Coronavirus disease 2019-associated pulmonary fibrosis: clinical findings, pathogenesis, and potential treatment

Ya-Le Jiang¹, Hua-Ping Dai², Chen Wang²,³

¹School of Medicine, Tsinghua University, Beijing 100084, China; ²Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, National Center for Respiratory Medicine, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, National Clinical Research Center for Respiratory Disease, Beijing 100029, China; ³Tsinghua University-Peking University Joint Center for Life Sciences, Peking Union Medical College, Beijing 100730, China.

An outbreak of coronavirus disease 2019 (COVID-19) has caught global attention and caused enormous damage. 2019 novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), shares remarkable homology with severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus. In the follow-up studies, 62% of SARS and 33% of MERS patients, who tended to be older and have longer intensive care unit admissions, had radiographic evidence of pulmonary fibrosis (PF) after hospital discharge.[1,2] The repercussions of COVID-19 may also lead to PF, impair pulmonary function, and threaten life quality.

As a progressive respiratory disorder characterized by scar formation of pulmonary tissue, the damage of fibrosis cannot be restored but the progression can be delayed or even prevented if intervened early. During the process of fibrosis, epithelial cells are abnormally activated, recruiting fibroblasts, and leading to airway contraction and impaired lung compliance. Extensive deposition of extracellular matrix causes progressive damage to the tissue structure and finally scar formation, clinically manifesting as progressive dyspnea and pulmonary hypertension. Given the epidemiological, viral immunological, and clinical evidence, PF will become one of the severe complications for COVID-19 patients. A total of 4.9% patients reported post-COVID-19 PF after recovery from the virus.[3] Compared with patients without PF, the fibrosis group tended to be older and had higher levels of serum C-reactive protein and interleukin (IL)-6, as well as a longer-term of hospitalization, pulsed steroid therapy, and antiviral therapy.[4] A female elderly without history of pulmonary diseases died due to severe bilateral PF after elimination of COVID-19 infection.[5] The autopsy showed scattered acute and organizing diffuse alveolar disease (DAD) and fibrosis with honeycomb-like remodeling, alarming the fatality of post-COVID-19 PF.

Irregular interface and parenchymal band were more common in the initial computerized tomography (CT) scans of COVID-19 patients with ultimate fibrosis, and potentially predictive for early formation of PF. Other typical imaging features included interstitial thickening, air bronchogram, and coarse reticular pattern.[4] Quantitative evaluation of chest CT features based on the abnormal manifestation found that fibrosis was seen in almost half of the cases and significantly increased with the disease duration.[6] Such time sequential finding was also observed in an autopsy study of acute respiratory distress syndrome.[7] The imaging features showed associations with clinical characteristics. Fibrosis scores weakly correlated with partial pressure of carbon dioxide in artery, and moderately correlated with oxygenation index, indicating that early notice of onset and prevention of fibrosis is crucial and may improve prognosis.[6] Although fibrous shadows were common in the early stage of the disease, slow absorption was observed in some patients. The improvement of CT abnormalities was found to be associated with the disease severity in the acute phase of COVID-19 infection, and the abnormalities were almost absorbed approximately 5 months after discharge.[8] Whether remaining pulmonary lesions will completely disappear and whether fibrosis will affect lung function requires further investigation.

The pathophysiology of severe COVID-19 is acute lung injury followed by inflammation and latent fibrosis.
Histologically, DAD, enormous macrophages infiltration, and serous fibrous exudation were found in both Chinese and Italian patients, as well as manifestations of hyperresponsive inflammation, such as capillary congestion, interstitial edema, dilated alveolar ducts, formation of hyaline membranes, and intra-alveolar hemorrhage. In the proliferative phase, hyperplasia of type II pneumocyte was also consistently observed. Platelet-fibrin thrombi in small arterial vessels, myofibroblast proliferation, alveolar granulation tissue, and obliterating fibrosis were solely present in partial Italian patients. The fibrotic phase was rarely observed, possibly due to the short course of the disease. In addition, secondary bacterial or fungal infection noticed in these two cohorts was also observed in the consecutive autopsies in Germany, where mixed forms of DAD and purulent pneumonia occurred in stages of squamous metaplasia and fibrosis. Biopsies from COVID-19 patients with carcinoma showed hyperactive inflammation, viral interstitial pneumonia, and extensive alveolar damage, even when they did not exhibit any symptom of pneumonia. Thus, mild patients with early-stage infection are also at potential risk to progress to PF.

In addition to virus-induced directional impairment, specific and non-specific immune responses also play significant roles in PF. The virus binding of alveolar macrophages activates differentiation of T helper (Th) cells. When humoral immunity is not sufficient to control transmission of virus, the balance state between Th1 and Th2 cells is broken, followed by over-activation of constant tissue damage and subsequent increased Th2 response. Macrophage-mediated non-specific immune responses participate in the first line of defense against virus once contact with angiotensin-converting enzyme 2. M1 macrophages induced by interferon and tumor necrosis factor-α released from Th1 subsequently secrete pro-inflammatory cytokines like IL-12, IL-1β, and IL-6. M2 macrophages secrete anti-inflammatory factor like IL-10, transforming growth factor-β (TGF-β), vascular endothelial growth factor, and platelet-derived growth factor, further inducing proliferation of fibroblasts and secretion of collagen to promote the progress of PF.

Cytokine storms play a key role in PF, where hyperfunction of non-specific immunity under the circumstance of defected specific immunity against virus, especially humoral immunity, leads to uncontrolled overproduction of inflammatory cytokines and imbalanced cytokine network. Capillary permeability is increased, leading to reduced alveolar surfactant, and finally alveolar collapse and atelectasis. Downstream leakage of interstitial fluid simultaneously results in reduced oxygen diffusion and impaired ventilation/perfusion ratio, which aggravates pulmonary ischemia and hypoxia, as observed in patients with severe COVID-19 infection. The hypoxic environment can also promote fibrosis through epithelial-mesenchymal transition, although precise mechanisms still lack reliable explanations. In addition, mechanical ventilation promotes release of local inflammatory factors, leading to sustained secondary damage and activation of tissue repairment; thus, collagen deposition and fibroblast proliferation finally contribute to PF.

Currently, there are no evidence-confirmed drugs for SARS-CoV-2. Promising interventions to alleviate PF have been proposed and experimentally applied to clinical practice.

1. Antiviral drugs. The viral assembly inhibitors lopinavir-ritonavir were recommended based on the experience of SARS treatment, but failed to show superiority over standard therapy in a randomized clinical trial. Patients treated with the triple antiviral therapy lopinavir-ritonavir, ribavirin, and interferon-β had a significantly shorter time for negative conversion of nucleic acid in nasopharyngeal swab, indicating the safety and superiority over lopinavir-ritonavir alone in patients with mild to moderate COVID-19. Anti-malarial chloroquine, favipiravir, and co-administration of darunavir and umifenovir were also reported to have certain anti-SARS-CoV-2 effects, but stringent clinical trials are still ongoing and we should be careful before drawing definitive conclusions. Remdesivir failed to show clinical benefits in adult patients with severe COVID-19 despite high anticipation due to positive results in animal models.

2. Corticosteroids and cytokine inhibitors. Glucocorticoids were controversial and not recommended for the treatment of COVID-19 owing to slower elimination of virus. Various scales of trials reported improved clinical outcomes in COVID-19 patients treated with steroids. The profibrotic factor IL-6 is currently the main therapeutic target for COVID-19 complicated with cytokine storm syndrome such as the use of tocilizumab. The two anti-fibrotic drugs, pirfenidone and nintedanib, targeting at TGF-β1 signaling pathway and tyrosine kinases respectively, are expected to alleviate the fibrotic consequences in COVID-19 patients and have been suggested as hypothetical treatment.

3. Mesenchymal stem cells (MSC). MSCs differentiate into pulmonary vascular endothelial cells and alveolar epithelial cells via intravenous infusion, increasing the secretion of alveolar surfactant. The immunomodulatory effect of MSCs could reduce the expression of TGF-β and prevent PF. Ongoing clinical trials on MSC-based approaches for the treatment of COVID-19 patients are in progress in many countries, including human embryonic stem cells-derived immunity- and matrix-regulatory cells.

4. Lung transplantation. Lung transplantation is currently the only way to improve survival rate of PF. However, it is still controversial due to concerns such as post-operative rejection, high price, and detrimental complications.

Coronavirus disease caused by SARS-CoV-2 has been causative of great global public health concern. The long-term consequences of COVID-19 remain speculative and can never be assumed without rigorous prospective study. PF caused by sustained injury of pulmonary tissue caused by viral inflammation may become one of the most serious complications after this pandemic. [Supplementary Figure 1, http://links.lww.com/CMJ/A642] Although some potentially effective therapeutic drugs have been proposed based on the pathogenesis of COVID-19-induced PF, most.
of them still need to be further verified for efficiency and safety.

**Conflicts of interest**

None.

**References**


