Review Article

Post-COVID-19 pulmonary fibrosis: An ongoing concern

Nuha Nasser Alrajhi

Department of Medicine, Pulmonary Unit, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Nuha Nasser Alrajhi, Department of Medicine, Pulmonary Unit, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia.
E-mail: nuha-alrajhi@hotmail.com

Submission: 05-01-2023
Revised: 05-02-2023
Accepted: 10-07-2023
Published: 17-10-2023

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.atm_7_23

Abstract:

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 rapidly spread across the globe causing over 6 million deaths and major compromization of health facilities. The vast majority of survivors post-COVID-19 are left with variable degrees of health sequelae including pulmonary, neurological, psychological, and cardiovascular complications. Post-COVID-19 pulmonary fibrosis is one of the major concerns arising after the recovery from this pandemic. Risk factors for post-COVID-19 pulmonary fibrosis include age, male sex, and the severity of COVID-19 disease. High-resolution computed tomography provides diagnostic utility to diagnose pulmonary fibrosis as it provides more details regarding the pattern and the extent of pulmonary fibrosis. Emerging data showing similarities between post-COVID-19 pulmonary fibrosis and idiopathic pulmonary fibrosis, finding that needs further exploration. The management of post-COVID-19 pulmonary fibrosis depends on many factors but largely relies on excluding other causes of pulmonary fibrosis, the extent of fibrosis, and physiological impairment. Treatment includes immunosuppressants versus antifibrotics or both.

Keywords:

COVID-19, pulmonary fibrosis, severe acute respiratory syndrome coronavirus 2

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in November 2019. Because it is highly contagious, it spread rapidly worldwide, being the largest pandemic of the 20th century and causing over 6 million deaths and a major compromise of health facilities.[1] Even after announcing the discovery of the COVID-19 vaccine, quarantine and social distancing were the major preventive strategies. Nevertheless, the vast majority of severe COVID-19 survivors have been left with variable degrees of health sequelae, including pulmonary, neurological, psychological, and cardiovascular complications. The major long-term complication of post-COVID-19 is pulmonary fibrosis.

Pulmonary fibrosis is a chronic progressive and mostly fatal disease characterized by interstitial collagen deposition with varying degrees of alveolar bronchiolization. There are many causes of pulmonary fibrosis including connective tissue disease (CTD), smoking, drugs, and family history. Idiopathic pulmonary fibrosis (IPF) is a diagnosis of exclusion, perhaps more common among elderly males who are active or former smokers. It is known that viral infection can be a co-factor for IPF pathogenesis.[2] This review focuses on post-COVID-19 pulmonary fibrosis.

Post-COVID-19 Interstitial Lung Disease–fact or Coincidence: Lessons from Previous Endemics

Pulmonary complications, particularly interstitial lung disease (ILD), are anticipated complications post-COVID-19. This theory proposes the virology as the cause and trigger of ILD pathogenesis. The strongest evidence was obtained from SARS CoV-1 survivors included in the longest longitudinal study by Zhang

How to cite this article: Alrajhi NN. Post-COVID-19 pulmonary fibrosis: An ongoing concern. Ann Thorac Med 2023;18:173-81.

et al., wherein 71 patients were included from a single medical institute in China and followed up for 15 years. During this time, high-resolution computed tomography (HRCT) and pulmonary function test (PFT) were conducted postrecovery and repeated over time. Their results showed that 38% of the patients had persistent interstitial lung abnormalities (ILA) described mainly as ground-glass opacities (GGO) and cord-like consolidation along with physiological impairment findings. Although these abnormalities improved, fibrotic abnormalities persisted over the course of their follow-up.[3]

In addition, persistent ILA post-Middle East respiratory syndrome coronavirus (MERS-CoV) has been documented. Das *et al*. examined the chest radiographs of 36 MERS-CoV survivors between 1 month and 8 months after hospital discharge. Although the radiological method was different, the incidence of parenchymal abnormalities (38%) post-MERS-CoV was like that seen in H1N1 viral infection cases. Older age and severe MERS-CoV infections requiring intensive care unit (ICU) admissions are considered risk factors for post-MERS-CoV pulmonary fibrosis.[4]

On the other hand, multiple viruses are implicated in the pathogenesis, progression, and exacerbation of IPF as well as other ILDs. For instance, cytomegalovirus, Epstein-Barr virus, and the herpes virus family are implicated in the pathogenesis of IPF.[2,5-7] Based on the aforementioned facts, we can conclude that anticipation of ILD as sequelae of COVID-19 is a valid hypothetical risk.

Epidemiology of COVID-19 Pulmonary Fibrosis

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.[8] Furthermore, pulmonary fibrosis causing refractory hypoxia accounted for 19% of ICU deaths in a single-center study.[9] 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. 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.[10] 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.[11] Although this was observed only in a few patients, it definitely signifies the short-term sequelae of COVID-19.

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. 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. 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. This functional reduction persisted during the 12-month follow-up period.[12] 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.[13]

Pathogenesis of COVID-19-related Pulmonary Fibrosis

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.

Two-hit hypothesis or virus-induced subclinical interstitial lung abnormalities: Genetic predisposition

Considering that pulmonary fibrosis secondary to COVID-19 is more frequent among old male patients who require intensive respiratory support, most experts have proposed the two-hit hypothesis to explain this devastating condition. In this hypothesis, the virus, reactive oxygen radicle, or other factors hit the lung that is either genetically predisposed to pulmonary fibrosis or the one that has subclinical ILA. ILA occurs in 7%–10% of the general population. In this case, the virus triggers a profibrotic cascade in the predisposed lung, and fibrosis persists even after recovery.

Direct effect of severe acute respiratory syndrome coronavirus 2 on profibrotic cascade

SARS-CoV-2 can induce a fibrotic cascade either directly or indirectly.

As the virus gains cellular entry primarily by binding to the angiotensin-converting enzyme 2 (ACE2) receptors, particularly angiotensin I (AT1R) and to a lesser extent αvβ3 and αvβ6 integrins, which are near the ACE2 receptors. Both high ACE2 and αVβ integrin stimulate the profibrotic cascade, including transforming growth factor-beta (TGF-β) and reactive oxygen species. TGF-β is one of the principal stimulators of fibroblast accumulation, maturation, and differentiation to myofibroblast, which is the factory of collagen deposition.[14-16]

In addition to its direct effect on ACE2, SARS-CoV-2 can indirectly stimulate fibrosis. Through the binding sites on the ACE2 receptors, SARS-CoV-2 causes alveolar epithelial cells type 2 (AEC2) injury that results in the activation of innate immune response with macrophage accumulation, AEC2 injury, and denudation of alveolar basement membrane. These processes precipitate the influx of local fibrocytes, which causes the release of inflammatory mediators, including interleukin (IL)-6, TNF-α, and TGF-β activation, leading to exaggerated inflammatory cascade and cytokine storm. Both injured AEC2 and macrophage activation result in the activation of TGF-β, which leads to the activation and proliferation of the fibroblasts along with their differentiation into myofibroblasts with subsequent collagen deposition. In genetically predisposed patients, it can lead to fissure cycle fibrosis.[17,18]

Risk Factors for Pulmonary Fibrosis

Pulmonary fibrosis secondary to COVID-19 is not uncommon complication of severe COVID-19; however, it is not a universal finding in this group of patients. The risk factors for pulmonary fibrosis have been studied in different aspects, including clinical and radiological risk factors, in genetically predisposed individuals. Figure 2 illustrate the risk factors for post COVID-19 pulmonary fibrosis.

Clinical risk factors

Clinical risk factors including age, male sex, smoking history, and comorbidities have been identified.

Many studies documented the association between age, sex, and medical comorbidities with the severity of COVID-19 and development of lung fibrosis. Several studies highlight

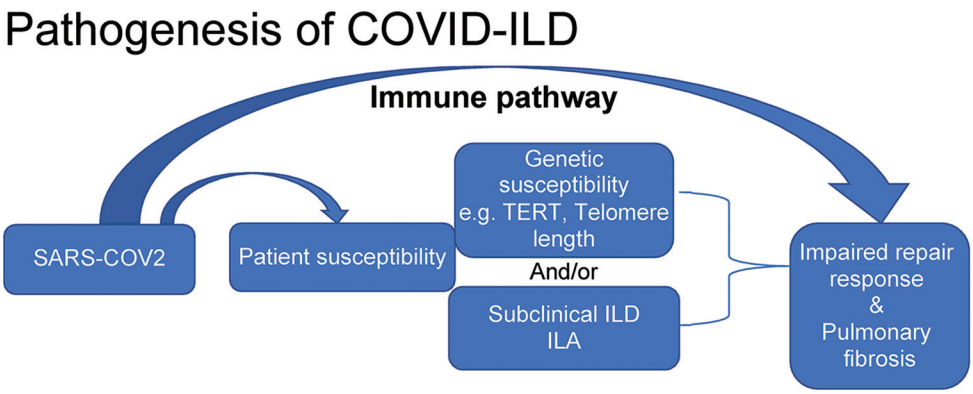

Figure 1: SARS-CoV-2 can cause ILD through either its immunological effect on alveolar epithelial cells or through two-hits hypothesis. in the immunological pathway, SARS-CoV-2 directly binds to ACE2 receptor with subsequent stimulation of the profibrotic cascade, leading to impaired repair response and pulmonary fibrosis. SARS-CoV-2 can also induce lung fibrosis in patients with either genetic predisposition or patients with subclinical ILA. ACE2: angiotensin-converting enzyme 2. ILA: Interstitial lung abnormalities, ILD: Interstitial lung disease, SARS- CoV-2: Severe acute respiratory syndrome coronavirus 2

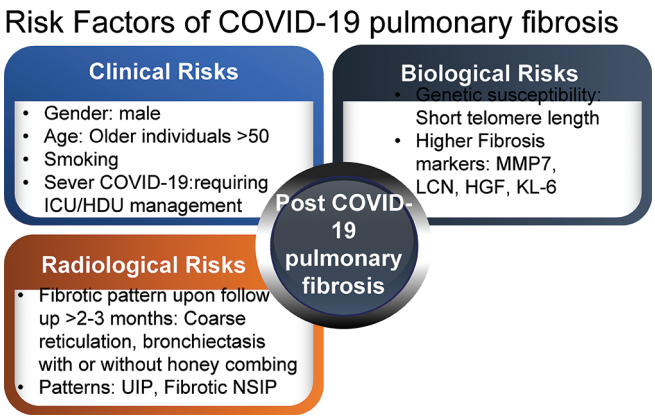

Figure 2: Risk factors for pulmoanry fibrosis. There are clinical, biological, and radiological risk factors. HGF: Hepatocyte growth factor, ICU/HDU: Intensive care unit/high dependency unit, KL-6: Krebs von den Lungen 6, LCN: Lipocalin 2, MMP-7: Matrix metalloproteinase-7, NSIP: Nonspecific interstitial pneumonia, UIP: Usual interstitial pneumonia

age as one of the main risk factors for pulmonary fibrosis complicating the course of COVID-19 and causing other complications. Currently, male sex is a known risk factor for severe COVID-19 and death.[12,14,19,20] Furthermore, a meta-analysis of studies on COVID-19-associated mortality revealed that smokers, active or passive, are at greater risk of having severe and complicated course of COVID-19 than nonsmokers.[21,22] When we analysed the risk factors according to the risk of developing pulmonary fibrosis particularly, we also found similar risk factors. Huang *et al*. examined the clinical risk factors associated with the potential development of pulmonary fibrosis and demonstrated that older age, male sex, and presence of comorbidities negatively affect the survival.[12] Nonetheless, the severity of COVID-19 itself is linked to the development of pulmonary fibrosis among survivors of this devastating infection. McGroder *et al*. studied pulmonary fibrosis complicating the recovery from SARS-CoV-2 infection and found that fibrotic abnormalities were detected on HRCT in 72% of mechanically ventilated patients as compared to 20% of nonmechanically ventilated patients.[23] Further emphasis on the severity of the disease in the development of pulmonary fibrosis was conducted by Huang *et al*., revealing high risk of chronic interstitial changes in patients who required more intense management with invasive or noninvasive treatment.[12] These clinical risk factors of post-COVID-19 pulmonary fibrosis are similar to the clinical characteristics of IPF patients.

Radiological Abnormalities Predicting Fibrosis as a Long-term Sequela of COVID-19

The presence of interstitial thickening and particularly coarse reticulation with associated bronchiectasis as well as parenchymal bands on HRCT may highlight the risk of a residual fibrotic change.[24] Furthermore, studying the Lung Severity Score on chest CT at baseline is a good predictor of future fibrosis recorded during the 6-month follow-up CT, and the risk increased with the addition of other clinical risk factors.[25]

Genetic and Biological Risk Factors

As the clinical risk factors of post-COVID-19 pulmonary fibrosis almost matched the clinical characteristics of IPF, genetic and biological similarities between post-COVID-19 pulmonary fibrosis and IPF could be considered. McGroder *et al*. found that not only does the severity of COVID-19 itself determine the fate of recovery, but there is also a negative correlation between age-adjusted telomere length and the odds ratio of developing pulmonary fibrosis after recovery from COVID-19. Their study showed that each 10% reduction of age-adjusted telomere length is associated with a 1.35-odd increased risk of developing fibrosis, as detected on chest CT.[23]

Fibrotic biomarkers, including matrix metalloproteinase-7, hepatocyte growth factor, and lipocalin 2, were investigated in 22 patients with COVID-19. Among them, 10 patients required ICU admission, whereas 5 and 7 patients required hospital admission and home treatment, respectively. Thus, they confirmed a positive correlation of the level of these biomarkers not only with the risk of ICU admission but also with PFT impairment after recovery from COVID-19.[26] Other biological markers like KL6 have been heavily investigated as a marker of fibrotic lung disease and an indicator of disease progression and prediction of the risk of exacerbation and prognosis as well.[27-30] Xue, and his colleges examined the effect of KL-6 on predicting the development of post COVID-19 pulmonary fibrosis.[31] This study included 289 patients admitted to the hospital with moderate or severe COVID-19. Moderate disease was defined as the presence of respiratory symptoms along with chest CT features suggestive of pneumonia, whereas severe disease was described as ICU admission with IMV/NIV and rapid disease progression on chest CT >50% over 24–48 h. Both moderate and severe disease patient groups underwent KL6 investigation and chest CT at admission and after 2 months. Chest CT findings were categorised as fibrotic or nonfibrotic according to the presence or absence of reticulation, respectively. Features suggestive of fibrosis were observed in 114 (39%) patients, with the proportion equivalent between both the groups. However, 30% of these patients had irreversible fibrosis, accounting for 12% of the study population. Regarding correlation with the KL6 levels, the researchers found that the KL6 level was not only elevated in patients with severe disease but also in those who initially presented with early COVID-19 fibrosis. Moreover, the baseline KL6 levels at admission were higher in patients with

irreversible fibrosis on follow-up CT than in those with reversible fibrosis. A cut-off level of 505 U/mL of KL6 was suggested to differentiate between COVID-19 patients with and without fibrosis and of 674 U/mL to differentiate between those with reversible and irreversible fibrosis, with fair sensitivity and specificity for both.

Since the clinical and biological risk factors for post-COVID-19 pulmonary fibrosis match the clinical and biological profile of IPF patients, there are concerns about the burden of pulmonary fibrosis complicating the COVID-19 course in the survivors. The next question would be about the severity of the fibrosis, fibrotic pattern, appropriate treatment options to treat/prevent post-COVID-19 pulmonary fibrosis, and the timing to starts treatment early or late in the course of the disease.

Patterns of Post-COVID Interstitial Lung Disease

Most of the studies published on long-term radiological sequelae of acute COVID-19 focus on describing the radiological abnormalities rather than radiological patterns. Most of these studies correlate that with a physiological impairment which reflects the significance of these parenchymal abnormalities. This lack of pattern identification when reporting such abnormalities could be partly due to the failure of grouping all the abnormalities into a specific pattern.

The long-term follow-up HRCT varied between different studies, ranging from 4 months to 1 year. The most common radiological abnormalities are reticular lines, GGO, parenchymal bands, and traction bronchiectasis. These abnormalities are predominant in the lower lobe of the lung, and all point toward the possibility of organizing pneumonia (OP) rather than fibrotic nonspecific interstitial pneumonia (NSIP); honeycombing was rarely reported.[32,33]

Interesting study presented at both ERS International Congress 2021 and American Thoracic Society 2021 International Conference was that by Tomassetti, but it was not published till the preparation of this article. It was a multicentre study conducted in Italy that enrolled 550 patients 6 months post-COVID-19. Among them, 193 patients (35%) had significant chest CT abnormalities involving >5% of the lung, while 209 patients (38%) presented insignificant parenchymal abnormalities. Among the 193 patients with significant radiological abnormalities, 18% had diffuse fibrotic ILA, 10% had diffuse nonfibrotic parenchymal abnormalities, and 6% had focal fibrosis. Of the 18% patients with diffuse fibrotic ILA, 11% had fibrotic NSIP/OP, 6% had intermediate probability of UIP, and 1% had definite/probable UIP.[34,35] Dhooria *et al*. reported the presence of OP pattern in 91% of their study cohort based on CT performed in the subacute phase 3–8 weeks post-COVID-19 associated with persistent dyspnoea.[33]

Detecting these radiological abnormalities would raise the next question regarding the most appropriate treatment option.

Approach for Post-COVID-19 Pulmonary Fibrosis Management

The approach for managing post-COVID-19 ILD and pulmonary fibrosis should be like any other disease. This includes first diagnosing ILD, excluding other causes of ILD, determining the ILD pattern on CT, and deciding about the need for further management including appropriate medical treatment through multidisciplinary discussion (MDD). For this, the detailed medical history including environmental exposure and occupational history, CTD-related symptoms, family history, and drug history should be recorded. This should be followed by meticulous physical examination to ensure the absence of subtle features of CTD, and then conducting laboratory investigations to exclude CTD/interstitial pneumonia with autoimmune features. Further need for lung biopsy (transbronchial lung biopsy, lung cryobiopsy, or surgical lung biopsy) should be assessed based on the individual clinical scenario and MDD recommendations. Figure 3 illustrates the approach for managing post-COVID-19 ILDs.

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

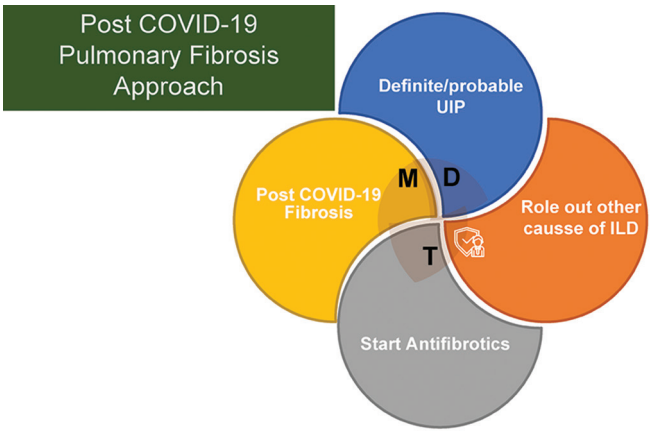

Figure 3: Approach to post-COVID pulmonary fibrosis: To determine the pattern of pulmonary fibrosis. If definite or probable usual interstitial pneumonia, to role out other causes of interstitial lung disease. If all other causes are ruled out, and after multidisciplinary team discussion discussion, consider starting antifibrotics. UIP: Usual interstitial pneumonia, ILD: Interstitial lung disease, MDT: Multidisciplinary team discussion

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. Figure 4 summarises the treatment approach for managing post-COVID-19 pulmonary fibrosis.

Immunosuppressant Agents

The role of immunosuppressants have been better studied in the acute phase of COVID-19, especially in patients with severe COVID-19. Multiple immunosuppressants/immunomodulator therapy have been approved in the management of the acute phase of COVID-19. Steroids are the most common Food and Drug Administration-approved medication for acute COVID-19 pneumonia, especially for patients requiring oxygen therapy. This was established after the RECOVERY trial and other studies proved the efficacy of steroids in the acute phase of COVID-19, where the cytokine storm occurs in the early or even later phase.[36,37] Hence, our knowledge on corticosteroids is adequate for treating acute respiratory distress syndrome (ARDS). Moreover, IL-6 and anti-JAKs showed effectiveness in severe COVID-19 cases with cytokine storm, and anti-IL-6 is a Grade 2b recommendation.[38-45]

On the other hand, long-term immunosuppressant therapy is not well studied, and most of the studies show long-term benefits among survivors of severe COVID-19 who had OP patterns on CT. For instance, Myall *et al*. reported significant clinical, physiological, and radiological improvements in patients with post-COVID-19 interstitial pneumonia.[32] In their study, telephone calls were made to patients 6 weeks after hospital discharge, and screening for post-COVID ILD was conducted only if the patients reported persistent symptoms. It should be further stressed that the radiological pattern in 59% of this cohort was OP, and its response is well known. Additionally, considering this methodology of screening only symptomatic patients. Musculoskeletal impairments and fatigue are well-described complications post-COVID-19, which might mask any respiratory symptoms; thus, a significant minority of patients who have post-COVID-19 ILD and are overwhelmed with nonrespiratory complications would be missed. Dhooria *et al*. compare the effect of high dose steroid versus low dose steroid therapy in patient with persistent radiological abnormalities of more than 20% after recovering the acute viral illness. Almost all patient (98%) were having severe COVID-19 and 91% of the study cohort are having OP pattern. The majority of study population experienced significant radiological improvement with near complete resolution in both study groups associated with clinical and physiological improvement.[33]

Antifibrotic Therapy

Multiple small case reports and series predict the response to antifibrotics administered early in the course of post-COVID-19 ILDs, especially with the presence of findings suggestive of fibrosis such as interlobular septal thickening with traction bronchiectasis, with or without honeycombing.

Theoretically and in animal models, the administration of antifibrotics early in the course of the disease could prevent or halt the progression of ILAs post significant injury. Both nintedanib and pirfenidone are approved for IPF patients and considered the standard of

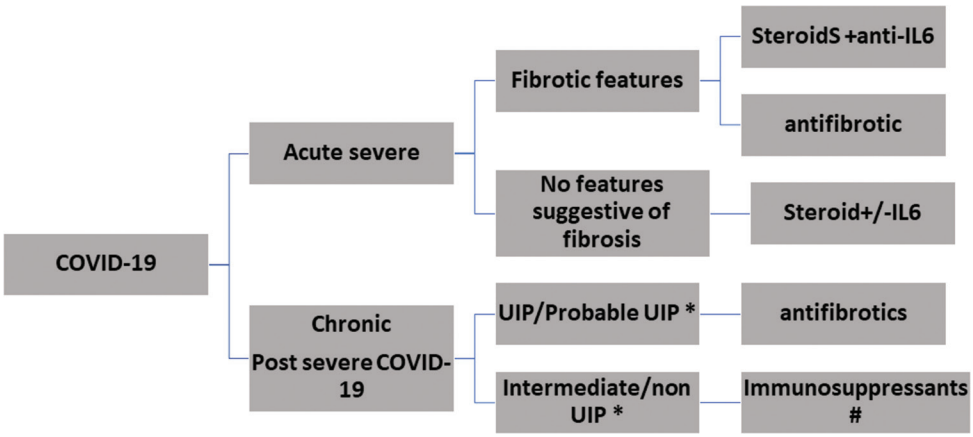

Figure 4: Schematic approach to manage post COVID-ILDs: The approach depends on the acuteness of presentation. Acute COVID-19 is managed by steroid therapy with or without Interleukin-6 therapy. The decision of starting antifibrotic therapy in acute severe COVID-19 depends largely on the radiological appearance of fibrosis described as significant reticulation, severe traction bronchiectasis, and architectural distortion with or with honeycombing. Managing chronic post-COVID-19 interstitial lung disease (ILD) largely depends on the radiological pattern. *After excluding other causes of ILDs. #Antifibrotics can be added if patients experienced progressive phenotype despite immunosuppressant therapy. UIP: Usual interstitial pneumonia, IL-6: Interleukin-6

care. The main goal of these therapies is to slow the progression and to delay the time to exacerbation, which is responsible for the highest risk of mortality in these patients. Similarly, antifibrotics are approved as part of the therapy for non-IPF fibrotic lung diseases of other aetiology, who exhibit progressive phenotype despite immunosuppressant therapy, and they showed similar expected effects. Considering this, it would be reasonable to consider these drugs for post-COVID-19 pulmonary fibrosis.

Pirfenidone

Pirfenidone, a TGF-β1 inhibitor, is a key player in fibrogenesis through fibrocyte activation and differentiation into myofibroblasts, which is the factory for collagen deposition. It also has an antioxidant and anti-inflammatory effect.[46-48] Pirfenidone decreases ACE expression through the AT1R/p38 mitogen-activated protein kinase pathway as well as its express potential in reducing ROS.[49,50] Pirfenidone can significantly ameliorate fibrosis and ARDS-induced fibrosis *in vitro* when it is started early in the course of the disease.[49,51] The pirfenidone effect in post-COVID-19 fibrosis was tested in a few studies. Acat *et al*. conducted a retrospective study on 22 critical patients with COVID-19. All patients received standard therapy recommended at that time for COVID-19, including favipiravir, systemic steroids, and anticoagulant therapy. Pirfenidone was added in the treatment of 13 out of 22 patients. CT was performed at the start of treatment and repeated 2 months later. The abnormalities were further analyzed through machine learning. Due to the high contagiousness of the disease, PFT was conducted only at the follow-up visit. Their study reported significant improvement in the overall parenchymal lung involvement in the group receiving pirfenidone as compared to the group receiving standard therapy, despite higher baseline interstitial involvement in the former, and this was consistent with the PFT values as well.[52] Few other case series and case reports have demonstrated similar findings.[53-55] Figure 3 illustrates the clinical consideration to start antifibrotics in patients with pulmonary fibrosis post-COVID-19.

Nintedanib

Nintedanib, a tyrosine kinase inhibitor, is a key inhibitor of the multiple cascades involved in IPF pathogenesis. It blocks platelet-derived growth factor receptor, vascular endothelial growth factor receptor, and fibroblast growth factor receptor, which regulate unrelenting pulmonary fibrosis. In animal models, nintedanib alleviated lung fibrosis caused by bleomycin.[56]

Similar to pirfenidone, there is a lack of studies evaluating nintedanib use in post-COVID-19 pulmonary fibrosis. Umemura *et al*. conducted a prospective, interventional study to examine the effect of nintedanib on acute severe COVID-19 pneumonia and showed that nintedanib decreases the time to withdrawal of mechanical ventilation. Although the inclusion criteria and primary outcomes did not examine its effects on the long-term sequelae of severe COVID-19, including pulmonary fibrosis, the nintedanib group showed a significant improvement in the radiological abnormalities after mechanical ventilation withdrawal as compared to the control group.[57] Few other case reports and case series have indicated the usefulness of nintedanib in severe fibrotic COVID-19 during the acute phase.[58-60]

Apart from these few case reports and case series, antifibrotics are prescribed less often than expected. One survey found that physicians are less enthusiastic about prescribing antifibrotics, with only 2.2% of the patients receiving this treatment in the multicentre survey.[61] The reasons behind this low rate of prescribing antifibrotics could be due to patient selection, as in that survey, the researchers included all ILD abnormalities after recovering the acute illness, the most common pattern of post-COVID-19 ILD is OP, followed by NSIP, where the most effective therapy would be immunosuppressant therapy rather than antifibrotics.[32,33] The timing of starting antifibrotics is also crucial, as most antifibrotics were started 3 weeks from the onset of symptoms, which is a bit early for starting antifibrotics in the course of the disease. Lastly, and more importantly, there is a lack of high-quality evidence of the effectiveness of antifibrotics.

Currently, there is a serious lack of high-quality evidence for using antifibrotics in the treatment of post-COVID-19 pulmonary fibrosis. Moreover, the theoretical concept of antifibrotics in severe COVID-19 patients with clinical and radiological risk factors for pulmonary fibrosis must be proved. We are a waiting with a great interest for the results of multiple ongoing double-blind randomized controlled trials conducted to examine the effect of antifibrotics in post-COVID-19 pulmonary fibrosis. In time, we will have a better understanding of the natural history and course of post-COVID-19 pulmonary fibrosis.

In conclusion, post-COVID-19 ILD is an emerging consequence of the pandemic. The risk of post-COVID-19 pulmonary fibrosis is highest among acute severe COVID-19. It's clinical significance and natural history are evolving. Furthermore, COVID-ILD and IPF share clinical and biological similarities. Lastly, the pattern of ILD involvement determines the appropriate therapy; hence, antifibrotics may be effective in post-COVID fibrotic ILD.

Acknowledgment

The authors would like to thank Interstitial Lung Disease

Center, KSU, Riyadh. KSA, for all work managing post-COVID-19 pulmonary fibrosis.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. WHO COVID-19 Dashboard. Geneva: World Health Organization; 2020, 2022. Available from: https://covid19.who.int. [Last accessed on 2022 Nov 19].
2. Sheng G, Chen P, Wei Y, Yue H, Chu J, Zhao J, *et al.* Viral infection increases the risk of idiopathic pulmonary fibrosis: A meta-analysis. Chest 2020;157:1175-87.
3. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, *et al.* Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: A 15-year follow-up from a prospective cohort study. Bone Res 2020;8:8.
4. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, *et al.* Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging 2017;27:342-9.
5. Marzouk K, Corate L, Saleh S, Sharma OP. Epstein-Barr-virus-induced interstitial lung disease. Curr Opin Pulm Med 2005;11:456-60.
6. 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.
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. Konopka KE, Perry W, Huang T, Farver CF, Myers JL. Usual interstitial pneumonia is the most common finding in surgical lung biopsies from patients with persistent interstitial lung disease following infection with SARS-CoV-2. EClinicalMedicine 2021;42:101209.
14. John AE, Joseph C, Jenkins G, Tatler AL. COVID-19 and pulmonary fibrosis: A potential role for lung epithelial cells and fibroblasts. Immunol Rev 2021;302:228-40.
15. Wigén J, Löfdahl A, Bjermer L, Elowsson-Rendin L, Westergren-Thorsson G. Converging pathways in pulmonary fibrosis and COVID-19 – The fibrotic link to disease severity. Respir Med X 2020;2:100023.
16. Guizani I, Fourti N, Zidi W, Feki M, Allal-Elasmi M. SARS-CoV-2 and pathological matrix remodeling mediators. Inflamm Res 2021;70:847-58.
17. Chilosi M, Poletti V, Ravaglia C, Rossi G, Dubini A, Piciucchi S, *et al.* The pathogenic role of epithelial and endothelial cells in early-phase COVID-19 pneumonia: Victims and partners in crime. Mod Pathol 2021;34:1444-55.
18. Doglioni C, Ravaglia C, Chilosi M, Rossi G, Dubini A, Pedica F, *et al.* COVID-19 interstitial pneumonia: Histological and immunohistochemical features on cryobiopsies. Respiration 2021;100:488-98.
19. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, *et al.* Estimates of the severity of coronavirus disease 2019: A model-based analysis. Lancet Infect Dis 2020;20:669-77.
20. Ioannidis JP, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environ Res 2020;188:109890.
21. Zhang H, Ma S, Han T, Qu G, Cheng C, Uy JP, *et al.* Association of smoking history with severe and critical outcomes in COVID-19 patients: A systemic review and meta-analysis. Eur J Integr Med 2021;43:101313.
22. Umnuaypornlert A, Kanchanasurakit S, Lucero-Prisno DE, Saokaew S. Smoking and risk of negative outcomes among COVID-19 patients: A systematic review and meta-analysis. Tob Induc Dis 2021;19:09.
23. McGroder CF, Zhang D, Choudhury MA, Salvatore MM, D'Souza BM, Hoffman EA, *et al.* Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. Thorax 2021;76:1242-5.
24. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the development of pulmonary fibrosis using serial thin-section CT and clinical features in patients discharged after treatment for COVID-19 pneumonia. Korean J Radiol 2020;21:746-55.
25. Caruso D, Guido G, Zerunian M, Polidori T, Lucertini E, Pucciarelli F, *et al.* Post-acute sequelae of COVID-19 pneumonia: Six-month chest CT follow-up. Radiology 2021;301:E396-405.
26. Chun HJ, Coutavas E, Pine AB, Lee AI, Yu VL, Shallow MK, *et al.* Immunofibrotic drivers of impaired lung function in postacute sequelae of SARS-CoV-2 infection. JCI Insight 2021;6:e148476.
27. Zhang T, Shen P, Duan C, Gao L. KL-6 as an immunological biomarker predicts the severity, progression, acute exacerbation, and poor outcomes of interstitial lung disease: A systematic review and meta-analysis. Front Immunol 2021;12:745233.
28. Yokoyama A, Kondo K, Nakajima M, Matsushima T, Takahashi T, Nishimura M, *et al.* Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology 2006;11:164-8.
29. Hanzawa S, Tateishi T, Ishizuka M, Inoue Y, Honda T, Kawahara T, *et al.* Changes in serum KL-6 levels during short-term strict antigen avoidance are associated with the prognosis of patients with fibrotic hypersensitivity pneumonitis caused by avian antigens. Respir Investig 2020;58:457-64.
30. Chiu YH, Chu CC, Lu CC, Liu FC, Tang SE, Chu SJ, *et al.* KL-6 as a biomarker of interstitial lung disease development in patients with Sjögren syndrome: A retrospective case-control study. J Inflamm Res 2022;15:2255-62.
31. Xue M, Zhang T, Chen H, Zeng Y, Lin R, Zhen Y, *et al.* Krebs Von den lungen-6 as a predictive indicator for the risk of secondary pulmonary fibrosis and its reversibility in COVID-19 patients. Int J Biol Sci 2021;17:1565-73.
32. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, *et al.* Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Ann Am Thorac Soc 2021;18:799-806.
33. Dhooria S, Chaudhary S, Sehgal IS, Agarwal R, Arora S, Garg M, *et al.* High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: An open-label, randomised trial (the COLDSTER

trial). Eur Respir J 2022;59:2102930.
34. Tomassetti S. A multidisciplinary multicenter study evaluating risk factors, prevalence and characteristics of post-COVID-19 interstitial lung syndrome PCOILS. Am J Respir Crit Care Med 2021;203:A1748.
35. Tomassetti S. A multidisciplinary multicenter study evaluating risk factors, prevalence and characteristics of post-COVID-19 interstitial lung syndrome (PCOILS). American Journal of Respiratory and Critical Care Medicine 2021;203.
36. Ma S, Xu C, Liu S, Sun X, Li R, Mao M, *et al.* Efficacy and safety of systematic corticosteroids among severe COVID-19 patients: A systematic review and meta-analysis of randomized controlled trials. Signal Transduct Target Ther 2021;6:83.
37. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693-704.
38. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021;397:1637-45.
39. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, *et al.* Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021;384:1491-502.
40. Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, *et al.* Interleukin-6 blocking agents for treating COVID-19: A living systematic review. Cochrane Database Syst Rev 2021;3:CD013881.
41. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JP, *et al.* Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A meta-analysis. JAMA 2021;326:499-518.
42. Kramer A, Prinz C, Fichtner F, Fischer AL, Thieme V, Grundeis F, *et al.* Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev 2022;6:CD015209.
43. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, *et al.* Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): A randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407-18.
44. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, *et al.* Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med 2021;384:795-807.
45. Wolfe CR, Tomashek KM, Patterson TF, Gomez CA, Marconi VC, Jain MK, *et al.* Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): A randomised, double-blind, double placebo-controlled trial. Lancet Respir Med 2022;10:888-99.
46. Cain WC, Stuart RW, Lefkowitz DL, Starnes JD, Margolin S, Lefkowitz SS. Inhibition of tumor necrosis factor and subsequent endotoxin shock by pirfenidone. Int J Immunopharmacol 1998;20:685-95.
47. Shi Q, Liu X, Bai Y, Cui C, Li J, Li Y, *et al. In vitro* effects of pirfenidone on cardiac fibroblasts: Proliferation, myofibroblast differentiation, migration and cytokine secretion. PLoS One 2011;6:e28134.
48. Hale ML, Margolin SB, Krakauer T, Roy CJ, Stiles BG. Pirfenidone blocks the *in vitro* and *in vivo* effects of staphylococcal enterotoxin B. Infect Immun 2002;70:2989-94.
49. Li Y, Li H, Liu S, Pan P, Su X, Tan H, *et al.* Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Mol Immunol 2018;99:134-44.
50. Fois AG, Posadino AM, Giordo R, Cossu A, Agouni A, Rizk NM, *et al.* Antioxidant activity mediates pirfenidone antifibrotic effects in human pulmonary vascular smooth muscle cells exposed to sera of idiopathic pulmonary fibrosis patients. Oxid Med Cell Longev 2018;2018:2639081.
51. Oku H, Shimizu T, Kawabata T, Nagira M, Hikita I, Ueyama A, *et al.* Antifibrotic action of pirfenidone and prednisolone: Different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol 2008;590:400-8.
52. Acat M, Yildiz Gulhan P, Oner S, Turan MK. Comparison of pirfenidone and corticosteroid treatments at the COVID-19 pneumonia with the guide of artificial intelligence supported thoracic computed tomography. Int J Clin Pract 2021;75:e14961.
53. Firdaus H. Clinical improvement with pirfenidone in two patients of COVID 19. J Clin Diagn Res 2020;14:14-6.
54. Zhou X, Yang D, Kong X, Wei C, LvQiu S, Wang L, *et al.* Case report: Pirfenidone in the treatment of post-COVID-19 pulmonary fibrosis. Front Med (Lausanne) 2022;9:925703.
55. Momen AB. Usefulness of pirfenidone in COVID lung: A case series. EJMED 2021;3:24-6.
56. Yu WK, Chen WC, Su VY, Shen HC, Wu HH, Chen H, *et al.* Nintedanib inhibits endothelial mesenchymal transition in bleomycin-induced pulmonary fibrosis via focal adhesion kinase activity reduction. Int J Mol Sci 2022;23:8193.
57. Umemura Y, Mitsuyama Y, Minami K, Nishida T, Watanabe A, Okada N, *et al.* Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: An interventional study. Int J Infect Dis 2021;108:454-60.
58. Ogata H, Nakagawa T, Sakoda S, Ishimatsu A, Taguchi K, Kadowaki M, *et al.* Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019. Respirol Case Rep 2021;9:e00744.
59. Marwah V, Choudhary R, Malik V, Pemmaraju A, Peter D. Early experience of nintedanib in COVID-19 ARDS-related pulmonary fibrosis: A case series. Adv Respir Med 2021;89:589-96.
60. Bussolari C, Palumbo D, Fominsky E, Nardelli P, De Lorenzo R, Vitali G, *et al.* Case report: Nintedaninb may accelerate lung recovery in critical coronavirus disease 2019. Front Med (Lausanne) 2021;8:766486.
61. Dhooria S, Maturu VN, Talwar D, Kumar S, Handa A, Agrawal PN, *et al.* A multicenter survey study of antifibrotic use for symptomatic patients with post-COVID-19 interstitial lung abnormalities. Lung India 2022;39:254-60.