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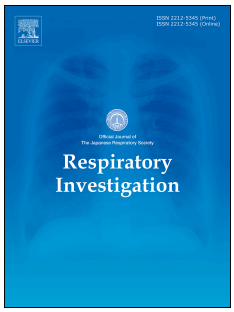

COVID-19 and interstitial lung diseases: a multifaceted look at the relationship between the two diseases

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COVID-19 and interstitial lung diseases: a multifaceted look at the relationship between the two diseases

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although it has been a fatal disease for many patients, the development of treatment strategies and vaccines have progressed over the past 3 years, and our society has become able to accept COVID-19 as a manageable common disease.

However, as COVID-19 sometimes causes pneumonia, post-COVID pulmonary fibrosis (PCPF), and worsening of preexisting interstitial lung diseases (ILDs), it is still a concern for pulmonary physicians. In this review, we have selected several topics regarding the relationships between ILDs and COVID-19.

The pathogenesis of COVID-19-induced ILD is currently assumed based mainly on the evidence of other ILDs and has not been well elucidated specifically in the context of COVID-19. We have summarized what has been clarified to date and constructed a coherent story about the establishment and progress of the disease.

We have also reviewed clinical information regarding ILDs newly induced or worsened by COVID-19 or anti-SARS-CoV-2 vaccines. Inflammatory and profibrotic responses induced by COVID-19 or vaccines have been thought to be a risk for *de novo* induction or worsening of ILDs, and this has been supported by the evidence obtained through clinical experience over the past 3 years.

Although COVID-19 has become a mild disease in most cases, it is still worth looking back on the above-reviewed information to broaden our perspectives regarding the relationship between viral infection and ILD. As a representative etiology for severe viral pneumonia, further studies in this area are expected.

(250 words)

Keywords

COVID-19

SARS-CoV-2

Interstitial lung disease

Pulmonary fibrosis

Vaccine

Abbreviations

ACE: angiotensin-converting enzyme

AE: acute exacerbation

AEC: alveolar epithelial cell

Ang: angiotensin

ARDS: acute respiratory distress syndrome

COVID-19: coronavirus disease 2019

CT: computed tomography

CTD: connective tissue disease

DAD: diffuse alveolar damage

DL_{CO}: diffusing capacity of the lungs for carbon monoxide

ECM: extracellular matrix

EMT: epithelial-mesenchymal transition

FGF: fibroblast growth factor

GGO: ground-glass opacity

HP: hypersensitivity pneumonitis

HR: hazard ratio

IL: interleukin

ILD: interstitial lung disease

IPF: idiopathic pulmonary fibrosis

MDA-5: melanoma differentiation-associated gene-5

NET: neutrophil extracellular trap

OP: organizing pneumonia

PCPF: post-COVID-19 pulmonary fibrosis

PDGF: platelet-derived growth factor

PM/DM: polymyositis/dermatomyositis

QOL: quality of life

RA: rheumatic arthritis

ROS: reactive oxygen species

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SSc: systemic sclerosis

STAT1: signal transducer and activator of transcription 1

TGF-β: transforming growth factor-β

TNF-α: tissue necrosis factor-α

UIP: usual interstitial pneumonia

VEGF: vascular endothelial growth factor

WHO: World Health Organization

1. Introduction

Interstitial lung disease (ILD) is a group of heterogeneous pulmonary diseases affecting the lung interstitium. Damaged interstitium that is thickened with infiltration of inflammatory cells and/or fibrosis reduces oxygen diffusion to the bloodstream and lung elasticity. ILDs have various causes, including connective tissue diseases (CTDs), occupational or environmental dust exposure, drugs, radiotherapy, and viral infections.

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After the first case was reported in December 2019 in Wuhan, China, over 600 million confirmed cases of COVID-19 across the world, including over 6 million deaths, had been reported to World Health Organization (WHO) by October 2022 [1]. Although it was a fatal disease for a significant number of patients at the beginning of the pandemic, the development of treatment strategies and vaccines have progressed through the 3-year experience of fighting against SARS-CoV-2, and our society has gradually become able to accept COVID-19 as a common and manageable disease.

However, as COVID-19 can sometimes present as pneumonia, including acute respiratory distress syndrome (ARDS), and cause post-COVID pulmonary fibrosis (PCPF), and as pulmonary infections generally worsen respiratory status in patients with chronic lung diseases, COVID-19 is still a concern for pulmonary physicians. In this review, we have selected the following topics to shed light on the relationships between ILDs and COVID-19: the pathogenesis of COVID-19 and the establishment of ILD, the impact of COVID-19 on preexisting ILDs, and ILDs newly induced by COVID-19 or anti-SARS-CoV-2 vaccines, including manifestation of latent CTD-ILDs. We hope this review will be helpful for understanding and managing ILDs in this “with-COVID-19” era.

2. Etiology of COVID-19, ARDS and following pulmonary fibrosis

The exact etiology of COVID-19 and subsequent pulmonary fibrosis is not yet fully understood. Although respiratory viral infections, not only from SARS-CoV-2 but also from other viruses, are strongly correlated with the development of pulmonary fibrosis [2], the molecular mechanisms that lead to fibrosis following viral infections have not been thoroughly investigated. Therefore, current understanding is partially based on similarities in clinical features and biomarker profiles with other diseases. The summary of this section is illustrated in Figure 1.

2.1. Establishment of SARS-CoV-2 infection in the respiratory tract

When SARS-CoV-2 establishes an infection, spike proteins on the surface of the virus bind to the angiotensin-converting enzyme (ACE)-2 receptors of host cells [3]. Type 2 alveolar epithelial cells (AECs) are one of the cell types known to express ACE-2 receptors [4] and may be the target cells for infection by SARS-CoV-2.

ACE and ACE-2 receptors are regulators of the renin-angiotensin system. ACE converts angiotensin (Ang) I to Ang II [7], which has proinflammatory and profibrotic properties through the activation of various signaling pathways, such as transforming growth factor-β (TGF-β) [8-10], interleukin (IL)-1β, tissue necrosis factor-α (TNF-α), IL-6 and IL-8 pathways [11, 12], other than releases aldosterone. On the other hand, ACE-2 mediates the conversion of Ang II into Ang1-7 [13], which has anti-inflammatory and antifibrotic roles [14], such as downregulation of TGF-β and its downstream pathways [15, 16] and reduction of reactive oxygen species (ROS) production [17]. Thus, these ACE and ACE-2 activities counteract each other.

In COVID-19, higher viral loads in airway secretions are accompanied by significantly increased serum Ang II levels in patients with severe COVID-19 pneumonia [19]. The

binding of SARS-CoV-2 to ACE-2 receptor and damage in type 2 AECs may cause downregulation of ACE-2 receptors and promote lung damage in COVID-19.

In addition to ACE-2 receptors, SARS-CoV-2 can also infect host cells via other receptors, such as integrins αvβ3 and 6 [20]. Integrin αvβ6 promotes the transdifferentiation of fibroblasts into myofibroblasts and the epithelial-mesenchymal transition (EMT) mediated by TGF-β1 in idiopathic pulmonary fibrosis (IPF) [21, 22]. Thus, the binding of SARS-CoV-2 to those integrins may be a trigger for fibrogenesis.

2.2. Cytokine storm induced in the early phase of COVID-19

Clinically, severe COVID-19 usually develops several days after the onset and can potentially worsen even after the viral antigens have decreased. Since the distribution of viral RNA and protein throughout the body does not correspond to the location of damaged tissues and organs [23], it is believed that the primary cause of severe COVID-19 is an over-reaction of activated immune cells, known as a "cytokine storm," which continues even after the virus has been eliminated. Pro-inflammatory and profibrotic cytokines such as IL-1β, IL-6, TGF-β, and TNF-α are secreted by activated AECs, fibroblasts, endothelial cells, and immune cells [24]. Alveolar macrophages produce IL-1, which stimulates mast cells to produce IL-6. IL-6 activates neutrophils and promotes their accumulation at the site of injury and the production of proteases and ROS, resulting in pulmonary interstitial edema and a severe inflammatory response causing ARDS.

Neutrophil extracellular traps (NETs) are currently in the spotlight as a promoter of cytokine storms. NETs are web-like structures composed of chromatin decorated with proteases and released from neutrophils through programmed cell death. NETs promote cytokine storms by mediating the interaction between neutrophils and macrophages [26], AEC death [27], and EMT [28]. SARS-CoV-2 promotes the production of NETs, and

serum NET levels are increased in correlation with the disease severity in ARDS induced by COVID-19 [29]. A decrease in NETs in the first 3 days of severe COVID-19 is shown to be correlated with better 28-day survival [30].

2.3. Three pathological phases of ARDS and transition to the wound healing process

Three sequential pathological phases are recognized in the clinical course of ARDS: the exudative, proliferative, and fibrotic phases [31, 32]. In the exudative phase, diffuse alveolar damage (DAD) characterized by alveolar interstitial edema, hyalin membrane formation and inflammatory infiltrate [32, 33] occurs, and the alveolar epithelial-endothelial barrier is disrupted. COVID-19-induced ARDS is specifically characterized by impairment of microvasculature, activation of endothelial cells, and coagulopathy [34, 35], which can cause thromboembolic diseases. In the proliferative phase, the injured lesions are repaired through re-establishment of the alveolar barrier by epithelial cell regeneration, fibroblast proliferation and clearance of exudative fluid. The fibrotic phase only occurs in a subset of patients subsequently.

2.4. Development of pulmonary fibrosis

2.4.1. Lung injury and secretion of TGF-β

Some reports on SARS-CoV, another coronavirus that causes SARS, suggested that the regulation of the immune response in the acute phase of infection may be related to the subsequent development of pulmonary fibrosis. For example, signal transducer and activator of transcription 1 (STAT1) mediates signals from interferons that are protective against viral infection and regulate the phenotype of macrophages to the more proinflammatory (M1) rather than the anti-inflammatory and profibrotic (M2) [36]. In mice infected with SARS-CoV, those lacking STAT1 have shown more severe disease and

extended pulmonary fibrosis [37, 38].

Additionally, though the mechanism is not well studied in COVID-19, injuries to alveolar epithelium or endothelium are generally thought to trigger profibrotic reactions. In the context of COVID-19, viral infection and subsequent inflammation causing DAD can cause injuries to both AECs and microvasculature. When the alveolar epithelium is damaged, type 2 AECs proliferate to cover the injured epithelium. Those stressed AECs induce cell senescence and secrete profibrotic mediators. Transitional epithelial cell types that express typical features of cell senescence are persistent in IPF lungs [39, 40], and they are also enriched in COVID-19 lungs [41]. As in IPF [42], shorter telomere length is associated with more severe disease and the development of pulmonary fibrosis in COVID-19 [43, 44].

TGF-β is one of the profibrotic mediators secreted by those injured AECs as well as by endothelial cells and activated inflammatory cells, and it plays a central role in the pathogenesis of pulmonary fibrosis. It promotes the accumulation of fibroblasts into the injured site by promoting the migration of fibroblasts all through the lung structures, recruitment of circulating fibrocytes [45, 46], transdifferentiation of epithelial cells and endothelial cells via EMT [21, 47, 48], and endothelial-mesenchymal transition [49, 50]. TGF-β also induces activation and proliferation of fibroblasts and their differentiation into myofibroblasts, and deposition of extracellular matrix (ECM), resulting in basal membrane disruption and abnormal wound repair.

Signaling from TGF-β is mainly mediated by the Smad2/3 pathway [51], while the interaction of TGF-β/Smad signaling with other profibrotic pathways, including the platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) pathways, has also been reported [52, 53]. In COVID-19, the biomarkers involved in the TGF-β pathway are increased in lung specimens from

PCPF patients [54]. Moreover, as plasma TGF-β, PDGF, FGF, and VEGF levels are increased in COVID-19 patients [10, 55], they may be factors correlated with the formation of PCPF.

2.4.2. Oxidative stress and ventilator-induced lung injury

Oxidative stress is considered to be another cause of AEC damage in the context of COVID-19. Hyperoxia promotes ROS production in mitochondria, which is observed in IPF pathogenesis [56]. ROS activates TGF-β, and TGF-β induces ROS production [57]. On the other hand, hypoxia may also cause pulmonary fibrosis via EMT induced by hypoxia-inducible factor-1α [58, 59]. Thus, excessive oxygenation, particularly during mechanical ventilation, as well as hypoxia due to pneumonia in severe COVID-19 patients, may lead to the formation of pulmonary fibrosis.

Pulmonary fibrosis can also be induced by excessive airway pressure due to mechanical ventilation [60, 61], especially under inappropriate ventilator settings. Mechanical stretching of alveolar spaces may induce profibrotic signaling, apoptosis, and EMT of type 2 AECs [60, 62]. Due to a similar etiology, intense inspiratory effort in spontaneous breathing may also cause self-inflicted lung injury [63]. Such ventilator-induced lung injury and post-ARDS pulmonary fibrosis can be reduced with adherence to lung-protective ventilation strategies, which have already been proven to be effective in reducing mortality in ARDS [64, 65]. Prone positioning therapy can reduce inspiratory oxygen concentration by attenuating ventilation-perfusion mismatch and facilitating lung-protective ventilation by reducing inspiratory driving pressure through a redistribution of pulmonary edema from the dorsal to the ventral region [66].

3. The impact of COVID-19 in patients with pre-existing ILD

The presence of comorbidities is a well-known predictor of severe disease in patients with COVID-19. Chronic lung disease is recognized as one of those comorbidities. However, not much has been elucidated about the impact of preexisting ILD on COVID-19. As there is significant concern about the development of acute exacerbation (AE) of ILDs by COVID-19, it is important to correctly understand how SARS-CoV-2 is transmitted and harms patients with preexisting ILD.

Moreover, since the use of immunosuppressants is regarded as one of the risk factors for the severity and mortality of COVID-19, there is also a concern for ILD patients who are on immunosuppressive treatments.

3.1. The impact of preexisting ILD on susceptibility to COVID-19

The combined evidence regarding chronic ILDs and COVID-19 suggests that patients with preexisting ILDs may be more susceptible to SARS-CoV-2 infection. The expressions of ACE-2 and integrin αvβ6 in AECs, which are the keys for SARS-CoV-2 in entering the body, are increased in patients with ILDs, particularly in those with IPF [67-69].

A report from South Korea analyzing the data from 8,070 COVID-19 cases and matched controls showed that the adjusted odds ratio for the presence of ILD compared with matched controls was 2.02 in the COVID-19 cohort, especially high in young people and males. IPF, CTD-ILDs, and other diseases were more frequent in the COVID-19 group, but hypersensitivity pneumonitis (HP) was not [70].

3.2. COVID-19 as a trigger of AE-ILD

Though not a major trigger, viral infection is regarded as one of the triggers of AE-IPF [71, 72], which is a fatal complication of both IPF and other fibrosing ILDs [73]. As AE-

IPF is more common in winter and spring than in summer and autumn [74, 75], there may be a significant number of AEs triggered by viral infections which are not recognized.

There are several case reports of AE-ILDs triggered by COVID-19 [76-79]. As the clinical symptoms, time course, and radiological features of severe COVID-19 and AE-ILD resemble each other; it is difficult to differentiate between cases that are simply severe viral pneumonia and AE-ILD triggered by COVID-19 [80, 81]. In any case, acutely worsened respiratory failure in COVID-19 patients with preexisting ILD is a devastating condition like AE-ILD, and some patients are refractory to treatment and pass away [79, 80]. A case series by Kondoh et al. revealed that AE-ILD triggered by COVID-19 showed higher 30- and 90-day mortalities (50% and 75%, respectively) than AE-ILD not related to COVID-19 (15% and 16%, respectively) [82]. Based on a review of the relevant literature, the majority of patients with AE-ILD triggered by COVID-19 are treated with medium-high dose corticosteroids, including steroid pulse therapy and antiviral agents, with or without immunosuppressants. COVID-19 should be kept in mind as a trigger when managing patients with AE-ILD in this COVID era, and further studies regarding proper treatment strategies are warranted.

3.3. The impact of preexisting ILD on the severity and prognosis of COVID-19

Preexisting ILDs have had a consistently negative impact on the clinical course of COVID-19 throughout all studies. According to a report from Wuhan, China, preexisting ILD was related to an elevated prevalence of cough, sputum, fatigue, difficulty in breathing, and diarrhea. It was also related to elevated blood neutrophil count and levels of IL-8, IL-10, IL-1β, and D-dimer [83], which might reflect increased disease activity in patients with preexisting ILD. In terms of the prognosis, preexisting ILD causes elevated mortality in COVID-19 [70, 83-90]. It was also associated with higher rates of

hospitalization, ICU admission, use of mechanical ventilation, and longer hospital stay [84-87], which reflect a higher severity in patients with preexisting ILD [70, 84]. Drake et al. reported that the hazard ratio (HR) for mortality in COVID-19 patients with preexisting ILD was 1.60 [88]. Aveyard et al. analyzed the data from a national registry including 7,454 patients with IPF and 5,677 with non-IPF ILDs and revealed similar trends in mortality (HR 1.47 for IPF and 2.05 for other ILDs) and hospitalization (HR 1.59 for IPF and 1.66 for other ILDs) [86].

The prognostic factors for COVID-19 patients with preexisting ILD were also assessed in several studies. Yamaya et al. reported that diabetes was a risk factor for more severe COVID-19 [84]. Older age, male sex, history of cancer/hemopathy, long-term oxygen therapy use, no use of antifibrotics, obesity, impaired diffusing capacity of the lungs for carbon monoxide (DL_{CO}) or forced vital capacity, and consolidation on chest computed tomography (CT) were reported to be factors correlated with mortality [85, 88, 89, 91].

Among ILD subtypes, Drake et al. revealed that IPF patients have a higher risk of death than non-IPF ILD patients [88]. Among non-IPF ILDs, HP and rheumatic arthritis (RA)-related ILD were associated with higher mortality, while other CTD-ILDs and sarcoidosis were associated with lower mortality [88]. According to a study from France, the 1-month mortality of COVID-19 patients with fibrotic idiopathic interstitial pneumonia was 35%. In contrast, the mortality of patients with other ILDs, including CTD-ILD, vasculitis, and sarcoidosis, was 19%, which was comparable with the mortality of all French COVID-19 patients [89]. On the other hand, there were also studies that found no adverse effect of IPF on survival and hospitalization [86, 90]. A study using a large-scale database with over 130 million patients with COVID-19 has revealed that IPF, RA-ILD, systemic sclerosis (SSc)-related ILD, and HP were associated with increased mortality, while Sjögren's syndrome-related ILD was associated with decreased mortality [90].

3.4. The impact of immunosuppressive treatment for preexisting ILDs on the severity and prognosis of COVID-19

The use of corticosteroids or other immunosuppressive drugs is generally regarded to be a risk for the elevated incidence and severity of COVID-19 [92-94]. Several reports insist that patients with autoimmune diseases, including CTD-ILD, have an increased risk of COVID-19 infection [95, 96] and severe COVID-19 [97]. Though it is unclear whether autoimmune diseases themselves could be a risk for COVID-19, as most patients with autoimmune diseases might be on treatment with immunosuppressive agents, it is not surprising that those patients showed worse outcomes.

Conversely, some articles have reported favorable outcomes in patients with CTD-ILD treated with immunosuppressants and/or corticosteroids [85, 98]. Ye et al. reported that though rheumatic diseases were associated with respiratory failure due to COVID-19, they were not related to the length of hospital stay or mortality rate [99]. Given that corticosteroids [100], baricitinib [101], and tocilizumab [102] are now used for treating moderate-severe COVID-19, those agents may possibly be effective in improving outcomes in COVID-19. Therefore, further information is necessary to confirm whether any immunosuppressive treatments for ILDs have a negative impact on COVID-19 management.

4. Pulmonary fibrosis as a sequelae of COVID-19

As longer-term follow-up data is accumulated, persisting symptoms after the recovery from acute COVID-19 have been recognized as post-COVID-19 complications [103]. Pulmonary fibrosis is one of them, which may deteriorate patients' quality of life (QOL) and pulmonary function significantly. As pulmonary fibrosis is a common complication of ARDS [104] and viral infection is suspected to cause chronic fibrotic ILDs [105, 106], it is not surprising that pulmonary fibrosis may also develop after COVID-19.

As the severity and mortality of COVID-19 have become much lower than at first due to the establishment of treatment/prevention strategies and possibly due to the repeated mutations of SARS-CoV-2, the prevalence of PCPF should have reduced significantly. However, as there is still a subset of patients with severe COVID-19 and following residual pulmonary fibrosis, we need to be familiar with the clinical features of PCPF and recognize SARS-CoV-2 as a potential inducer of pulmonary fibrosis.

4.1. Pulmonary function impairment and radiological abnormalities in PCPF

In findings within a few weeks from disease onset, "fibrotic" abnormalities on chest CT can be seen as early as 3 weeks after the onset, regardless of the original severity [107, 108]. Baseline chest CT abnormality of moderate COVID-19 is mainly comprised of ground-glass opacity (GGO) and consolidations [109]. In terms of pulmonary function, the prevalence of DL_{CO} and total lung capacity impairment was reported to be 25-50% at discharge and was particularly worse in patients with severe disease [110]. Though PCPF is generally thought to be formed in the acute phase of COVID-19 and become stable afterward, there are several reports describing cases with extensive pulmonary fibrosis that progressed over several weeks after recovery from COVID-19 [111-114].

At several months after the diagnosis of COVID-19, the prevalence of consolidation on

chest CT becomes lower, while GGO is still a predominant finding [115, 116]. Additionally, mosaic attenuations, reticulation, architectural distortion, and, particularly in patients recovered from ARDS, bronchiectasis/bronchiolectasis are common CT abnormalities at 3-4 months [115, 117].

According to findings at 1-year follow-up after hospitalization, there were still 25% of patients who showed CT abnormalities, the majority of which were GGO, reticulation, and traction bronchiectasis/bronchiolectasis [118, 119]. As GGO represents not only alveolar exudate in the acute phase of inflammation but also fine fibrotic lesions, GGO observed at 1-year follow-up may reflect the latter. Thus, fibrotic abnormalities are thought to become a more common finding as time passes.

In a meta-analysis of 70 studies conducted by Fabbri et al., inflammatory findings on chest CT, such as GGO and consolidation, were observed in 50% of follow-up CTs within 1 year, while fibrotic findings such as reticulation, architectural distortion, interlobular septal thickening, traction bronchiectasis, and honeycombing were observed in 29% [120]. The prevalence of DL_{CO} impairment was 38%, and of restrictive disorder was 17%. Among the above parameters, the prevalence of CT inflammatory findings was the only parameter that significantly reduced over time (3.6%/month) [120]. However, the prevalence of each radiological and functional parameter varied significantly among studies, partly because the definition of fibrotic and inflammatory CT findings and disease severity of the included patients varied from study to study and because most studies included in this meta-analysis were cross-sectional and lacked longitudinal follow-up data from the same patients.

From 2022 onwards, a number of reports with relatively longer-term longitudinal follow-up data have become available. Bocchino et al. have reported that the prevalence of GGO was high at 3-month follow-up (94%) but dropped to 20% at 6 months and 2% at 1 year. The prevalence of consolidations dropped from 71% to 13% at 3 months and totally

disappeared at 6 months, while fibrotic abnormalities became evident at 3 months (2%) and persisted until the 1-year follow-up [109]. Other studies also showed that the prevalence of chest CT abnormality and DL_{CO} impairment gradually reduced over time until 1-year follow-up [116, 119, 121, 122]. Meanwhile, some reports showed no significant improvement in those parameters, particularly in fibrotic CT abnormalities, between 6 and 12 months [123, 124].

Although data on longer-term follow-up are lacking in the field of COVID-19, we can assume the natural course of PCPF through our experience of the previous coronavirus outbreak. According to 15-year observational data on patients with severe acute respiratory syndrome, the severity and prevalence of residual pulmonary fibrosis was reduced within the first year after recovery from the acute phase but remained unchanged in the next 14 years [125]. We should obtain further observational data on COVID-19 in the near future.

4.2. Histopathology of PCPF

The early reports on lung histopathology of COVID-19 were mainly on findings from autopsy or explant samples from patients with fatally severe disease in the acute phase. According to those reports, a significant number of patients showed a histopathological transition from DAD to pulmonary fibrosis [126, 127].

In recent studies, biopsy findings from milder diseases and particularly from PCPF have been reported. Doglioni et al. performed transbronchial lung cryobiospy in patients with non-severe COVID-19 within 20 days from the onset. The distortion of alveolar architecture, type 2 AEC hyperplasia, diffuse vascular dilatation, and hyperplastic interstitial capillaries/venules were observed [128]. In another study, transbronchial biopsy samples from 6 patients with PCPF 4-15 months after discharge showed bronchiolocentric interstitial pneumonia, most of which presented with architectural distortion and

peribronchial remodeling with ECM deposition [129]. In findings from surgical lung biopsy samples obtained at 2-4-month follow-up, diffuse interstitial fibrosis and areas of microscopic honeycombing were present [130]. Konopka et al. summarized the findings from 18 PCPF patients at 3-6 months after the onset, which showed that a usual interstitial pneumonia (UIP) pattern [131] was the most common finding (7 out of 18 cases), while a mixture of organizing DAD with fibrotic changes (cicatricial organizing pneumonia (OP) or nonspecific interstitial pneumonia-like fibrosis) was also common. Patients with a UIP pattern were older than those without and likely presented persistent respiratory symptoms [132].

4.3. Risk factors of PCPF

Various clinical and radiological parameters have been reported to be correlated with the development of PCPF, such as older age [119, 124, 133-139], male sex [133-135, 140], higher body mass index [136, 137], comorbidities [134-136], parameters related to disease severity such as mechanical ventilation or ICU admission [124, 133, 134, 138-140], dyspnea [134, 138, 140], lower blood lymphocytes [134, 141], higher C-reactive protein level [134, 138], and more severe and broader abnormalities on the initial or the worst chest CT [124, 138]. In a meta-analysis, older age, chronic obstructive pulmonary disease, higher CT score, ICU admission, mechanical ventilation, and longer hospital stay were significantly associated with the development of PCPF, and cough, chest pain, and fever were more common in the acute phase in patients who eventually developed PCPF [142]. As the severity of COVID-19 is an important predictor of PCPF, these clinical parameters are in common with the prognostic factors of COVID-19 itself. In addition to those cross-sectional parameters, Huang et al. studied the impact of changes in several blood test markers over time. In patients who developed PCPF, lactate dehydrogenase levels

increased in the first 4 weeks and decreased afterward, and C-reactive protein was consistently high even 4 weeks after the onset of COVID-19. In patients who did not develop PCPF, those parameters started to decline at 2 weeks after the onset [134].

Though not routinely measured in clinical practice, some experimental markers related to the severity of inflammatory and fibrotic reactions have also been reported to be related to an elevated risk of PCPF. McGroder et al. revealed that shorter age-adjusted telomere length was independently associated with PCPF at 4 months after hospitalization [44]. Circulating IFN-γ has also been reported to be correlated with PCPF [143]. Krebs von den Lungen-6, which is a glycoprotein and an extracellular region of human MUC1 mucin cleaved from the cell surface in response to injury of type 2 AECs [144], is increased in the acute phase in patients who later develop PCPF [145, 146]. It predicts the reversibility of the CT fibrotic changes, and it may decrease after the formation of fibrosis [147].

4.4. Prevention and treatment of PCPF

For the moment, there is no specific drug that has been shown to be effective for PCPF. Based on the experience of other fibrotic diseases and theoretical background, several treatments have already been tried for PCPF. We have picked out some of them here and introduced the information available so far.

4.4.1. Antifibrotics

Pirfenidone and nintedanib have become key drugs for controlling the disease progression of IPF and other fibrotic ILDs in the last 8 years. Pirfenidone regulates the levels of TGF-β and TNF-α *in vitro* [148, 149] and reduces the proliferation of fibroblasts and the production of collagen in animal models of lung fibrosis [150, 151]. It is also a scavenger of ROS [152] and downregulates ACE receptor expression [153]. Nintedanib is

an inhibitor of receptor tyrosine kinases of multiple growth factors, including VEGF, FGF, and PDGF [154], whose downstream pathways interact with the TGF-β pathway.

In 2014, two large-scale international phase 3 randomized controlled trials revealed a positive effect of pirfenidone and nintedanib in suppressing disease progression and preventing AE of IPF [155, 156]. Moreover, these drugs have shown a survival benefit as well [157, 158], though this was not proven as a primary outcome in a clinical trial. More recently, these drugs have shown a similar treatment effect on non-IPF fibrosing ILDs, which are progressive despite other possible treatments, such as anti-inflammatory agents [159, 160].

There are some case reports of PCPF treated by pirfenidone or nintedanib, which were well tolerated, resulting in the improvement of fibrosis [161-163]. In an interventional study from Japan, nintedanib led to improvement in the length of mechanical ventilation and CT volumetry in patients with mechanically ventilated COVID-19, though no benefit on mortality was found [164]. According to a recent randomized controlled trial for pirfenidone in severe COVID-19 conducted in China, pirfenidone did not improve chest CT findings, but the levels of inflammatory markers such as IL-2R, TNF-α, and D-dimer were decreased [165]. As some other clinical trials of those agents for PCPF are or soon will be underway (Table 1), evidence is expected to be updated in the near future.

4.4.2. Corticosteroid

Dexamethasone was the first drug proven to have a positive effect on acute COVID-19 [100]. As disease severity is one of the robust predictors of PCPF, it may be true that prevention of deterioration in the acute phase is important for preventing the development of PCPF. However, the effect on PCPF of corticosteroids commenced after recovery from the acute phase has not been well studied.

In a preliminary study from the UK, patients with abnormal parenchymal shadows on chest CT at 6 weeks after a diagnosis of COVID-19 took up to 0.5 mg/kg/day of prednisolone for their extensively remaining OP-like shadows. All patients showed significant improvement in their breathlessness, pulmonary function, and chest CT findings 3 weeks later [166]. The dose of prednisolone was evaluated in a controlled trial comparing a high dose (starting from 40 mg/day and tapered every 1-2 weeks down to 10 mg/day) and a low dose (10 mg/day), both of which were started 3-8 weeks after the onset of COVID-19, continued for 6 weeks and showed a similar effect on dyspnea and radiological improvement. Treatment-related adverse events were not different between the groups [167]. Although these studies showed a potential benefit of corticosteroid on PCPF as long as it is commenced within 2 months after disease onset, it is still unknown whether the improvement was due to the treatment or was just the natural course of the disease since they lacked control groups.

4.4.3. Other therapeutic strategies

Though the evidence in the field of pulmonary fibrosis is limited, some other drugs, such as sirolimus (rapamycin), treamide, and the Chinese herbal medicine fuzheng huayu, are now under study for the treatment of PCPF (Table 1). In addition, medicines used for controlling acute COVID-19, such as remdesivir, baricitinib, and tocilizumab, are also considered to be important drugs that can attenuate the severity of the disease.

Apart from drug therapies, a lung-protective mechanical ventilation strategy may also be important [64, 65], as discussed in section 2.4.3. Moreover, pulmonary rehabilitation is generally effective for decreasing dyspnea and improving exercise capacity and QOL in patients with pulmonary fibrosis [168]. In a randomized controlled trial for the efficacy of pulmonary rehabilitation on post-COVID-19 conditions, a 6-week intervention group

showed significant improvement in pulmonary function, exercise capacity, QOL, and anxiety/depression assessment score [169].

Further treatment approaches may be presented in the near future through the various trials that are already underway.

5. ILD induced by mRNA vaccine for SARS-CoV-2

COVID-19 vaccination induces a Th1-cell response [170], releasing cytokines such as IL-2, TNF-α, and IFN-γ, which upregulate macrophage activation and may cause acute lung injury. Alternatively, it is possible that the adjuvants included in the vaccines could also induce abnormal immune reactions causing lung injury. Although no vaccine-related ILD or death has been reported in large clinical trials of mRNA vaccines for SARS-CoV-2 [171, 172], as those vaccines have become used broadly, it has been revealed that some people experience development or exacerbation of ILD possibly induced by the vaccines. The WHO global pharmacovigilance database (VigiAccess) shows 5,262 cases, which account for 0.05% of all registered vaccine shots, of abnormal lung shadows or pneumonitis, such as the words “ARDS,” “ILD” and “pulmonary fibrosis” after administration of the BNT162b2 vaccine (Pfizer/BioNTech) [173].

To date, case-based information has been accumulated, starting with the first case report of vaccine-related ILD induced by an mRNA vaccine [174]. These cases have consistently shown that ILD occurred within 1-10 days after the first or second shot of the vaccine and sometimes improved spontaneously [175-177] but sometimes was accompanied by respiratory failure and treated with corticosteroid (methylprednisolone 0.5-1mg/kg and/or pulse therapy) [177-182]. The major radiological findings are GGO and consolidation represented by an HP or OP pattern [175, 181]. Histopathological lymphocytic alveolitis, or OP, was proven in some of these cases [181, 182]. Barrio Piqueras et al. reported a case of acute eosinophilic pneumonia induced by mRNA vaccine [176].

For the viral vector vaccines, there is a reported case of acute eosinophilic pneumonia induced 1 day after the first vaccination [183]. Another report showed ILD induced 18 days after vaccination and successfully treated with methylprednisolone pulse therapy followed by gradual tapering of prednisone [184]. For the inactivated vaccines, there is a

case report of ILD induced 2 days after administration that required mechanical ventilation, which was treated with methylprednisolone pulse therapy [185].

Vaccines may also cause AE of preexisting ILDs. There are some case reports of AE-ILDs induced 1-14 days after administration of mRNA vaccines that were successfully treated with corticosteroids and/or immunosuppressants [186-189] or were refractory to the treatment and resulted in death [189, 190].

Although ILD and AE-ILD are relatively rare among the complications induced by vaccines, physicians, especially those who care for patients with ILDs, should be aware of those complications.

6. Manifestation of latent CTD-ILD induced by COVID-19 or anti-SARS-CoV-2 vaccines

Molecular mimicry, which happens when the same lymphocyte receptor recognizes both a self-protein and a foreign antigen due to their structural similarity, plays an important role in the pathogenesis of various autoimmune diseases [191]. Vojdani et al. reported that human monoclonal antibodies against SARS-CoV-2 had reactivity with 28 out of 55 human tissue antigens [192]. Various autoantibodies are induced in patients with COVID-19, such as antinuclear antibody, lupus anticoagulant, anti-melanoma differentiation-associated gene-5 (MDA-5) antibody and anti-neutrophilic cytoplasmic antibody [193-196], which induce or exacerbate autoimmune diseases [196-198]. In addition to SARS-CoV-2 infection, mRNA vaccines also induce autoimmune syndromes, not only due to the similarities in the immune responses induced by COVID-19 and mRNA vaccines but also to the adjuvants contained in the vaccines, which is referred to as "autoimmune/inflammatory induced by adjuvants (ASIA)" [199].

Among these autoimmune diseases, the clinical features of anti-MDA-5 antibody-positive polymyositis/dermatomyositis (PM/DM)-ILD (including clinically amyopathic dermatomyositis) are recognized to resemble COVID-19, including serum cytokine profiles such as elevated IL-6, IL-8 and IL-10 [200]. These two diseases share several pathogenic pathways through activation of the type 1 interferon pathway, which may explain their similarities. MDA-5 is a cytoplasmic viral RNA sensor for viruses such as coronavirus and picornavirus and promotes the production of type 1 interferon and activation of downstream signaling for viral clearance [201, 202].

After the beginning of the COVID-19 pandemic, the incidence of anti-synthetase antibody-positive patients has increased. The most common antibodies were anti-MDA-5 and some anti-aminoacyl tRNA synthetase antibodies [203]. As PM/DM positive for those

antibodies is frequently associated with rapidly progressive ILD, the incidence of PM/DM-ILD might be increased after the COVID-19 pandemic. Particularly, PM/DM-ILD induced by vaccination needs to be cared for cautiously as an iatrogenic adverse event. There are several case reports of PM/DM-ILD induced by mRNA vaccines [204-206], including those with positive anti-Jo-1 antibody [204] or anti-MDA-5 antibody [205, 206], induced by both mRNA and virus vector vaccines.

Though it is not easy to pick out people at risk for having latent autoimmune diseases, we should be aware of the possibility of the development of *de novo* autoimmune diseases when managing systemic symptoms induced after COVID-19 or anti-SARS-CoV-2 vaccination.

7. Conclusions

Over the 3 years of the COVID-19 pandemic, various facts have been revealed regarding the relationships between COVID-19 and ILDs. However, there are still plenty of things that remain unknown in the context of COVID-19, which are so far assumed with reference to the evidence of ILDs. For instance, the etiology of COVID-19-induced acute lung injury and PCPF is mostly unknown. Possible etiologies have been assumed based on the cytokine profile in the acute phase of COVID-19, but the real correlations between those cytokines and the etiology of COVID-19 need to be studied.

In terms of clinical information, the currently available epidemiological data are based mostly on COVID-19 patients diagnosed in the early phase of the pandemic (by the middle of 2020). In this early phase, no treatment/prevention strategies, such as corticosteroids or vaccines, had been established yet. In addition, as SARS-CoV-2 has mutated repeatedly, the virus might have become less virulent. Thus, the disease we experienced in the early phase may be different from that in the current clinical practice.

Nevertheless, we think it is still worth looking back at those data for an understanding of viral pneumonia and ILD affected by viral infection. There are likely to be plenty of similarities in the underlying mechanisms of severe viral pneumonia, cytokine storm, development of pulmonary fibrosis, and the manifestation of latent immune reactions between those induced by SARS-CoV-2 and those induced by other respiratory viruses. Therefore, abundant information containing a significant amount of data from patients with severe COVID-19 is undoubtedly important not only as records of the past but also as a legacy for broadening our perspectives in the field of viral infections. Further studies to elucidate the detailed etiology and management of PCPF and provide longer-term follow-up data as sequels to the current reports and characterization of ILDs induced by viral infections are expected.

Conflict of Interest

Yasuhiro Kondoh received lecture fees from Boehringer Ingelheim Co., Ltd. Jun Fukihara has no conflict of interest.

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Table 1. Clinical trials for treatment or prevention of post-COVID-19 pulmonary fibrosis [207]

	Phase	Location	Treatment agent	Comparator	Primary outcomes	Status
NCT04619680	4	USA	Nintedanib	Placebo	Change in FVC (180 days)	Recruiting
NCT04338802	2	China	Nintedanib	Placebo	Change in FVC (8 weeks)	
NCT04607928	2	Spain	Pirfenidone	Placebo	Change in FVC (% predicted) (24 weeks) Change in percentage of fibrosis on HRCT (24 weeks)	Recruiting
NCT04856111	4	India	Pirfenidone	Nintedanib	Change in FVC (24 weeks)	
NCT04948203	2/3	USA	Sirolimus	0.5 mg vs. 1 mg vs. 2 mg daily	Number of patients with >10% pulmonary fibrosis on chest CT (12 weeks)	Recruiting
NCT05516550	2/3	Russia	Treamide	Placebo	Change in 6-minute walk distance and Borg score (29 days)	Not yet recruiting
NCT04527354	2	Russia	Treamide	Placebo	Rate of relative ≥10% increase in FVC (28 days) Rate of relative 5-10% increase in FVC and ≥15% in DL_{CO}	Completed
NCT04551781		Egypt	Prednisone (20 mg)	Placebo	HRCT score (day 14)	Completed
NCT04279197	2	China	Fuzheng Huayu	Placebo	Improvement of HRCT score (24 weeks) FVC, FEV_1, FVC/FEV1 (24 weeks)	Completed
NCT04482595	2	USA	Nanosuspension of genistin	Placebo	Change in DL_{CO} (12 weeks) Change in 6-minute walk test (12 weeks)	Recruiting
NCT04645368		Russia	Bovhyaluronidase azoxymer	No therapy	Severity of pulmonary tissue lesions with fibrosis (75 days) Interstitial changes (%) on HRCT (75 days)	Recruiting
NCT05387239	1	USA	EV-Pure™ and WJ-Pure™	Placebo	Adverse events due to treatment (3 months) 6-minute walk test	Recruiting
NCT04789395		Turkey	Ozone		Prevention of pulmonary fibrosis (1 year)	Recruiting
NCT05299333		Turkey	Telerehabilitation	Physical activity recommendation	6-minute walk test (8 weeks) Hand-held dynamometer (8 weeks)	Not yet recruiting

COVID-19: coronavirus disease 2019; FVC: forced vital capacity; HRCT: high resolution computed tomography; FEV_1: forced expiratory volume in 1 second; DL_{CO}: diffusion capacity of lungs for carbon monoxide.

Figure caption

Figure 1. Suggested etiology of COVID-19, ARDS, and subsequent pulmonary fibrosis. COVID-19: coronavirus disease 2019; ARDS: acute respiratory distress syndrome; ACE-2: angiotensin-converting enzyme-2; AEC: airway epithelial cell; NET: neutrophil extracellular trap; ROS: reactive oxygen species; TGF-β: transforming growth factor-β; PDGF: platelet-derived growth factor; FGF: fibroblast growth factor; VEGF: vascular endothelial growth factor.