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Around 15% of patients in the PePS2 study remained on treatment having completed 17–33 cycles of pembrolizumab, showing that a subset of patients with a poor PS can still gain long-term benefits with immune checkpoint inhibitor therapy. Despite these positive outcomes, the short median progression-free survival of 4.4 months and median overall survival of 9.8 months highlight the need to develop improved therapeutic strategies for this population. Additional information should emerge from larger prospective studies to identify biomarkers and clinical stratification factors to assign patients of poor PS to the safest and most effective regimens. The CheckMate 817 study will assess first-line ipilimumab combined with nivolumab in patients with either a poor PS or with a comorbidity (eg, asymptomatic untreated brain metastases, hepatic or renal impairment, HIV),¹⁰ and the eENERGY trial (NCT03351361) will compare first-line ipilimumab plus nivolumab to carboplatin-based doublet chemotherapy specifically in patients with NSCLC of PS2. With the large numbers of patients who have an impaired PS at the time of their initial lung cancer diagnosis, PePS2 and other studies dedicated to the inclusion of this historically trial-ineligible population will hopefully expand immunotherapy treatment options and lead to meaningful improvements in their lives.

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COVID-19 interstitial pneumonia: monitoring the clinical course in survivors

COVID-19 is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first case was identified,¹ the rapid emergence of new cases, admissions to hospital, and deaths required that public health officials focus on prevention through infection control measures, clinicians focus on diagnosis and supportive care, and medical scientists focus on the development of new vaccines and therapeutics. Attention is now turning towards understanding the natural course of COVID-19 in survivors and optimising follow-up to prevent, identify, and treat any undesirable long-term sequelae.

Distinct patterns of disease progression were documented in early clinical descriptions of the first COVID-19 cases.² Many patients with acute COVID-19 have involvement of their respiratory system, characterised by dry cough, dyspnoea, hypoxaemia, and abnormal imaging results.³ Although most patients had mild-to-moderate disease, 5–10% progress to severe or critical disease, including pneumonia and acute respiratory failure.^{4,5} Severe cases can occur early in the disease course but clinical observations typically describe a two-step disease progression, starting with a mild-to-moderate presentation, followed by a secondary respiratory worsening 9–12 days after the first onset of



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symptoms.^{4,6,7} Respiratory deterioration is concomitant with extension of ground-glass lung opacities on chest CT scans, lymphocytopenia, and high prothrombin time and D-dimer levels.⁴

Early evidence supports the hypothesis that some survivors might develop long-term respiratory sequelae. Fibrotic abnormalities of the lung have been detected as early as 3 weeks after the onset of symptoms regardless of whether the acute illness was mild, moderate, or severe.^{3,8-10} Abnormal lung function (ie, restrictive abnormalities, reduced diffusion capacity, and small airways obstruction) has also been identified at the time of discharge from hospital and 2 weeks after discharge.¹¹⁻¹³ These lung function abnormalities appear to be more common among patients whose acute COVID-19 was severe with high levels of inflammatory markers, and are often accompanied by evidence of pulmonary fibrosis including interstitial thickening, coarse reticular patterns, and parenchymal bands.¹²

It is too soon to determine which patients with COVID-19 are at greatest risk for developing long-term pulmonary abnormalities, if such sequelae will resolve, improve, or become permanent, and how the pulmonary abnormalities might be affected by therapeutics such as remdesivir, dexamethasone, and

others under investigation. We hypothesise that most COVID-19 survivors will manifest early pulmonary abnormalities, which could range from being asymptomatic, to mild to severe, and debilitating. We further hypothesise that among patients without pre-existing lung disease, the duration of pulmonary abnormalities will be related to the severity of their acute COVID-19 course, with complete or near complete resolution within 6 months in patients who had a mild course (ie, did not require admission to hospital) and within 12 months in patients who had a moderate course (ie, admitted to hospital but did not require intensive care). However, persistent lung function abnormalities, including restrictive lung disease, decreased diffusing capacity, and fibrosis, are expected in patients who had a severe course, particularly those who required mechanical ventilation. These hypotheses need to be tested, which requires a systematic approach. We call on the pulmonary community to work together to develop a uniform and systematic approach to follow-up of COVID-19 survivors. Such an approach should facilitate research and knowledge generation and, ultimately, improve patient outcomes.

An approach to deciding when it is safe to schedule COVID-19 survivors for elective in-person visits has

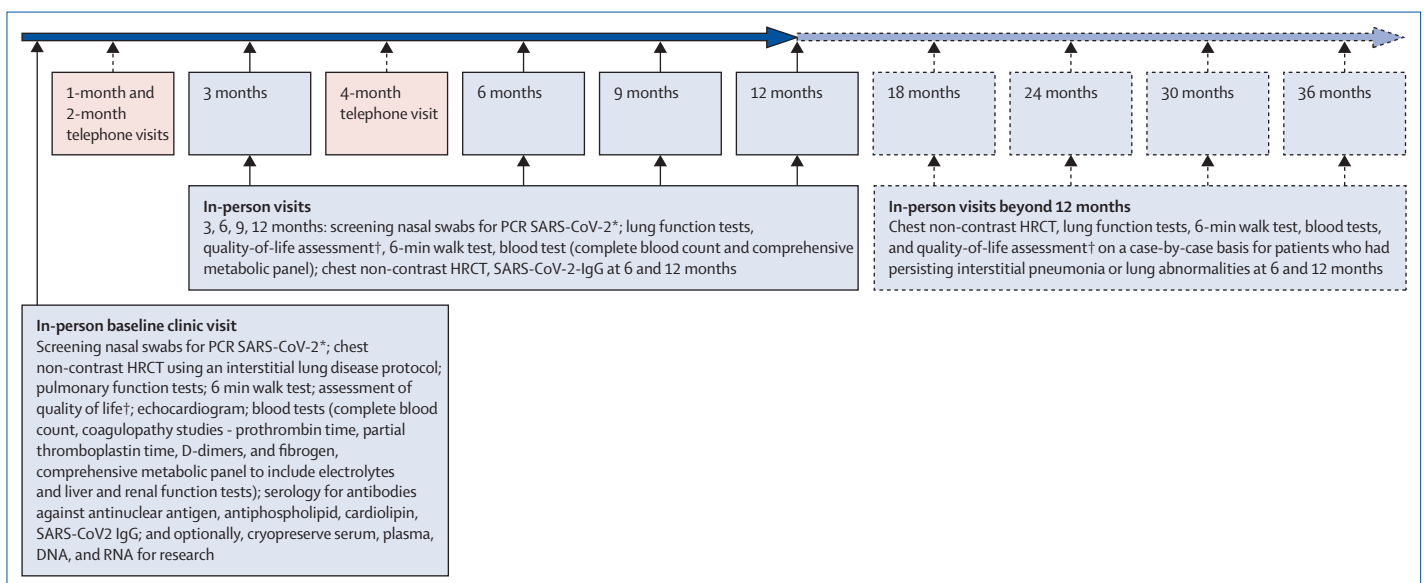


Figure: Suggested follow-up care for COVID-19 survivors

HRCT=high-resolution CT. SARS-CoV-2= severe acute respiratory syndrome coronavirus 2. *Nasal swab testing during the 3–5 days before visit is to make sure that the survivors are not shedding the virus particles and thus ascertain the status of infectivity at baseline and during follow-up visits. The intended in-person baseline and follow-up visits could then be converted to telemedicine visits if found to be positive for SARS-CoV-2, on a case-by-case basis, or appropriate precautionary measures could be taken with personal protective equipment by health-care workers. †Quality of life assessment via patient reported outcomes with standard questionnaires used for respiratory diseases, fatigue, anxiety, and depression.

been published.¹⁴ However, no empirical evidence or consensus exists on how patients should be followed-up. Here, we propose an approach for consideration, which is based upon evolving clinical knowledge, clinical experience and rationale.

The initial in-person visit should target the establishment of a patient's baseline after COVID-19. This process would require a thorough investigation of present and past medical, social, and family history, physical examination, and blood testing, including the following: a complete blood count; comprehensive metabolic panel; coagulopathy studies (prothrombin time, partial thromboplastin time, D-dimers, and fibrinogen); serology for antiphospholipid and anticardiolipin antibodies; SARS-CoV-2 IgG antibody levels; and cryopreservation of serum and plasma, including RNA and DNA for genotype research studies. Additionally, a baseline non-contrast high-resolution CT scan (HRCT), pulmonary function tests (spirometry, lung volumes, and diffusion capacity), 6-min walk test, assessment of quality of life (including fatigue, anxiety and depression) by patient reported outcomes, pulse oximetry on room air at rest and during the 6-min walk test, pulse oximetry with supplemental oxygen if the pulse oximetry on room air is less than 88%, and an echocardiogram should be considered, if resources permit.

Once the COVID-19 survivor's baseline has been established, a follow-up evaluation during a structured protocol visit should aim to better understand the natural course of disease and identify new abnormalities early. A reasonable plan would be to follow-up patients with mild impairment of lung function by phone visits or videoconferencing, or both, at 1, 2, and 4 months and in-person at 3 and 6 months, and subsequently at 9, 12, 18, 24, 30, and 36 months based on the degree and extent of lung involvement and impairment on a case-by-case basis (figure). During the initial 12 months of follow-up, the in-person visits could be accompanied by repeat testing for COVID-19 infectivity, repeat pulmonary testing, 6-min walk test, monitoring of quality of life, fatigue, and some blood testing (eg, complete blood count, comprehensive metabolic panel, coagulopathy studies, and SARS-CoV-2 IgG antibody levels). Imaging by non-contrast HRCT of the chest at the 6-month and 12-month in-person visits could be done to assess improvement, resolution, persistence,

or worsening of any fibrosis. Beyond 12 months, most tests could be ordered on a case-by-case basis, although patients with fibrosis on their 6-month or 12-month HRCT of the chest might warrant additional scans at 24 and 36 months to understand long-term sequelae of interstitial pneumonia or pulmonary fibrosis.

In summary, the varying extent of pulmonary fibrosis and lung function impairment among survivors of COVID-19, and the unknown course of such abnormalities, highlight the need for pulmonary clinicians to closely monitor disease course in survivors. Such follow-up will generate knowledge about the natural course of disease and facilitate enrolment in clinical trials assessing the treatment of abnormalities with immune modulating drugs and antifibrotic drugs.¹⁵ A standard approach from institution to institution will facilitate research and could improve outcomes.

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Gender equity in interstitial lung disease



We have witnessed transformative events in the field of interstitial lung disease over the past decade. Multiple international consensus guidelines have unified our clinical approach and best practices for the diagnosis and management of patients with idiopathic pulmonary fibrosis.¹ The results of positive clinical trials for pharmacological treatments for idiopathic pulmonary fibrosis have also led to renewed hope and enthusiasm for finding a cure for what has traditionally been considered a terminal disease.^{2,3} Similarly, considerable advances have been made in the treatment of systemic sclerosis-associated lung disease and progressive fibrosing interstitial lung diseases with the completion of large multicentre trials and new indications for therapies.^{4–6} Although we acknowledge these advances, we are prompted to reflect on the composition of the teams driving the work forward, viewed through the lens of diversity and growing calls for inclusiveness. Herein we address the issue of gender inequity.

Women are under-represented in leadership roles in the field of interstitial lung disease. This might be because of a historical predominance of men in this field, particularly in its early years. However, during the past decade, the proportion of women doing clinical research in interstitial lung disease has grown, as reflected in the authorship of original papers, narrowing the gender gap. Furthermore, women increasingly are elected as interstitial lung disease representatives in respiratory societies, such as the European Respiratory Society. Despite this, women remain a minority in some positions. We summarised the authorship of major publications from 2010 to 2019 on interstitial lung disease, with a focus on guidelines and large clinical trials, where authorship contribution typically occurs by invitation (appendix). To date, not one published industry-sponsored clinical

trial of pulmonary fibrosis therapy has been led by a woman.^{2–6} Furthermore, the contribution of women to clinical guidelines (the authors of which are usually designated by international societies), is also strikingly rare.⁷

Although gender inequality in medicine might be unintentional, research suggests it is the effect of both implicit and explicit biases.⁷ Sociocultural factors also contribute to gender inequality, especially for women with caregiver and home responsibilities.⁸ The pattern of gender inequity has been consistent across high impact publications, with the magnitude of the gap varying among countries and regions, suggesting that its causes relate more to structural and systemic barriers than to individual preferences.

The paucity of women in leadership roles is a reflection of historical systemic biases in academia and medicine, which lead to, and perpetuate, the so-called glass ceiling and leaky pipeline effects. Although for more than 2 decades at least half of graduating medical students have been women, women still represent a disproportionately small number of medical school deans,⁹ department chairs, and full professors. A robust and growing body of evidence shows gender inequity in conference presentations and authorship of peer-reviewed publications across diverse fields.^{10–13} With increased awareness of this issue, there are evolving and concerted endeavours to improve gender equity in leadership roles within the broad field of pulmonary medicine, and specifically in the field of interstitial lung disease. Notable efforts have been made by different interstitial lung disease representatives (such as organisers of the International Colloquium on Lung and Airway Fibrosis, and the International School for Interstitial Lung Disease) to highlight women leaders, speakers, and session chairs.

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