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Review

Pulmonary Fibrosis in SARS-CoV-2 Infection: The Beginning of the End

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INTRODUCTION

The world has been battling a pandemic of a novel Coronavirus named SARS-COV-2 and witnessing the frantic dance of COVID-19 in the year 2020-21 and much more to be seen in the time ahead. Despite being a respiratory infection, COVID-19 has been proven to complicate by affecting other systems and an even dreaded outcome in patients with comorbidities[1]. Epidemiological and Clinical research has concluded that most of the COVID – 19 patients elicit a milder form and good response to recommended medical treatment, resulting in recovery. Around 5% of the cases ended up in ICU , 2.3% were mechanically ventilated and mortality rate was steady around 2%[2,3]. This still does not undermine the fact that millions of lives were lost in this horror. The economic, humanitarian, social and mental impact of this pandemic is insurmountable.

Given the recent advances and the state of medical science that is today, a pandemic was probably the least of our concerns. But that is exactly what happened. And all we are left with is with unanswered questions. Mankind is not new to global pandemics. The shift of our species from hunter – gatherers to an agrarian household has mitigated the spread of infectious disease in communities. Increasing interaction, expansion, trade lead to exponential outreach of diseases. The bubonic plague is written in the history books as he first pandemic. Tales from the past still sends shivers down the spine. From the year 541 till 2019 we saw many pandemics, but none albeit studied in such detail and still left us puzzling.

Viruses are notorious for spreading quickly and dying slowly. And COVID – 19 is no exception. It has affected 200 million people worldwide and killed about 100,000 till date[4]. The storm, has left many traces behind. COVID-19 affects almost all the system in body. Severe COVID-19 infections are dealing with numerous health issues. Fibrosis is one such but the most dreaded aftermath. The eponym "Fibrosis" denotes a state of pathologic process in which the lung tissue and parenchyma is undergoing irreversible damage in form of hardening, damage to cell line and excessive deposition of Collagen fibres, extracellular matrixes. Pulmonary Fibrosis (PF) is an end, a dead end of a destroyed lung parenchyma, seen in end stage Interstitial Lung Diseases (ILDs)[5]. A severely infected COVID-19 survivor, after beating the virus is ending up with devastating fibrosis. This potentially is an urgent health crisis, which will require a lifetime of Oxygen dependence. Slowly an increasing number of patients are being diagnosed with post COVID residual pulmonary fibrosis and requiring Long Term Oxygen Therapy (LTOT).

What we are still left to identify is how and when we can predict PF in a patient of COVID-19 with the limited but substantial set of diagnostic methods we have.

Any sort of infection be it viral or bacterial can cause injury to airway epithelium and undergo cell death in form of apoptosis, both the organisms carry the potential to alter or modulate host response towards invasion and injury. Previous viral epidemics have taught us the mechanism of post viral lung fibrosis extensively. And carrying that knowledge in today's scenario, can help tackle the

unknown. The cytokines involved in host immune response are quantifiable via a blood test, and the amount of damage done by the virus is possible to demonstrate via a basic CT Scan of the lungs. And comparing out both these parameters through a sequence in tandem with disease progression can identify PF and quite possibly plan necessary interventions.

There can be a potential link between the inflammatory markers and development of PF, as the entire process at its core is exaggerated inflammation which persisted. The gold standard test to diagnose is PF is High Resolution CT Scan thorax. Thin section chest CTs are the best tool for us in disease evaluation and progression for COVID-19.

Atypical Pneumonia of viral aetiology is the leading cause of hospitalization in COVID-19 patients, majority of mortality noted were due to complications suffered in form of ARDS, Residual fibrosis and refractory respiratory failure. But survivors of the disease are yet to be studied for any long term or chronic complications. Pulmonary Fibrosis being one of the most important of such complication. It is a debilitating and limiting condition severely affecting the remaining quality of life. The observational studies have shown similar findings in long term follow up of COVID-19 survivors[6]. What we saw from a 15 year follow up of SARS patients, they were ending up with chronic lung diffusion abnormalities, and COVID-19 has its own share of similarities with SARS in itself[7].

Researchers in radiology have reported that typical imaging features of COVID-19 patients include ground-glass opacity (GGO)[8,9] crazy-paving pattern, and consolidation[9]. Once discharged, a sizable amount of patients had almost no CT abnormalities[10]; yet many still demonstrated apparent residual parenchymal abnormalities on follow-up chest CT scans[11]. However it has rarely been reported whether discharged patients develop fibrosis, and/or which group of patients is more likely to develop pulmonary fibrosis.

The state of medical science as of today has no approved therapy of COVID-19. Potential treatment or even a substantial evidence of established risk factors, mortality predictors, complications are having evidence which is circumstantial at best. Severe patients of COVID-19 have proved reduced lung diffusion and oxygenation as compared to mild or moderate category patients. The delta in knowledge remains here, to stratify whether these patients will develop chronic pulmonary fibrosis, or they will heal with healthy breathing lung tissue. Interestingly and unfortunately, it has been observed that COVID – 19 patients develop devastating fibrosis as early as 3 weeks, which is a grave concern[14]. Long COVID Syndrome is a published term and upcoming data is indicating long-term symptomatically active post covid patients are increasing in number[15].

Recently published guidance by the NHS lays out the likely aftercare needs of patients recovering from covid-19 and identifies potential respiratory problems including chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease. The evidence for these possible sequelae is largely derived from acute manifestations of covid-19, along with extrapolations from the 2003 outbreak of severe acute respiratory syndrome (SARS) and data on acute respiratory distress syndrome (ARDS)[16].

We are still left with more questions than answers about the pandemic. The research is still required to understand how can fibrosis occur, and will these be permanent or temporary, or rather dreadful – progressive. In this study we have tried to better understand Development of Pulmonary Fibrosis in Post COVID -19 patients, especially the moderate and critically ill patients, possibly find out a positive between fibrosis and inflammatory markers so we can catch the complication early and help the recovery phase of the disease progress uneventful.

Background

Interstitial lung diseases comprise several inflammatory disease (ILDs) chronically affecting the lung parenchyma, interstitium and the vasculature. Chronic inflammation, collagen deposition more specifically in the interalveolar spaces can mean a fibrotic lung. The emerging cause of Fibrosis has been infectious diseases leading up to dysregulated host immune response. PF is the flag bearer of various ILDs. The primary failure seen in PF is defect in Oxygen and CO_2 transport across the alveolar surfaces[17]. One such example being Idiopathic Pulmonary Fibrosis (IPF). IPF carries the maximum mortality with only 2-5 years of median survival (which is actually worse than malignancy), hence research on PF will help improve clinical outcomes[18,19].

The Basic Principle of Breathing Physiology

Pathogens and inhaled particles are continuously exposed to the respiratory system. As a result, it is bordered by a highly specialised epithelium that can be classified as conducting airways or alveoli depending on where it is located and what it is used for. A protective layer of mucus is produced towards the lumen by secretory club and goblet cells, which are found in the pseudostratified epithelium of the proximal airways. To remove particles that have become stuck, the terminally developed ciliated cells move the mucus layer upward. Although most cell types of the airway epithelium are very malleable, basal cells are thought to represent the progenitor cells of the airway epithelium since they can develop into secretory or ciliated cells[20].(Figure 1-A)

The conducting airways split out at the distal end and eventually ended up in the alveoli. One of the largest body surfaces in continuous touch with the environment, these sac-shaped units are crucial for effective gas exchange. Highly specialised flattened type I alveolar epithelial (ATI) cells cover around 95% of the alveolar surface[21]. Together with the pulmonary microvasculature endothelial cells, they provide an incredibly thin epithelial-blood barrier that facilitates effective CO_2 and oxygen passive diffusion[22]. Alveolar macrophages (AM), microvascular cells, and fibroblasts are just a few of the surrounding cells in the niche that interact with type II alveolar

epithelium (ATII) cells, together with ATI cells, to form the highly differentiated alveolar epithelium. (Figure 1:B)

In this figure: (A) In the airways' pseudostratified epithelium, mucus is produced by secretory goblet and club cells and transported by ciliated cells to protect the lung from micro-injuries and infection. Basal cells, which are progenitor cells, reside at the lamina propria. The composition and frequency of these cell types vary among different anatomical sites in the nose, trachea, bronchi, and bronchioles.

(B)The alveolar epithelium is designed for gas exchange. Flattened ATI cells form an ultra-thin barrier for oxygen and CO_2 diffusion. Cuboidal ATII cells are progenitor cells of ATI cells and produce pulmonary surfactant to prevent alveolar collapse. Lung fibroblasts maintain the ATII stem cell niche while resident alveolar macrophages and immune cells defend against infection.

(C) SARS-CoV-2 initially infects the airway epithelium and can replicate efficiently in ciliated and secretory cells, resulting in mild to moderate COVID-19 symptoms.

(D) The respiratory epithelium exhibits differential susceptibility to SARS-CoV-2 infection. In correlation with ACE2 expression, SARS-CoV-2 infection is most efficient in the upper airways, particularly in the nasal epithelium. Infectivity decreases toward the alveoli but can result in severe COVID-19 manifestation when it reaches there.

(E) SARS-CoV-2 enters the alveoli and infects the endothelium and epithelial cells of the alveoli, resulting in viral pneumonia. Syncytial and apoptotic alveolar epithelial cells, which lead to the loss of lung surfactant and barrier integrity, are clear signs of SARS-CoV-2's cytopathogenic effects. Alveolar injury in some patients leads to a compromised immune system and life-threatening microvascular activation. Fibrin deposition, ATII cell hyperplasia, and thickening of the alveolar wall are indications that tissue regeneration is already occurring during acute COVID-19. Furthermore, patients with COVID-19 who are critically ill still show radiological fibrosis long after they

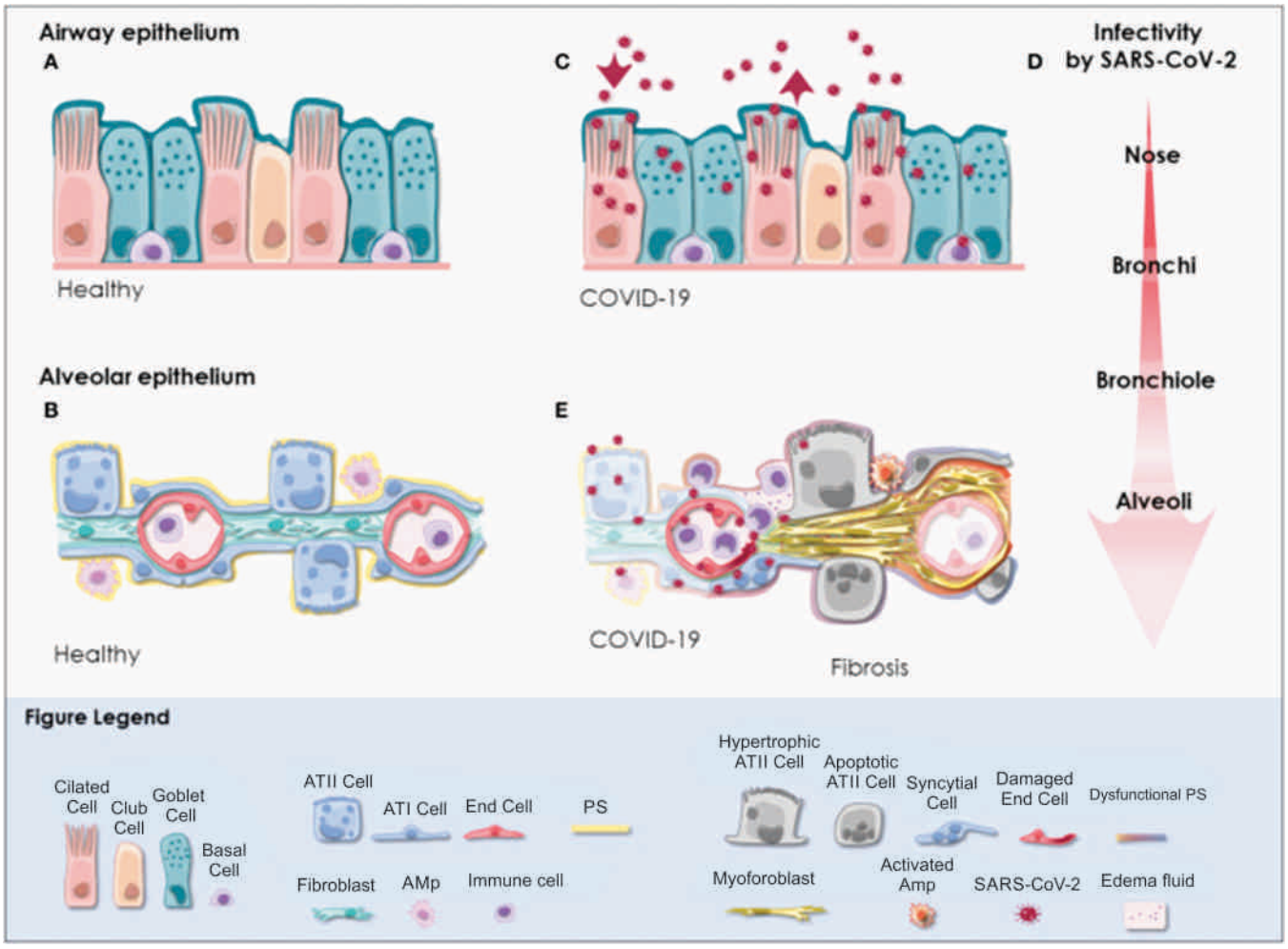

Figure 1: SARS CoV–2 in the Respiratory Tract

have recovered, suggesting that COVID-19-associated fibrosis has been induced. ATI cell, type I alveolar epithelial cell; ATII cell, type II alveolar epithelial cell; COVID-19, coronavirus disease 2019; End. cell, endothelial cell; AM, alveolar macrophage; PS, plasma renin-angiotensin-converting enzyme 2; pulmonary surfactant; SARS-CoV-2, severe acute respiratory syndrome coronavirus[23].

ATII cells serve as facultative stem cells in response to injury, triggering their regenerative response and causing them to become hyperplastic. Apoptosis, migration to the site of injury and differentiation into ATI cells, or self-renewal are the possible outcomes for these ATII cells. These mechanisms rely on the equilibrium of many mediators and a complex interaction between cells, in which stromal cells and AM play a key role[24]. According to some research, the mouse's pro-inflammatory and oxidative environment acts as a catalyst for ATII cell differentiation and repair, with Wnt signalling serving as a major regulator[25]. Studies showing that ATII-targeted injury or cellular intrinsic changes, rather than genetic or related to ageing, result in abnormal tissue remodelling highlight the importance of ATII cells in the repair process[26,27].

Pulmonary Fibrosis in the setting of COVID-19

Alveolar Damage

After five years of follow-up, it has been shown that ARDS can cause physical disability that lasts a lifetime[28], including fibrotic lung alterations brought on by aberrant wound healing. Acute alveolar injury, such as that caused by a viral infection, triggers inflammatory and apoptotic responses[30,31]. Damage to the alveolar epithelial cells starts a chain of events that includes the release of pro-inflammatory cytokines, which activates the local immune system, regulated fibroblast proliferation, and interstitial fibrogenesis, which starts the main wound healing mechanisms[32,33]. Recovery of the basal lamina, re-epithelialization of the alveolar epithelium34, and breakdown and clearance of ECM proteins[35]are typical ways to restore these effects. To stop the evolution of the disease after alveolar injury, a precise and controlled repair mechanism is essential.

New Evidence

As long-term follow-up information on recovered COVID-19 patients becomes available, predictions can be made using lessons learned from previous coronavirus epidemics. SARS-CoV, the coronavirus that causes severe acute respiratory syndrome, is to blame for the first coronavirus outbreak of the twenty-first century (SARS). SARS is a condition that manifests conventional infection-related symptoms, such as fever and pneumonitis, and that most individuals recover from 12 weeks after contracting the infection. SARS patients may experience severe respiratory problems in up to one-third of cases, necessitating oxygen therapy[36].

Beginning with early lung injury and oedema, bronchiolar sloughing of ciliated epithelial cells, and the deposition of hyaline-rich alveolar membranes, the acute phase of SARS eventually leads to decreased oxygen exchange, which appears clinically. The subsequent 25 weeks are divided into a progressive phase that is characterised by the deposition of fibrin and the invasion of inflammatory and fibroblastic cells. After a year, the last stage of pulmonary fibrosis consolidates with collagen deposition and interstitial fibroblast proliferation[37,38].

Early research suggests that COVID-19 individuals who are critically unwell experience fibrotic remodelling and scarring in their lungs, similar to what happened in SARS and MERS cases. In numerous independent surveys[39,40], an unacceptably high percentage of COVID-19 patients reported continuing symptoms, primarily fatigue and dyspnea, even months after first diagnosis. Many survivors show diminished diffusion ability and persistent radiological anomalies three months later, whereas others make a full recovery[41,42]. More research is being done to determine whether radiological and functional abnormalities are persistent and even deteriorating. The abnormal localization of mucus to the alveolar parenchyma, pathologic indications of proliferative DAD, and thickening of the alveolar wall found during lung autopsies of deceased COVID-19 patients are concerning[43,44,45].

Pathogenic Mechanisms

In prior analogous viral epidemics like influenza and SARS, the process of post viral lung fibrosis has been thoroughly explored, and understanding the past may help us prepare for an uncertain future. In a research from China of 16 patients who were hospitalised with pneumonia brought on by the 2009 H1N1 influenza, significant levels of transforming growth factor-beta 1 (TGF-1)46 were found. This study is relevant since it focuses on severe H1N1. This cytokine is known to cause fibrosis by a number of mechanisms, including a rise in extracellular matrix protein deposition, promotion of fibroblast chemotactic migration, and the transition from fibroblast to myofibroblast.

The influenza virus stimulates toll-like receptor 3, which activates TGF-1 in the lungs and results in increased amounts of collagen deposition, according to animal research by Jolly *et al*[47] using a mouse model. They were able to show that collagen 1, 111, 1V, and V1 significantly increased in their trials as early as 5 days after an influenza infection. High amounts of TGF-1 were also seen in blood, bronchial epithelial cells, and alveolar epithelial cells during the previous SARS-CoV-1 outbreak in 2002[48].

The molecular foundation of the present SARS-CoV-2 pandemic's progression to pulmonary fibrosis and PC-ILD is yet unknown, however it is thought to be complex (Figure 2). Direct viral effects, the virus' ability to make cytokines like TGF-1 more active, and an increase in oxidative stress have all been hypothesized[4]. Since it has been demonstrated that the angiotensin-converting enzyme-2 (ACE-2) receptor is downregulated by the high-affinity binding of the SARS-CoV-2 viral spike protein to this receptor, the participation of the renin-angiotensin system has also attracted considerable

attention[5]. When it comes to lung fibrosis, ACE-2 is thought to be protective. High angiotensin 2 (ANG II) levels are caused by the reduced ACE-2 expression. A strong vasoconstrictive peptide directly connected to development is ANG II.

Along with controlling blood pressure, ANG II is essential for the fibrotic process because it signals cellular and molecular actions that result in the development of pulmonary fibrosis and abnormal wound healing. These include I the production of pro-inflammatory cytokines like interleukin-6 (IL-6) and IL-8, (ii) the release of reactive oxygen species by infected alveolar cells, and (iii) the activation of TGF-1, which in turn causes fibroblasts to proliferate, migrate, and differentiate into myofibroblasts, where collagen and fibronectin are then deposited (Figure 2).

Patients with post-COVID fibrosis are almost always sicker, initially have more widespread bilateral involvement, and hence were more likely to need high oxygen concentrations, frequently for extended periods of time, during the acute stage of their illness. It is known that prolonged exposure to high oxygen concentrations increases the formation of oxygen-derived free radicals, which can harm the pulmonary epithelium. [6] The sickest COVID-19 pneumonia patients are also more likely to have needed extended mechanical ventilation, frequently with development of high plateau pressures in an effort to ventilate their stiff, noncompliant lungs. The role of mechanical stress as an inciting factor for lung injury is also well recognized and it is likely that VILI may also be contributing to the pulmonary fibrosis encountered in these patients[49].

Historical Take

Globally, SARS-CoV-2 has now infected more than 50 million people. The majority of patients have mild or moderate infections, but a small number of patients—a few million—will have considerable pulmonary involvement because roughly 10% will have severe COVID-19 pneumonia and 5% will develop ARDS. While the majority of cases will clear up without any lasting lung injury, it's likely that a sizable portion will still have fibrotic sequelae. Regardless of the aetiology, it is known that a sizeable fraction (about 25%) of patients with ARDS in the pre-COVID era sustained long-term, persistent impairment of their pulmonary function as well as radiographic indications of pulmonary fibrosis on computed tomography (CT)[50]. If we narrow our attention once more to other influenza pneumonias, specifically, fibrosis complicates H1NI only sporadically[51], whereas up to 22% of patients with

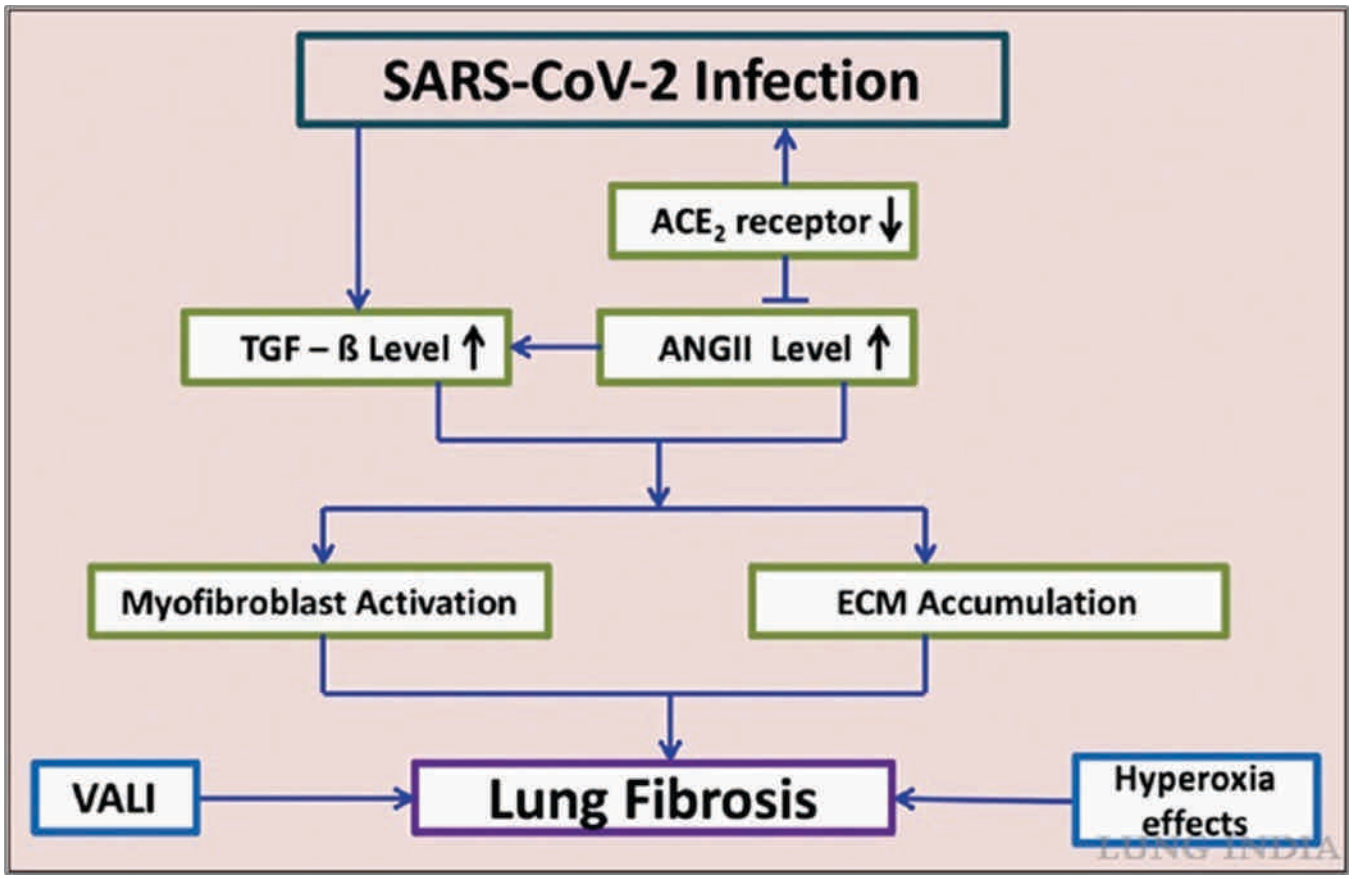

Figure 2: Postulated mechanism of SARS-CoV-2 induced fibrosis stressing the pivotal role of Angiotensin 2 (Image reproduced with permission from Wolters-Kluwer – Lung India[14])

H7N9 pneumonia[52] had fibrosis at 6 months. Data from other coronavirus diseases like SARS and Middle East respiratory syndrome are much more sparse (MERS). Fibrosis was uncommon in both epidemics of the disease.

According to a research by Chang *et al.*[53] in SARS patients, parenchymal bands, traction bronchiectasis, and even honeycombing had significantly decreased when a second CT scan was performed 4-6 months after the original scan in patients with these two viral pneumonias. Progressive fibrosis was uncommon, despite reports of it in some survivors. The study by Zhang *et al.*, which followed 81 healthcare workers from Beijing Peoples Hospital over a period of 15 years[54], provides the only long-term longitudinal data on MERS. At 15 years, they discovered that only 5% of patients still had interstitial fibrosis. In most patients at serial follow-up, alterations declined throughout the first two years before stabilising. COVID-19, however, differs from these other coronaviruses primarily due to the scope of the pandemic and the enormous number of infected people. Although steroids are currently the mainstay of therapy for the majority of critically ill hospitalised COVID-19 patients, the typical amounts most of them get do not seem to be enough to stop some of them from developing lingering lung shadows. Just now are follow-up statistics on SARS-CoV-2 infection survivors starting to become available. In a study of Italian COVID-19 pandemic survivors, it was discovered that up to 45% of them still complained of dyspnea at a subsequent appointment, which was held on average 60 days (SD, 13.6) after the symptom had started.

In a follow-up research by Zhao *et al.*[55] of the pulmonary function and radiography in 55 COVID-19 survivors 3 months after recovery, it was discovered that 71% still had interstitial thickening evidence in their CT scans. At the time of hospital discharge and two weeks following discharge, aberrant lung function (such as decreased diffusion capacity, restrictive anomalies, and small airways obstruction) has also been found[56,57,58,59]. The most prevalent aberration of lung function in COVID-19 released survivors was impairment of diffusion capacity, which occurred in up to 47% of cases. Restrictive ventilatory deficits were next, occurring in about 25% of cases, and were more severe in patients with severe acute disease. Importantly, it was discovered that the ratio of TLco to alveolar volume (Kco) was considerably smaller in patients with severe disease than in those with mild-to-moderate disease, suggesting a degree of pulmonary vasculopathy[57].

The severity of cardiac injury was assessed in a prospective, multicenter, observational analysis of 86 severe SARS-CoV-2 survivors who were already receiving close follow-up in Austria. According to preliminary prepublication results presented at the ERS meeting in 2020[60], the majority of patients had persistent dyspnea (37 percent), decreased diffusion capacity (28 percent), and abnormal CT scans (88 percent) at six weeks after discharge. At 12 weeks, the CT abnormalities were decreased to 56 percent, from 8 points on the 6-week CT scans to 4 points on the 12-week scans. Data from the 24-week follow-up is eagerly expected. Fortunately, the authors state that none of their patients had progressive lung fibrosis. Additionally, lung function improved. By contrast, we have been struck with the speed of progression to PC-ILD in several of our patients.

In 42 COVID-19 survivors who underwent retrospective analysis with follow-up imaging at a median of 11.6 days, Xiong *et al.*[61] found indications of advancement in 83 percent of cases, including progressive opacifications, interstitial thickening, and fibrous strips. On the follow-up CT, the progression was substantially correlated with the degree of opacifications assessed on the initial CT (P 0.001). The discovery of extensive pulmonary fibrosis, including sizable areas of disturbed architecture with fibromuscular structure and collagenized fibrosis, was made public for the first time in a recent autopsy study by Schwensen *et al.*[62] Additionally, IPF-like remodelling and honeycombing were observed.

It is still too early in the pandemic to predict with certainty what the normal course of post-COVID fibrosis will be. The key query is: Are the changes so often identified on CT scan likely to (1) continue, (2) gradually improve, or (3) even worsen with time? Follow-up of cohorts of post-COVID survivors are now beginning at numerous centres. This has effects on both the treatment and patient prognosis. As we will show [Figure 3], antifibrotics may play a significant impact in individuals who advance but less or no involvement in the first two scenarios.

Regardless of the severity of the acute illness, radiological signs such as fibrotic abnormalities of the lung have been found as early as 3 weeks following the onset of symptoms[63,64,65]. The clinical hallmark of COVID-19 fatal cases is organised diffuse alveolar damage (DAD), which is accompanied by pulmonary fibrosis of varied severity[66]. Relevantly, many COVID-19 patients get ARDS, and a significant fraction of these patients may die from progressive lung fibrosis[67].

Ground-glass opacities (GGOs) with or without consolidation, crazy-paving pattern, interstitial thickening, and parenchymal bands, which are primarily bilateral with a preference for the peripheries of the lower lobes[64,65], are radiologic imaging findings in COVID-19 pneumonia. Foci of organised pneumonia, DAD, and oedema are seen, as with other inflammatory pneumonitis. In a recent study comparing CT imaging, the fibrosis group showed more interstitial thickening, air bronchogram, uneven interface, coarse reticular pattern, parenchymal bands, and pleural effusion than the fibrosis-free group.

Inferred indicators of pulmonary fibrosis in these patients include interstitial thickness, uneven interface, coarse reticular pattern, and parenchymal bands that emerge over the course of the disease[68]. Although uncommon, there have been reports of rapid advancement to honeycombing[69,70]. To ascertain whether the reticulation indicates irreversible fibrosis, long-term follow-up will be required[71]. The degree of reticulation on a CT scan is correlated with lower diffusion capacity, a restrictive pattern on a pulmonary function test, and quality of life (QOL). However, in older patients with COVID-19, many of whom are elderly and may already have lung diseases, even a little

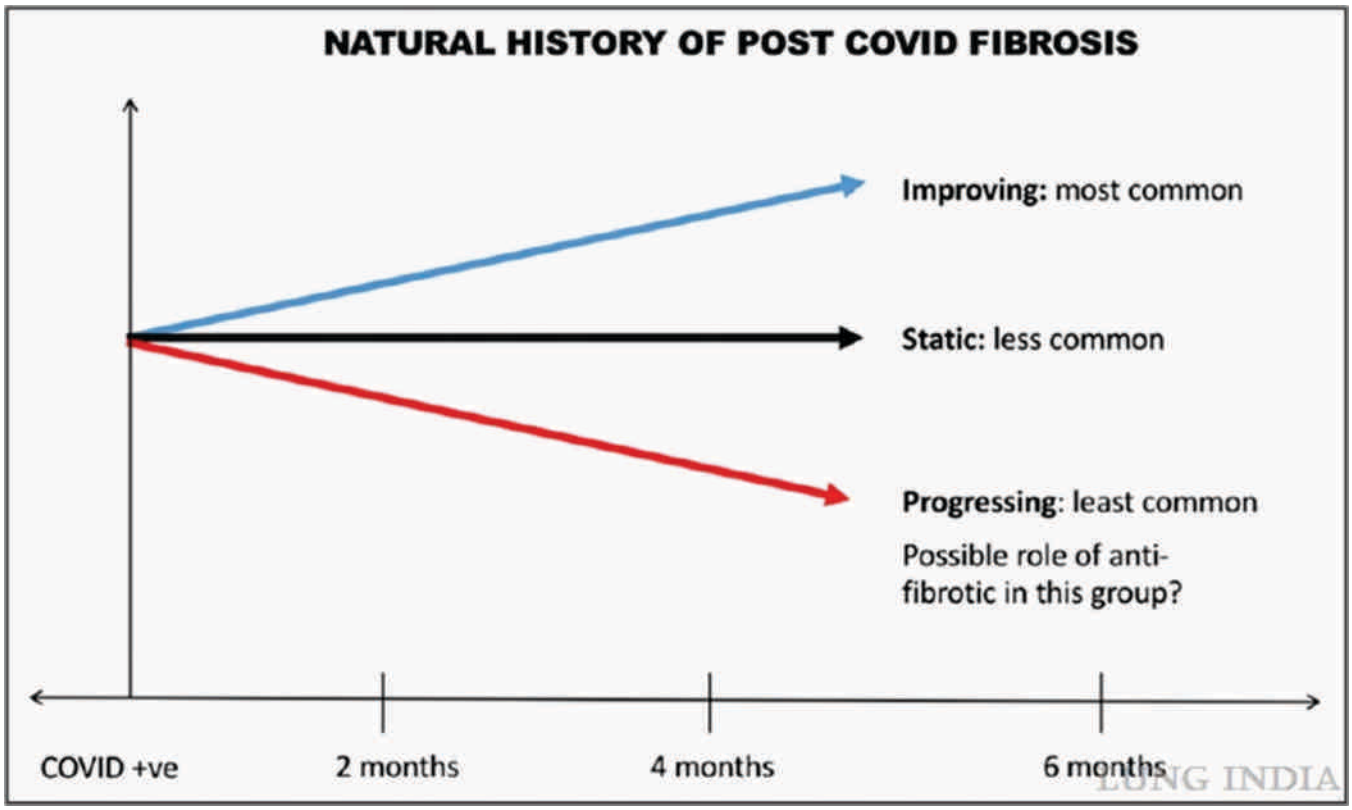

Figure 3: Possible courses of Pulmonary Fibrosis.
(Image repurposed under CC from Wolters – Kluwer, Lung India[14])

amount of residual fibrosis could lead to significant morbidity and mortality[72].

Predicting Post COVID Interstitial Lung Disease

As information on post-COVID fibrosis becomes available, various potential predictors have been found. There have been a number of them, including advanced age, serious disease, a protracted hospital or ICU stay requiring mechanical breathing, a history of smoking, and chronic alcoholism[73]. It is well known that the degree of fibroblastic response necessary to repair the injury correlates with the severity of the lung injury and the inflammatory response[74]. The development of fibrosis during recovery may be caused by higher levels of CRP and IL-6 during sickness. Other coronavirus infections, such as MERS-CoV infection[75] and SARS infection[76], were similarly observed to substantially correlate with the likelihood of lung fibrosis following high LDH levels during acute illness. In contrast to the nonfibrotic group, patients with COVID-19 who developed PC-ILD also received pulsed steroid therapy and antivirals for longer lengths of time, suggesting that those who develop fibrosis after discharge typically had more severe illness while they were in the hospital.

It is too soon to say which COVID-19 patients are more likely to experience long-term pulmonary abnormalities, whether these sequelae will disappear, get better, or stay there, or how treatments might alter the pulmonary abnormalities. Clinical reassessment and more research are necessary for those with a history of moderate or severe disease, persistent symptoms, or radiological abnormalities. It would be extremely helpful to have a precise biomarker that might identify COVID-19 infected patients who are more prone to develop fibrosis.

Fibroblast mediated fibrotic changes.

In this review, we have attempted to synthesise the existing knowledge of potential mechanisms that might connect initial infection to the development of lung tissue remodelling. There is now abundant emerging evidence that COVID-19 can cause fibrotic changes in the lungs, and this is supported by the clear emerging data. In Figure 4, we have attempted to condense this knowledge and depict the probable interaction between the pathways covered above. SARS-CoV2 may induce fibrogenesis in a variety of ways, including by triggering

inflammatory pathways, harming the alveolar epithelium, and causing vascular alterations. To thoroughly define the underlying pathogenic pathways that underlie COVID-19-induced lung fibrosis, more study is urgently required.

Lung injury is brought on by SARS-CoV-2 infection, which damages the alveolar epithelium and triggers the release of inflammatory and immunological cytokines produced from the epithelium and macrophages. In response to TGFb, PDGF, and IL-6, interstitial fibroblasts migrate and grow in the alveolar space due to denudation of the basement membrane caused by activated inflammatory cells and injured epithelial cells. Infection with SARS-CoV2 also damages endothelial cells, causing bleeding and plasma leaking into the alveolus. Urokinase and PAI1 are released by the injured alveolar epithelium, and this causes coagulation pathways to become active and deposit fibrin. Myofibroblasts multiply and fibrosis develops as a result of persistent alveolar stimulation of TGFb, immune cells' production of PDGF and IL-6, and myofibroblast proliferation.

Stability of Fibrosis

Growing evidence suggests that many COVID-19 patients experience fibrotic sequelae and changes in their lung function that are suggestive of restrictive lung disease two years after the COVID-19 pandemic began[76,77,78,79,80]. However, research thus far suggests that fibrosis lingers for several months after the virus has cleared up[81,82]. It is currently too early to say if such alterations occur solely as a temporary reaction to viral infection and will naturally resolve with time. Whether post-COVID-19 fibrotic changes in the lung are stable after they have established or progressive, as in fibrotic lung disorders such as IPF, is a critical topic in the management and therapy of such individuals in the years to come.

Numerous variables could affect whether post-COVID 19

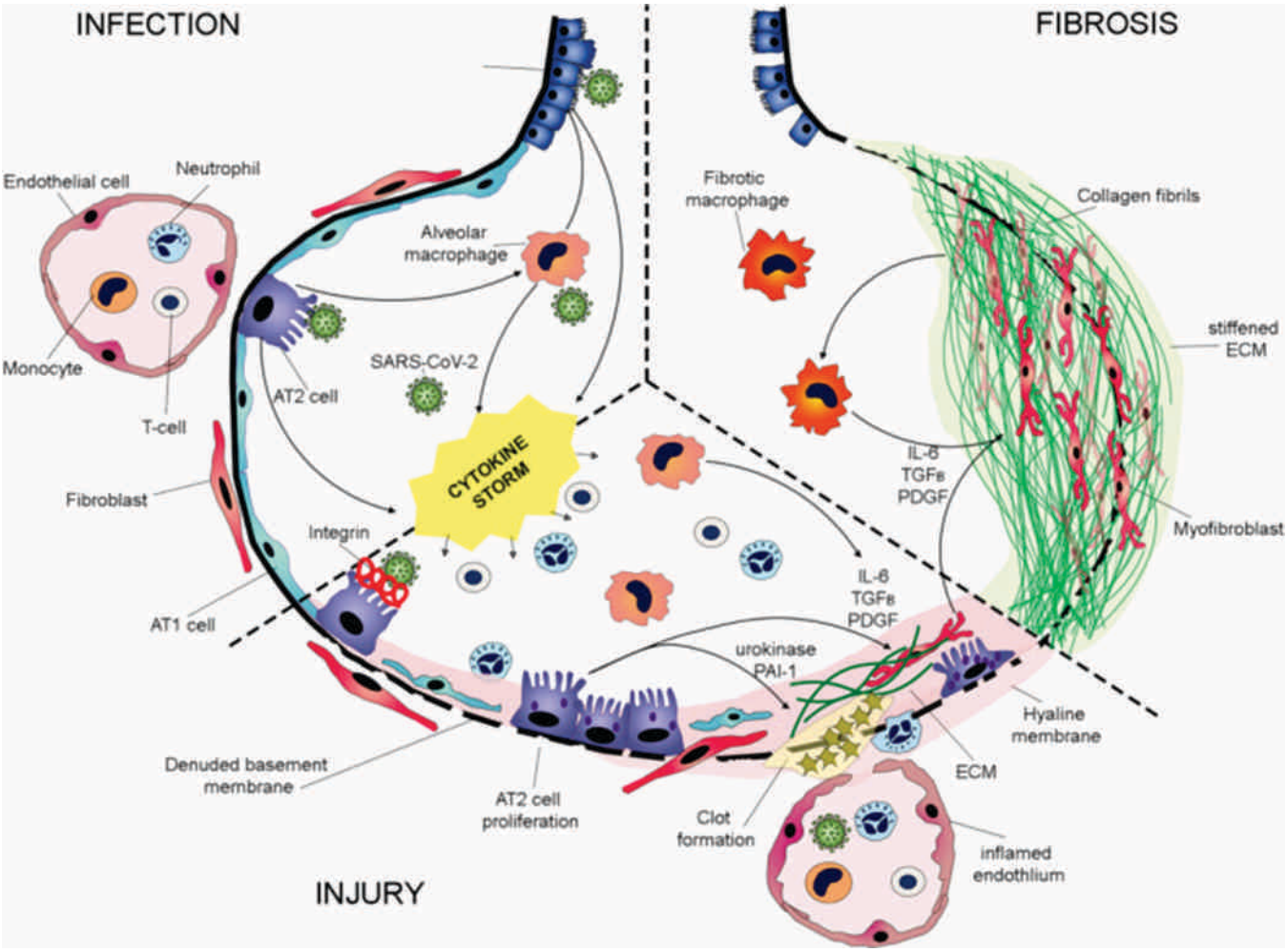

Figure 4: Fibroblast facilited mechanism

pulmonary fibrosis has the potential to advance and be fatal. Genetics is probably going to be important. Life-threatening COVID19[83,84] is connected with genes related to innate antiviral defences, inflammatory lung damage, and the ABO blood group system, according to genetic studies. Genome-wide association studies have identified a number of genes associated with the onset of pulmonary fibrosis, even though no research have specifically examined genetic connections with post-COVID-19 fibrosis to date[86,86,87]. This suggests that COVID-19 infection may cause a more advanced post-COVID-19 fibrosis among people who have genetic variations known to be linked to the onset of lung fibrosis.

As being older is a major risk factor for both pulmonary fibrosis and COVID-19[88,89,90], it may also play a role in determining whether post-COVID-19 fibrosis progresses. The lung parenchyma becomes stiffer with advancing age[91,92], which may have significant effects on TGF activation and the emergence of lung fibrosis[93]. The pro-fibrotic potential of lung fibroblasts is also influenced by age. Aged mice's fibroblasts exhibit decreased Thy1 expression, which is linked to a pro-fibrotic phenotype[94,95]. They also have decreased apoptosis and enhanced responses to TGF[96]. Additionally, growing fibroblasts and lung epithelial cells on decellularized, aged ECM results in changes to the ECM that the cells deposit[97]. Importantly, lung fibrosis in old mice is aggravated by viral lung injury[98,99,100].

Metabolic syndrome and obesity are frequent risk factors for COVID-19[101,102]. Diabetes type 1 and type 2 are both related with a noticeably higher risk of dying from COVID19[103,104]. Similar to those with pulmonary fibrosis, patients with these conditions are more likely to be overweight[105,106] and to have a clinical history of hypertension or diabetes, which is suggestive of the metabolic syndrome[107]. Additionally, in at-risk patients[108], a higher body mass index (BMI) is linked to a higher chance of developing ARDS. There isn't any concrete proof that obesity and /or metabolic changes cause COVID-19 to develop fibrosis, although a number of studies have suggested a possible mechanism of action[109,110,111]. The contractility of fibroblasts is increased and they deposit more collagen I and fibronectin when the signalling of the transcriptional co-activator peroxisome proliferator activated receptor gamma co-activator 1alpha (PGC1) is disrupted at the cellular level. Similar to this, decreased expression of PTEN, a protein that regulates the metabolism of glucose and fatty acids, results in transdifferentiation of fibroblasts and myofibroblasts as well as increased collagen production[113]. In addition, the anti-diabetic medication metformin can slow the progression of experimental pulmonary fibrosis and inhibit TGF-induced fibrotic responses in lung fibroblasts *in vitro*[114]. It's significant that metformin, especially in women, is linked to decreased mortality in COVID-19 patients[115,116]. This confirms the involvement of metabolic changes in the pathophysiology of COVID-19; however, the relative contribution of these changes to either stable or progressive.

Identifying Pulmonary Fibrosis

The most popular techniques for identifying and assessing pulmonary fibrosis are high-resolution CT (HRCT) and PFT[117]. Serum biomarkers have undergone extensive research to determine new ways to forecast the severity, responsiveness to treatment, and progression of any fibrotic process[117]. Fibroblast proliferation and ECM remodelling are involved in the pathogenic mechanisms of idiopathic pulmonary fibrosis (IPF), which create an environment that is conducive to the development of fibrotic scarring. Selman *et al.* hypothesised that not all inflammatory lesions may cause lung tissue to fibrose[118]. Despite this assertion, current research by Zhou *et al.* suggests that individuals with severe or critical COVID-19 pneumonia had a considerably higher risk of lung fibrosis than people with intermediate COVID-19[119].

Risk Factors and Prediction

There are possible risk factors which can enforce the danger of complicating the disease to the stage of fibrosis -

1. Age

- It is said to be an incredibly significant risk factor. The risk of Pulmonary fibrosis increases with advancing age. This has also been observed during the MERS outbreak[120].

2. Disease Severity

- Duration of disease along with severity are important determinants for the development of Pulmonary fibrosis in post COVID-19 Pneumonia. Study in patients with COVID-19 pneumonia in Wuhan showed that Pulmonary Fibrosis was observed in 4% of patients, who had the duration of disease of <1 Week. While 61% of patients had lung fibrosis with disease duration of >3 Weeks[121].

3. Pre-existing Comorbid Conditions

- Comorbid conditions also increase the risk of disease severity. Pre-existing Diabetes, Coronary Artery Disease, Hypertension etc. in all these conditions the clinical course of the disease is quite severe. According to WHO around 14% of COVID-19 patients have a severe form of the disease[122].

4.Duration of ICU Stay and Ventilatory Support

- If the patient has a severe form of the disease, there are ample chances of prolonged hospitalisation, especially ICU stay and use of mechanical ventilation. The longer the ICU stay the severe the disease becomes. The mechanical ventilation comes with its own complication such as Ventilator Associated Lung Injury. Risk of mortality is significantly higher in such patients and those who have survived are at risk of developing Pulmonary Fibrosis[123].

5.Chronic Smoking

- Smokers have an increased likelihood of developing severe form of the disease (1.4 times) and they are twice more likely to require ICU admissions and mechanical ventilation. They are more at risk of higher mortality as compared to non-smokers[124,125].

6.Chronic Alcoholism

- WHO and National Institute on Alcohol Abuse and Alcoholism (NIAAA) have warned people to avoid excessive alcohol consumption, stating that habit can increase the severity and susceptibility of COVID-19 and increases the risk of complications[126,127].

The best way to predict development of Pulmonary Fibrosis is by HRCT Scanning of Thorax. To identify prediction of Pulmonary Fibrosis development by CT Scan imaging, Minhua *et al.* studied 32 patients with confirmed COVID – 19 rtPCR status and divided them into two groups according to the evidence of Fibrosis on their latest CT Imaging. These CT Findings showed that 14 patients developed Fibrosis while 18 patients had a clear CT scan. The fibrotic group of patients were older in age and the median levels of their Infective markers were also raised significantly compared to the non-Fibrotic group. Conclusion was made that Fibrosis was more likely to develop in patients with severely clinical conditions, especially with high inflammatory indicators[59].

Based on these risk factors described above there are some risk reduction strategies which can be followed such as. 1. Use of Anti Virals and Immunomodulatory medications, 2. Minimize ventilatory induced lung injury with protective lung ventilation, 3. Limit exposure to environmental factors and encourage for smoking cessation.

Pathogenetic Understanding and Mechanisms

Pulmonary fibrosis is a well-known complication of Acute Respiratory Distress Syndrome (ARDS), the latter occurs in 40% of COVID-19 patients. However, the current understanding suggests that more than 30% of patients develop fibrotic changes in lung[127].

Even though ARDS is a strong predictor of Pulmonary Fibrosis in COVID -19, the type of ARDS seen in COVID -19 is varied from classic ARDS. Hence the mechanism of COVID-19 related Pulmonary Fibrosis is different from classical Idiopathic Pulmonary Fibrosis.

To start with there is invasion of Type 2 Alveolar Epithelial cells via ACE-2 receptor. After the invasion, the virus goes through replication in order to form even more nucleocapsids.

These pneumocytes now release plethora of inflammatory markers and cytokines such as IL-6, IL-1, IL-8, TNF – α, IFN – λ, IFN – β, CXCL-10, etc, This is what is termed as "Cytokine Storm" which acts as attractant for Neutrophils, T Cells, CD4, 8 and helper cells starts getting sequestrated into lung tissue.

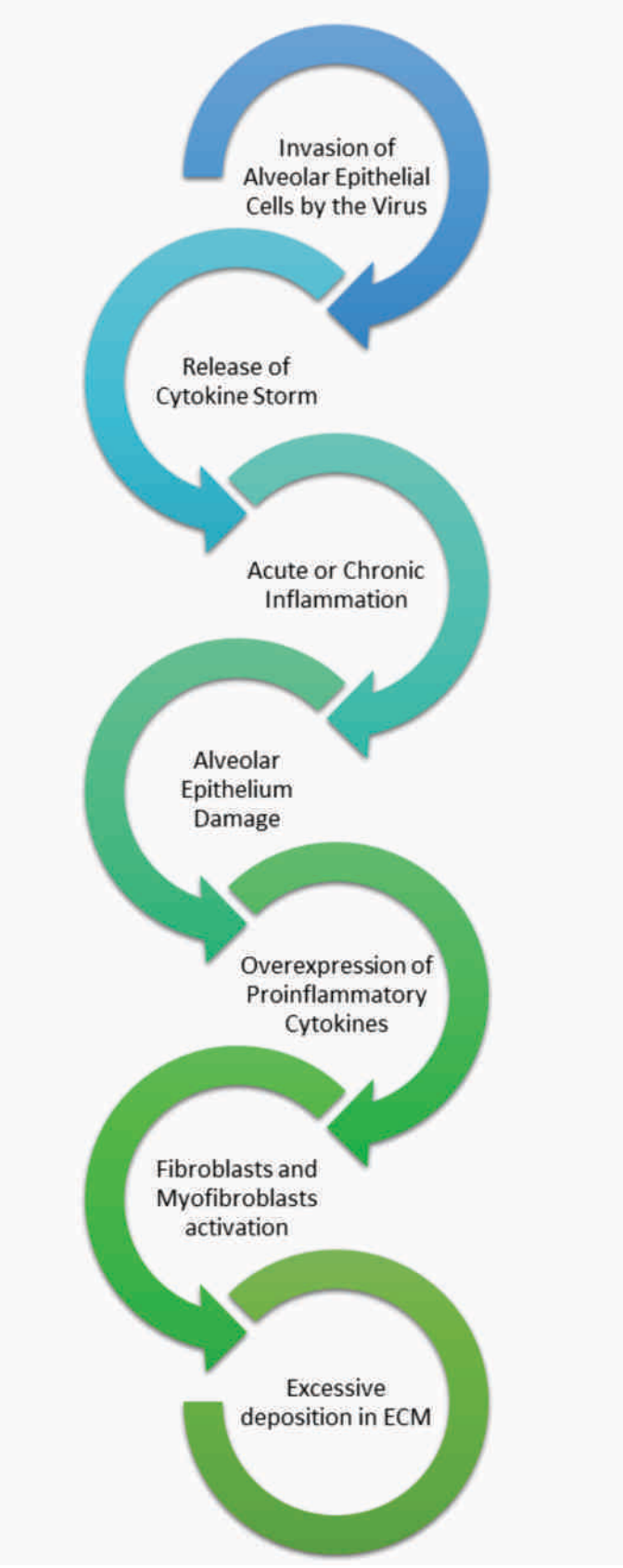

Figure 5: Pathophysiology of Pulmonary Fibrosis in COVID -19[129]

This leads to persistent damage to Type 1 and Type 2 pneumocytes by inflammatory cells and replication which results in Diffuse Alveolar Damage causing Acute Respiratory Distress Syndrome[129]. (Fig.5)

Exaggerated inflammatory response in COVID – 19 along with Cytokine Storm, the regulatory pathways come in use to deal with the damaged lung tissue. Prolongation of this response forms a fibrotic response which can be seen as Interstitial Septal Thickening, Ground Glass Opacities, Fibrotic Bands, Crazy Paving Patterns, Tractional Bronchiectasis in CT scans.

Since a few years ago, viral and bacterial infections have been recognised as contributing factors to the development of PF[130]. This theory has recently received additional support from the SARS-CoV-2. Due to the significant fibrotic outcome of infection, the SARS-CoV-2 is a positive-sense single-stranded RNA virus[130] that is linked to considerable lung involvement, in the worst cases indicated by ARDS, which can be worsened by PF[131,132].

Despite the fact that SARS-CoV-2 infection is frequently curable, the occurrence of lung fibrotic consequences as a result cannot be ruled out[133]. ARDS, which can occasionally lead to pulmonary fibrosis as a long-term outcome[134], develops in about 40% of COVID-19 patients, and PF is more common in patients with severe or critical COVID-19[132]. Age, smoking status, ethnicity, and male sex are among recent risk variables that have been linked to the development of severe SARS-CoV-2 infection. In addition to these risk factors, various comorbidities, such as chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and obesity[135] increase hospitalisation and mortality in COVID-19 disease. Additionally, the transcriptome analysis of cells derived from patients with chronic lung diseases found that these individuals had higher levels of genes directly linked to the effectiveness of viral replication and to an improved inflammatory microenvironment, supporting their susceptibility to severe COVID-19 infection[135]. Statin and anti-diabetic medication like metformin, on the other hand, have been shown to reduce the risk of death in COVID-19 patients when taken at home[136,137].

Post-COVID-19 fibrosis has been linked in a small subset of individuals to an aggravation of underlying ILD. It's interesting that these conclusions came from a follow-up that lasted no more than six months, and information on the long-term effects of COVID-19 infection on lung health is still absent. Infections with the severe acute respiratory syndrome coronavirus 1 (SARS-CoV) and the middle east respiratory syndrome coronavirus (MERS-CoV), for which the onset of lung fibrosis has been reported to occur to a similar extent to SARS-CoV-2 (33 percent and 27.8-62 percent of patients, respectively), have also been investigated for the fibrotic disease resulting from virus dependent-ARDS[138]. Patients with SARS-CoV experience functional deterioration and lung interstitial abnormalities, which improve over the first two years after infection and then remain stable. Of note, in 4.6% of survivors, the changes persisted after 15 years of follow-up long-term studies[133,139].

The pathophysiology of COVID-19 is characterised by the early infection's activation of adaptive immunity as well as respiratory dysfunction brought on by lung damage and hypoxia. Local cytokine storms and a phase of systemic hyperinflammation are brought on by the disease[140,141]. In fact, PF and COVID-19 patients share a number of pathological characteristics, including diffuse alveolar damage (DAD), altered epithelial function, impaired vascular and microvascular function due to the presence of microthrombi, acute fibrinous pneumonia, ECM accumulation, and immune system activation with ongoing inflammatory processes. Epithelial and vascular changes typically take place in the early stages of infection, while fibrotic characteristics appear 3 weeks after the onset of symptoms[142].

However, an innate immune response, altered myeloid gene expression profile, hyperactivation of alternatively activated macrophages, high levels of proinflammatory and profibrotic factor production, as well as coronavirus infection, particularly with SARS-CoV-2, all contribute to the pathological processes that result in the lungs. Indeed, the influx of immune cells into the lung, which led to the development of lung hyperinflammation and fibrosis, has been linked to the lung inflammation brought on by SARS-CoV-2 infection from a molecular perspective[143,144]. The fibrotic event is brought on by the increased macrophage activation seen in severe COVID-19 patients, which results in dysregulation of the tissue healing mechanisms[145]. It's interesting to note that there are now two distinct patterns that can characterise the deadly COVID-19 infection: either a lung with a high viral load and cytokine expression but minimal morphological alterations, or a lung with a low viral load and cytokine expression but increased numbers of immune cells[146]. Essentially, the damage to the alveolar epithelial cells causes fibroblast infiltration and the activation/release of pro-fibrotic mediators like TGF- and PDFG, which results in the production and buildup of ECM[147]. In particular, AT2 cells express and release several growth and fibrogenic factors as well as cytokines, such as monocyte chemoattractant protein-1 (MCP-1), TGF-1, TNF-, IL-1, and IL-6 once the injury occurs in the lung. These substances then promote AT2 cell hyperproliferation, draw fibroblasts to the fibrotic locus, and trigger fibroblast transdifferentiation / activation into myofibroblasts, which impairs alveolar function, particularly with regard to alveoli-capillaries gas exchange[148,149].

These PF-related pathways, however, are not explicitly set off by viral infection. Contrarily, several recent data have identified potential distinctive pathways by which SARS-CoV-2 infection results in the start of PF. One of these examines the function of angiotensin-converting enzyme-2 (ACE2), a crucial enzyme required for SARS-CoV-2 binding and entry into host cells[150].

There is no doubt that the lung changes brought on by SARS-CoV-2 infection play a role in the development of PF, and even

if the relevant pathogenic mechanisms are not fully understood, potential routes are hypothesised and graphically shown in Figure 6.

The viral infection has a cytolytic effect on alveolar epithelial type II cells (AT2), the main source of ACE2, which causes AT2 to differentiate into alveolar epithelial type I cells (AT1) pneumocytes and increases AngII, which binds to its receptor AT1R and stimulates the expression of pro-inflammatory factors like cytokines as well as increased tPA accumulation in the blood. The pro-inflammatory chemicals' release aids in the remodelling of the ECM, which causes fibrogenesis. KL-6 is released from AT2 cells as a result of the pro-inflammatory cytokines TNF- and IL-8. The virus causes NET to develop, which in turn reinforces epithelial damage (yellow cells) and encourages the EMT process, which results in an accumulation of myofibroblasts.

We may therefore state with certainty that two pathologies have resulted in two other considerations. The link between lung infection, alveolar injury, and circular thrombosis has first been highlighted by COVID-19[151]. The inquiry into the potential function that this process might play in the progression of PF was prompted by scientists' growing understanding of the causal involvement of neutrophils and their activation (NETosis) in the promotion of lung diseases. Additionally, it has shown that there may be novel targets that can be discovered to treat or delay COVID-19, post-COVID-19 lesions, and IPF. The second factor is how crucial ageing is to the fibrotic process. The elderly make up the majority of COVID-19 patients who develop lung fibrosis lesions. Given that several authors highlight ageing as a major characteristic to distinguish, this is not shocking[152,153].

A Note on Management

Although not the focus of our present study we will try to summarise to the current position of treating the fibrotic progression. There has been severe lack of scientifically proven methods to treat Post COVID-19 Pulmonary Fibrosis. Various studies are going for newer treatment options which are at different stages of development. Corticosteroid

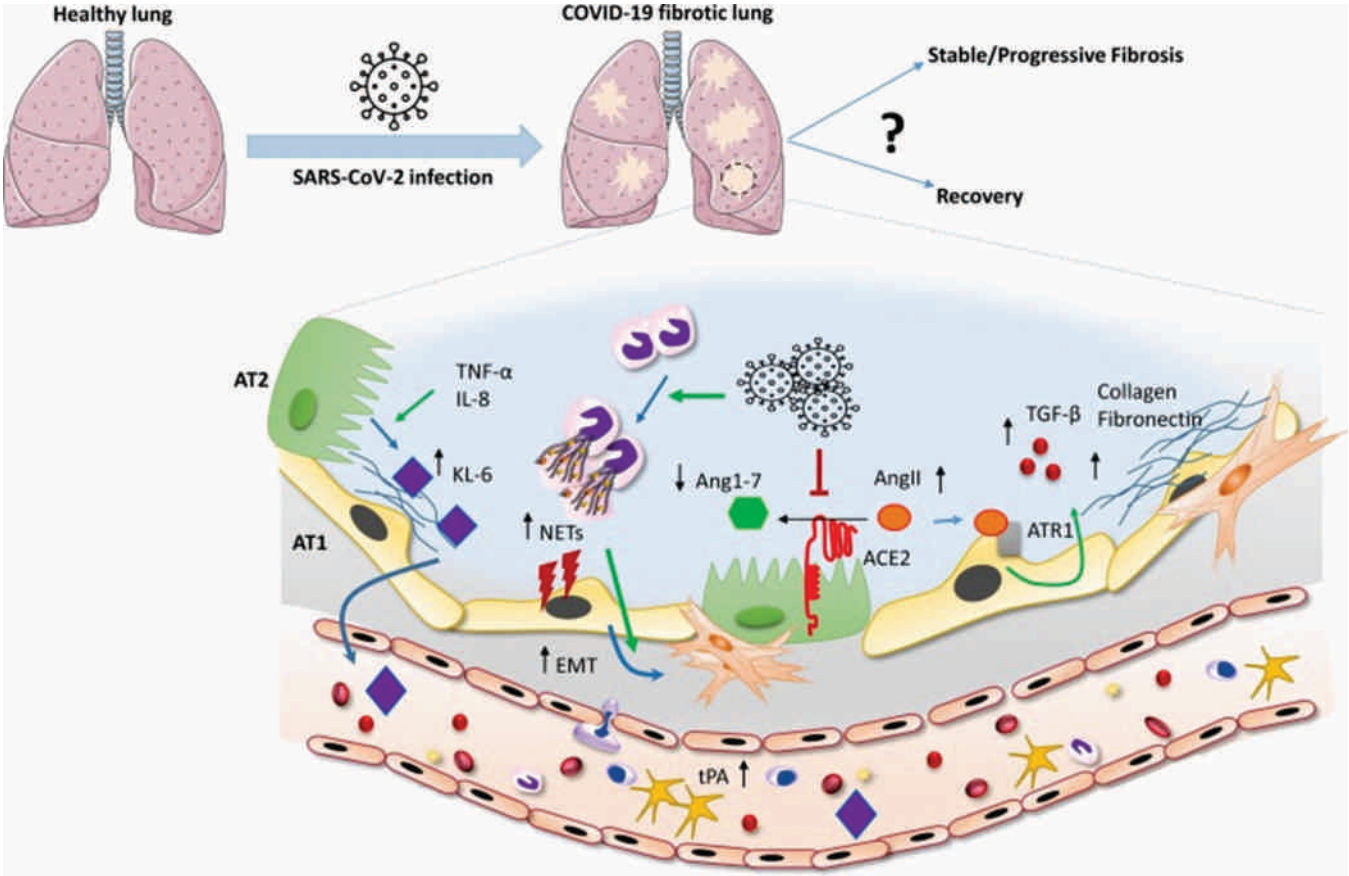

Figure 6: Possible Characteristic Mechanism

(Dexamethasone, Methylprednisolone) have been widely used as one of the treatment options for COVID-19. It has been observed that prolonged use of low dose or pulsed steroid therapy may have some benefit in lung protection[154,155].

Besides this there are Anti Fibrotic agents available to use such as Nintedanib and Pirfenidone. These agents not only have anti fibrotic effect, but also have some Anti Inflammatory and anti-oxidative properties; thus, they can be used in the acute phase of the disease. The hepatotoxicity of both these drugs should not be overlooked, and Nintedanib is linked to higher risk of bleeding in patients who are on anticoagulant therapy.

There is literature available which supports the use of Anti Fibrotic agents in the first week of ARDS onset to prevent Pulmonary Fibrosis. This calls for an urgent need of understanding Biomarkers which signifies risk of developing pulmonary fibrosis early in the disease stage[156,157].

There is some benefit of Endurance Exercise, Physiotherapy, Rehabilitation especially in early phase of disease have some benefit to improve lung function. However, this data needs to be backed with more scientific evidence to have a conclusion[158].

Duncan Richards, Professor of Clinical Therapeutic at University of Oxford, commented that drug-based treatments for this condition are not highly effective and are associated complications. Ideally, treating doctors are the right person to accurately predict which patients have the greatest risk of developing fibrosis, and select drugs designed to tackle this judiciously before serious symptoms develop[159].

Lung transplantation is emerging as a final hope in patients with Pulmonary Fibrosis and Respiratory Failure due to COVID-19. There was a study by Jing-Yu Chen *et al*. in China where three critical patients with COVID -19 underwent lung transplant with full ethical review. Out of those three, two patients survived and started active participation in rehabilitation programme. There is still scarcity of literature available for lung transplant as a potential option and further clinical resource is required[160].

Prospective information from up to two years after the onset of the pandemic on the COVID-19 effects on the chronic pulmonary system is only now starting to become available. One year after being hospitalised, a group of patients who had recovered from severe COVID-19 were monitored, and roughly 25% of them exhibited ongoing radiographic abnormalities with fibrosis-specific symptoms such septal thickening, reticular opacities, and traction bronchiectasis[161]. The fact that these radiologic alterations were found in patients who were not ventilated and so presumably on the less severe end of the acute lung damage spectrum is perhaps the most relevant discovery. The proportion of individuals with radiologic findings suggestive of fibrotic changes as well as functional abnormalities increased significantly with increasing disease severity in other cohorts that included critically ill patients requiring mechanical ventilation, reaching up to 50%–66% of patients at 4 months[162]. As previously mentioned, upon follow-up, SARS and MERS survivors both demonstrated persistent function and radiologic abnormalities[163,164,165]. According to preliminary COVID-19 data, functional and radiologic impairment is at least as common as, if not more so than, in SARS and MERS cohorts at comparable follow-up time points. This may be because the severely ill COVID-19 patients who contracted the disease early in the pandemic were older and more medically comorbid than in previous pandemics[166,167]. Patients with long-term pulmonary and extra-pulmonary COVID-19 problems will invariably present a challenge to the global health care system due to the significantly larger clinical impact of COVID-19 compared to other pandemics.

It is yet unknown whether ARDS brought on by COVID-19 would cause gradual and permanent lung fibrosis, similar to IPF, from which there is no cure. The lungs of COVID-19 victims with explanted lungs and those who died from the disease had traction bronchiectasis, interstitial fibrosis, bronchial metaplasia, and radiographic and microscopic honeycombing, among other characteristic hallmarks of progressive fibrotic disease[168,169,170]. More recent studies show that fatal COVID-19 cases have dramatically more fibroblasts and collagen deposition[171]. There is currently no proof that people who fully recover from ARDS caused by COVID-19 will have progressive fibrosis, despite case reports describing histopathologic evidence of DAD (the pathologic manifestation of ARDS) in these fatal cases. Instead, ARDS-induced fibrotic alterations tend to stabilise after early recovery and may disappear over following years, as was previously shown with SARS and H1N1. However, the course of post-COVID-19 ARDS fibrosis is yet unknown, and many patients may need a lot of clinical care to recover.

Strategies

We assume a similar probability of development of lung fibrosis given the many parallels between COVID-19 and SARS. It appears vital to look into whether survivors may indeed be at danger of having chronic pulmonary sequelae given the severity of the COVID-19 pandemic. Additionally, since patients with established cardiovascular disease appear to be more susceptible to COVID-19, it is important to consider the possibility of functional capacity decline in these patients once they have recovered from the acute illness[172]. Furthermore, dyspnea and weariness may be symptoms of both illnesses, and the effect of lung remodelling may be more prominent in patients with prior heart dysfunction. Dedicated outpatient ambulatories for COVID-19 survivors might be established at that point, and a multidisciplinary strategy comprising both cardiologists and pneumologists may be beneficial.

However, the true pulmonary outcomes of COVID-19 survivors may be revealed by the use of serial PFT and/or imaging tests in the early post-discharge period as well as in the mid- and long-term. The identification of risk factors and early markers of lung fibrosis would also become significant should

the risk of long-term lung fibrosis be verified, favouring the deployment of preventative measures in the fraction at higher risk. (Figure-7)

In this regard, three complimentary methods to lower the risk of lung fibrosis development may be suggested: (a) a more intense and longer inhibition of viral replication; (b) a persistent inhibition of the inflammatory response; and (c) the use of anti-fibrotic medications. It is currently uncertain if early and/or prolonged antiviral treatment can prevent lung remodelling or whether particular antiviral medications are more effective than others. Although the use of anti-inflammatory medications during the initial phase of COVID-19 is still debatable, ARDS survivors may benefit from a protracted course of low-dose corticosteroids because it may prevent maladaptive lung remodelling. However, the benefit-risk ratio of these medications should be carefully assessed, particularly in patients with prior comorbidities such type 2 diabetes, hypertension, and chronic kidney disease. The use of either angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, however, may shield patients from the chronic effects of Ang II, which may also play a significant role in the development of lung fibrosis, but this point needs further clarification[173].

Index Case

A 65-Year-Old male presented in Pacific Medical College and Hospital with cough and difficulty in breathing since 10 days. He was a known case of Hypertension (7 Years) and Type – 2 Diabetes Mellitus (15 Years).

Initial Lab Workup

- Hb – 11.0 gm% (13.5-18 gm%)
- TLC – 11,800 /mm^3 (4000-11000 /mm^3)
- CRP – 3.23 mg/L (<5 mg/L)
- Ferritin – 259.8 ng/mL (30-400 ng/mL)
- D Dimer – 3980 ngFEU/ml (<710 ng FEU/mL) IL-6 – 9.0 pg/ml (<7 pg/mL)

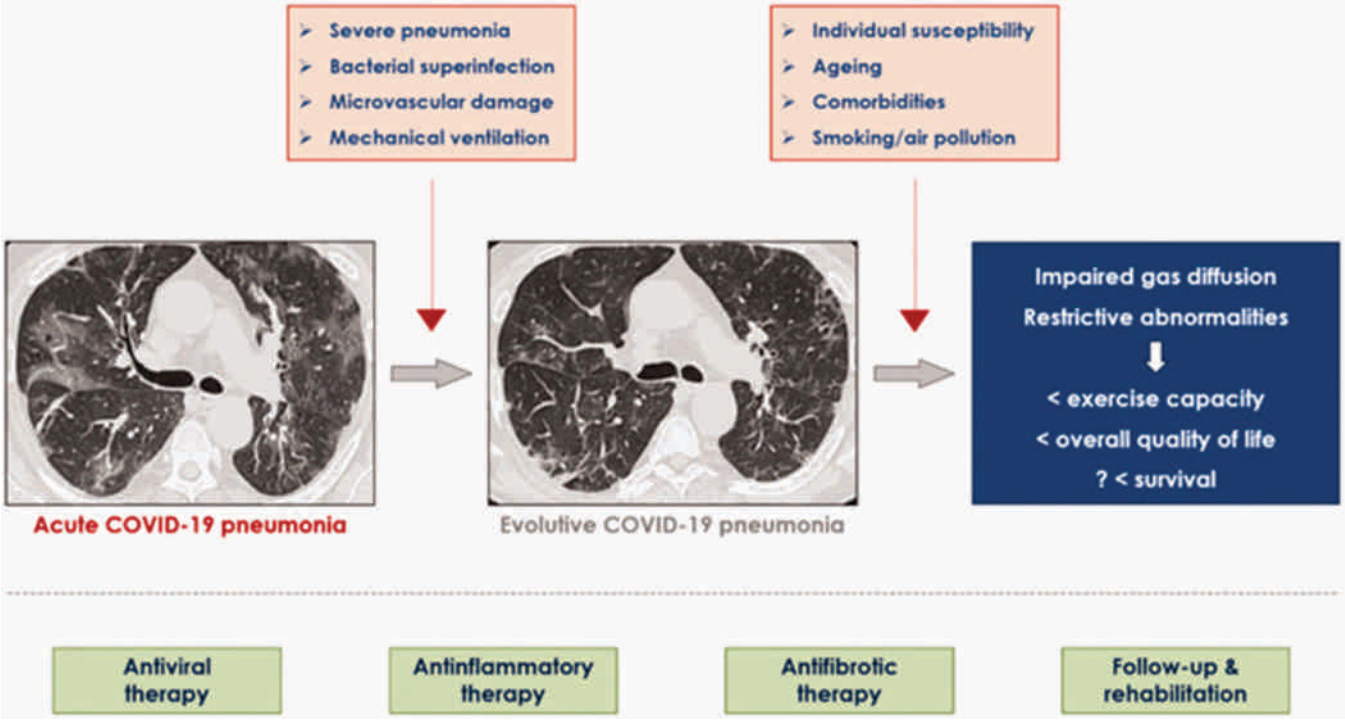

Figure 7: Possible strategies for prevention

Admission CT scan **(Plate.1)** showed Ground Glass opacities and Interstitial Septal Thickening and a severity score of 15/25

Patient had a month long stay in the ICU but did not require any mechanical ventilation. He was kept on Non-Invasive Ventilation through BiPAP mask, and intermittently on NRBM mask. Patient was given IV Antivirals (Remdesivir), IV Corticosteroids (Methylprednisolone), S/C Low Molecular Weight Heparin (Enoxaparin) and appropriate Antibiotics. With Oral Pirfenidone for anti-fibrotic treatment. After being shifted to wards form ICU a repeat CT scan **(Plate 2)** showed widespread fibrotic changes in the lungs. There was significant reticulation and patchy areas of consolidation in both lungs, mainly in the peripheries with relatively sparing lung apices along with bronchiolar and vascular dilatation. Keeping with post COVID status and distribution of fibrosis, these features favored fibrosing stage of disease process (Moderate). His CT Scoring was 13/25.

Patient was in a high-risk category and developed Pulmonary Fibrosis as a terminal complication. Patient was discharged with O_2 support at home after 34 days of hospital stay.

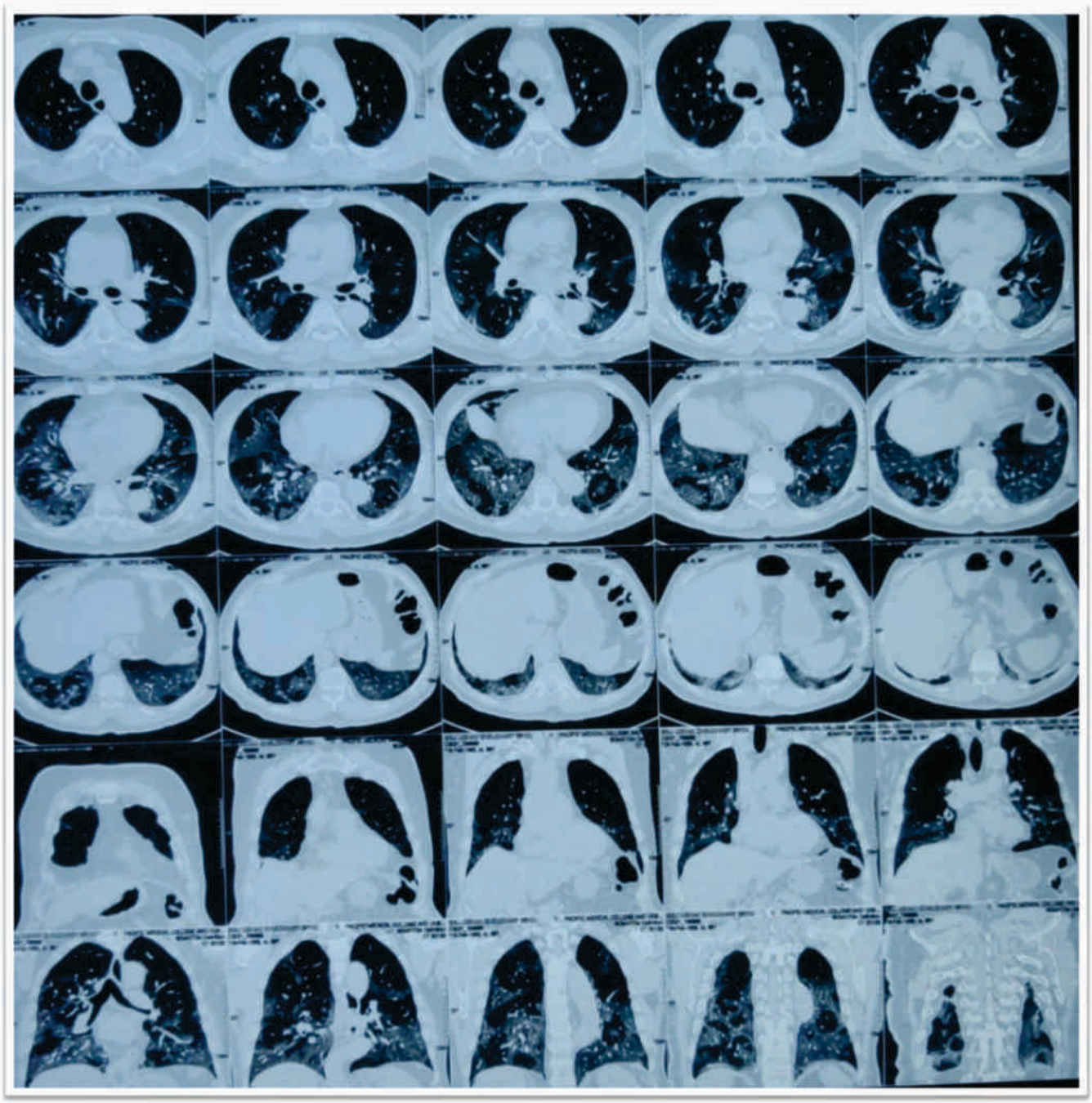

Plate 1: Admission CT Scan with CT Score 15/25

His Pirfenidone was continued at home along with anti-coagulation cover. His lab workup at time of discharge showed high D - Dimer (3876 ngFEU/ml) and almost normal inflammatory markers. This is a classic case of COVID -19, with risk of advancing age and pre-existing Hypertension and Type 2 Diabetes Mellitus, landing in Pulmonary Fibrosis. The only laboratory correlation that existed was significantly higher D – Dimer even at the end of 1 month with normal levels of other inflammatory markers.

Last but not least, there has been much discussion over the potential usefulness of anti-fibrotic drugs in preventing or treating the possibility of ARDS-induced fibrosis, and there are currently numerous trials investigating these treatments. The only drugs currently licenced for the treatment of IPF are nintedanib[174] and pirfenidone[175], both of which have been demonstrated to slow the loss of lung function. It makes sense that these medications could hasten recovery in the most severe instances given the likelihood that post-ARDS fibrosis will be generally stable and slowly resolve months to years after the initial COVID-19 sickness. However, these medications come with a heavy burden of side effects, such as severe nausea, weight loss, diarrhoea, sun sensitivity, and liver failure. It is vital to take into account that fibrosis is closely linked to the healing process and that many of the pathways that are implicated as "pro-fibrotic" are required for physiologic lung maintenance in order to avoid the fibroproliferative cascade from starting in ARDS. Therefore, when focusing on these pathways, it's important to strike a balance between promoting lung regeneration and reducing the mechanisms that lead to fibrosis.

CT Scan of 100% Lung Involvement

The CT Scan Plates 3 and 4 show the near total lung involvement in a 67-year-old male with no-morbidities. Patient's illness was fatal after 34 days of hospitalisation, Plate 4 shows the repeat CT Scan of almost same state with widespread devastating lung fibrosis.

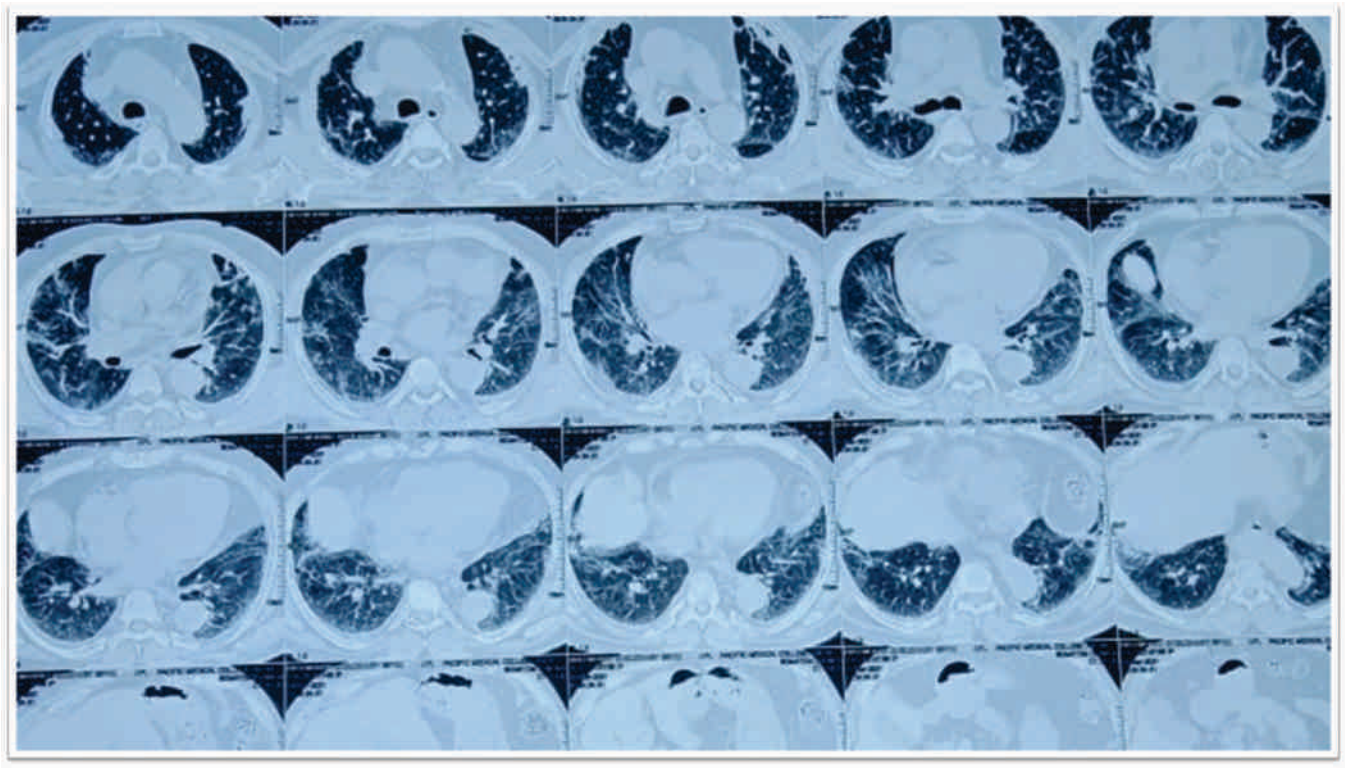

Plate 2: Discharge CT scan with CT Score 13/25

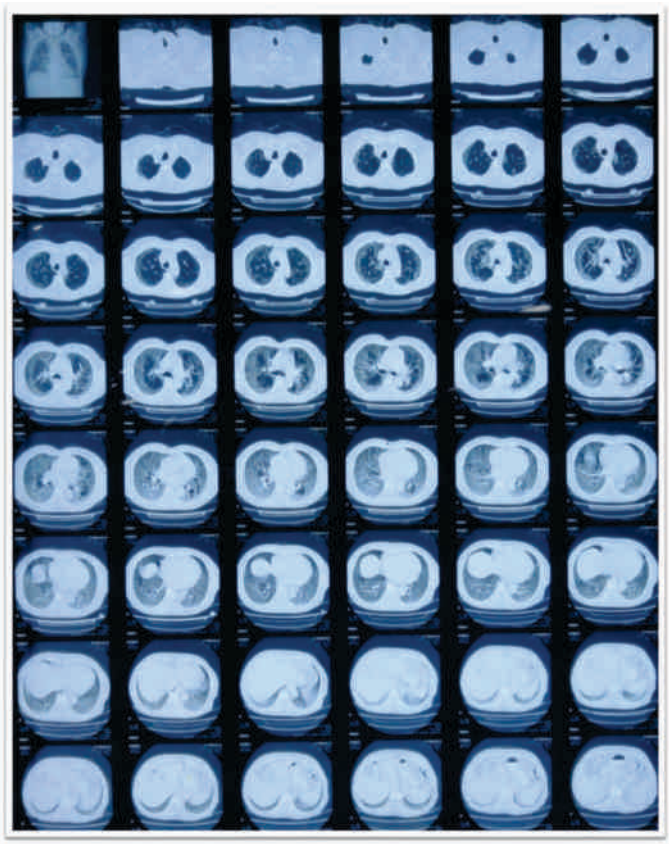

Plate 3 and 4: CT Scan with 100% Lung involvement

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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