



Post COVID Interstitial Lung Abnormalities—Incidence and Management

Mark Robertshaw¹ · Corey D. Kershaw¹

Accepted: 27 March 2023 / Published online: 11 April 2023

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

Abstract

Purpose of Review This review aims to summarize the available literature to identify the incidence and risk factors for persistent interstitial lung abnormalities (ILAs) following hospitalization for COVID-19. The current and prospective treatment options are reviewed in an effort to help pulmonary practitioners care for this burgeoning patient population.

Recent Findings Statistical modeling suggests that 11.7% of all patients hospitalized with COVID-19 have irreversible fibrotic features on long-term follow-up imaging.

Summary The available evidence suggests that up to 30% of patients have ILAs following COVID-19 hospitalization. The radiographic abnormalities improve or resolve in a majority of these patients. However, estimates suggest that up to one-third of these patients have irreversible fibrotic features. Clinical trials of the impact of anti-fibrotic agents are ongoing. As there continue to be thousands of COVID-19 hospitalizations in the USA each week, the management of post-COVID ILAs will become a common problem for the pulmonary practitioner.

Keywords COVID-19 · Post-COVID · Post-COVID fibrosis · Interstitial lung abnormality · Interstitial lung disease

Introduction

Since late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for causing COVID-19 illness has resulted in a global pandemic which impacts nearly every aspect of human society. As of February 2023, there have been over 750 million cases of COVID-19 worldwide and 6.8 million deaths [1]. There exists a wide spectrum of clinical presentation of COVID-19 illness including asymptomatic viral shedding, lower respiratory tract infection, or severe ARDS and death. In some cases, patients may continue to experience persistent symptoms including dyspnea, exercise intolerance, and fatigue months—or even years—after the infection has cleared. This constellation of symptoms is sometimes referred to as “post-acute sequelae of COVID-19” and in some cases may be the result of fibrotic lung disease which was not present prior to SARS-CoV-2

infection. Given the staggering number of total cases and hospitalizations caused by COVID-19, even a low incidence of post-COVID pulmonary fibrosis can have profound impacts on the field of pulmonary medicine. This review will summarize the existing literature on the known incidence and risk factors of post-COVID pulmonary fibrosis and provide a brief overview of its current and prospective treatments.

Incidence

Following viral transmission and infection of the lower respiratory tract, SARS-CoV-2 generates a radiographic lung injury pattern that is generally similar to that caused by other viral respiratory pathogens. In the early stages of COVID-19 pneumonia, the most common parenchymal abnormality is ground glass opacity, followed by consolidation [2]. Autopsy studies performed on patients with severe COVID pneumonia suggest these radiographic findings most likely represent alveolar hyaline membranes and reactive type II pneumocytes seen in the exudative diffuse alveolar damage phase [3]. Beyond the acute stage of infection, there is typically more radiographic heterogeneity including complete radiographic resolution, the persistence of ground glass opacities, or the development of other interstitial lung abnormalities (ILAs)

✉ Corey D. Kershaw
corey.kershaw@utsouthwestern.edu

Mark Robertshaw
mark.robertshaw@utsouthwestern.edu

¹ Division of Pulmonary and Critical Care Medicine,
University of Texas Southwestern Medical Center, 5939
Harry Hines Blvd, 75390-8558 Dallas, TX, USA

such as reticulation, architectural distortion, or traction bronchiectasis (Figs. 1, 2, 3, and 4). Notably, ILAs must involve at least 5% of a lung zone and do not include radiographic features suggestive of alternative etiologies such as dependent atelectasis, focal fibrosis adjacent to spinal osteophytes, isolated nodularity, or interstitial edema [4]. This variability in radiographic features was demonstrated in a study of 52 hospitalized patients with COVID-19 pneumonia who underwent follow-up CT imaging approximately 4 months after discharge. The most common radiographic abnormalities identified on this follow-up scan were mosaic attenuation (30 of 52), reticulations (27 of 52), and architectural distortion (24 of 52). The authors did not report what proportion of patients had a normal 4-month follow-up CT scan. Patients in this cohort with severe or critical COVID-19 pneumonia—defined by the presence of hypoxia, tachypnea, or multiorgan failure—had a higher prevalence of mosaic attenuation pattern with hypoattenuated areas (66% versus 13%) and reticulations (59% versus 13%) on the follow-up CT scan when compared to patients with mild or moderate infection. There was also a non-significant trend towards more architectural distortion (52% versus 13%) in patients with severe or critical disease suggesting that increased disease severity is associated with a greater risk of post-COVID ILAs [5]. Similarly, a large single-center cohort study of 353 subjects from Wuhan, China, found that ground glass

opacities (159 of 353) and irregular lines (56 of 353) were the most common radiographic features identified on CT scans performed six months after hospitalization for COVID-19 pneumonia. This study also identified a positive association between the increasing severity of COVID-19 pneumonia and the likelihood of persistent ILAs at 6 months [6]. This heterogeneity in radiographic features seen on initial follow-up CT imaging makes it challenging to predict which patients go on to develop post-COVID fibrosis, though recently published studies with longer follow-up periods offer slightly more clarity.

It remains unclear whether radiographic abnormalities which may persist for several months after COVID-19 pneumonia represent slowly resolving diffuse alveolar damage or the emergence of fibrotic lung disease from aberrant repair mechanisms. Several meta-analyses have attempted to answer this question by characterizing the evolution of these radiographic abnormalities over a longer period of follow-up after hospitalization for COVID-19 pneumonia. The largest of these meta-analyses done by Fabbri and colleagues compiled 46 studies examining the persistent radiographic sequelae up to twelve months after SARS-CoV-2 infection. They noted that patients with ground glass or consolidative opacities during the initial hospitalization had a higher rate of radiographic improvement on follow-up imaging when compared to patients with ILAs (0.92 to 0.44 and 0.32 to 0.26, respectively). The timing of the follow-up scan in this

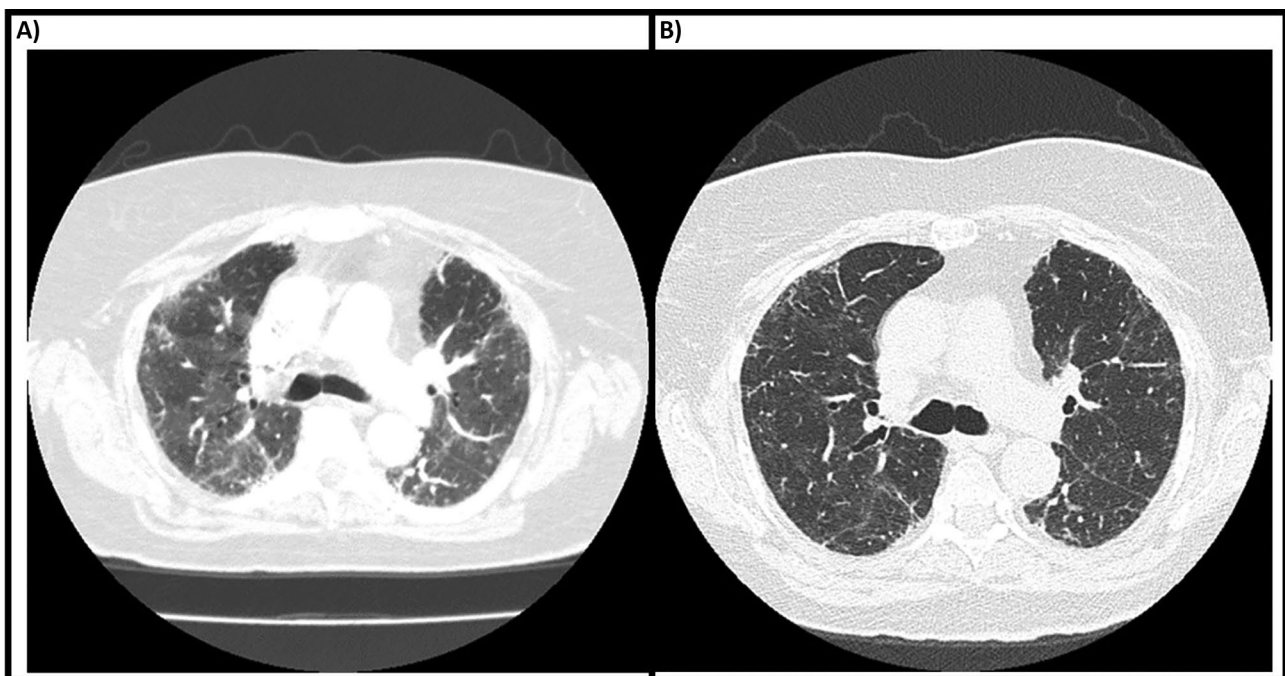


Fig. 1 Representative axial CT scan slices of a patient with post-COVID interstitial lung abnormalities. **A** CT chest has done 2 months after discharge. Prominent radiographic features include ground glass opacities

with mosaic attenuation, reticulations, and irregular lines. **B** CT chest has done 1 year later with improved ground glass opacities and scattered irregular lines

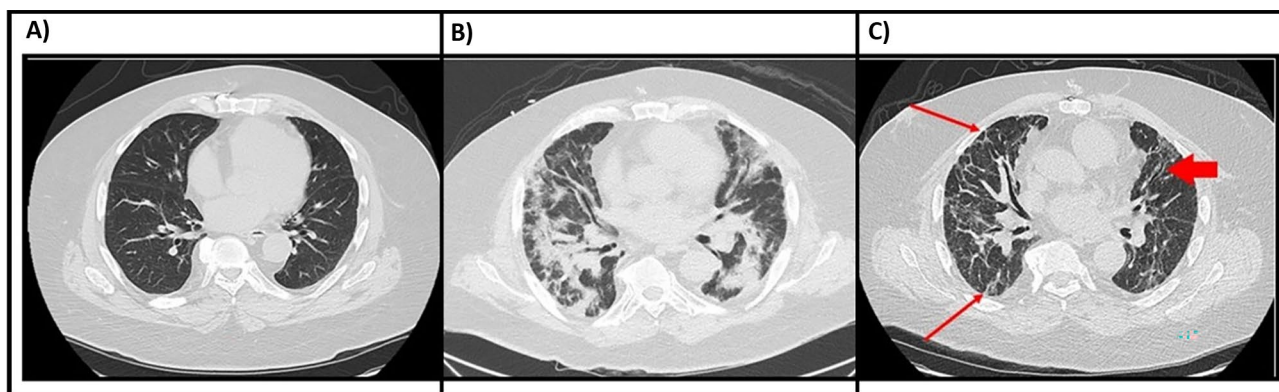


Fig. 2 Representative axial CT scan slices of a common pattern of radiographic progression after COVID-19 pneumonia. **A** Baseline CT chest has done before the COVID-19 infection showing normal lung parenchyma. **B** CT chest done on admission for COVID-19 pneumonia showing peri-bronchovascular ground glass opacities and consoli-

datations. This patient was treated with a course of systemic corticosteroids. **C** CT chest was done 10 months after hospitalization with minimal ground glass opacities but the architectural distortion was not present before COVID. Subpleural reticulations (arrow) and traction bronchiectasis (arrowhead) identified

study was positively associated with the improvement or resolution of the ground glass or consolidative changes. In other words, taken collectively the ground glass and consolidative opacities became less prominent the farther out from COVID-19 hospitalization. The authors suggest this association reflects the typical course of resolving diffuse alveolar damage. In contrast, there was no such temporal association in patients with ILAs suggesting these findings represent an irreversible process [7•]. Similar findings were seen in a prospective cohort study of 62 participants from Wuhan, China, published in 2021. In this study, 56% of participants had ILAs on follow-up CT imaging done 6 months after hospitalization with COVID-19. All of these participants demonstrated persistent ILAs on another follow-up CT scan done 6 months later; however, approximately 25% (8 of 35) showed a slight reduction in severity suggesting that some

patients may continue to show slow radiographic improvement for several years after hospitalization with COVID-19. Additionally, of the remaining participants with non-fibrotic abnormalities on 6-month follow-up imaging, 85% (23 of 27) showed partial or complete resolution on the 1-year CT scans [8]. This slow improvement was also seen in a study by Pan et al. of 209 subjects hospitalized with severe COVID-19. The CT abnormalities seen during the index hospitalization in this study resolved in 61% of participants (128 of 209) at 3 months and in 75% of participants (156 of 209) at 6 months [9]. These studies suggest that while a significant proportion of patients hospitalized with COVID-19 have persistent abnormal findings on follow-up imaging, many of these patients show partial or complete resolution over the following months. However, those with ILAs—non-dependent reticulation, architectural distortion, traction

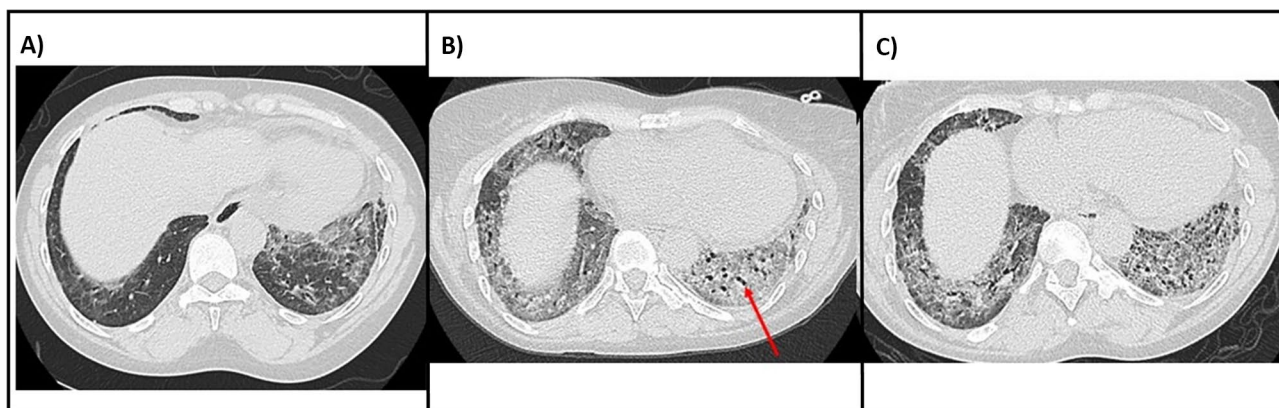


Fig. 3 Representative axial CT scan slices of a patient with baseline SSc-ILD exacerbated by COVID-19 pneumonia. **A** Baseline CT chest has done before the COVID-19 infection showing minimal ground glass opacities and reticulations in the left lung base. **B** CT chest has

done 2 months after COVID-19 hospitalization showing a significant increase in diffuse ground glass opacities and traction bronchiectasis (arrow) not present before COVID. **C** CT chest has done 1 year later showing no significant improvement

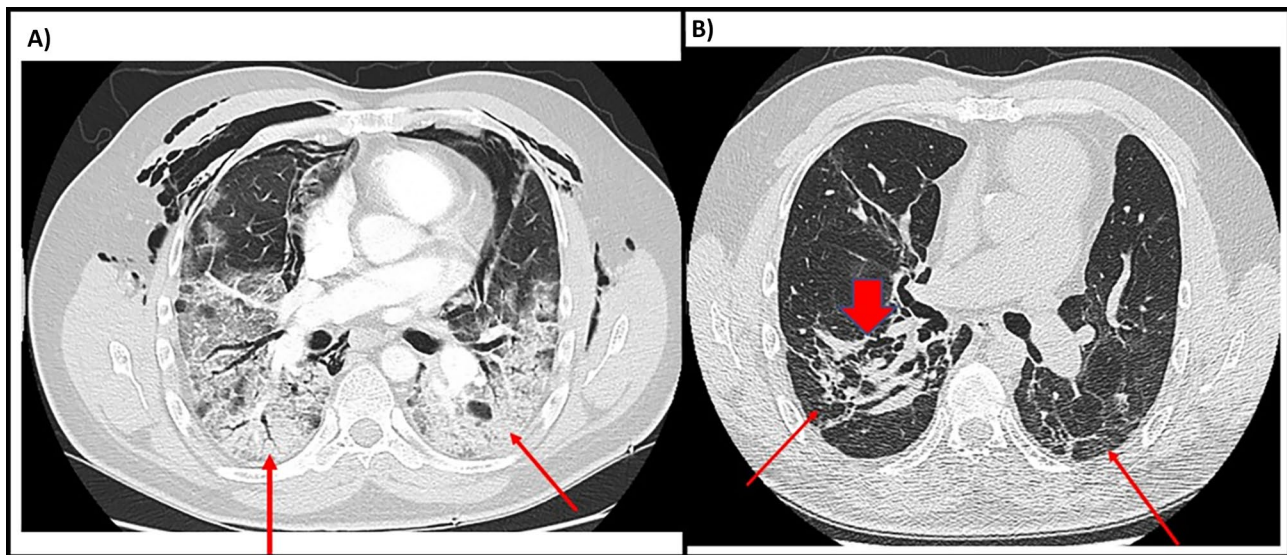


Fig. 4 Representative axial CT scan slices of a patient with post-COVID interstitial lung abnormalities. **A** CT chest has done during hospitalization for COVID-19 pneumonia demonstrating bilateral ground glass opacities, bibasilar consolidation (arrows), and pneumomediastinum. **B** CT chest

has done 1 year after discharge shows improved ground glass opacities and residual architectural distortion with both peri-bronchovascular and subpleural reticulations (arrows). New traction bronchiectasis (arrowhead)

bronchiectasis, honeycombing—on initial follow-up imaging typically do not show significant improvement over time.

As residual ILAs are an emerging complication following COVID-19 infection, there is increasing interest in defining both the prevalence and risk factors associated with persistent ILAs after COVID-19 hospitalization. The largest study to date of residual lung abnormalities following COVID-19 is currently being performed by the PHOSP-COVID Study Collaborative Group in the UK. Interim analysis of this UKILD study released in December 2022 found residual lung abnormalities—defined as ground glass opacities or reticulations—in nearly 80% of CT scans performed at a median follow-up time of 140 days after COVID-19 hospitalization. Twenty-six out of the twenty-eight subjects that had a second follow-up CT scan done at least 3 months later still had residual abnormalities. Based on Bayesian modeling, the authors of the UKILD study estimate the prevalence of residual lung abnormalities to be up to 11.7% in patients hospitalized with COVID-19. The clinical indicators with the strongest association with residual lung abnormalities in this cohort were severe illness requiring NIPPV, IMV, or ECMO (RR 1.40, 1.23–1.63), abnormal CXR findings at follow-up (RR 1.40, 1.22–1.61), and post-hospitalization percent predicted DLco < 80% (RR 1.26, 1.02–1.58) [10••]. Other risk factors identified as being associated with residual lung abnormalities after COVID-19 hospitalization include older age, male sex, comorbid hypertension, longer length of stay, prior tobacco use, higher C-reactive protein, lower circulating interferon gamma, and lymphopenia [11–13]. Additional studies, including the secondary analysis of the

UKILD study, will likely better define the risk factors associated with residual ILAs after COVID-19 hospitalization and may lead to the creation of scoring systems to facilitate more targeted surveillance and treatment of such a large patient population.

While longer-term studies are ongoing, the preponderance of the available evidence suggests that approximately 30% of patients have residual lung abnormalities 6 months after COVID-19 hospitalization. Most patients continue to have slow improvement in imaging over the following months or years; however, it is estimated that up to 12% of patients have persistent ILAs consistent with irreversible fibrotic lung disease.

Treatment

While the majority of patients with abnormal chest imaging after COVID-19 hospitalization demonstrate gradual radiographic improvement over the course of several months, those with persistent parenchymal lung disease are faced with a paucity of available treatments. Clinical trials examining agents currently in use for other fibrotic lung diseases have started to shed light on the role of these treatments for patients with post-COVID ILAs.

Similar to that of other infections, the immune response to SARS-CoV-2 infection can become dysregulated and result in a post-infectious organizing pneumonia [14]. As secondary-organizing pneumonia is known to be a corticosteroid-responsive process, there has been

considerable attention focused on the effect of corticosteroids on patients with COVID-19. Dexamethasone became a cornerstone of treatment for patients with severe COVID-19 after the RECOVERY trial demonstrated that its use resulted in a significant reduction in mortality in patients requiring supplemental oxygen or invasive mechanical ventilation [15]. Corticosteroids were first studied in patients with persistent ILAs after COVID-19 by Myall and colleagues in 2021. This prospective observational study treated 30 patients with functional or physiologic impairment and radiographic features of organizing pneumonia 4 weeks after COVID-19 hospitalization with a 3-week tapering dose of oral prednisolone. All 30 patients reported improved breathlessness after treatment and pulmonary function testing showed a mean relative increase in FVC of 9.6%. Post-treatment CT images were reviewed in a multidisciplinary team conference, and all patients were felt to have improved radiographic features [16••]. This observational study suggests that corticosteroids may also be effective in the treatment of post-COVID organizing pneumonia; however, their role in the treatment or prevention of post-COVID fibrosis is uncertain.

Arguably, the most intriguing prospective treatments for post-COVID fibrosis are the anti-fibrotic agents nintedanib and pirfenidone. Both agents are currently approved for use in idiopathic pulmonary fibrosis, and nintedanib is approved for other forms of progressive fibrotic lung disease. Given their role in stabilizing lung function in patients with interstitial lung disease, these anti-fibrotic agents quickly emerged as potential treatments for patients with persistent ILAs after COVID-19 hospitalization. A small prospective trial published in 2021 suggested that nintedanib may be beneficial in the treatment of COVID-19 pneumonia; however, the long-term impact of anti-fibrotic therapies on patients with persistent lung disease after COVID-19 remains unclear. The high expectations for these agents may be tempered by the fact that prior studies have not shown a progressive fibrotic phenotype in patients with post-COVID fibrosis. The results of the two largest ongoing randomized clinical trials, ENDCOV-I and NINTECOR, are estimated to become available in early 2024.

There are a variety of approaches by pulmonary clinicians at our institution on how to treat patients seen in the clinic with post-COVID ILAs. Most are in agreement that a course of oral corticosteroids is appropriate for the management of secondary organizing pneumonia after COVID-19 infection. Further courses of corticosteroids beyond the treatment of suspected organizing pneumonia are uncommon and are only employed in patients who remain symptomatic and have radiographic features which suggest a steroid-responsive process (e.g., a preponderance of ground glass opacities). Those with significant reticulations, traction bronchiectasis, or honeycombing are rarely treated with additional corticosteroids. The majority of pulmonary clinicians at this institution also do

not typically use anti-fibrotic agents citing the lack of strong evidence supporting their use and the lack of clear data showing disease progression in patients with post-COVID ILAs. In this latter group, most of us adopt a close-monitoring strategy, with follow-up visits 3–4 times per year with pulmonary function testing. Routine CT scans after the initial consultation are rarely done unless there is a change in the patient's symptoms and/or lung volumes.

As clinical trials examining the impact of corticosteroids and anti-fibrotic agents are continuing, the non-pharmacologic treatments used in the treatment of other chronic lung diseases are likely beneficial in the treatment of patients with post-COVID fibrosis as well. A comprehensive approach to treatment including pulmonary rehabilitation, supplemental oxygen, risk factor modification, screening for comorbid conditions, and appropriate vaccinations is required when caring for patients with post-COVID fibrosis.

Some patients may continue to have severe functional or physiologic impairments despite maximal medical therapy. In such refractory cases, lung transplantation can be an effective treatment. There are no consensus criteria for transplant referral or listing; however, many transplant centers utilize the criteria for other progressive fibrotic interstitial lung diseases.

Conclusion

With incomplete vaccination rates and the emergence of new variants of the SARS-CoV-2 virus, COVID-19 remains a global pandemic, responsible for millions of cases and thousands of deaths. While the majority of patients hospitalized with COVID-19 survive to discharge, many experience a significant decline in exercise tolerance and health-related quality of life. In some cases, this functional decline may be the result of persistent ILAs caused by the aberrant injury repair of diffuse alveolar damage. The available evidence suggests that as many as one-third of patients hospitalized with COVID-19 have these radiographic features 6 months after discharge. Many of these patients show gradual radiographic improvement or resolution in longer-term studies; however, some estimates suggest that these ILAs remain persistent in up to one out of every eight hospitalized patients. As the best treatment approach of patients with persistent ILAs after COVID-19 is being elucidated, pulmonary specialists must be prepared to care for these patients for decades to come.

Compliance with Ethical Standards

Conflict of Interest Dr. Robertshaw has no relevant conflicts of interest to report. Dr. Kershaw reports advisory board work for Boehringer Ingelheim.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. World Health Organization. WHO Coronavirus (COVID-19) dashboard | WHO Coronavirus (COVID-19) dashboard with vaccination data, <https://covid19.who.int/>. Accessed 20 Feb 2023.
2. Wang Y, Dong C, Hu Y, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. *Radiology*. 2020;296(2):E55–64. <https://doi.org/10.1148/radiol.202000843>.
3. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77(2):198–209. <https://doi.org/10.1111/his.14134>.
4. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a position paper from the fleischner society. *Lancet Respir Med*. 2020;8(7):726–37. [https://doi.org/10.1016/S2213-2600\(20\)30168-5](https://doi.org/10.1016/S2213-2600(20)30168-5).
5. Guler SA, Ebner L, Aubry-Beigelman C, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J*. 2021;57(4):2003690. Published 2021 Apr 29. <https://doi.org/10.1183/13993003.03690-2020>
6. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–32. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8).
- 7.● Fabbri L, Moss S, Khan FA, et al. Parenchymal lung abnormalities following hospitalisation for COVID-19 and viral pneumonitis: a systematic review and meta-analysis. *Thorax*. 2023;78(2):191–201. <https://doi.org/10.1136/thoraxjnl-2021-218275>. **Largest meta-analysis of post-COVID radiographic findings.**
8. Han X, Fan Y, Alwalid O, et al. Fibrotic interstitial lung abnormalities at 1-year follow-up CT after severe COVID-19. *Radiology*. 2021;301(3):E438–40. <https://doi.org/10.1148/radiol.2021210972>.
9. Pan F, Yang L, Liang B, et al. Chest CT patterns from diagnosis to 1 year of follow-up in patients with COVID-19. *Radiology*. 2022;302(3):709–19. <https://doi.org/10.1148/radiol.2021211199>.
- 10.●● Stewart I, Jacob J, George PM, et al. Residual lung abnormalities following COVID-19 hospitalization: interim analysis of the UKILD post-COVID study [published online ahead of print, 2022 Dec 1]. *Am J Respir Crit Care Med*. 2022. <https://doi.org/10.1164/rccm.202203-0564OC>. **Multicenter prospective cohort study of patients after COVID-19 hospitalization.**
11. Huang W, Wu Q, Chen Z, et al. The potential indicators for pulmonary fibrosis in survivors of severe COVID-19. *J Infect*. 2021;82(2):e5–7. <https://doi.org/10.1016/j.jinf.2020.09.027>.
12. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the development of pulmonary fibrosis using serial thin-section CT and clinical features in patients discharged after treatment for COVID-19 pneumonia. *Korean J Radiol*. 2020;21(6):746–55. <https://doi.org/10.3348/kjr.2020.0215>.
13. Hu ZJ, Xu J, Yin JM, et al. Lower circulating interferon-gamma is a risk factor for lung fibrosis in COVID-19 patients. *Front Immunol*. 2020;11:585647. Published 2020 Sep 29. <https://doi.org/10.3389/fimmu.2020.585647>.
14. Vadász I, Husain-Syed F, Dorfmueller P, et al. Severe organising pneumonia following COVID-19. *Thorax*. 2021;76(2):201–4. <https://doi.org/10.1136/thoraxjnl-2020-216088>.
15. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704. <https://doi.org/10.1056/NEJMoa2021436>.
- 16.●● Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. *Ann Am Thorac Soc*. 2021;18(5):799–806. <https://doi.org/10.1513/AnnalsATS.202008-1002OC>. **First therapeutic trial of corticosteroids in post-COVID fibrosis.**

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.