosis. They are most beneficial in the early inflammatory phase of lung injury rather than in established fibrosis.

In selected patients, particularly those with radiologic or histopathologic features suggestive of organizing pneumonia, corticosteroids may provide symptom relief and improve radiographic appearance.

However, prolonged use of systemic steroids is associated with adverse effects including hyperglycemia, osteoporosis, increased infection risk, and muscle wasting.

Current guidance recommends short-term, carefully titrated corticosteroid therapy for patients with evidence of persistent inflammation. It is critical to distinguish between inflammatory and fibrotic processes, often via HRCT and inflammatory markers, before initiating therapy.

3. Pulmonary rehabilitation: Pulmonary Rehabilitation (PR) is a cornerstone in the management of chronic respiratory diseases, and its role in COVID-related pulmonary fibrosis is increasingly recognized. These structured pulmonary rehabilitation protocols including aerobic exercise, physiotherapy, and respiratory training aim to enhance physical and emotional well-being.

Components of PR include:

- Supervised aerobic and resistance training
- Breathing exercises (e.g., diaphragmatic and pursed-lip breathing)
- Education on energy conservation and respiratory hygiene
- Psychological support services and individualized nutritional counselling

Studies show that patients undergoing PR experience significant improvements in exercise tolerance (e.g., 6MWT distance), dyspnea scores, and health-related quality of life (HRQoL). It is particularly effective for patients experiencing deconditioning and fatigue post-COVID.

Home-based or virtual PR programs have gained attention, particularly in response to pandemic-related restrictions, especially during pandemic-related restrictions, and can be integrated into long-term care.

4. Oxygen therapy: For patients with persistent hypoxemia following COVID-19, long-term oxygen therapy (LTOT) is essential to improve functional status and reduce complications.

Indications for oxygen therapy include:

- Resting oxygen saturation < 88%
- Significant desaturation on exertion (e.g., during 6MWT)
- Development of pulmonary hypertension or right heart strain due to chronic hypoxia

LTOT has been shown to improve survival in hypoxemic patients with chronic lung disease, reduce hospitalizations, and enhance activity levels. Oxygen therapy must be carefully titrated, and patients should be monitored for oxygen toxicity and CO_2 retention, particularly those with underlying COPD.

5. Stem cell therapy and regenerative medicine: Stem cell therapy is an emerging and experimental field in the management of pulmonary fibrosis, including post-COVID fibrosis.

- Mesenchymal Stem Cells (MSCs) derived from bone marrow, adipose tissue, or umbilical cord have anti-inflammatory, immunomodulatory, and tissue regenerative properties.
- MSCs secrete paracrine factors that modulate immune responses, reduce cytokine storm intensity, and promote alveolar epithelial repair.

Preliminary studies and early-phase clinical trials indicate potential benefits, though evidence remains inconclusive, with improvements in oxygenation, radiological findings, and inflammatory markers. However, larger randomized controlled trials are required to establish efficacy and safety.

Other avenues under regenerative medicine include:

- **Exosome-based therapies**: Leveraging extracellular vesicles for targeted repair.
- **Lung bioengineering and transplantation**: Still experimental but hold promise for end-stage disease.

Multidisciplinary Approach and Personalized Medicine

Given the heterogeneity of post-COVID lung involvement, a Multidisciplinary Team (MDT) approach is critical. This includes pulmonologists, radiologists, physiotherapists, psychologists, and palliative care specialists.

Future therapeutic directions may include targeted anti-cytokine therapies (e.g., anti-TGF-β agents), novel anti-fibrotics, and personalized immunomodulatory regimens based on genetic and molecular profiling.

Patient engagement, regular follow-up, and inclusion in registries and trials are key components in improving care and advancing our understanding of post-COVID pulmonary fibrosis.

Conclusion

Post-COVID pulmonary fibrosis is a rising clinical entity with potential long-term morbidity. Comprehensive diagnostic evaluation and timely initiation of appropriate therapies are crucial. While current treatments are largely extrapolated from idiopathic pulmonary fibrosis management, ongoing clinical trials and integration of long-term care models are crucial for future management strategies. Multidisciplinary collaboration, patient education, and policy-level initiatives targeting long-term COVID care are essential for healthcare preparedness to combat this looming public health challenge.