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Review Article

Post-COVID-19 Pulmonary Fibrosis: An Update

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A B S T R A C T

Coronavirus disease 2019 (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most common cause of hospitalisation for COVID-19 is interstitial pneumonia that may be complicated by Acute Respiratory Distress Syndrome (ARDS). With an increasing magnitude of COVID-19 survivors, post-COVID interstitial lung disease and pulmonary vascular disease are likely to be the most important long term respiratory complications. Data from previous coronavirus infections such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), as well as emerging data from the COVID-19 pandemic, suggest that there could be substantial pulmonary fibrotic consequences following SARS-CoV-2 infection. Thus, the long-term consequences of COVID-19 appear crucial. Here, we have discussed the pathogenesis, natural history, and radiological aspects of such patients and the possible predictors which might lead to the development of lung fibrosis. Older age, severity of illness, prolonged ICU stay, history of smoking and alcoholism are few of the risk factors for the development of post-COVID-19 pulmonary fibrosis. Therapeutic options like antifibrotic drugs such as pirfenidone, nintedanib, pulmonary rehabilitation, SARS-COV-2 vaccine etc. have been described. The role of steroids and antifibrotics in the prevention of post-COVID fibrosis is still controversial. Careful longitudinal follow-up of multiple cohorts of post-COVID-19 survivors with serial lung function testing and imaging is required to complete the knowledge about natural history of the disease and the response to various therapies.

Keywords: SARS-CoV-2, Post-COVID-19 Pulmonary Fibrosis, Antifibrotics, Pulmonary Rehabilitation

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Till 25th May 2021, around 167,034,523 cases of COVID-19 and 3,472,568 deaths had been reported worldwide.[1] Increasing number of COVID-19 survivors continue to battle the symptoms of the illness long after they have been clinically tested negative for the disease. They are called as long–haulers. Various studies have reported that around 70-80% of patients who recovered from COVID-19 present with persistence of at least one or more symptoms, even after being declared

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COVID-free.[2] Post-COVID pulmonary fibrosis is one of the most worrying long-term complications. This review is to present an update on different aspects of post-COVID pulmonary fibrosis.

Pulmonary Fibrosis: General Overview

Interstitial Lung Disease (ILD) refers to a heterogeneous collection of more than one hundred distinct lung disorders that tend to be grouped together because they share clinical, radiographic, and pathologic features. The term interstitial lung disease, in general, implies the clinical manifestation of inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells. In many of the ILDs, interstitial fibrosis follows injury to the gas-exchanging units. Fibroblastic proliferation and excessive collagen deposition, the histological hallmarks of pulmonary fibrosis, either result directly from the initial injury, from the inflammatory cell response that releases proinflammatory and profibrotic cytokines, or from the regenerative and reparative processes taking place at the epithelial and endothelial surfaces.[3] Pulmonary fibrosis develops late or even in early stages of some diseases like smoking-related connective tissue disease-associated ILDs, hypersensitivity pneumonitis, occupational ILDs, and drug-induced ILDs. Other idiopathic ILDs can even present with pulmonary fibrosis like IPF and fibrotic NSIP.[4] A variety of viruses such as the Epstein–Barr virus, influenza virus, cytomegalovirus, and hepatitis C have been implicated in lung fibrosis.[5] DNA from herpes virus has been identified in 33 patients with IPF.[6] SARS-COV-2 is now emerging as a cause of pulmonary fibrosis. A substantial proportion (about 25%) of patients who developed ARDS in the pre-COVID era, irrespective of aetiology, experienced residual and long-term impairment of their pulmonary function, with radiographic evidence of pulmonary fibrosis on Computed Tomography (CT).[7] Early analysis of patients with COVID-19 on hospital discharge suggested that more than a third of recovered patients developed fibrotic abnormalities.[8] Previous studies highlighted that duration of the disease was an important determinant for lung fibrosis post ARDS. In the study done by Rai DK et al., 4% of patients with a disease duration of less than 1 week, 24% of patients with a disease duration between weeks 1 and 3, and 61% of patients with a disease duration of greater than 3 weeks, developed fibrosis.[9] Many patients who recovered from acute phase of COVID-19 are developing residual pulmonary fibrosis which is responsible for their persistent respiratory symptoms. How to prevent and manage post-COVID-19 pulmonary fibrosis, remains a challenge.

Pathogenesis of Post-COVID-19 Pulmonary Fibrosis

In general, the pathogenesis of pulmonary fibrosis due to any cause is the result of persistent remodelling (abnormal wound healing) of the lung parenchyma. Multiple microinjuries damage and activate alveolar epithelial cells, which in turn provoke a profibrotic microenvironment. Alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myofibroblasts. Aggregates of subepithelial fibroblasts-myofibroblasts (fibroblastic foci) and alveolar epithelial cells produce matrix-metalloproteinases 2 and 9 that may increase basement membrane disruption and allow fibroblast-myofibroblast migration into the alveolar spaces. In addition, alveolar epithelial cells induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation.[10] Current evidence suggests that the tissue-factor-dependent extrinsic pathway is the predominant mechanism by which the coagulation cascade is locally activated in the lungs of patients with pulmonary fibrosis. Both intra-alveolar and interstitial myofibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between interstitial collagenases and tissue inhibitors of metalloproteinases provokes the progressive deposition of extracellular matrix. These myofibroblasts produce angiotensinogen and hydrogen peroxide that have been implicated in alveolar epithelial cell death, further impairing reepithelialization.[11]

In the current SARS-CoV-2 pandemic, the molecular basis of progression to pulmonary fibrosis and post-COVID interstitial lung disease (PC-ILD) is still unclear but it is believed to be multifactorial. During the acute phase of COVID-19 pneumonia, lung injury mainly occurs due to the inflammatory response to viral infection with possible bacterial superinfection leading to ARDS. Other possible determinants of lung damage are endothelial dysfunction and microvascular damage by local thromboembolic events.[12] Similar to SARS, COVID-19 pneumonia progresses histopathologically as intra-alveolar and interstitial fibrin deposition and chronic inflammatory infiltrates, few weeks after the initial diagnosis. The renin-angiotensin system also plays a role because of high affinity binding between the SARS-CoV-2 viral spike protein and the angiotensin converting enzyme-2 (ACE-2) receptor, and has been shown to down regulate the level of the ACE-2 receptor. ACE-2 is believed to have a protective role in lung fibrosis.[13] The decreased ACE-2 expression, in turn, leads to an increase in the level of angiotensin 2 (ANG II). Being a potent vasoconstrictor peptide, ANG II is directly involved in the development of inflammation and fibrosis. Cellular and molecular signalling events of ANG ll, that lead to the development of aberrant wound healing and pulmonary fibrosis are - (i) production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-8, (ii) production of reactive oxygen species among infected alveolar cells, and, (iii) activation of TGF-β1 which in turn lead to proliferation, migration, and differentiation

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of fibroblasts to myofibroblasts with resultant deposition of collagen and fibronectin.[14] High levels of TGF-β1 in serum, bronchial epithelial cells and alveolar epithelial cells were observed in the earlier SARS-CoV-1 outbreak in 2002.[15]

Oxygen toxicity and Ventilator-Induced Lung Injury (VILI) are the iatrogenic factors potentially contributing to the fibrosis, encountered very frequently in survivors of severe COVID-19 pneumonia. Patients who developed post-COVID pulmonary fibrosis were invariably sicker, had extensive, bilateral involvement initially, and hence were more likely to have required high concentrations of oxygen, often for prolonged periods during the acute stage of their illness, resulting in heightened production of oxygen-derived free radicals which damage the pulmonary epithelium.[16] Patients with severe COVID-19 pneumonia related ARDS are more likely to be managed with prolonged mechanical ventilation with high plateau pressures in an attempt to ventilate their stiff, noncompliant lungs. It is well recognised that mechanical stress, an inciting factor for lung injury, might have contributed to the pulmonary fibrosis encountered in these patients.[17]

Risk Factors for Post-COVID-19 Pulmonary Fibrosis

Based on the previous studies on SARS and MERS outbreaks, the risk factors for developing lung fibrosis include older age (> 65 years), severity of the illness (increased LDH level), prolonged ICU stay, history of smoking, and chronic alcoholism. The severity of the lung injury and the inflammatory response were known to correlate with the extent of fibroblastic response required to repair the injury. Higher levels of CRP, IL-6, and LDH levels during acute illness were also found to significantly correlate with the risk of pulmonary fibrosis.[18]

As the data regarding post-COVID-19 fibrosis are still emerging, same predictors have been putatively identified like male gender, advanced age, severe illness, prolonged ICU/ hospital stay, mechanical ventilation, a history of smoking, and chronic alcoholism.[19,20] An Egyptian study revealed that the patients with a history of cigarette smoking showed a much higher incidence of post-COVID pulmonary fibrosis than non-smokers. Out of a total of 30 smoker patients, 18 patients developed pulmonary fibrosis (60%). In this study, post-COVID-19 pulmonary fibrosis correlated well with the age of the patient. Prevalence of pulmonary fibrosis was 43.3% (13/30 patients) in the age group of 60-75 years and 28% (7/25 patients) in the age group of 45-60 years followed by 20% (5/25 patients) in the age group of 25-45 years. This study showed that males were 1.5 times more susceptible to develop post-COVID-19 pulmonary fibrosis than females, as 37.5% of male patients developed fibrosis in comparison to 25% of female patients.[21] CT severity score (CT-SS) also played an important role in the prediction of disease progression. CT-SS is a score for the degree of lung affection based on dividing the lung into five lung lobes and affection of each lobe scored visually on a scale of 0–5 depending on the degree of their involvement, 0 indicating no involvement, 1 indicating less than 5% involvement, 2 indicating 5–25% involvement, 3 indicating 26-49% involvement, 4 indicating 50–75% involvement, and 5 indicating more than 75% involvement. The total CT score, the sum of individual lobar scores, ranges from 0 to 25.[22] A correlation was observed between CT-SS during acute phase and incidence of post-COVID lung fibrosis. Post-COVID-19 pulmonary fibrosis was seen in 18.4% of mild group patients (CT-SS of 1–17) (n = 38) in comparison to 42.8% in the severe group (CT-SS of 18–25) (n = 42).[21]

According to one study, pulmonary fibrosis developed more in patients managed in an intensive care unit (ICU) or high-dependency unit (HDU), patients discharged with a new oxygen prescription, patients with protracted dependency on high inspired fractions of oxygen, continued positive pressure ventilation and bi-level non-invasive ventilation.[23] Mc Groder et al. found that fibrotic-like patterns were more common in those who were mechanically ventilated compared to those who were not mechanically ventilated (72% vs 20%, p = 0.001). In unadjusted analyses, those with fibrotic-like patterns were significantly more likely to be male, had shorter telomeres, higher admission Sequential Organ Failure Assessment (SOFA) scores, higher lactate dehydrogenase (LDH) levels, and have received steroids or anti-interleukin-6 receptor blockade.[24]

Post-COVID-19 Pulmonary Fibrosis - Radiology

In general, pulmonary fibrosis shows hazy opacities with reduction in lung volume that progresses to a reticular pattern and finally ends in coarser, cystic areas of honeycombed lung. HRCT of lung, being more sensitive than chest x-ray, is useful in the differentiation of various ILDs, determining the extent and severity of disease activity, and most importantly, the detection of disease, especially in patients with normal or minimal change on chest radiography. Early disease appears as patchy, predominantly peripheral, subpleural reticular opacities, and minor degrees of honeycomb changes. In more advanced disease, a more diffuse reticular pattern in the lower lung zones with thickened interlobular septa and intralobular lines progresses to traction bronchiectasis and subpleural fibrosis.[25] In COVID-19 patients, as early as 3 weeks after the onset of symptoms, fibrotic abnormalities of lungs have been detected on radiology. Radiologic findings in COVID-19 pneumonia include ground-glass opacities (GGO) with or without consolidation, crazy-paving pattern, interstitial thickening, and parenchymal bands which are mainly bilateral with a predilection for the peripheries of

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the lower lobes.[26] Foci of oedema, organising pneumonia, and diffuse alveolar damage (DAD) are observed, similar to other inflammatory pneumonitis. CT findings like interstitial thickening, air bronchogram, irregular interface, coarse reticular pattern, parenchymal bands, and pleural effusion were seen more commonly in the fibrosis group as compared to those where fibrosis did not persist.[27]

A 3-weeks follow up study in Wuhan on hospitalised patients revealed that most of the patients predominantly showed patterns such as ground-glass opacity with ill-defined margins, air bronchograms, thickening of adjacent pleura and smooth or irregular interlobular or septal thickening with diffuse distribution. Other findings included progressive intra or inter septal thickening, crazy-paving patterns, and interstitial changes. These findings suggested the development of pulmonary fibrosis, though it was too early to label these lung changes as irreversible fibrosis in a time range of 3 weeks.[7] Pan et al. had found that maximum involvement of lungs occurred approximately 10 days after the initial symptom and in most of the cases these post-COVID changes resolved with time.[28] However, the cases taken in this study were of mild category. In one of the studies, a chest CT scan was performed on the last day before discharge, two weeks, and four weeks after the discharge. On follow up of these patients, the abnormalities (including focal/ multiple GGO, consolidation, interlobular septal thickening, sub-pleural irregular lines) in lungs were gradually absorbed in the first and second follow-ups after discharge as compared with the scan before discharge. The lung lesions of 64.7% of the discharged patients were fully absorbed after a 4-week follow-up, indicating that the damage to lung tissue by COVID-19 could be reversible for most of the COVID-19 patients.[29]

In a prospective, multicentric, follow-up observational study on 86 severe SARS-CoV-2 survivors in Austria, the extent of cardiopulmonary damage was evaluated. The preliminary prepublication findings reported that majority of the patients were left with persisting dyspnoea (37%), reduction in diffusion capacity (28%), and CT abnormalities (88%) at 6-week post discharge. At 12 weeks, the CT abnormalities had decreased to 56%, from 8 points on the 6-week CT scans to 4 points on the 12-week scans. Reassuringly, the authors also reported that progressive pulmonary fibrosis was not encountered in any of their patients, while data from the 24-week follow-up is keenly awaited. There was also an improvement in lung function from 6- to 12-week follow-up.[30] These data suggested that the majority of patients infected with coronavirus were discharged from hospitals with persisting radiological change but by 12 weeks, approximately most of the patients had full CXR resolution. The optimal time for follow-up imaging to assess for radiological clearance in COVID-19 is unknown. Current BTS guidelines recommend a repeat CXR 6 weeks after a (bacterial or viral) community-acquired pneumonia; the rationale being exclusion of primary bronchial neoplasms that can contribute to lobar or segmental pneumonia.[31] The ATS does not recommend routine follow-up imaging for patients recovering satisfactorily from community-acquired pneumonia.[32] So, as the data suggest, a 12-week time point may be considered to be optimal in providing sufficient time for imaging resolution while also ensuring that non-resolving changes are addressed sufficiently early. It is too early in the course of the pandemic to predict the natural history of post-COVID-19 pulmonary fibrosis. Follow-up of cohorts of post-COVID-19 survivors are already underway at several centres with the pivotal question: Are the changes seen on CT scan likely to (1) persist, (2) gradually improve, or (3) even worsen with the passage of time? This has implications not only for prognosis but also for treatment. Antifibrotics may have an important role in those who progress but a lesser role in the first two scenarios.

Pulmonary Function Test (PFT) in Post-COVID-19 Pulmonary Fibrosis

Pulmonary function testing is useful in establishing the presence of functional impairment in pulmonary fibrosis and following its course and response to therapy. The lung volumes like total lung capacity (TLC), functional residual capacity, and residual volume are reduced in pulmonary fibrosis. Expiratory flow rates (FEV1) and forced vital capacity (FVC) may be decreased because of reduction in lung volume, but FEV1/ FVC ratio is maintained. The decrease in diffusion capacity of lungs for Carbon Monoxide (DLCO) results from both the contraction of the pulmonary capillary volume and the presence of ventilation-perfusion abnormalities. Resting arterial blood gases are usually abnormal, revealing hypoxemia, and respiratory alkalosis. The major cause of resting hypoxemia is ventilation-perfusion mismatch. With exercise, the (A−a) PO_2 widens, and arterial PO_2 and oxygen saturation fall. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of abnormalities seen with exercise. In addition, gas exchange during exercise has been demonstrated to be a sensitive parameter for following the clinical course. The severity of the initial abnormalities in FVC, DLCO, arterial PO_2, and (A−a) PO_2, as well as oxygen desaturation on a 6MWD test, correlate with poorer survival.[33]

In a study of 110 discharged patients of COVID-19 including 91 (83%) patients of mild-moderate disease and 19 (17%) patients with severe disease, almost 50% had impairment of the transfer factor of the lung for carbon monoxide (TLCO). The interval between onset of illness and PFT was on an average 20 days in mild cases to 34 days in severe pneumonia. The TLCO was lower in patients with severe disease and was more sensitive to disease severity than other lung function parameters such as FVC and

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TLC. Interestingly, in this study the TLCO/ alveolar volume (KCO) was significantly lower in those with severe disease than those with mild-moderate COVID-19 cases, possibly implying a degree of pulmonary vasculopathy.[34] Zhao et al. conducted a 3-months follow up study of 55 COVID-19 patients in which PFT and radiological evaluation were done. It revealed that 71% had residual CT abnormalities, including evidence of interstitial thickening in 27%. PFT was abnormal (i.e. reduced diffusion capacity, restrictive abnormalities, and small airways obstruction) at the time of discharge and 2 weeks after discharge. Impairment of diffusion capacity, being the most common abnormality, was seen in up to 47% of the cases followed by restrictive ventilatory defects seen in about 25% of cases.[35]

In a study on SARS survivors, 36% of patients had residual CXR abnormalities after 12 weeks of discharge and 30% had it at 6 months predominantly in the form of airspace opacification and reticulation. These radiological findings correlated well with PFT parameters including FVC, TLCO, and TLC. At six months, 16% of patients had persistent impairment of transfer factor of the lung for carbon monoxide (TLCO) with the preservation of the alveolar volume (KCO), implying that these CXR imaging abnormalities were due to parenchymal lung disease.[36] Similar findings were seen in MERS survivors at 6 weeks median follow-up point (range 32-230 days), wherein residual CXR abnormalities were seen in 36% of patients, with the predominant pathology being pulmonary fibrosis.[16]

Given that persistent imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease and are the group in whom closer follow-up and further investigation are indicated.[37]

Treatment

Pharmacological Treatment

Steroid: Some forms of ILD, including cryptogenic organising pneumonia (COP), connective tissue disease-associated ILD, and sarcoidosis, may demonstrate a favourable response to corticosteroids and other immunosuppressive agents. However, in diseases such as IPF, what was once thought to be the standard of care (prednisone plus azathioprine) has been demonstrated to carry harm without any potential for benefit.[38] While considering the use of these drugs, an assessment should be made regarding the risks and benefits of the therapy. The role of steroids in preventing and treating post-COVID-19 pulmonary fibrosis is controversial. Most of the patients who develop PC-ILD are hypoxic during acute phase and had severe COVID-19 pneumonia. On the basis of results of RECOVERY trial, steroids became the standard of care in hypoxic COVID-19 patients in ICUs across the world, in modest doses of 4-6 mg dexamethasone for no more than 10 days.[39] As is seen in various follow-up studies, merely giving steroids does not seem to be enough for preventing fibrosis. This does not change the fact that most of the patients nowadays are provided equivalent or higher doses of steroids.[40] Steroids should be continued on discharge if the CT scan prior to discharge continues to show significant GGOs and the patient remains hypoxic. But the treating physician should also have a concern about the adverse effect of long-term large dose steroids like worsening hyperglycaemia and proximal myopathy which in turn would retard the patients' mobility and rehabilitation. The usual given dose is 20–30 mg of prednisolone at discharge and tapering is to be done on follow up depending on the patient's response. Cough can be quite problematic and difficult to control; low-dose opiates may be of some benefit and low dose corticosteroids are occasionally used, understanding their long-term risk.[38] Evaluation and treatment for acid and non-acid reflux should be considered whenever intractable cough persists.

Antifibrotic Agents: Pirfenidone is an orally administered agent with anti-inflammatory, antioxidant, and antifibrotic properties. There is evidence to suggest that pirfenidone has efficacy in slowing the progression of fibrosis in IPF. In recently published data from the ASCEND trial, pirfenidone was associated with a significant reduction in the proportion of patients who had a decline of 10% or greater in their predicted FVC. Additionally, there was a significant increase in the numbers of patients who demonstrated no decline in FVC. In a combined analysis of the ASCEND and CAPACITY trials, pirfenidone was associated with a decrease in both all-cause and IPF-related mortality.[41,42] Nintedanib (BIBF-1120) is a tyrosine kinase inhibitor that targets the platelet-derived growth factor receptor, vascular endothelial growth factor receptors, and fibroblast growth factor receptors. A 12-month, randomised, double-blind, placebo-controlled, phase 2 trial with 432 IPF patients showed the trend towards a reduction in the decline of lung function with fewer acute exacerbations and preserved quality of life. Two recent, multinational, randomised, placebo-controlled, parallel group trials (INPULSIS-1 and INPULSIS-2) showed that nintedanib slowed disease progression by significantly reducing the rate of decline in FVC.[43] Nintedanib has been approved for the treatment of IPF in the United States.

Both PC-ILD and IPF share many common demographic factors like disproportionately affecting males, the elderly, smokers. Autopsy and histopathology of the involved lung in COVID-19 patients showed fibrosis with fibroblasts and honeycombing. For all these reasons, it is reasonable to assume that antifibrotic drugs may have a potentially valuable role in the setting of COVID-19. However, there are a few concerns regarding the use of these antifibrotics in acute phase of COVID-19 pneumonia, like many COVID-19 patients have hepatic dysfunction in the form of raised

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transaminases and both antifibrotics pirfenidone and nintedanib can cause hepatotoxicity. As most of the COVID-19 patients are on an anticoagulant, nintedanib might be associated with an increased risk of bleeding.[44]

The choice of drugs that should be used is less clear. It is worth noting that INBUILD, INPULSIS, and ASCEND trials have shown that both these antifibrotic drugs took at least 1-3 months to demonstrate an effect in the form of FVC improvement.[43] Addition of antifibrotics in the standard treatment protocol is riddled with uncertainties in terms of timing in acute phase and patients' characteristics at discharge or follow up (clinical, radiological, biomarkers parameters). In the study conducted by Umermura Y, et al. 30 patients were enrolled who were administered 150 mg of nintedanib via nasogastric tube twice daily from day 1 to liberation from mechanical ventilation within 28 days. The nintedanib group had a significantly higher PaO_2/ FiO_2 ratio, shorter lengths of mechanical ventilation and lower volume of high-attenuation areas on CT images. These findings clearly suggested that the administration of nintedanib could ameliorate the lung injury induced by COVID-19, potentially by modulating the progression of pulmonary fibrosis. The widely recognised and alarming sequelae of COVID-19 on respiratory function can be reduced by nintedanib as evidenced by findings of CT.

Despite the favourable effects of nintedanib on respiratory function, the 28-day mortality rate was not significantly different between the two groups.[45] So, in the acute phase, adding them at a late stage in patients already needing ventilator support, may not be beneficial. Since it has already been well observed by the follow-up studies, as mentioned earlier, that the patients with severe ARDS are more likely to develop lung fibrosis, so, this group of patients might get benefitted from treating with antifibrotics. Such patients will generally require prolonged ventilation with high oxygen requirements and perhaps antifibrotics along with steroids might have a role in preventing or retarding the fibrosis. In the case series by Momen et al., five patients who developed pulmonary fibrosis after COVID-19 which did not improve with standard care, were started on pirfenidone with individualised dosing and showed marked improvement of both the patients' symptoms and improvement of the radiological findings over 6-12 weeks.[46] A study is being conducted by Pratima et al. in Kalinga Institute of Medical Science, Orissa, India, to find out the role of nintedanib on improvement in CT severity score at 6 and 12 weeks in acute moderate hospitalised COVID-19 patients; its results are awaited.[47] A biomarker that can identify and predict which patient will develop fibrosis, would indeed be invaluable. But, till one emerges, evidence of fibrosis on CT with traction bronchiectasis and/ or honeycombing would be useful to identify which patients would potentially get benefitted from antifibrotics.

As of now, antifibrotics should be reserved for those post-COVID patients who demonstrate evidence of progression of fibrosis, deterioration in PFT parameters suggestive of restrictive lung disease or increased domiciliary oxygen requirement in the recovery phase, provided other causes for the same have been ruled out. Giving these drugs to those who are spontaneously improving over time or whose fibrosis is static, is unlikely to be useful. However, at present, it is very difficult to identify which patient is likely to progress and get benefitted from antifibrotics as progression will be apparent only over time.

The role of renin-angiotensin-aldosterone system (RAAS) is well known in the development of post-COVID-19 pulmonary fibrosis. The spironolactone-dependent up-regulation of the adenosine A2A receptor (A2AR) has recently been shown to play a role in the endothelial–mesenchymal transition, suggesting a possible mechanism for spironolactone in the reduction in fibrosis.[48] It is likely that spironolactone may modulate the extracellular matrix and fibrosis via interaction with this receptor. Lieber et al. showed that the use of spironolactone alleviated pneumonia induced by liposaccharides and bleomycin by reducing the number of inflammatory cells such as lymphocytes, neutrophils, macrophages and eosinophils in the alveoli.[48] Ji et al. demonstrated the therapeutic effect of spironolactone by reducing the inflammatory response in the lungs.[49] Atalay et al. demonstrated a positive effect of spironolactone in the treatment of acute lung injury.[50] Overall, the effect of aldosterone on the pathophysiology and incidence of fibrosis is not fully understood, most of the studies of these effects of aldosterone have been conducted in animal models. Nevertheless, considering the above findings, it seems likely that spironolactone may be effective in the prevention of COVID-19 infection-related pulmonary fibrosis, but further experimental research is needed to elaborate the mechanisms of involvement of this medication in the pathology of pulmonary fibrosis and its utility.

It is important to reduce the viral load and hence the duration of viral pneumonia for preventing pulmonary fibrosis. The therapeutic options for this are hydroxychloroquine, remdesivir, and ivermectin. However, recently WHO has given strong recommendations against the use of hydroxychloroquine whereas conditional recommendatiosn against the use of remdesivir. Ivermectin is recommended in mild and early cases.[51]

Pulmonary Rehabilitation

Pulmonary rehabilitation designed to optimise patients' exercise capacity, breathlessness, health status, and psychological well-being, is already established as a key management strategy in those with chronic respiratory diseases. Pulmonary rehabilitation leads to increased

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muscle strength and improved endurance in patients with COPD. Similar improvements may be evident in fibrotic lung diseases as well. In addition to the potential benefits of improved muscle strength and stamina, patients with PC-ILD may also get benefited from the ongoing education regarding oxygen use, breathing and pacing techniques, and social support.[52] In a study on SARS patients, residual mild pulmonary function defects were detected in over half of the recovered SARS patients at 3 months after hospital discharge, 41% had impaired exercise capacity that could not be accounted for by ventilatory limitation.[53] Critical illness muscle weakness and deconditioning were likely to be the contributing factors. Pulmonary rehabilitation should be commenced as soon as the patient is shifted out of the ICU and should be continued at home after discharge of the patient from the hospital. Liu K et al. recruited 72 participants in their study, out of which 36 patients underwent respiratory rehabilitation and the rest without any rehabilitation intervention. After 6 weeks of respiratory rehabilitation in the intervention group, they disclosed significant differences in FEV1(L), FVC(L), FEV1/FVC%, DLCO% and 6-min walk test.[54] Domiciliary Oxygen support is required for many patients with PC-ILD and this should be provided via oxygen concentrator with patients being instructed to keep monitoring their saturations at rest and after exertion and targeting SpO_2 according to comorbidity of the patient.

Vaccination

Chronic lung disease is an indication to get vaccinated against influenza and pneumococcal pneumonia, so all patients with PC-ILD should receive these vaccinations. It is worth mentioning here that many different kinds of vaccines against SARS-COV-2 have been developed. It has been shown that these vaccines prevent infection by this virus, and if infected, they decrease the severity of the disease. As it has been already mentioned in the above text that disease severity is the most important risk factor to develop long term complications of COVID-19 like PC-ILD, so a vaccine is a direct preventive modality for COVID related lung fibrosis.[55,56]

Anticoagulation

Patients with PC-ILD continue to be at high risk for clotting complications after discharge. Even a minor pulmonary embolism at this stage in a hypoxic patient can cause major harm. As prolonged immobilisation and systemic inflammation are indications to use prophylactic anticoagulation, these agents should be used in these patients as they are not yet fully mobile because of muscle wasting and breathlessness and may be continued for few weeks to months post discharge until their mobility improves, irrespective of any other indication.[57]

Lung Transplantation

Since late 1980s, lung transplantation has been used for the management of a wide range of severe lung disorders with progressive disease unresponsive to pharmacologic treatment, with evidence supporting quality of life and survival benefit for lung transplant recipients. Lung transplantation could be the only treatment option for patients with end-stage lung fibrosis due to COVID-19. However, only a few patients have received this therapy till date. Chen et al. reported three patients who received lung transplantation for COVID-19 related lung fibrosis. Two out of them survived.[58] In future, selection criteria need to be formulated for post-COVID-19 pulmonary fibrosis patients to undergo lung transplantation. Multipotent mesenchymal stem cells, which have the capacity to replace damaged alveolar cells, secrete anti-inflammatory factors and reduce fibro-proliferation.[59]

Pulmonary hypertension contributes to progressive diffusion impairment and may contribute to progressive respiratory failure. Post-COVID-19 pulmonary fibrosis can cause the development of pulmonary hypertension and cor pulmonale in a similar fashion.[60] Common causes of pulmonary hypertension, such as left-sided systolic or diastolic cardiac dysfunction may also be present.[61] So, if pulmonary hypertension or cor pulmonale is diagnosed, it should be treated.

Follow Up of Post-COVID Interstitial Lung Disease

As we have mentioned that there are uncertainties about the natural history of PC-ILD, accurate longitudinal studies with serial imaging and PFT are the only way to complete gaps. Raghu et al. have proposed a scheme for the follow-up of these post-COVID survivors. An initial baseline visit should be established once the patient is SARS-COV-2 RT-PCR negative with a baseline non contrast high-resolution CT scan (HRCT), PFTs (spirometry, lung volumes, and diffusion capacity), 6-min walk test, and assessment of QOL with standard questionnaires and follow up visits up to a total duration of 36 months, based on the degree and extent of the lung involvement.[62] It seems reasonable that 3 monthly lung function tests, walk tests, QOL questionnaires, and annual HRCT should be done for all patients till clinical, physiological, and radiological stability has been documented.

Conclusion

Patients with severe COVID-19 infection are often complicated by ARDS. Post-COVID-19 pulmonary fibrosis is one of the most worrying pulmonary complications developing in a substantial proportion of survivors of COVID-19 infection. Older age, severity of illness, prolonged ICU stay, history of smoking and alcoholism are a few of the risk factors for development of post-COVID-19 fibrosis. Knowledge of these

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predictors guides us in identifying high risk patients for the development of pulmonary fibrosis and provides us with a subset of patients in whom early treatment should be given which might help in preventing pulmonary fibrosis in these patients. Post-COVID pulmonary fibrosis needs to be diagnosed as early as possible so that treatment can be started timely. Options like steroids, antifibrotic drugs such as pirfenidone and nintedanib, pulmonary rehabilitation, and SARS-COV-2 vaccine are available for prevention and treatment of post-COVID pulmonary fibrosis. However, role of steroids and antifibrotics in prevention of post-COVID fibrosis is still controversial. More studies are required to assess the effects of antifibrotics, pulmonary rehabilitation, long term steroid, anticoagulant therapy or any other therapy in prevention and treatment of post-COVID-19 pulmonary fibrosis.

Conflict of Interest: None

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