



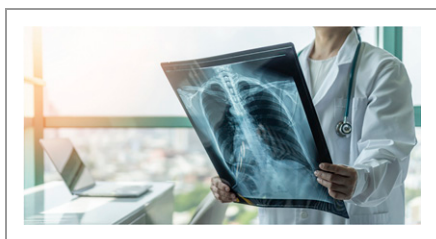
Lungs after COVID-19: Evolving Knowledge of Post-COVID-19 Interstitial Lung Disease

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Emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 resulted in a global pandemic with more than 100 million people infected to date (1). In the early months of the pandemic, healthcare providers grappled with uncertainty about the clinical course and appropriate management of the coronavirus disease (COVID-19). Over time, well-designed observational studies, collaborative networks, and innovative clinical trial platforms led to significant advances in knowledge about the acute care of COVID-19. As more people recover from COVID-19, many are wrestling with the long-term sequelae of the disease, and more questions have arisen about the prevalence and appropriate management of residual lung disease in survivors of COVID-19 (2–4). Persistent inflammatory abnormalities on chest imaging beyond the acute illness period have been reported in several cohorts, and observational studies have suggested development of pulmonary fibrosis in a subset of patients (5–7).



However, existing studies are largely limited to case series and small cohorts with convenience sampling. No prior studies have systematically and rigorously evaluated patients who survived COVID-19 for residual lung disease. Without large prospective studies, we are often left to extrapolate from other viral infections and speculate on the incidence and appropriate management of post-COVID-19 interstitial lung disease (ILD) (8).

In this issue, Myall and colleagues (pp. 799–806) report on the incidence and clinical features of persistent inflammatory ILD after hospitalization for COVID-19 (9). In this prospective observational study of 837 patients who survived hospitalization for SARS-CoV-2 infection at a single center in the United Kingdom, the authors found that 7% of patients had persistent interstitial changes on chest computed tomography (CT) 6 weeks after hospital discharge. The majority of these (35 out of 59, or 4% of the entire cohort) had an organizing pneumonia (OP)-like pattern, with bilateral subpleural ground-glass infiltrates in a mid- to lower-zone distribution, at times associated with subpleural and peribronchial linear dense consolidation, and traction bronchiectasis in some patients. These patients were offered treatment with corticosteroids (0.5 mg/kg prednisolone) with a taper over 3 weeks, on average. All 30 patients who received corticosteroid treatment reported subjective improvement in breathlessness and physical functioning and had objective improvements in lung function and chest imaging.

The strength of the study is the authors' rigorous, systematic, and comprehensive approach to documenting follow up of this large cohort of patients hospitalized with COVID-19. Their protocol provides a paradigm for a structured postdischarge assessment of patients recovering from

COVID-19. All patients that met criteria (based on imaging, symptoms, and physiologic testing) were reviewed at a weekly post-COVID-19 multidisciplinary discussion prior to a decision to offer therapy. This rigorous and comprehensive follow up ensured that each patient had access to state-of-the-art multidisciplinary care and allowed healthcare providers to improve their knowledge of this novel and complex condition in real time. This approach also allowed for thorough characterization of a large cohort of patients recovering from COVID-19 with respect to residual pulmonary disease and accurate reporting of the incidence of post-COVID-19 inflammatory ILD.

This study also provides incremental knowledge about treatment of post-COVID-19 inflammatory ILD. Myall and colleagues report a 4% incidence of this condition among a large cohort of patients that required hospitalization. In real-world settings, many clinicians are seeing patients with post-COVID-19 inflammatory ILD and have adopted treatment with corticosteroids despite little evidence to support their use. The improvements in symptoms and physiologic parameters reported here are encouraging. However, we must caution against generalizing these treatment effects to a larger group of patients. This was an observational cohort of 30 patients without a comparator group of untreated patients. As such, there is no way to know whether these patients would have recovered on their own without therapy. Corticosteroid treatment may shorten the time to recovery and return to functioning for patients recovering from COVID-19 with an OP-like pattern on chest CT. However, without a randomized controlled trial, this inference is largely based on extrapolation from studies of patients with other causes of OP (10).

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DOI: 10.1513/AnnalsATS.202102-223ED

Additionally, patients in this study were given a clinical diagnosis of OP based on CT imaging and multidisciplinary discussion without a lung biopsy. Although the patients were treated as having OP, the underlying histopathology is not known.

We found it encouraging that only a small number of patients in this cohort developed symptomatic post-COVID-19 ILD associated with physiologic impairment. Interestingly, a much larger number of patients (nearly 40%) had persistent symptoms 4 weeks after hospital discharge, consistent with other studies (2, 11). However, almost half of these had no evidence of physiologic or radiographic abnormalities. Another third had functional or physiologic impairment but normal imaging. These findings highlight the wide range of abnormalities and complex needs of patients recovering from COVID-19.

Despite the significant contribution that this study adds to our understanding of post-COVID-19 ILD, many questions remain unanswered. The short-term follow up of patients, with imaging and treatment at 6–8 weeks after discharge, ensured a timely intervention with the goal of preventing fibrosis. However, without

longer follow up, there is no way to know how many patients with SARS-CoV-2 infection develop chronic fibrosing ILD and whether steroid treatment actually prevents fibrosis in the long term. The etiology of post-COVID-19 fibrotic changes remains unclear. It is possible that another insult during the hospitalization aside from infection with SARS-CoV-2, such as ventilator-induced lung injury, hyperoxia, or superimposed bacterial pneumonia, contributed (12). The majority of patients with persistent inflammatory ILD in this study required supplemental oxygen therapy during the hospital stay, and 46% required mechanical ventilation. Does this indicate that those who were requiring supplemental oxygen, intensive care unit admission, and mechanical ventilation may have had higher risk of developing ILD? Without a comparator group, there is no way to know.

It is also important to note that only those patients with findings of OP and restrictive physiology in the absence of improving symptoms were offered steroid therapy. Those who had OP changes on CT but had <15% lung involvement and/or no restrictive abnormality (21/59 patients or 2.5% of the overall cohort) were not offered steroids,

and neither were the 3 patients with fixed changes. Similarly, patients who were not hospitalized with SARS-CoV-2 infection were not included in this study. Therefore, we still lack data on the management and long-term outcomes of these groups of patients.

Future studies should build on the work by Myall and colleagues to advance our knowledge of the long-term pulmonary sequelae of SARS-CoV-2 infection. There is a pressing need for rigorous follow up of multi-center cohorts of COVID-19 survivors with attention to lung function, imaging abnormalities, and symptoms. More data on corticosteroid treatment is needed, although a randomized clinical trial will be difficult to justify given existing data on the efficacy of steroids for other causes of OP. Collaborations among institutions and additional observational studies that include a comparator group of untreated patients would be a step in the right direction. If done in a rigorous manner such as by Myall and colleagues, we are positioned to gain a large amount of knowledge about the natural history and response to therapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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