Post-COVID Interstitial Lung Disease—The Tip of the Iceberg

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KEYWORDS

• COVID-19 • Post-COVID-19 condition (long COVID) • Interstitial lung disease
• Post-COVID fibrosis • Long-term impact

KEY POINTS

- Some patients have persistent symptoms, lung function impairment, and radiological abnormalities post-severe acute respiratory syndrome coronavirus 2 infection.
- Post-COVID-fibrotic changes have shown resolution at 12 months, however, in a cohort of patients, the changes persist.
- The long-term impact of post-COVID fibrosis remains unknown and ongoing studies are aimed at assessing the frequency and consequences of this new disease entity.
- Post-COVID interstitial lung disease may represent a significant burden on the health care systems.

INTRODUCTION

On the March 11, 2020, the World Health Organization (WHO) declared the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a global pandemic, commonly referred to as coronavirus 2019 (COVID-19).[1] The first documented case was recognized in Wuhan, China, in December 2019.[2] As of November 2022, there have been over 550 million cases worldwide and over 6 million deaths associated with COVID-19.[3] The spectrum of presentations and symptoms of COVID-19 can vary widely from asymptomatic carriers to life-threatening respiratory and multi-organ failure. The risk factors for the severity of COVID-19 are thought to

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correlate with increasing age, body mass index (BMI), and comorbidities such as diabetes, obesity, cardiovascular disease, hypertension, and chronic kidney disease.[4–7]

The widespread collaborative efforts of governments, public health, pharmaceutical industry, and researchers have led to a wealth of expertise in tackling the pandemic over a relatively short time. We have effective therapies that can reduce the symptom burden and risk of hospitalization and in-hospital mortality with COVID-19. Antivirals, monoclonal antibodies, and immunomodulatory drugs have emerged through robust trials as treatments for SARS-CoV-2 infection.[8,9] Several therapies have been shown to reduce the risk of hospitalization in patients with mild to moderate disease. Treatment of symptomatic COVID-19 with Paxlovid, a SARS-CoV-2 protease inhibitor consisting of nirmatrelvir and ritonavir, has led to a reduction of severe COVID-19 by 89%, without evident safety concerns.[10] In non-hospitalized patients with mild to moderate COVID-19 disease, Molnupiravir reduces the risk of hospitalization or death by approximately 50%.[11–13] Coupled with the rollout of mass vaccination programs worldwide, we have seen the mortality from COVID-19 declining despite continued high rates of infection.[14,15]

Although we are grappling with the changing nature of the virus and attempting to rebuild our lives and economies, we are now faced with an emerging yet unquantifiable health epidemic –post-COVID-19 condition (long COVID). This review will discuss the emerging evidence for the development of post-COVID interstitial lung disease (PC-ILD) focusing on the pathophysiological mechanisms, incidence, diagnosis, and impact of this potentially new and emerging respiratory disease.

PATHOPHYSIOLOGY OF POST-COVID INTERSTITIAL LUNG DISEASE

Data from previous coronavirus outbreaks of Middle East respiratory syndrome (MERS) and SARS suggest that between 25% and 35% of survivors will experience long-term respiratory complications with lung function and radiographic abnormalities consistent with the development of pulmonary fibrosis, therefore, raising the suspicion that persistent respiratory symptoms post-SARS-CoV-2 infection may have similar pathophysiological mechanisms to MERS and SARS infections.[7,16–20]

Several histopathological findings have been identified among COVID-19 cases. Gross examination of postmortem specimens revealed that tissue damage was more severe in the lung peripheries, where fibrous tissue proliferation in the alveolar septa and alveolar destruction was remarkably abundant. In the central areas, the alveolar structure was roughly preserved with only focal fibrosis.[21] The most commonly reported histological pattern of lung injury is diffuse alveolar damage (DAD) with two identifiable stages; an acute stage, defined by scattered or diffuse hyaline membranes, associated with alveolar edema, an alveolar eosinophil exudate, and few vacuolated macrophages, and a more organized stage of parenchymal collapse, enlargement of alveolar septa, alveolar fibrin deposits, hyperplasia of type-2 pneumocytes, sparse multinucleated giant cells, and minor fibroblast proliferation[22,23] A lung cryobiopsy study performed in patients with a mean disease duration of 31.3 days observed marked fibrotic lung parenchymal remodeling, characterized by fibroblast proliferation, airspace obliteration, and micro-honeycombing.[24]

According to a meta-analysis of COVID-19 inpatients, 14.8% developed acute respiratory distress syndrome (ARDS).[25] DAD has long been considered the hallmark histologic finding in acute ARDS.[26] Pulmonary fibrosis (PF) subsequent to ARDS is well-recognized and given the relatively high incidence of ARDS among COVID-19 patients,[25,27] PC-ILD as a potential long-term outcome of COVID-19 is concerning. Distinct from the idiopathic form of PF or other progressive ILD, fibrosis resulting from ARDS is largely stable. However, whereas some patients with fibrosis post-ARDS may fully recover, some may have lasting symptoms of decreased lung function.[28] In postmortem studies of those with COVID-19 features suggestive of a fibrotic phase, such as mural fibrosis and microcystic honeycombing, these findings were observed to be focal, rather than widespread. This may be due to the short duration of the disease at the time of death.[22]

The underlying pathology of ARDS is complex, and the inflammatory response and immune system play a critical role.[29] In general, there is conflicting evidence regarding the possibility that viral infection may predispose one to the development of fibrosis. It is postulated that chronic viral infection may contribute to the fibrotic response through the promotion of a state of mild but chronic inflammation, which disrupts homeostasis and healing, thereby leading to increased susceptibility to a secondary insult. The coronavirus infection tends to have an acute duration; however, there is evidence from ARDS that even a duration of less than 1 week can lead to fibrosis.[30] Inflammation promotes viral clearance, but excessive cytokine response can be damaging.[31]

Viruses can upregulate the expression of critical host cell surface receptors, signaling pathways, and production of growth factors. The angiotensin-converting enzyme 2 (ACE2) receptor, which is engaged by the S1 subunit of the SARS-CoV-2 spike protein, acts as a regulator of the renin-angiotensin system (RAS), which activates a broad range of signaling pathways including proinflammatory and profibrotic effects. Inflammation promotes viral clearance, but excessive cytokine response can be damaging.[31] Cytokines such as transforming growth factor (TGF)-β, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and chemokines promote activation of immune populations that clear infection and promote immunity through T-cell and B-cell recruitment. They also activate macrophage populations that clear apoptotic cellular debris. In acute lung injury, activated macrophages also contribute to the induction of neutrophil recruitment and activation.[32] Neutrophilic infiltrate, in turn, contributes to the generation of reactive oxygen species (ROS) and both neutrophilic infiltrate and ROS may contribute to tissue injury.[33,34] In response to injury, the alveolar epithelial cells recruit fibroblast and inflammatory cells to initiate wound healing by reshaping the extracellular environment to restore tissue integrity and promote the replacement of parenchymal cells.[35] Usually, this pro-fibrotic process is turned off once the tissue heals. However, repeated damage and repair, such as that seen in SARS-CoV-2 infection, can lead to the imbalance of this process, resulting in excessive pathological deposition of extracellular matrix protein, accompanied by upregulation of myofibroblast activity, resulting in a chronic inflammatory environment of macrophage and immune cell infiltration. This is supported by a study on lung samples from individuals who succumbed to COVID-19 and control individuals using single-nucleus RNA sequencing. They noted a reduction in the epithelial cell compartment, of both alveolar type 1 and 2 cells, and an increase in monocytes/macrophages and fibroblasts in COVID-19 patients as compared with control lungs.[36] Furthermore, in a multi-omics study of postmortem COVID-19 patients, there was hyperinflammation, alveolar epithelial cell exhaustion, vascular changes and fibrosis, and parenchymal lung senescence as a molecular state of COVID-19 pathology. A forkhead transcription factor, FOXO3A suppression was implicated as a potential mechanism underlying the fibroblast-to-myofibroblast transition associated with PC-ILD.[37] In this cellular environment, massive proinflammatory and profibrotic cytokines are released, thus, activating fibrosis-related pathways including the TGF-β signal pathway, wingless/integrated (WNT), signal pathway and yes-associated protein/transcriptional cofactor with PDZ binding motif signal pathways.[38,39]

Fig. 1 illustrates how viruses can upregulate the expression of critical host cell surface receptors, signaling pathways, and production of growth factors. The ACE2 receptor acts as a regulator of the RAS which activates a broad range of signaling pathways including proinflammatory and profibrotic effects.

A significant proportion of patients with severe COVID-19 required invasive mechanical ventilation (IMV). IMV can induce stretch force injury and alveolar injury and may contribute to ARDS. Increased lung stretch can induce oxidative injury, increase cytokine production, increase epithelial-mesenchymal transition (EMT),[40,41] and increase collagen deposition in the lungs which contributes to the development of PF. Careful ventilation of injured lungs, or lungs that may have increased stiffness, could potentially help to minimize ventilator-induced profibrotic signaling.[40]

PERSISTENT SYMPTOMS POST-COVID

Although the majority of patients' symptoms recover within 4 to 8 weeks of a SARS-CoV-2 infection, some find their symptoms will persist beyond 12 weeks, leading to the term "long COVID".[42,43] The WHO has defined "post-COVID-19 (long COVID)" as a condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Studies have shown up to 48.8% of individuals reporting not feeling fully recovered from COVID-19 with a median of nine persistent symptoms 1 year following the SARS-CoV-2 infection (Box 1) with the most reported symptoms being breathlessness and fatigue.[44–47] Female gender, being middle age (40–59 years), having two or more self-reported comorbidities and experiencing a more severe form of COVID-19 at the time of diagnosis and resultant hospitalization had a lower rate of self-reported recovery[6,44,45]

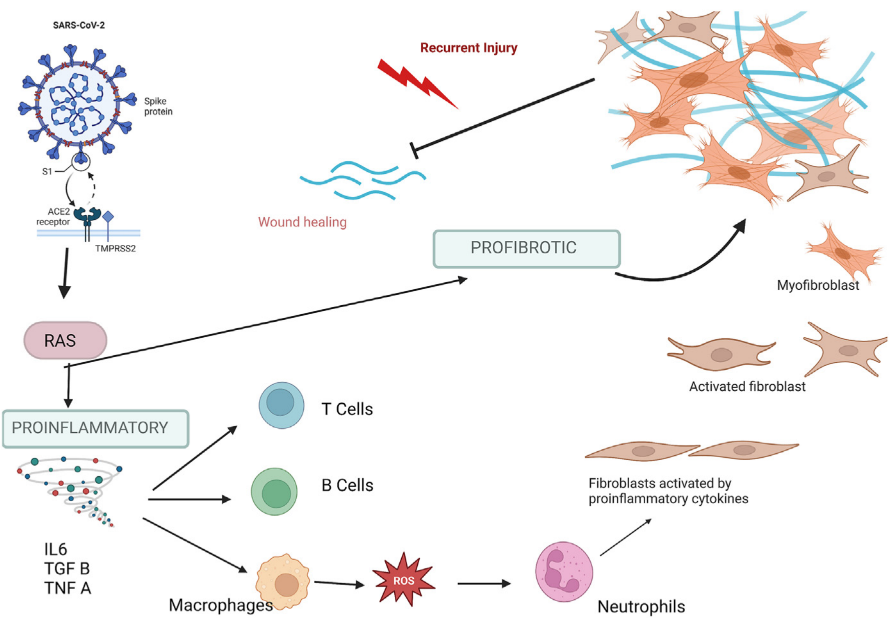

Fig. 1. Pathophysiology of Post-COVID ILD. (Created with BioRender.com.)

Box 1
Commonly reported persistent symptoms post-COVID-19

- Breathlessness
- Fatigue
- Impaired sleep quality
- Aching of muscles (pain)
- Physical slowing down
- Joint pain or swelling
- Limb weakness
- Pain
- Short-term memory loss
- Slowing down in thinking

Data from Refs.[44–47]

Persistent symptoms of COVID-19 have been reported in the early phases and late phases of follow-up (**Table 1**). As time has elapsed since the emergence of the novel SARS-CoV-2 infection, we are beginning to appreciate the long-term symptom burden. Two large prospective observational studies looking at long-term outcomes after SARS-CoV-2 infection, the Lung Injury COVID-19 study and the Post-Hospitalization COVID-19 study (PHOSP-COVID) have followed up 305 Spanish and 1077 UK patients, respectively.[46,48] The Lung Injury COVID-19 study stratified patients according to the severity of SARS-CoV-2 infection as a moderate disease (features of pneumonia with oxygen saturations above 90% requiring supplemental oxygen, n = 162) or severe disease (patients who required either non-invasive ventilation, high flow oxygen, or intubation and IMV, n = 143). At medium term follow-up classed as less than 180 days from the initial symptoms, 55.5% of patients with severe disease and 44.1% of patients with moderate disease had persistent dyspnea with a modified Medical Research Council (mMRC) dyspnea scale of above 2. Dyspnea was significantly more prevalent in the severe group than in the moderate group ($P = 0.042$). At this time point, only 13.5% of patients had symptom resolution and other persistent symptoms included chest pain, fatigue, and cough with no differences in frequency between the moderate and severe groups.[48] Beyond 10 months, one-third of patients' symptoms had resolved; however, breathlessness (mMRC>2) remained in 18.4 and 20% of the moderate and severe groups, respectively. Intriguingly, patients with moderate disease severity had a higher symptom burden at this later time point than those with severe disease, including cough (11.9% vs 3%; $P = 0.03$), chest pain (14% vs 4.4%; $P = 0.025$), and fatigue (20% vs 7.7%; $P = 0.017$). This suggests that the ongoing symptoms do not correlate with the severity of the acute COVID-19 illness.[49] In the PHOSP-COVID study only 239 of 830 (28.8%) individuals described themselves as fully recovered at a median of 5.9 months (interquartile range 4.9–6.5) post-hospital discharge; 632 of 855 (92.8%) individuals had at least one persistent symptom with a median of nine symptoms (see **Table 1**).[45]

A persistence of respiratory symptoms at 1-year follow-up in a subset of patients after acute COVID-19 highlights the potential for ongoing respiratory sequelae and the need for continued monitoring of this group of patients. With over 550 million people affected worldwide,[3] up to 20% may have continued respiratory symptoms in a

Table 1
Published reports on symptoms post-severe acute respiratory syndrome coronavirus 2 infection

	Mandel et al,[44] 2021	Carfi et al,[47] 2020	Willi et al,[50] 2021	Froidure et al,[51] 2021	Boari et al,[52] 2021	Robery et al,[53] 2021	Faverio et al,[54] 2021	Han et al,[55] 2021	Hama Amin et al,[56] 2022	Zangrillo et al,[57] 2022	Huang et al,[58] 2021	Faverio et al,[59] 2022	Evans et al,[45,46]
Type of study	Cross-sectional study	Prospective cohort	Systematic literature search of 31 studies	Single-center cohort study	Prospective Cohort	Retrospective analysis	Multicenter prospective observational cohort	Prospective longitudinal study	Meta-analysis of 618 articles	Prospective observational study	Ambidirectional cohort study	Multicenter prospective observational cohort	Prospective, longitudinal cohort study
Country	UK	Italy	Switzerland	Belgium	Italy	UK	Northern Italy	China	Worldwide	Italy	Wuhan, China	Northern Italy	Multicenter, UK
Duration of follow-up	Median 54 days (IQR 47–59)	Mean 60.3 days (SD 13.6)	9–90 days	Median 95 days	Average 4 months	8–18 weeks	6 months	6 months	Up to 7 months	12 months	6 and 12 months	11–13 months	2–14 months post-discharge
Number of patients	384	142	48,258	134	94	221	312	114	2018	116	1276	287	2320 at 5 months 807 at 1 year
Persistent symptoms	71.9%	87.4%	66%–87.4%	-	-	100%[d] 21%[e]	-	-	-	-	68%[h] 49%[i]	-	54.9%[j] 48.8%[i]
Specific symptoms													
Fatigue	67.3%[a] 73.3%[b] 76.9%[c]	53.1%	16.36%– 72%	25%	52%	-	-		38.7%[f] 80%[g]	-	52%[h] 20%[i]	-	-
Dyspnea	54.8 %[a] 63.3%[b] 57.7%[c]	43.4%	14.55%–74.3%	35%	36%	-	38%	6.1%	26.6%[f] 50%[g]	7% (at rest) 46% (on exertion)	26%[h] 30%[i]	40%	-
Cough	32.2%[a] 36.7%[b] 46.2%[c]	-	61%	10%	-	-	-	10%	15.5%[f] 31.6%[g]	-	-	-	-
Joint/muscle pain	-	27.3%	27.3%	-	-	-	-	-	15.4%[f] 58.3%[g]	-	11%[h] 12%[i]	-	-
Chest pain	-	21.7%	21.7%	-	-	-	-	-	8%[f] 30.5%[g]	39%	5%[h] 7%[i]	-	-
Poor sleep quality	61.1%[a] 93.3%[b] 76.9%[c]	-	24%	-	31%	-	-	-	-	-	27%[h] 17%[i]	-	-

Headache	-	-	18.18%–61%	-	-	-	-	-	-	-	2%[h] 5%[i]	-	-
GI symptoms	-	-	31%	-	-	-	-	-	-	-	1%[h] 1%[i]	-	-
Physiological distress	-	-	23.5%–46.9%	-	21%	-	-	-	-	36%	23%[h] 26%[i]	-	-
Comments		-	11 prospective cohort 11 retrospective cohort 4 cross-sectional 5 case reports	-			-	-	13 studies used	-		-	

Abbreviations: CPAP, continuous positive airway pressure; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, inter quartile range; SD, standard deviation.

[a] Oxygen alone.
[b] CPAP.
[c] IMV.
[d] Required ICU.
[e] Did not require ICU.
[f] Non-fibrotic group.
[g] Fibrotic group.
[h] 6 months.
[i] 12 months.
[j] 5 months.

year equating to a staggering 110 million people. This proportion of symptomatic patients with post-COVID-19 condition (long COVID) represents a significant burden on the individual as well as on the health care systems. A greater understanding of the natural evolution of symptoms over a longer period and the impacts of interventions will improve our understanding of the long-term impacts of the COVID-19 disease. Persistent respiratory symptoms have a complex etiology and are not always attributable to the underlying parenchymal disease. Although the natural assumption is that these symptomatic patients may have underlying structural changes such as PF, one needs to be mindful that deconditioning. overall well-being such as the presence of anxiety and depression and muscle weakness/fatigue may also be contributing to ongoing breathlessness. Objective evidence of pulmonary abnormalities with pulmonary physiology and advanced radiology is therefore paramount.

Pulmonary Function Impairment Post-COVID-19

Pulmonary function abnormalities are seen as early as 2 weeks post-discharge of an acute SARS-CoV-2 infection. In a retrospective observational study of 137 patients from China, 81% of patients demonstrated an inspiratory vital capacity of less than 80% predicted and 24.1% of patients had a forced vital capacity (FVC) of less than 80% predicted. The degree of restrictive ventilatory impairment correlates with the severity of acute SARS-CoV-2 infection[60,61] and impairment was greatest in those patients who required intensive care unit (ICU) admission, of which 50% required intubation and IMV.[49] Lung function impairment had poor correlation with the presence of respiratory symptoms, however, a correlation between biomarkers involved in host defense reflecting neutrophil activation (lipocalin-2), fibrosis signaling (matrix metalloproteinase-7) and alveolar repair (hepatocyte growth factor), and reduction in FVC and diffusing capacity for carbon monoxide (DLCO) was found.[49]

Several studies have shown persistent lung function abnormalities at 3 and 4 months follow-up[20,51,53,62–65](**Tables 2**). The principal study out of Wuhan, China, showed that in 83 patients who did not require IMV, 55% of patients had a DLCO less than 80% predicted and 23% had an FVC of less than 80% predicted at 3 months post-discharge.[20] Similar findings in DLCO and FVC decline were seen in Canadian, Belgian, French, and UK cohorts.[51,53,62,63] Impairments in lung function do not correlate with persistent symptoms,[51] however, were related to the severity of COVID-19 as defined as the need for IMV,[63,65] ICU admission,[51,53,63] percentage inspired oxygen,[53,65] and days on inspired oxygen.[62] Correlations were also seen with age and severity of initial lung involvement.[63]

Longitudinal follow-up has shown that lung function impairments improve over time.[20,54,59,66,67] However, even after a year post-COVID-19, a proportion of patients will continue to have lung function impairment, raising the suspicion of long-term pulmonary complications such as the development of PF. In a Chinese study of 83 patients, 33% of patients had a DLCO less than 80% predicted at 12 months compared with 55% at 3 months and 11% of patients had an FVC less than 80% predicted at 12 months compared with 23% at 3 months.[20] Similar improvements albeit persistent impairments in lung function parameters were observed in a Dutch study of 92 patients where the frequency of impaired FVC improved from 25% at 6 weeks to 11% at 6 months, and for DLCO, this percentage improved from 63% to 46%.[66] Larger multicenter prospective studies have corroborated these findings and have identified risk factors for persistent lung function impairment as having asthma as a comorbidity,[54,59] female gender,[67] and age.[48,67] Persistent lung function abnormalities highlight underlying structural lung involvement as a mechanism of ongoing respiratory symptoms post-COVID and necessitate further radiological assessment.

Table 2
Published reports on pulmonary function testing post-severe acute respiratory syndrome coronavirus 2 infection

Study	Type of Study	Country	Population/ Data	Duration of the Study	DLCO % Predicted	Alterations in DLCO (<80% Predicated)	FVC % Predicted	Alterations in FVC (<80% Predicated)	Comments
LV et al,[61] 2020	Retrospective analysis	Taizhou, China	137 patients	2 weeks following discharge	-	-	-	55.6%	The degree of restrictive ventilatory impairment correlated with the severity of acute SARS-CoV-2 infection. Evidence of small airway dysfunction at a much lower frequency
Froidure et al,[51] 2021	Single-center cohort study	Belgium	134 patients	Median 95-day interval	Median 74%	46%	Median 88%	-	Impairments in lung function do not correlate with persistent symptoms. Impairments in lung function correlated with ICU admission
Robey et al,[53] 2021	Retrospective analysis	United Kingdom	221 patients	8–18 weeks	Mean 76.6%	53%	Mean 86.5%	-	Alterations more common in patients requiring ICU. DLCO alterations more frequent with abnormal CT findings

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Table 2
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Study	Type of Study	Country	Population/ Data	Duration of the Study	DLCO % Predicted	Alterations in DLCO (<80% Predicated)	FVC % Predicted	Alterations in FVC (<80% Predicated)	Comments
Frija-Masson et al,[63] 2021	Retrospective study	Paris, France	137 patients	3 months after symptom onset	Median 49%	-	Median 98%	-	Alterations in PFT correlated to age, degree of initial lung involvement, and endotracheal intubation
Guler et al,[64] 2021	Multicenter prospective cohort	Switzerland	113 patients	4 months	Mean 73.2	-	Mean 86.6%	-	Alterations more pronounced in patients who had severe/critical COVID-19 vs mild/ moderate COVID-19
Safont et al,[67] 2022	Multicenter prospective cohort	Spain	313 patients	2 months (mean 63 ± 12 days) and 6 (mean 181 ± 10 days) months after discharge	Mean 77.25% (2 months) 81.50 (6 months)	54.63% at 2 months 46.96% at 6 months	Mean 99.02 (2 months) Mean 100.59 (6 months)	14.38% (2 months) 9.27% (6 months)	FVC % predicted improved over time. Increased risk of DLCO impairment at 6 months was age D-dimer peak value, female sex, and peak RALE score
Faverio et al,[54] 2021	multicenter, prospective, observational cohort study	Northern Italy	312 patients	6 months from discharge	Median 76.0% vs 84.0% vs 77.4% (oxygen vs CPAP vs IMV.	58% vs 36% vs 54% (oxygen vs CPAP vs IMV.	Median 107.2% vs 106.4% vs 102% (oxygen vs CPAP vs IMV.	-	Patients with COVID-19 who required oxygen have less impairment on PFT compared with patients requiring CPAP and patients requiring IMV

Faverio et al,[59] 2022	multicenter, prospective, observational cohort study,	Northern Italy	287 patients	11–13 months from discharge	Median 79.0 vs 88% vs 80% (oxygen vs CPAP vs IMV.	53% vs 29% vs 49% (oxygen vs CPAP vs IMV.	Median 108.0%, 110.0% vs 106.5% (oxygen vs CPAP vs IMV.	-	Improvement from 6 to 12 months. Patients who required less respiratory support had fewer alterations in PFT
Tarraso et al,[68] 2022	Multicenter prospective observational cohort study	Spain	284 patients	12 months	-	53.8% vs 46.8% 39.8% 60 days vs 180 days vs 365 days	-	14.32% vs 9.29% 6.69% 60 days vs 180 days vs 365 days	Age, female sex, and BMI risk of DLCO impairment at 365 days

Abbreviations: CPAP, continuous positive airway pressure; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ICU, intensive care unit; IMV, invasive mechanical ventilation; RALE, radiological assessment of lung edema.

Radiological features post-COVID-19

Radiology has been a very helpful tool in helping us understand the disease process[44, 70, 73, 63, 53, 50, 71, 54, 67, 59, 74] (**Table 3**).[68] In a retrospective study out of the Lombardy region in Italy, the worst hit region in Europe, 90 consecutive hospitalized patients had computerized tomography (CT) performed on admission and 60 days post-discharge. On admission, 90% of patients had bilateral lung disease with an 80% peripheral and 63% mid-zone and lower-zone predominance; 54.4% demonstrated diffuse ground glass opacities (GGO) and 46.6% had both GGO and consolidation. CT images were reported as fibrotic based on the presence of reticulation, architectural distortion, traction bronchiectasis, and honeycombing. Twenty-three (25.5%) patients were defined as having a non-specific interstitial pneumonia (NSIP) pattern by two thoracic radiologists with over 30 years of experience. Patients with features of fibrosis on their imaging were older and had evidence of systemic inflammation with statistically higher lactate dehydrogenase (LDH), c-reactive protein, erythrocyte sedimentation rate (ESR), D-dimer, evidence of bone marrow suppression with reduced hemoglobin, white cell counts and platelets, and corresponding reductions in lung function parameters (FVC and DLCO) compared with individuals without features of fibrosis on their imaging[69] These findings were similar to studies out of Wuhan, China, where 46% of patients at a median of 56 days follow-up had CT evidence of fibrotic changes manifesting as parenchymal bands (76%), irregular interface (32%), traction bronchiectasis (38%), lung distortion (25%), and honeycombing (9%). The fibrosis was predominantly peripheral in distribution (89%), corresponding with the areas of acute COVID-19 changes, and the overall burden of fibrosis was minimal or mild in the majority (84%) of patients[70] In 50% of this cohort, initial features of lung distortion attributed to improved fibrosis, suggesting a reversible element to these changes. On multivariate analysis, fibrosis was associated with higher ESR, eosinophil counts, and advancing age. More patients in the fibrosis cohort required non-invasive ventilation and 77% of the overall cohort was defined as having severe SARS-CoV-2 infection.[70] A further study of 216 discharged patients found that 85.1% had CT abnormalities at 3 months and these were more frequent in patients defined as severe/critical or required IMV or high-flow oxygen. There was also a significant negative correlation between total lung capacity (TLC) and residual volume and a weaker correlation to DLCO on lung function testing ($P < 0.05$).[71] These early studies raised several questions as to whether features defined as fibrotic during early imaging are reversible over time and thus highlighted the need for longer follow-up studies, or whether the severity of COVID-19 or the need for IMV is driving the development of fibrosis. One such study found that at 4 months follow-up, 44.4% of patients had a multi-disciplinary diagnosis of ILD on CT imaging; 56% had evidence of architectural distortion and this correlated with reductions in DLCO. The majority of patients with ILD at 4 months were admitted to ICU (6.3% vs 93.8%; $P = 0.001$) and required IMV, high flow oxygen, or underwent prone ventilation, and also had more complications of venous thromboembolism (VTE) and ARDS during their acute illness.[65] Highlighting a potential role of severity of infection and IMV as risk factors and contributors to the development of fibrosis. Furthermore, in a study of 220 patients with 20% incomplete CT resolution at 6 months, predicators of persistent CT abnormalities were older age, prolonged hospital stay, a lower PaO2/FiO2 at hospital admission, a higher degree of support, and higher oxygen requirements.[72] The presence of reticulations and consolidation on CT at hospital admission predicted the persistence of radiological abnormalities during follow-up.[72]

Table 3
Published reports on radiology findings post-severe acute respiratory syndrome coronavirus infection

	Mandel et al,[44] 2021	Yang et al,[70] 2020	Zhang et al,[73] 2021	Frija-Masson et al,[63] 2021	Robey et al,[53] 2021	Willi et al,[50] 2021	Zhou et al,[71] 2021	Faverio et al,[54] 2021	Safont et al,[67] 2022	Faverio et al,[59] 2022	Besutti et al,[74] 2022	Tarraso et al,[68] 2022
Type of study	Cross-sectional study	Retrospective study	Retrospective longitudinal study	Retrospective study	Retrospective analysis	Systematic literature search of 31 studies	Prospective cohort study	Multicenter prospective observational cohort	Multicenter prospective cohort	Multicenter prospective observational cohort	Retrospective study	Multicenter prospective observational cohort study
Country	UK	Greece	China	Paris, France	UK	Switzerland	Wuhan, China	Northern Italy	Spain	Northern Italy	Italy	Spain
Duration of follow-up	Median 54 days (IQR 47–59)	Median 56 days after symptom onset	Various time points up to 12 weeks	3 months	8–18 weeks	9–90 days	4 months	6 months	2 months and 6 months after discharge	11–13 months	12 months	2 months and 12 months
Number of patients	384	116	310	137	221	48,258	216	312	313	287	65	325[a] 156[b]
Abnormal radiology	38% CXR remained abnormal 9% CXR deteriorating	46% with CT evidence of fibrotic changes	60.7% of CT had abnormalities after 12 weeks	Overall % of abnormalities on CT not declared	65% of CT scans had abnormalities	54.3–83% had CT abnormalities	Abnormalities on CT scans 85.1%[a] 68.0%[b] 22.2%[c] (*P*-value <0.001)	Abnormalities on CT scans 25%[a] 24%[b] 44%[c] (*P* < 0.001)	Abnormalities on CT scans 52.38%[a] 91.14%[b] (*P*-value 0.001>)	Abnormalities on CT scans 46%[a] 65%[b] 80%[c] (*P* < 0.001)	86.2% had ongoing CT abnormalities Residual non-fibrotic abnormalities (37.5%)[a] Residual fibrotic abnormalities (4.4%)[b] Post-ventilatory abnormalities (2.5%)[c]	At 2 months 61.6% (200/325) had CT abnormalities and at 12 months 78.8% (123/156)
Specific findings on CT scans												
GGO			51.6%	75%	44%		79.3%[a] 60.0%[b] 22.2%[c] (*P*-value <0.001)	16%[a] 7%[b] 12%[c] (*P* = 00186)	36.73%[a] 68.35%[b] (*P* = 0.001)	30%[a] 48%[b] 71%[c] (*P* < 0.001)	32.1% at 5–7 months [a] 3.5% at 5–7 months[b] 2.2% at 5–7 months[c]	73.5% [a] (32% of cohort) 45.5%[b] (15.8% of cohort)
Parenchymal bands		76%	32%		-				13.60%[a] 38.46%[b] (*P* = 0.001)		2.7% at 5–7 months[a]	33.4%[b] (11.6% of cohort)

(*continued on next page*)

Table 3 (*continued*)

	Mandel et al,[44] 2021	Yang et al,[70] 2020	Zhang et al,[73] 2021	Frija-Masson et al,[63] 2021	Robey et al,[53] 2021	Willi et al,[50] 2021	Zhou et al,[71] 2021	Faverio et al,[54] 2021	Safont et al,[67] 2022	Faverio et al,[59] 2022	Besutti et al,[74] 2022	Tarraso et al,[68] 2022
Bronchiectasis		32%	11.5%		-		4.6%[a] 0.0%[b] 0.0%[c]		8.16%[a] 44.30%[b] (*P* = 0.001)	4%[a] 2%[b] 11%[c] (*P* = 0.03)	12.8% at 5–7 months[a] 4.0% at 5–7 months[b] 2.2% at 5–7 months[c]	30.8%[b] (10.7% of entire cohort)
Lung distortion		25%		-	-					-		
Honeycombing		9%			-					0%[a] 2%[b] 1%[c]	0.5% at 5–7 months[b] 0.2% at 5–7 months[c]	
Reticulation			5.7%	30%			11.5%[a] 16.0%[b] 0.0%[c] (*P*-value = 0.019)	19%[a] 19%[b] 34%[c] (*P* < 0.042)	10.88%[a] 34.17%[b] (*P* = 0.001)	27%[a] 42%[b] 29%[c] (*P* < 0.001)	3.7% at 5–7 months[b] 1.7% at 5–7 months[c]	33.9%[b] (11.8% of entire cohort)
Fibrotic changes		89%	36.1%	18%	21%	1.8%–47%		-			4.4%	65.4%[b] (22.7% of entire cohort)
Comments		Patients more likely to have fibrotic changes were older and had a more severe form of COVID-19	Severe COVID-19 more likely to cause CT changes which persist longer	Patients with fibrosis on Ct also had impairments in PFT	Features of fibrosis on CT felt to be significant to patients who required ICU (*P* = 0.0259		Severe/critical[a] Mild/moderate[b] Asymptomatic[c]	[a] = Oxygen alone [b] = CPAP [c] = IMV Abnormalities on CT were more frequent in patients requiring higher respiratory support	Moderate[a] Severe[b]	[a] = Oxygen alone [b] = CPAP [c] = IMV	70.8%[a] at 5-7 months, of which 20 (30.8%) had residual changes. The remaining 10 (15.4%) with fibrotic c abnormalities remained unchanged at 12 months	2 months[a] 12 months[b]

A systematic review of 31 studies found abnormal CT findings in 39 to 83% of patients with five studies describing PF at 3 months.[50] Longitudinal serial CT studies over 3 and 6 months showed that fibrosis-like findings were more prominent with severe SARS-CoV-2 infection (24.3% (17/70) vs 52.0% (53/102)), and that even with severe disease, these findings could improve over time with 24% and 52% improvement seen in severe and moderate disease, respectively. Radiological abnormalities persisted and were slower to resolve in the severe group.[73] A further large retrospective Italian study of 405 patients with follow-up between 5 and 7 months showed CT resolution in 55.6% of patients. Residual non-fibrotic and fibrotic abnormalities were noted in 37.5% and 6.9% of patients, respectively. Non-fibrotic changes were described as overt GGO (4.9% of whole population) or barely visible GGO (27.2% of whole population), peripheral predominant bronchiectasis (12.8%), peri lobular opacities (7.9%), and peripheral parenchymal bands (2.7%), resembling an NSIP pattern with or without organizing pneumonia features. Residual fibrotic abnormalities were found in 6.9% of patients of which a third were attributed to post-ventilatory abnormalities. Fibrotic abnormalities included subpleural reticulation (3.7%), bronchiectasis (4%), and volume loss (2.2%).[74] A subset of 65 patients had further CT imaging at 12 months follow-up. Nine (13.8%) had complete resolution at 12 months, 46 had non-fibrotic residual abnormalities at 5 to 7 months, of which 26 (40%) completely resolved and 20 (30.8%) had improvement but with residual changes. The remaining 10 (15.4%) with fibrotic abnormalities remained unchanged at 12 months.[75] In multivariate analysis, length of hospital admission, smoking history, and obesity have been identified as risk factors for persistent radiological abnormalities.[75]

The Emergence of Post-COVID Interstitial Lung Disease

Persistent symptoms, lung function, and radiological abnormalities have been reported post-COVID-19 (see **Box 1**, **Table 1, 2 and 3**). Several studies have demonstrated the gradual resolution of these findings over time including improvements in lung function impairment and radiological abnormalities.[20,48,54,56,58,59,68,76] The COVID-FIBROTIC study of 448 patients demonstrated ongoing radiological abnormalities in 27.4% of the patients at 12 months, with GGO being the most common abnormality (15.8%) followed by reticular pattern (11.8%), traction bronchiectasis (10.7%), and parenchymal bands (11.6%). Overall residual fibrotic changes were noted at 12 months in 22.7% of the cohort. Residual fibrotic features have been noted at varying time points in studies extending out to a year.[68] Risk factors for developing PC-ILD include increasing age (mean age 59 in fibrotic group vs 48.5 non-fibrotic group), chronic obstructive pulmonary disease (HR 2.88; 95% CI 1.27, 6.52), and severity of COVID-19 stratified according to baseline CT, a requirement for non-invasive or IMV and prolonged length of stay.[51,53,54,56,58,59,63,65,71,72,74,76,77]

A systematic review and meta-analysis of 46 studies assessing radiological features in 2811 CT images within 12 months found great heterogeneity in fibrotic findings between studies with a mean estimate of 29% (95% CI 22–37%).[77] Other meta-analyses have described the presence of fibrosis as high as 45%.[56]

There remain several unanswered questions regarding PC-ILD. There is little doubt that a cohort of individuals have residual fibrotic changes at 12 months ranging from 1 to 29% in studies,[48,59,78] however, pathologically whether that is related to fibrosis promoted by coronavirus itself or sequelae of severe infection and IMV remains to be determined. Certainly, studies have shown the presence of fibrosis being highest among those mechanically ventilated.[54,58,59,65] Similarly, it is unclear if COVID-19 unmasks and accelerates an undiagnosed pre-existing ILD or if it acts as a provoking viral agent triggering ILD.[79] Long-term studies are also needed to ascertain whether the fibrotic changes observed at a year, and consequently pulmonary function impairment and symptoms, continue to improve or remain static (similar to that seen in ARDS) over time. One such study, The UK Interstitial Lung Disease Long COVID study (UKILD-Long COVID) aims to investigate the prevalence and risk factors for PC-ILD looking at clinical, functional, and imaging parameters over time.[7]

Treatment of Post COVID Interstitial Lung Disease

A greater understanding of the pathophysiological mechanisms by which COVID-19 contributes to the development of lung fibrosis is key to our understanding of the natural history and development of PC-ILD. This, in turn, may lead us to the development of therapies that could ameliorate or hasten resolution.

The beneficial role of Dexamethasone in acutely unwell COVID-19 patients has been demonstrated in a randomized controlled trial.[80] There is limited trial evidence of therapy for PC-ILD. The majority of data are from observational cohorts. In a study of 837 patients followed up 4 weeks after discharge, 325 had ongoing symptoms and were offered further investigations and assessment; 35 (4.8%) patients were given the diagnosis of PC-ILD–predominantly an organizing pneumonia pattern; 30 patients were treated with corticosteroid therapy at day 61 ($\pm$ 19) post-COVID which was weaned over a period of 3 weeks. Patients reported symptomatic (median MRC improved from 3 ($\pm$2) to 2 ($\pm$1); $P = 0.002$), physiological (mean relative increase in FVC of 9.6% ($\pm$13.6); $P = 0.004$ and mean increase in Tl_{CO} of 31.49% ($\pm$27.7); $P < 0.001$), and radiological improvements. There was no observation of the progression of CT findings or change to fibrosis after treatment with corticosteroids. This study was limited due to the lack of randomization and control arm.[81]

Furthermore, the potential role of antifibrotics has been studied in a small retrospective, matched case-control study of 21 patients who received nintedanib therapy. There were improvements in SpO2/FiO2 ratio ($P = 0.006$) with no differences in chest imaging or oxygenation between the nintedanib and the control group.[82] To date, only a few observational studies have investigated the role of immunomodulatory and antifibrotic therapies highlighting the great need for randomized control trials.[83]

Novel therapies targeting histone deacetylase 88 and hepatocyte growth factor secreted by mesenchymal stem cells have been proposed due to their antifibrotic effects.[84,85] A phase 1 clinical trial in 27 patients with COVID-19 PF using human embryonic stem cell-derived immunity and matrix-regulatory cells during the SARS-CoV-2 outbreak in Wuhan City showed improvements in exercise capacity and resolution of fibrotic changes on CT.[86] There are ongoing trials of Sirolimus, Pirfenidone, and Colchicine assessing the impact on the development of PC-ILD[83,87,88] and we eagerly await robust trials investigating therapies in PC-ILD.

SUMMARY

The long-term impact of the COVID-19 pandemic remains to be elucidated. The SARS-CoV-2 virus triggers a significant inflammatory and immune response, which causes lung damage. Though the majority of patients will improve and recover fully, some have persistent symptoms, reduced lung function, and radiological abnormalities at 12 months. With over 550 million people affected worldwide, the significance of persistent pulmonary abnormalities in the form of PF cannot be underestimated in terms of ongoing morbidity. The incidence of PC-ILD is very heterogenous and varies from study to study, according to varied factors including the duration of follow-up, severity of SARS-CoV-2 infection, and need for IMV. as well as other potential risk factors. Further studies are eagerly awaited that will glean more light on the risk factors for developing PC-ILD, the role of therapies in preventing or treating PC-ILD, and give a greater understanding of the clinical significance of this new disease.

CLINICS CARE POINTS

- Persistent pulmonary symptoms are commonly reported post-SARS-CoV-2 infection and risk factors include increased length of stay in hospital with COVID-19, severe COVID-19 pneumonitis on initial CT, the need for higher respiratory support, female gender, and increasing age.
- Lung function impairment improves over time, however, can persist in a proportion of patients post-SARS-CoV-2 infection.
- CT abnormalities at 1 year include mostly non-fibrotic changes (like GGO, bronchiectasis, peri lobular opacities, and parenchymal bands), and less commonly, peripheral fibrotic changes.
- The long-term consequences of persistent fibrotic changes post-COVID-19 remain to be elucidated and studies need to assess the significance of these findings.

DISCLOSURE

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