Interstitial lung disease before and after COVID-19: a double threat?

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Pre-existing ILD and pulmonary fibrosis increases the risk to manifest severe COVID-19. Residual interstitial lung changes and sequelae have been observed in COVID-19 survivors. A closer and standardised long-term follow-up of these patients is needed. https://bit.ly/3jWBPCG

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Introduction

Sadly, there have already been nearly 200 million confirmed cases of coronavirus disease 2019 (COVID-19) and more than 4 million deaths [1]. The true toll is certainly much higher. We have learned much about the wide spectrum of disease due to COVID-19 over the past 18 months, ranging from asymptomatic infection to severe pneumonia, respiratory failure and death [2]. There is growing concern about whether survivors of COVID-19 will have long-term pulmonary sequelae, including fibrotic interstitial lung disease (ILD) and/or manifest progressive pulmonary fibrosis [3].

Several clinical features and comorbidities are associated with a poor prognosis and a higher risk of mortality of COVID-19. These include pre-existing health problems such as hypertension, diabetes, cardiovascular disease, obesity, cancer, chronic kidney, liver and lung diseases, and older age, male sex, smoking and race [4–7]. Whether these risk factors are also predictors of longer-term outcomes from COVID-19 is currently unclear. Although bilateral parenchymal airspace densities, organising pneumonia, and diffuse alveolar damage are known acute features of COVID-19 [8], their severity and duration need to be determined.

Three important clinical questions have arisen around the interaction between COVID-19 and ILD: 1) Are patients with pre-existing ILD at higher risk of pulmonary complications from COVID-19? 2) Do survivors of COVID-19 without known pre-existing ILD manifest pulmonary fibrosis? and 3) What is the appropriate management of post-COVID-19 interstitial lung changes?

Are patients with pre-existing ILD at higher risk of pulmonary complications from COVID-19?

While COPD has been associated with poor outcomes as a consequence of COVID-19 [7], data on patients with ILD are limited. As patients with ILD have both impaired lung function and increased risk of acute exacerbations driven by viral infection, COVID-19 is of particular concern [9].

In this issue of the *European Respiratory Journal*, Lee *et al.* [10] investigated the relationship between ILD and COVID-19. They report on a Korean nationwide cohort of 8070 patients with COVID-19, and an age, sex and region-matched cohort derived from a pool of 121 050 subjects. Of the 8070 COVID-19 patients, 67 (0.8%) had ILD. Their findings suggest that patients with ILD have a higher risk of both acquiring COVID-19 and having worse outcomes. The reason for patients with ILD to have an apparently increased susceptibility is unclear. However, patients with ILD were over-represented in the COVID-19 cohort (0.8% *versus* 0.4%), with an adjusted odds ratio of 2.02 (95% CI 1.54–2.61). As there is no theoretical reason that patients with pre-existing ILD would be more frequently infected with SARS-CoV-2, this observation suggests that ILD may predispose to develop more symptomatic disease.

Not surprisingly, COVID-19 patients with pre-existing ILD required more often oxygen therapy (46.3% *versus* 12.3%), had a higher rate of intensive care unit admission (10.5% *versus* 2.9%) and mechanical ventilation (11.9% *versus*1.9%), and a higher mortality (43.3% *versus* 13.1%). Using a composite end-point, they showed that patients with ILD were more likely to have severe COVID-19 than those without (adjusted OR 2.23, 95% CI 1.24–4.01), including those with idiopathic pulmonary fibrosis (IPF) (adjusted OR 14.82, 95% CI 3.96–63.74) [10].

Other studies have reported similar findings (table 1). In a European multicentre study, Drake *et al.* [11] found that pre-existing ILD was associated with significantly higher mortality from COVID-19. A four-fold increase in the adjusted risk of death in patients with pre-existing ILD was found in another case–control study of 46 patients with COVID-19 and 92 controls [12]. More recently, Gallay *et al.* [13] reported a case fatality rate of 35% among subjects with idiopathic fibrotic ILD and 19% in those with other ILDs, the latter being comparable to that reported in the global French population hospitalised for COVID-19 at that time.

These prior studies and the report by Lee *et al*. [10] confirm that ILD patients, most of them requiring hospitalisation, have worse outcomes from COVID-19. This knowledge should alert clinicians and patients of their particular need to minimise risks for exposure to SARS-CoV-2 by taking appropriate proactive, preventive measures, including vaccination [14].

TABLE 1 Published reports on pre-existing interstitial lung disease (ILD) and COVID-19

Study	Type of study	Country	Population/data	Key results	Risk factors for mortality
Esposito *et al.* [12]	Multicentre retrospective case–control study, 1 March to 8 June, 2020	USA (6 centres in Boston, MA)	Hospitalised and non hospitalised patients • 46 COVID-19/ILD • 92 COVID-19/non-ILD (controls matched for age, sex, and race)	Mortality • COVID-19/ILD 33% • COVID-19/non-ILD 13% Increased aOR of death 4.3 (95% CI 1.4–14.0; p=0.01) Likely to be hospitalised • COVID-19/ILD 74% • COVID-19/non-ILD 58% Need for ICU • COVID-19/ILD 47% • COVID-19/non-ILD 23%	• Older ages • Lower D_{LCO} UIP pattern in CT scan (although not statistically different from survivors)
Drake *et al.* [11]	International multicentre analysis, 1 March to 1 May, 2020	UK and European ILD centres	Hospitalised patients • 161 COVID-19/ILD • 322 COVID-19/non-ILD (propensity-score matched for age, sex, and comorbidities)	Mortality • COVID-19/ILD 49% • COVID-19/non-ILD 35% Increased risk of death in adjusted analysis (HR 1.60, 95% CI 1.17–2.18; p=0.003)	• Male sex • Older age • Obesity • IPF • FVC <80% pred
Gallay *et al.* [13]	Multicentric observational survey, from onset of the outbreak in France to 28 May, 2020	France: French rare lung disease network (OrphaLung)	123 COVID-19/ILD • 48 fibrotic idiopathic ILD • 75 other types of ILD	Mortality at 30 days • Fibrotic idiopathic ILD 35% • Other types of ILD 19% Hospital admission • 84% (21% in ICU) • 90% fibrotic idiopathic ILD • 80% other types of ILD	• Increasing age • Male sex • History of cancer/ haemopathy • Chronic use of oxygen supplementation at home

aOR: adjusted odds ratio; HR: hazard ratio; ICU: intensive care unit; D_{LCO}: diffusing capacity of the lung for carbon monoxide; UIP: usual interstitial pneumonia; CT: computed tomography; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity.

Do survivors of COVID-19 without pre-existing ILD manifest pulmonary fibrosis?

Several observational studies have reported the natural course of patients recovering from COVID-19, with results varying from full recovery to lung function impairment and persistence of air space densities and pulmonary fibrosis (table 2). Interstitial lung and fibrotic abnormalities have been described after infection by other coronaviruses, such as SARS-CoV-1 in 2002 and MERS-CoV in 2012, in approximately one third of patients [15, 16].

Factors predicting evolution of COVID-19 pneumonitis were first reported by Marvisi *et al*. [17] in 90 hospitalised patients. In another study, preliminary data at follow-up from a cohort of 837 COVID-19 patients revealed that 325 (39%) had persistent symptoms. At 6 weeks from discharge, persistent parenchymal abnormalities were found in 59 (76.6%) of 77 patients assessed in the ILD service who had an abnormal chest computed tomography (CT), predominantly suggesting organising pneumonia; 30 of

TABLE 2 Published reports on interstitial lung disease (ILD) in survivors of COVID-19 without pre-existing ILD

Study	Type of study	Country	Population/data	Duration of the study	Results
Marvisi *et al*. [17]	Restrospective evaluation of clinical and HRCT features	Italy	90 Caucasian patients	Admission and 8 weeks later	• Pulmonary fibrosis (n=23) 25% • 15 were males with age 75±15 years • GGOs in 90% on admission • Residual GGOs in ∼50% at 8 weeks
Lerum *et al*. [20]	Prospective trial; self-reported dyspnoea, QOL, pulmonary function and chest CT findings	Norway	103 patients	3 months following hospital admission for COVID-19	• Parenchymal bands in 19% • Residual GGOs in 25% • Median FVC, FEV_1 and D_{LCO} were 94%, 92% and 83% pred, respectively
Han *et al*. [19]	Assessed pulmonary sequelae and risk factors for fibrotic-like changes	UK	114 patients	At 6 months after severe COVID-19 pneumonia	• Fibrotic-like changes in 35% • Residual GGOs/interstitial thickening in 27% • Complete resolution in 38%
Myall *et al*. [18]	Observational study of corticosteroid treatment	UK	837 COVID-19 patients	Assessed *via* telephone 4 weeks after discharge; 77 patients referred to post-COVID-19 lung disease MDT after CT at 6 weeks	• 39% (325/837) reported ongoing symptoms • 59 (76.6%) of those imaged at 6 weeks were found to have persistent parenchymal abnormality • 30 of these patients received steroid treatment based on CT scan (prednisolone 0.5 $mg \cdot kg^{-1}$ with rapid wean over 3 weeks)
Sonnweber *et al*. [21]	Prospective, multicentre, observational study	Austria	145 COVID-19 patients (133 follow-up at 100 days)	60 and 100 days after confirmed diagnosis	• 41% persistent symptoms at 100 days • 63% radiological lung abnormalities (GGOs, consolidation and reticulation) • Majority of COVID-19 patients improved symptoms and lung abnormalities within 3 months
Wu *et al*. [22]	Prospective, longitudinal, follow-up study,	China	399 patients admitted to hospital (severe COVID-19); 135 (34%) patients met the inclusion criteria	Follow-up at 3, 6, 9 and 12 months	• 65 (78%) had residual changes on CT at 3 months (mostly GGO) • 20 (24%) patients had abnormal radiological changes at 12 months

(HR)CT: (high-resolution) computed tomography; QOL: quality of life; MDT: multidisciplinary team; GGO: ground-glass opacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

them received treatment with corticosteroids and had improvement of forced vital capacity and carbon monoxide transfer factor after 3 weeks [18]. These findings, observed relatively soon after discharge, are therefore somewhat expected, and in keeping with studies of survivors of acute respiratory distress syndrome (ARDS) from other similar viral infections.

Recently, Han *et al*. [19] assessed pulmonary sequelae at chest CT at 6-month follow-up in 114 survivors of severe COVID-19 pneumonia, and found fibrotic-like changes on chest CT in 35% of patients; 27% had residual ground-glass opacities or interstitial thickening, and only 38% had complete radiological resolution. Variables associated with lung fibrotic changes at 6 months identified by multivariable analysis included age over 50 years, heart rate >100 beats per min at admission, hospital stay of 17 days or more, ARDS, noninvasive ventilation, and an initial total CT score equal to or greater than 18.

Recent reports demonstrated an improvement of symptoms and of CT abnormalities at 3 months and over 6–12 months in patients who survived COVID-19 [20–22]. Persistent radiological changes were found in 24% of 83 patients at 12 months after discharge [22].

What is the appropriate management of post-COVID-19 interstitial lung changes?

Radiological and histological features observed in the acute phase of COVID-19 pneumonia correspond to the hyper-inflammation phase of the disease, and corticosteroid therapy has been the first line treatment since the findings of the RECOVERY trial [23]. However, management after the initial phase is not well established. In post-COVID-19 follow-up, our clinical experience and some emerging data suggest that persistent changes mostly consist of ground-glass opacities or consolidations corresponding to organising pneumonia at imaging, and corticosteroids may be beneficial in a number of cases [18]. In isolated cases, genuine pulmonary fibrosis may occur, although it seems to be less frequent than initially speculated [24]. It is currently unknown whether antifibrotic drugs indicated and used for IPF, other fibrotic ILDs with a progressive phenotype, and systemic sclerosis-associated ILD, also have a role in the treatment of fibrotic ILD following COVID-19 [24]. Results of ongoing clinical trials are eagerly awaited to determine the risk and benefits of antifibrotic treatment in patients with fibrotic lung involvement following COVID-19 (pirfenidone *versus* placebo: NCT04607928 and NCT04652518; nintedanib: NCT04541680 and NCT04619680; and comparing both antifibrotics: NCT04856111). More data is also likely to become available on the impact of acute COVID-19 therapies on long-term pulmonary outcomes, with particular interest in drugs that affect immune function, such as corticosteroids, tocilizumab and tofacitinib [23, 25, 26].

Future directions

Evolving knowledge raises the concern of residual pulmonary sequelae in survivors of COVID-19. Monitoring disease course longitudinally in survivors of COVID-19 will hopefully shed useful insights and enhance our understanding of the factors driving the resolution, evolution or stability of pulmonary fibrosis following COVID-19 [27]. Prospective, clinical, physiological and radiological assessment of the lung in well-designed studies is needed to differentiate fibrotic sequelae without physiological impairment in asymptomatic patients from fibrosis associated with functional impairment and reduction in quality of life. The efficacy and safety of antifibrotic agents in the setting of COVID-19 need to be determined in well-designed studies.

Summary

The report by Lee *et al*. [10] in this issue of the *European Respiratory Journal* highlights that pre-existing ILD increases the risk of manifesting severe COVID-19. Therefore, this is a group of patients in whom additional preventive measures, such as vaccination, is particularly indicated.

Emerging data documenting the residual interstitial lung changes and sequelae warrant future studies to determine the risk of pulmonary fibrosis in COVID-19 survivors. The need for a close and standardised long-term follow-up of these patients to understand disease behaviour is evident.

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