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# Interstitial lung diseases and COVID-19

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## Abstract:

There is continued lack of knowledge of the physiopathology and recovery processes of the new coronavirus pneumonia. The complications are similar to those experienced with severe acute respiratory syndrome and Middle East respiratory syndrome, since the new coronavirus is part of the same family. The new coronavirus infects both the epithelial cells of the airway and also alveolar epithelial cells (Type I and Type II pneumocyte). The Type I and Type II pneumocytes infected with the human coronavirus (hCoV) play a critical role in mediating the lung pathology and host sensitivity. Both human and animal studies have demonstrated that an inflammatory process starts in the lungs following hCoV infection and that an accumulation of monocyte–macrophage and neutrophils occurs. One of the earliest outcomes of rapid virus replication and increased proinflammatory cytokine/chemokine response is apoptosis of the epithelial and endothelial cells of the lung. The main effect of the new coronavirus on the body is an imbalance in the ratio of the cytokines produced by the body in response to the abnormal immune reaction, resulting from the invasion of the virus. This manuscript details the pathophysiology of the new coronavirus associated with fibrosis and makes recommendations for cases with interstitial lung disease.

## Keywords:

Coronavirus disease-2019, fibrosis, interstitial lung disease

## Introduction

Following the outbreak of the new severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2) in the city of Wuhan in Hubei province of China in December 2019, the World Health Organization identified it as a “global pandemic” on March 11, 2020.<sup>[1]</sup> According to the daily pandemic report on the official website of the World Health Organization, the confirmed number of cases of coronavirus disease-2019 (COVID-19) had reached 1,521,252 globally by April 10, 2020.<sup>[2]</sup>

There is little knowledge on the long-term complications of the disease, since the COVID-19 pandemic is still in a critical status. There has yet to be a study into the effect of SARS-CoV-2 on interstitial lung disease (ILD). Since the virus causing COVID-19 comes from the same family as SARS and Middle East respiratory syndrome (MERS), the possible mechanisms of complications are predicted to be through the effects of SARS-CoV and MERS-CoV.<sup>[3]</sup> Since the etiological and clinical properties of SARS-CoV-2 resemble those of SARS and MERS, it is believed that the experience obtained from these pulmonary syndrome may help in the management of the

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COVID-19 outbreak.<sup>[4]</sup> The mechanisms of fibrosis and recommendations for the management of ILD in the COVID-19 pandemic will be addressed in this manuscript in light of the current findings in literature.

## Mechanisms of Fibrosis

### Inflammatory response

The specific host factors producing the lung pathology after infection with the human coronavirus (hCoV) are not completely known, despite the many investigations evaluating the pathogenesis of SARS and MERS. That said, some factors that may play an important role in the initiation of exacerbated inflammatory response have been identified in previous studies of the pathogenesis of SARS-CoV and MERS-CoV in human and animal models.<sup>[3]</sup>

### Rapid virus replication

One remarkable feature of pathogenic hCoVs such as SARS-CoV and MERS-CoV is that both viruses are replicated in high titers in the very early periods of both *in vivo* and *in vitro* infections. This high rate of replication causes an increase in cytopathic effects and production of greater proinflammatory cytokines and chemokines in the infected epithelial cells. Studies of hCoV infections performed on the humans and experimental animals have identified a powerful correlation between the SARS-CoV and MERS-CoV titers and disease severity.<sup>[5-8]</sup>

### Human coronavirus infection of the airways and/or alveolar epithelial cells

Animal studies, especially in rats, have demonstrated that the virus infects both the airway epithelial cells and alveolar epithelial (Type I and Type II pneumocytes) cells.<sup>[3]</sup> Type I and Type II pneumocytes infected with hCoV are shown to play a critical role in the lung pathology and the mediation of host sensitivity.

### Delayed interferon response

Both SARS-CoV and MERS-CoV code structural and nonstructural proteins that antagonize interferon (IFN) reactions and reach high titers immediately after hCoV infection. Delayed IFN signals affect monocyte macrophage inflammatory response and sensitize T-cells to apoptosis, resulting in an irregular inflammatory response.<sup>[5]</sup>

### Monocyte-macrophage and neutrophil accumulation

Both human and animal studies have revealed an accumulation of inflammatory monocyte-macrophages and neutrophils in the lungs following hCoV infection. These cells are an important source of the cytokines and chemokines associated with mortality in the hCoV disease and have been observed in both human and animal models.<sup>[5,9]</sup>

### Cytokine storm and results of immunopathology

#### *Epithelial and endothelial cell apoptosis and vascular leak*

One of the earliest results of rapid virus replication and increased proinflammatory cytokine/chemokine response is the lung epithelial and endothelial cell apoptosis. IFN- $\alpha\beta$  and IFN- $\gamma$  induce inflammatory cell infiltration and, through the mechanisms bound to Fas-Fas ligand or tumor necrosis factor (TNF)-related apoptosis-inducing ligand DR5, cause airway and alveolar epithelial cell apoptosis.<sup>[10-12]</sup> The apoptosis of epithelial and endothelial cells disrupts the lung microvascular and alveolar epithelial cell barrier, leading consequently to vascular leak and edema and finally hypoxia.<sup>[3]</sup>

#### *Suboptimal T-cell response*

CoV-specific T-cells are highly important for viral clearance and thus limit damage to the host. In the case of SARS-CoV infections through TNF-mediated T-cell apoptosis, the vital inflammatory responses caused by pathogenic hCoV decrease T-cell response, leading to an uncontrolled inflammatory response.<sup>[13-16]</sup>

#### *Accumulation of alternatively activated macrophages and changing tissue homeostasis*

Fibrosis of the interstitial and alveolar spaces and hyperplasia of the pneumocytes are seen in some SARS patients, leading to an extended disease course in addition to widespread lung damage.<sup>[17,18]</sup>

#### *Acute respiratory distress syndrome*

Inflammatory mediators play an important role in the pathogenesis of acute respiratory distress syndrome (ARDS), which is the primary cause of mortality in patients infected with SARS-CoV and MERS-CoV. Many proinflammatory cytokines, including chemokines such as interleukin (IL)-6, IL-8, IL-1 $\beta$ , as well as granulocyte-macrophage colony-stimulating factor (GM-CSF), reactive oxygen species, and monocyte chemoattractants, contribute to ARDS.<sup>[19-22]</sup> In addition, uncontrolled epithelial cell proliferation and impaired tissue remodeling in the advanced stages cause pulmonary fibrosis and mortality.

Tse *et al.* evaluated pulmonary pathology in a study of seven patients who died of SARS (duration of hospitalization: 4–20 days) and reported the histopathological observation of a marked lung edema and hyaline membrane production, in addition to diffuse alveolar damage, in all patients.<sup>[23]</sup> Interstitial fibrosis to an intermediate degree has been detected in some regions. A disproportional infiltration of inflammatory cells (including multinucleated forms and lymphocytes in general) are seen in these areas. Dilation in airspace areas was observed as focal honeycomb fibrosis. A positive correlation was found between the duration of

the disease and the degree of interstitial fibrosis but only in a small number of cases. It was interpreted from the results that the pulmonary fibrosis seen in these mortal cases could be related to SARS, rather than the previously present lung lesions.<sup>[24]</sup> Follow-up radiological studies demonstrated pulmonary fibrosis in 62% of the surviving patients. Accordingly, a relatively rapid development of pulmonary fibrosis is possible at least in patients with severe SARS. That said, since the respiratory function of many patients is severely impaired, and ventilation and oxygen support is required, the factors that cause pulmonary fibrosis have been accepted as speculative.<sup>[24]</sup>

Both humoral and cellular immunity work in collaboration to eradicate viruses, together with all these possible mechanisms, alveolar macrophages activate T-helper (Th) cells through Toll-like receptors following the introduction of the virus to the lungs. Th cells comprise two subgroups: Th1 and Th2. Th1 cells, together with proinflammatory cytokines (IFN- $\gamma$ , IL-2, TNF- $\alpha$ , and GM-CSF), play a role in antiviral immunity. Th2 cells, working together with cytokines such as IL-4, IL-5, IL-6, IL-10, and IL-13, have anti-inflammatory effects. Cytokines such as IL-4, IL-6, and IL-13 stimulate the B-lymphocytes to produce immunoglobulin and fibroblasts to synthesize collagen. For this reason, Th2 elevation is an important factor triggering pulmonary fibrosis.<sup>[25]</sup> Under normal circumstances, Th1 and Th2 antagonize each other and find balance; however, with the increased viral load, this balance is impaired in favor of Th2, and tissue damage is overcome with fibrosis. Pulmonary fibrosis may increase substantially similar to this mechanism in patients with COVID-19.<sup>[25,26]</sup>

The primary effect of the new coronavirus on the body is an abnormal immune reaction resulting from the invasion of the virus, and consequently, the imbalanced ratio of cytokines produced by the body. During this process, epithelial cells in the lung and alveolar microvascular endothelial cells become targets for attack by inflammatory mediators and cause the characteristic damage of ARDS.<sup>[27]</sup> First, vasoconstriction, increased vascular permeability, blood leakage, and inflammatory factors occur following the vascular endothelial cell damage and the activation of inflammatory mediators.<sup>[28]</sup> Fluid entering the alveolar cause interstitial and alveolar edema, destroy the permeability of the alveolar epithelial barrier, and cause atelectasis by decreasing alveolar surfactant. Eventually, the epithelial cells in the lung and vascular endothelial cells suffer considerable damage. Second, tissue ischemia and hypoxia increase the severity of lung damage. This in turn causes lung ischemia and decreased oxygen diffusion, intensifying hypoxia and disrupting the ventilation/perfusion ratio. As a result, patients with COVID-19 generally experience progressive hypoxemia. The hypoxic environment has been reported

to support the progression of fibrosis through epithelial-mesenchymal transformation.<sup>[28]</sup> A hypoxic state, in addition, not only damages the lung tissue directly but also intensifies inflammation and oxidative stress. Furthermore, mechanical ventilation increases the release of local inflammatory factors in the body, while mechanical stress causes secondary lung damage through the inflammatory process. The above mechanism causes continuous lung damage before the improvement of status, followed by the start of the damage repair mechanism in the lung in the intermediate and latter stages of ARDS, and the development of fibrosis.<sup>[26]</sup>

One of the targets when treating COVID-19 is the prevention and treatment of pulmonary fibrosis. Treatment methods, such as the administration of cytokine inhibitor drugs, plasma replacement, and blood/plasma filtration, can be used in severely ill patients, with the aim of preventing the damage from the cytokine storm and eliminating the inflammatory factors. Tocilizumab is an antibody against IL-6 and may be used in these patients as part of a clinical study. Pirfenidone and nintedanib have been globally approved for the treatment of idiopathic pulmonary fibrosis (IPF). There is no information on the use of these drugs in pulmonary fibrosis induced by COVID-19.<sup>[26]</sup> Antiviral agents may also be used as a part of clinical studies based on the experience of SARS treatment. Mesenchymal stem cells (MSCs) are those with multidirectional differentiation potential and may repair damaged alveolar epithelium, inhibit pulmonary fibrosis, and regulate abnormal immunity reactions. MSC, after being placed into the lungs, differentiate into pulmonary vascular endothelial cells and alveolar epithelial cells.<sup>[26]</sup> Vascular endothelial cells increase the secretion of alveolar surfactants and initiate alveolar-epithelial cell repair. They also decrease collagen production and decrease pulmonary fibrosis by decreasing the expression of the transforming growth factor.<sup>[29]</sup> Currently, the efficacy of MSC has been confirmed in the treatment of ARDS and may be a good application for the treatment of severe COVID-19 by preventing pulmonary fibrosis. Currently, lung transplantation is the single treatment modality that may increase the survival of patients with pulmonary fibrosis and is also an alternative treatment that should be considered in the terminal phase in cases with complicated COVID-19.<sup>[26,30]</sup>

### **Recommendations for the Management of Interstitial Lung Disease in the Coronavirus Disease-19 Pandemic**

The British Thoracic Society has made recommendations for patients with ILD during the pandemic in a document published in March 2020.<sup>[31]</sup> These recommendations,

although only general suggestions, are directed at preserving the health of patients and workers and can also be individualized. Patients with ILD are in a “high-risk” group due to both their age and the treatment they are receiving. Social isolation and work from home are recommended for all such patients.

It is recommended that doctor appointments be conducted by phone or any means other than face-to-face consultations, since many tests such as pulmonary function tests (PFTs), bronchoscopic examinations, and computed tomography screening have been put on hold in this period. Possible symptoms of COVID-19 should be inquired in all patients presenting to the emergency services. Those with suspicious symptoms should not be allowed to enter the clinic, and the body temperatures of all patients should be measured when entering the facility. Telemedicine refers to the distribution of health-related services and information through knowledge and telecommunication technologies. It enables possibilities to patients and clinicians to contact, care, recommendation, reminder, education, intervention, observation, and distant admission. China first attempted to use telemedicine applications during the SARS pandemic, as the first such use of this method, and continued its use thereafter.<sup>[32]</sup> Telemedicine may be beneficial for the application of a treatment process and for advising of preventive measures in diffuse parenchymal lung diseases in the pandemic period. In this way, hospital visits are kept to a minimum, thus lowering the risk of transmission of the disease.

Antifibrotic drug use represents no additional risk for COVID-19 in patients with IPF, and the drugs should be continued, if possible. Drugs should be supplied by the hospital and delivered directly to the home of the patient or by family members not exposed to risk. Blood tests should be continued to identify any adverse effects; and if not possible, decisions should be made based on a risk analysis. Follow-up tests for Pulmonary Function Tests (PFT) should not be carried out. Follow-up visits to clinics may be postponed for 4–6 months. It is recommended that drugs may be stopped for 4–8 weeks in patients with IPF using antifibrotic drugs when diagnosed with COVID-19.<sup>[31]</sup> However, it would be more appropriate to continue with medications, considering that we are across a progressive disease and the possibility of the development of exacerbations if medications are discontinued. Such drugs may cause increased liver enzymes and are not recommended if the creatinine clearance is under 30 ml/min. Antifibrotic drugs can be started based on a phone consultation, provided that an PFT was performed within the last 6 months, and forced vital capacity (FVC) matched the criteria (50%–80%) in patients with IPF in a new diagnosis. If no PFTs is

present and the old FVC value is compatible with the criteria, an PFTs can be performed in patients with no symptoms of COVID-19. The results of a blood test performed within the last 6 weeks for any reason will be adequate. Follow-up blood tests should be performed after medication is started; however, this would be difficult should the outbreak progress. The cessation of treatment in patients receiving immunosuppressive treatment may aggravate the findings of the disease. Obeying social isolation measures is, therefore, mandatory. Medications should be continued when there are no signs of infection in patients, and as long as blood tests can be taken and adverse effects can be observed, but in the lowest dose possible. Patients should receive early medical help, and broad-spectrum antibiotics should be started as soon as any signs or symptoms of lower respiratory tract infections develop. Immunosuppressive treatments may be needed to be put on hold during an infection and 2 weeks after the infection, and for even longer periods in hospitalized patients. Patients should be carefully evaluated, and if the patient can tolerate it, doses of immunosuppressive drugs may be decreased (especially prednisolone) and even discontinued if possible. Obtaining blood tests may be difficult if the duration of the pandemic is extended. Cases should be individualized and treatments may be switched to prednisolone for several months (in a minimal dose that provides control), while second-line drugs such as mycophenolate mofetil and methotrexate (MTX) may be discontinued in this period. Long-term lymphocytopenia is common in patients with sarcoidosis, whether or not they are on immunosuppressive drugs, and this represents no special risk. The presence of lymphopenia does not necessitate a change of the immunosuppressive treatment of such patients.

An immunosuppressive drug to be started for the first time in nonrapidly progressive ILD (i.e., chronic hypersensitivity pneumonia) should be postponed during the pandemic, if possible; however, if required, it should be started as prednisolone treatment in doses of 20 mg/day or lower. High-dose steroids may lead to a poor prognosis in the event of a possible COVID-19 infection. Starting second-line treatments such as MTX should be postponed until after the pandemic, since the follow-up of blood tests would be challenging.

Treatment may be started in rapidly advancing ILD (i.e., vasculitis-and soft tissue disease-associated ILD). If steroid treatment be insufficient; cyclophosphamide can be added to the treatment. Treatment with rituximab should be postponed until after the pandemic, if possible. Prophylactic antibiotic use is recommended in patients on an intravenous regimen.

The dose should be escalated gradually in the event of an increased risk of an adrenal crisis in patients with a long-term steroid use, and the dose should be gradually decreased when the findings subside. Patient visits should be performed as distance visits where possible in ongoing clinical studies. The drugs used in the studies should be sent to the homes of the patients by courier, and such studies should be put on hold if the follow-up of adverse effects cannot be performed. Signs of COVID-19 should be questioned if the studies in which the patients are required to present to the clinic are to be continued. PFTs should not be performed during routine follow-up visits. ARDS is a known factor that increases the development of fibrosis, along with genetic tendency. Considering a great number of ARDS patients due to COVID-19, the workload of the clinics following patients with ILD may be increased after the pandemic due to the development of new cases. Accordingly, service plans should be made in advance for the postpandemic period.

These recommendations have been prepared for clinicians to aid in the treatment of patients with ILD during the COVID-19 pandemic. Information on the issue will be updated regularly in this period, when there are rapid change and flow of information.

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### Conflicts of interest

There are no conflicts of interest.

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