Review Article

Access this article online
Quick Response Code:

Website:
https://eurasianjpulmonol.org
DOI:
10.14744/ejp.2023.1004

Pulmonary fibrosis as a sequela of COVID-19 infection: What do we know?

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Abstract:

Coronavirus Disease 2019 (COVID-19), a highly infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has emerged as a global pandemic. The disease has a range of manifestations in terms of severity; it mainly causes respiratory dysfunction but can also lead to damage in multiple organs. Although the majority of COVID-19 patients can fully recover, severe cases may result in post-infectious complications. Pulmonary fibrosis is one of the severe long-term complications reported in COVID-19 that may lead to permanent lung damage or death. The long-term sequelae of COVID-19 raise significant global health concerns related to the pandemic. Currently, there is no proven effective strategy for managing post-COVID-19 pulmonary fibrosis. As its incidence is estimated to increase in the near future, it is important to learn about and stay updated on the progress of this disease. This article explores and discusses the latest clinical evidence on post-COVID-19 pulmonary fibrosis, including the underlying mechanisms, potential risk factors, and appropriate management options.

Keywords:

COVID-19, post-COVID, pulmonary fibrosis, risk factors

Introduction

Coronavirus Disease 2019 (COVID-19), a highly infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a global pandemic. Since its first reported cases in 2019 until the end of 2022, it has infected over 650 million individuals, resulting in more than 6.6 million deaths.[1] The virus can be transmitted from one person to another through respiratory droplets, close contact, and airborne routes. COVID-19 manifests with a range of symptoms, from mild manifestations like fever, fatigue, cough, and loss of smell or taste, to severe manifestations primarily characterized by respiratory dysfunction, such as acute respiratory distress syndrome (ARDS), and can also lead to multiple organ failure.[2] COVID-19 causes injuries to multiple organs and tissues, with extensive pulmonary involvement, and its pathology is similar to that of other coronavirus strains that cause Middle East Respiratory Syndrome (MERS) and Se-

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Received: 23-01-2023
Revised: 11-03-2023
Accepted: 09-07-2023
Published: 04-08-2023

How to cite this article: Putri SNV. Pulmonary fibrosis as a sequela of COVID-19 infection: What do we know? Eurasian J Pulmonol 2023;25:145-51.

vere Acute Respiratory Syndrome (SARS). Although the majority of COVID-19 patients will fully recover, recent studies estimate that around 70% of COVID-19 patients will continue to experience post-infectious complications, particularly in severe cases.

The World Health Organization (WHO) proposed a definition for "post-COVID-19 condition" or "Long COVID," which is defined as the presence of persisting or developing new symptoms three months after the initial infection, with the symptoms lasting for more than two months. Long after the primary infection, COVID-19 survivors may suffer significant parenchymal, functional, and physiological abnormalities.[3] Pulmonary fibrosis is one of the severe reported long-term complications of COVID-19 that may lead to permanent lung damage or death.[4] A previous study found that in four months post-hospitalization, 20% of non-mechanically ventilated and 72% of mechanically ventilated severe COVID survivors had fibrotic-like radiographic abnormalities.[5] The long-term sequela of COVID-19 might generate global health concerns related to the pandemic. This review explored the latest clinical evidence, including the underlying mechanism, potential risk factors, and management options for post-COVID-19 pulmonary fibrosis (PCPF).

Post-COVID-19 Pulmonary Fibrosis Mechanism

The COVID-19 infection mainly damages the lungs, resulting in acute respiratory distress syndrome (ARDS) in severe cases. Pulmonary fibrosis is an interstitial lung disease (ILD) well-known as a sequela of acute respiratory distress syndrome (ARDS). It is identified by gradual lesions of the lung tissue and impaired lung function.[6] Lung fibrosis may develop as a result of viral and immune-mediated mechanisms. The mechanism of post-COVID-19 pulmonary fibrosis (PCPF) was found to be different from that of idiopathic pulmonary fibrosis (IPF) and other fibrotic lung diseases. Pathological findings in PCPF revealed that the site of injury was in alveolar epithelial cells rather than endothelial cells.[7]

The most commonly acknowledged cause of lung fibrosis pathogenesis is due to epithelial cell injury, which then stimulates a fibroproliferative pathway.[8] The epithelial layer of the airway is a pseudostratified mucosa composed of cells that serve as barriers to pathogens, including SARS-CoV-2. An initial lesion in ARDS, through disfiguration of the alveolar-endothelial interface, leads to the loss of epithelial barrier function. This epithelial injury in extra-pulmonary sources of ARDS is probably caused by oxygen toxicity and inflammation, both of which can result in alveolar cell death, negatively charged glycocalyx loss, and the buildup of protein-rich alveolar edema.[8] As type II alveolar cells specifically express the angiotensin-converting enzyme-2 (ACE-2) receptor, there is significant binding between the SARS-CoV-2 virus and the ACE-2 receptor.[9]

In the lung fibrosis mechanism, ACE-2 is known to have a protective role. The diminished expression of the ACE-2 receptor results in an increase in angiotensin II levels, which plays a significant role in inflammation and the fibrotic process by releasing reactive oxygen species, pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), and activating transforming growth factor beta (TGF-ß1). This condition causes fibroblasts to proliferate, migrate, and differentiate into myofibroblasts, where collagen and fibronectin are then deposited.[8,9] Bronchoalveolar epithelial repair and surfactant generation are hindered by this directly viral-mediated cell death of the stem cells, which accelerates the course of severe COVID-19 into ARDS.[8]

Fibrosis can manifest as either a stable or progressive disease. Due to the excessive deposition of extracellular matrix (ECM) components, such as collagen, laminin, and fibronectin, in the parenchymal lung tissue, both stable and progressive fibrotic lung diseases are linked to considerable morbidity. As a result, alveolar walls become thickened, impairing gas exchange and increasing the likelihood of dyspnea, exhaustion, and exercise intolerance. One of the principal initiating mechanisms of the disease is considered to be alveolar epithelial damage, while the activated fibroblast is thought to be its main effector.[10]

The development of pulmonary fibrosis may also occur as a result of a cytokine storm brought on by an abnormal immune mechanism. The dysregulation of matrix metalloproteinases in the inflammatory phase of ARDS leads to endothelial and epithelial damage. In addition to vascular endothelial growth factor (VEGF), cytokines such as IL-6 and tumor necrosis factor-α (TNFα) are thought to play a role in the fibrosis process.[11]

Potential Risk Factors

Although it has not been completely defined yet, multiple studies have found some risk factors that have been linked to the development of pulmonary fibrosis as a result of COVID-19. Several risk factors associated with PCPF are age, genetics, gender, smoking status, the presence of underlying disease, COVID-19 severity, and Intensive Care Unit (ICU) admission/use of mechanical ventilation.[4,6,7]

Age: Advanced age is considered a prominent risk factor susceptible to the development of PCPF. Increased age is associated with lung parenchyma stiffening, disruption of intracellular communication, stem cell exhaustion, extracellular matrix (ECM) dysregulation, and a decreased immune response, all of which lead to poor outcomes. A prior study found that the median ages for PCPF and deceased COVID-19 patients are 56 and 62 years old, respectively. Elderly patients were also found to be associated with the risk of pulmonary fibrosis development at six months post-hospitalization. Although the reason has not been fully defined, a current study revealed that older age is more vulnerable to both SARS and MERS, which are similar to SARS-COV-2 infection, and more likely to develop severe complications, including pulmonary fibrosis.[12]

Genetics: Previous studies have demonstrated that severe COVID-19 is associated with genes evolved in innate antiviral defenses, inflammatory lung damage, and the ABO blood group system.[13] Genome-wide association studies have observed various genes related to the development of pulmonary fibrosis, although no study to date has specifically examined genetic associations with PCPF. This suggests that COVID-19 infection may result in more advanced pulmonary fibrosis in patients who have genetic changes associated with lung fibrosis development.[13]

Gender: Multiple studies have reported that men are more likely to experience pulmonary fibrosis following a COVID-19 infection.[14] A possible explanation for this condition is the presence of androgens, which can improve the fusion of host cells and viruses by promoting transmembrane serine protease 2 (TMPRSS2). TMPRSS2 is an endothelial cell surface protein that plays a role in SARS-CoV-2 entry and transmission.[6]

Smoking status: Various pulmonary diseases, such as pulmonary fibrosis and chronic obstructive pulmonary disease (COPD), have been linked to smoking as risk factors. Several studies have also reported that smoking history is a potential risk factor for PCPF patients. Smoking triggers oxidative stress, increased inflammation of the mucosa, and inflammatory cytokines, resulting in severe manifestations.[6]

Presence of underlying diseases: Several diseases have been connected to the progression of pulmonary fibrosis. Hypertension and diabetes were identified in 65% of PCPF patients. Lung diseases such as bronchial asthma and COPD were also shown to be significant risk factors for PCPF.[4,6] A recent meta-analysis found that PCPF was almost three times more common in patients with COPD.[4]

Severe COVID-19 related to ICU admission and mechanical ventilation: In a previous cross-sectional study, it was reported that 52% of moderate to severe COVID-19 patients have pulmonary fibrosis demonstrated on follow-up Computed Tomography (CT) scans.[15] ICU admission, particularly a prolonged ICU stay, along with the use of mechanical ventilation, has been found to be significantly associated with the development of pulmonary fibrosis. The use of mechanical ventilation carries a higher risk of ventilator-induced lung injury (VILI).[6,12] A previous study found that 85% of ARDS patients who received mechanical ventilation developed pulmonary fibrosis that was related to the duration of pressure-controlled inverse-ratio ventilation.[8] Prolonged use of mechanical ventilation will trigger proinflammatory mediators, worsening acute lung injury, which increases the risk of pulmonary fibrosis and mortality.

Radiological Findings

Post-COVID-19 Pulmonary Fibrosis (PCPF) can be identified on radiological examinations, especially on follow-up CT scans. A prior study explained that post-COVID-19 sequalae can show fibrosis-like manifestations, including a honeycomb appearance, reticular opacities, traction bronchiectasis, parenchymal bands, as well as non-fibrotic features such as ground glass opacities (GGOs), consolidation, or nodules. However, the development of a honeycomb appearance, which is a true fibrosis marker, is rarely seen in COVID-19.[16]

Fibrotic changes without honeycombing, but with histological evidence of fibrosis, are the most common findings of PCPF in CT scan evaluations. These fibrotic changes are mostly bilateral and located in the periphery of the lower lobe, similar to acute SARS-COV pneumonia. They usually coincide with the areas where existing ground glass opacity was observed.[17] It was also revealed that, compared to true fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF), the fibrotic and non-fibrotic changes in post-COVID-19 patients can disappear over time and are not as progressive as true fibrotic lung diseases.[16]

Management Options

There is currently no specific proven therapeutic strategy to manage pulmonary fibrosis post-COVID-19 infection. The management approach to PCPF can generally be divided into non-pharmacological and pharmacological therapies.

For non-pharmacological therapy, respiratory rehabilitation and oxygen supplementation could be beneficial for PCPF patients. The literature reveals that six months of respiratory rehabilitation may improve the quality of life, particularly in patients with mild pulmonary fibrosis. The latest studies in Japan and the UK have shown a beneficial effect of oxygen supplementation for patients with lung fibrosis. The use of oxygen was correlated with reduced dyspnea and improved patients' quality of life. Supplemental oxygen is recommended for PCPF patients with a resting Peripheral Oxygen Saturation (SpO_2) of 88% or those who desaturate during activity.[18]

Lung transplantation (LT) is an option for patients with end-stage PCPF if there are no post-operative aggravating conditions and if donors and transplants are available.[19] Nevertheless, there are still some concerns regarding lung transplantation, including the appropriate timing of the procedure, confirmation of negative virological status, immunosuppressive therapy, and the risk of COVID-19 recurrence. Further studies regarding the risks and benefits of LT for PCPF patients are strongly needed.[18]

For pharmacological therapies, several trials are investigating the use of oral corticosteroids, spironolactone, and anti-fibrotic agents as treatments for PCPF. In a prior study, patients with PCPF were prescribed prednisolone as their first-line therapy. It was reported that corticosteroids can reduce the short and long-term effects of COVID-induced pneumonia and also reduce the risk or severity of PCPF.[6,20] Corticosteroids act as anti-inflammatories and are useful in ARDS during the fibroproliferative phase. The use of corticosteroids as the initial therapy is associated with significant improvement, and it is also well tolerated in the majority of PCPF patients.[6]

A previous case report on an elderly PCPF patient showed a good response to corticosteroid and anti-fibrotic therapy. The patient was given 40 mg of oral prednisone daily for ten weeks, then switched to 20 mg for a month. Later on, the dose was maintained at 10 mg daily. This study proposed that steroid treatment may be beneficial for pulmonary fibrosis treatment.[21] Another study evaluated the efficacy of steroid therapy in a PCPF patient after two months. The patient was given methylprednisolone 1000 mg per day for four days and 500 mg per day for three days, followed by 20 mg prednisone per day. After discharge, he was given 10 mg of prednisone and then gradually reduced to 5 mg. A follow-up High Resolution CT Scan after two months showed a significant reduction in Ground Glass Opacities absorption. This study suggested that the administration of corticosteroids may prevent lung fibrosis but was not effective enough to reduce structural distortion, traction bronchiectasis, and honeycombing fibrosis. Nevertheless, the use of corticosteroids for severe and critical COVID-19 is strongly recommended by WHO. Future multicenter and randomized controlled studies regarding corticosteroid therapy for PCPF, including its dose and duration, are highly needed.[22]

Anti-fibrotic drugs show pleiotropic therapeutic effects by acting as anti-inflammatory and cytoprotective agents that mainly target the TGF-ß pathway.[3] Recent literature has described several potential therapeutic anti-fibrotic agents for PCPF, including pirfenidone, deupirfenidone, nintedanib, IN01 vaccine, colchicine, treamid, and Fuzheng Huayu.[23] To date, pirfenidone and nintedanib are the most studied antifibrotics and may be the most effective drugs in the treatment of pulmonary fibrosis. Both are also the only antifibrotics that have been approved by the U.S. Food and Drug Administration (FDA). Even though they have different mechanisms of action, both drugs have been shown to lower the decline of lung function in Idiopathic Pulmonary Fibrosis (IPF) and severe pulmonary fibrosis patients.[23,24]

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) has antifibrotic, antioxidant, and anti-inflammatory effects. Previous findings have demonstrated that pirfenidone is able to reduce inflammatory cells, ECM accumulation, and fibroblast proliferation.[25] This drug slows down fibrosis by blocking pro-inflammatory and pro-fibrotic cytokine cascades, particularly TGF-signaling, which is crucial to the pathogenesis of IPF. Based on *in vitro* and *in vivo* studies, pirfenidone acts as an anti-inflammatory agent by inhibiting the production of tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), interleukin-1beta (IL-1β), and IL-6.[26] For its antioxidant properties, pirfenidone inhibits Nicotinamide Adenine Dinucleotide Phosphate-dependent (NADPH-dependent) microsomal lipid peroxidation in the liver.[23]

A recent randomized clinical study, comparing the use of pirfenidone and placebo as a control, revealed that pirfenidone can slow down the progression of idiopathic pulmonary fibrosis.[27] The latest study also found that pirfenidone therapy decreased the incidence of lung fibrosis and its mortality rate.[28] Early use of pirfenidone is associated with better outcomes and reduces the need for corticosteroid therapy. In the study, patients receiving pirfenidone therapy reported an increase in D-Dimer levels. However, another research showed a contradictory result which found that pirfenidone may reduce D-Dimer level in pulmonary fibrosis patients.[28]

The efficacy of pirfenidone has not yet been established. Based on the recommended initial dose, the first week of treatment is 267 mg three times daily, followed by 534 mg three times daily for the second week, and 801 mg three times daily for the third week and thereafter, taken with or after meals. Pirfenidone is usually prescribed for four weeks or more, depending on the patient's response. A liver function test is necessary before starting pirfenidone, once a month for the first six months, and then every three months since pirfenidone is associated with hepatotoxicity. Rash, dizziness, nausea, fatigue, abdominal pain, and diarrhea are common adverse effects of the drug.[23,25]

Nintedanib is a small molecular tyrosine kinase inhibitor that acts as an anti-fibrosis and anti-inflammatory agent. It inhibits the signaling pathway of fibroblasts, myofibroblasts, and cells involved in lung angiogenesis by targeting fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), VEGF, and non-receptor kinases. A previous study reported a significant improvement in lung function in a critical COVID-19 patient after three months of nintedanib administration. Thorax CT findings also showed resolved lung fibrosis within two months.[19]

A previous case series reported that the use of oral nintedanib tablets, 150 mg twice a day for a month, in post-COVID-19 fibrosis patients resulted in significant clinical improvement.[29] A prospective study comparing the effectiveness of nintedanib and pirfenidone in COVID-19 pulmonary fibrosis reported significant lung improvement with nintedanib compared to pirfenidone.[30] Nintedanib therapy showed notable advancement in chest radiological examination at 6 and 12 weeks. This finding is in line with another study that also found that the nintedanib group had better clinical improvement after 12 weeks of follow-up compared to the pirfenidone group.[31] However, nintedanib should be avoided in patients on anticoagulation therapy or with coagulation disorders since it may cause gastrointestinal bleeding.[30]

The suggested dose is 150 mg twice daily for 12 months, taken 30 minutes after meals to increase gastrointestinal tolerance and enhance absorption by 20%. However, for patients with mild liver injury, the dose is reduced to 100 mg twice daily. Similar to pirfenidone, a liver function test is necessary to be evaluated before and during treatment. Common side effects include diarrhea, nausea, abdominal pain, and vomiting.[23,25]

Spironolactone may have several advantages in COVID-19 patients: it has anti-inflammatory, antioxidant, antifibrotic, and antiviral properties. Spironolactone increases the circulating levels of ACE-2 and inhibits SARS-CoV-2 from entering the cells. It also has antiandrogenic action by downregulating transmembrane serine protease 2 (TMPRSS2) and blocks the mineralocorticoid receptor. Aldosterone, a mineralocorticoid receptor activator, may be related to an inflammatory response that leads to fibrosis and hyperplasia. Both ACE-2 and TMPRSS2 are important regulators for SARS-CoV-2 cell entry. Spironolactone acts as an antifibrotic by affecting the extracellular matrix, which influences collagen synthesis in order to prevent fibrosis. It also has an antioxidant function that protects tissues from oxidative stress.[32] Hence, spironolactone may

have an impact on the hyper-inflammatory response related to severe COVID-19 and the prevention of post-COVID-19 pulmonary fibrosis.[20]

Currently, there is still inadequate clinical research regarding the use of spironolactone in post-COVID-19 pulmonary fibrosis patients. Previous clinical studies using animal models have suggested that spironolactone is an effective drug for pulmonary fibrosis due to its dual action as a mineral corticoid receptor antagonist and androgen inhibitor.[33,34] Spironolactone may be helpful in lowering inflammatory reactions in the early stage of ARDS and preventing pulmonary fibrosis.[18] Another study has also revealed that spironolactone can lower acute pneumonia due to lipopolysaccharide or bleomycin. Further clinical trials related to spironolactone's efficacy for COVID-19 are highly needed.[33,34]

Conclusion and Future Direction

In conclusion, pulmonary fibrosis is a severe COVID-19 sequela that may result in permanent lung damage and death. Risk factors reported to be linked with the development of PCPF include older age, genetics, male gender, smoking, ICU admission, and presence of underlying diseases. Currently, there is no proven effective strategy for PCPF management. Pharmacological therapies such as antifibrotics, corticosteroids, and spironolactone, as well as non-pharmacological therapies such as respiratory rehabilitation and oxygen supplementation, are considered. There is still much to be explored about this disease. It is estimated that the incidence of PCPF may increase in the near future. This condition is also complicated by the ongoing mutations of the virus, making it challenging to treat and potentially leading to an increase in global morbidity and mortality rates. Therefore, further continuous research on PCPF is highly required to establish more comprehensive knowledge specifically regarding its therapeutic modalities, which may improve patients' survival rates and prevent mortality.

Conflicts of interest
There are no conflicts of interest.

Financial support and sponsorship
Nil.

Peer-review
Externally peer-reviewed.

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