Post-acute Sequelae of COVID-19 1

Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation

Sally J Singh, Molly M Baldwin, Enya Daynes, Rachael A Evans, Neil J Greening, R Gisli Jenkins, Nazir I Lone, Hamish McAuley, Puja Mehta, Joseph Newman, Petr Novotny, David J F Smith, Stefan Stanel, Mark Toshner, Christopher E Brightling

Although the exact prevalence of post-COVID-19 condition (also known as long COVID) is unknown, more than a third of patients with COVID-19 develop symptoms that persist for more than 3 months after SARS-CoV-2 infection. These sequelae are highly heterogeneous in nature and adversely affect multiple biological systems, although breathlessness is a frequently cited symptom. Specific pulmonary sequelae, including pulmonary fibrosis and thromboembolic disease, need careful assessment and might require particular investigations and treatments. COVID-19 outcomes in people with pre-existing respiratory conditions vary according to the nature and severity of the respiratory disease and how well it is controlled. Extrapulmonary complications such as reduced exercise tolerance and frailty might contribute to breathlessness in post-COVID-19 condition. Non-pharmacological therapeutic options, including adapted pulmonary rehabilitation programmes and physiotherapy techniques for breathing management, might help to attenuate breathlessness in people with post-COVID-19 condition. Further research is needed to understand the origins and course of respiratory symptoms and to develop effective therapeutic and rehabilitative strategies.

Lancet Respir Med 2023

Published Online
May 19, 2023
https://doi.org/10.1016/S2213-2600(23)00159-5

This is the first in a Series of three papers about the post-acute sequelae of COVID-19

Institute for Lung Health, NIHR Leicester Biomedical Research Centre—Respiratory and Infectious Diseases, Leicester, UK (Prof S J Singh PhD, M M Baldwin PhD, E Daynes PhD, R A Evans PhD, N J Greening PhD, H McAuley MBBS, P Novotny MD, Prof C E Brightling PhD); **Imperial College London National Heart and Lung Institute, London, UK** (Prof R G Jenkins MD); **Department of Anaesthesia, Critical Care and Pain Medicine, Usher Institute, The University of Edinburgh, Edinburgh, UK** (N I Lone PhD); **Centre for Inflammation and Tissue Repair, Division of Medicine, University College London, London, UK** (P Mehta MD); **Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK** (J Newman MRCP); **Royal Brompton and Harefield Hospitals, London, UK** (D J F Smith MBBS); **Manchester University NHS Foundation Trust, Manchester, UK** (S Stanel MD); **NIHR Cambridge Biomedical Research Centre, Cambridge, UK** (M Toshner MD)

Correspondence to:
Prof Sally Singh, Department of Respiratory Sciences, University of Leicester, Biomedical Research Centre, Leicester LE3 9QP, UK
ss1119@le.ac.uk

Introduction

Over the first 3 years of the COVID-19 pandemic, worldwide mortality among people infected with SARS-CoV-2 has reduced from a peak of 101 600 deaths per week in January 2021 to 6500 deaths per week in March 2023.[1] Similarly, hospital admissions have reduced—for example, in the UK, 36·7 per 100 000 people were admitted to hospital in January 2021, whereas 10·6 per 100 000 were admitted in March 2023.[2] These improvements are due in part to the availability of effective vaccines, leading to a reduction in the severity of acute illness,[3] and the use of acute treatments such as dexamethasone, anti-interleukin-6 (IL-6) therapies, antivirals, and baricitinib.[4] As with other acute respiratory viral infections that cause acute lung injury, such as SARS-CoV and MERS-CoV,[5,6] long-term sequelae have been described after COVID-19 and are likely to increase in prevalence with increasing survivorship.

The post-acute sequelae of COVID-19 affect multiple organ systems and include a range of symptoms—among them breathlessness (dyspnoea), fatigue, and brain fog (cognitive impairment)—that persist or emerge after SARS-CoV-2 infection. These sequelae are collectively referred to as post-COVID-19 condition or long COVID (the term originally used by people with the condition), which is broadly defined internationally as the persistence of symptoms, usually for 3 months or more, and for at least 2 months, after acute SARS-CoV-2 infection that cannot be explained by an alternative diagnosis.[7] The exact prevalence of long COVID is not known and differs according to how it is measured, the cohort being studied, the SARS-CoV-2 variant, and vaccination status. Triple vaccination against COVID-19 appears to reduce the likelihood of persistent sequelae but does not prevent the development of long COVID. In a UK survey of private households, 4·5%, 4·2%, and 5·0% of triple-vaccinated adults had persistent symptoms 12–16 weeks after confirmed SARS-CoV-2 infection with omicron BA.1, omicron BA.2, and delta variants, respectively.[8]

Risk factors for long COVID include severe acute disease (including receipt of invasive mechanical ventilation), female sex, obesity, socioeconomic deprivation, and pre-existing disease.[9–11] These risk factors were established in high-income countries, but many are mirrored in middle-income and low-income countries where access to services might be compromised.[12,13] Although people with poorly controlled chronic lung disease have an increased risk of severe acute COVID-19 or death,[14,15] those in whom the pre-existing disease is well controlled do not appear to have an increased risk of severe disease, but they often have a worsening of respiratory symptoms after COVID-19. Whether worsening of symptoms in these people is due to destabilisation of the underlying chronic condition or to other COVID-19-related effects is uncertain. Potential mechanisms associated with long COVID include ongoing systemic inflammation (including activation of type I and III interferons and IL-6),[16] autoimmunity, microclotting, hypoadrenalism, and viral persistence.[17–21]

Respiratory symptoms are an important cluster of symptoms defined from a large dataset of published studies of post-acute sequelae of COVID-19.[22] Respiratory symptoms (breathlessness, breathing pattern disorders such as erratic breathing and hyperventilation, and persistent cough) and underlying pulmonary disease (lung

Key messages

- Post-COVID-19 condition (also known as long COVID) is a heterogeneous clinical syndrome that affects multiple organ systems and encompasses pulmonary sequelae and extrapulmonary disruption that can result in persistent disabling breathlessness (dyspnoea)
- The pulmonary sequelae of COVID-19 include thromboembolic disease, with thrombi and microvascular thrombi identified in the pulmonary vasculature; further work is needed to define the underlying mechanisms of chronic vascular disease after COVID-19 to inform diagnostic and therapeutic approaches
- Severe COVID-19 causes alveolar injury and induces profibrotic pathways similar to those seen in IPF, resulting in pulmonary fibrosis, particularly in individuals with genetic susceptibility; therapies that attenuate COVID-19-induced lung injury are likely to mitigate these effects, but long-term outcomes are unknown
- Individuals with well controlled pre-existing respiratory conditions, including mild-to-moderate asthma and COPD, do not appear to be at increased risk of severe COVID-19; however, people with asthma or COPD might have an increase in symptoms after COVID-19
- Extrapulmonary sequelae that might contribute to disabling dyspnoea in people with post-COVID-19 condition include physical deconditioning, and new-onset frailty or prefrailty; a range of factors, including forced inactivity, malnutrition, hypoxia, systemic inflammation, and immune-mediated damage might underlie these sequelae
- Current rehabilitation strategies to manage post-COVID-19 breathlessness have been modified from post-ICU services and chronic respiratory disease practice; common interventions include adapted pulmonary rehabilitation programmes and physiotherapy techniques

COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. IPF=idiopathic pulmonary fibrosis.

For more on **PHOSP-COVID** see https://www.phosp.org/

fibrosis and thromboembolic disease) need to be assessed in clinical care and might require specific interventions. In this Series paper, we first describe the multisystem nature of long COVID before reviewing specific pulmonary sequelae, pre-existing respiratory conditions, and selected extrapulmonary complications that might contribute to post-acute respiratory symptoms. Finally, we consider approaches to pulmonary rehabilitation and evaluate non-pharmacological therapeutic interventions for individuals with disabling dyspnoea after COVID-19.

Post-COVID-19 condition

Breathlessness, fatigue, muscle pain, brain fog, sleep disturbance, and headache are the most prevalent symptoms reported in long COVID, independent of the severity of acute illness (defined according to whether or not hospital admission was required). In a systematic review with an average follow-up time of 126 days, 22·6% of people who required hospital admission and 20·4% of people who did not require hospital admission reported persistent breathlessness.[9,10,23] By contrast, cough, fever, and loss of taste (ageusia) and smell (anosmia) are highly prevalent during acute illness but are less prevalent in post-COVID-19 condition. Clustering of individual symptoms has generally not led to the identification of disease-specific clusters of symptoms, except for a potential respiratory cluster dominated by shortness of breath and chest pain.[10] Nevertheless, in a meta-analysis of 54 published studies and two medical record databases,[22] respiratory symptoms (dyspnoea and persistent cough) were identified as an important cluster alongside fatigue and cognitive problems. By contrast, clusters in the PHOSP-COVID (Post-hospitalisation COVID-19 study) cohort were mostly defined by the burden of symptoms and ongoing health impairments, and symptom severity was positively associated with the total number of symptoms.[9] The more severe symptom clusters in PHOSP-COVID were also associated with lower exercise tolerance,[9] and people in these clusters were less likely to have returned to work 6 months after hospital admission.[24] There were intriguing associations between obesity and ongoing systemic inflammation, with elevated blood C-reactive protein and IL-6 concentrations in the more severe clusters compared with the mild cluster, highlighting different phenotypes and potential therapeutic targets.[25]

Although it is helpful to define a group of people who have not recovered on the basis of ongoing symptoms, we need to further understand the precise mechanisms that underlie symptoms, ongoing organ impairment, and the relationship between symptoms and organ damage and pathology. Acute lung injury is the dominant insult in severe acute COVID-19 (ie, in patients requiring hospital admission for respiratory support), in contrast to mild-to-moderate acute COVID-19 (in patients not requiring hospital admission), and any post-COVID-19 sequelae might differ between these groups, requiring specific assessments and interventions.

During the first quarter of 2020, around one in six immune-naive patients who were admitted to hospital with COVID-19 developed severe disease requiring an intensive care unit (ICU) admission, with the majority requiring respiratory support (non-invasive or invasive mechanical ventilation).[26] The current risk of developing severe COVID-19 in immune-naive patients is less clear owing to the increase in SARS-CoV-2 exposure and the difficulty of ascertaining a true immune-naive population. Nevertheless, similar to other critical illnesses, severe COVID-19 can leave patients with long-term morbidity involving any organ system and affecting health-related quality of life and wellbeing. These consequences might be related to the underlying disease process itself or to treatments administered in the ICU to facilitate life-support therapies, or both.

In PHOSP-COVID, a large, multicentre follow-up study of patients admitted to hospital with COVID-19, those who required invasive mechanical ventilation were less likely to report full recovery at 6 months after discharge than were those who required supplemental oxygen only (18·8% *vs* 36·3%), confirmed in analyses that adjusted for differences in patient characteristics.[24] In unadjusted comparisons, those requiring invasive mechanical ventilation also had lower physical performance (percentage of predicted incremental shuttle walk test distance 39·4% *vs* 50·1%) and worse lung physiology measured by spirometry and pulmonary diffusion capacity than did those who did not receive mechanical ventilation.[24] However, severity of acute COVID-19 illness was not associated with clusters representing phenotypes of patient-reported recovery, supporting the idea that some of the mechanisms that underlie post-COVID-19 condition are not directly related to acute lung injury. Furthermore, in a follow-up study of patients who were admitted to hospital with COVID-19, improvements in symptoms were noted at 2 years, but the symptom burden remained high for those who received ventilatory support in hospital compared with a control group without previous SARS-CoV-2 infection.[27]

Most critically ill patients with COVID-19 disease develop an extensive inflammatory insult that is driven by COVID-19 pneumonitis leading to acute respiratory distress syndrome (ARDS). ARDS is an inflammatory lung injury that leads to increased vascular permeability, which can be caused by various acute insults, only one of which is viral pneumonia.[28] A well developed evidence base has described the sequelae of ARDS in the pre-pandemic era, which can provide insights into recovery trajectories for patients with COVID-19-associated ARDS, given the currently limited evidence base for this group of patients. Follow-up studies show that people who survive ARDS can have substantial long-term respiratory morbidity. Reports detailing pulmonary evaluation have most frequently identified mild-to-moderate reductions in pulmonary diffusion capacity at 1-year follow-up in patients with non-COVID-19-related ARDS.[29] Reduced exercise capacity, most commonly measured with the 6-min walk test, is evident in cohorts of patients with ARDS, improving from 60–71% of predicted distance at 12 months to 71–76% of predicted distance at 5 years after hospital discharge.[30]

An important feature of the non-COVID-19 ARDS literature is the broader impact of post-acute sequelae on patients and their families. The consequences of critical illness extend beyond the respiratory system and might contribute to the increased incidence of physical and mental health impairments,[31] impaired quality of life,[32] socioeconomic effects as a result of not being able to work,[33] and broader effects on the family unit (eg, if family members have to adopt caregiver roles) after discharge from the ICU.[34] Data on long-term outcomes and the course of recovery after COVID-19 are limited; however, in the UK (table) and elsewhere, major research funding has been allocated to understand the determinants, clinical and biological features, underlying mechanisms, and natural history of post-COVID-19 condition, to explore its wider health, social, and economic effects, and to develop strategies for management and support.

Pulmonary sequelae of COVID-19

There is growing awareness of an increased risk of thromboembolic disease and lung fibrosis in survivors of COVID-19, both of which could contribute to persistent breathlessness.[35] At present, insufficient evidence exists for an increased incidence of other chronic respiratory diseases after COVID-19.[36,37] Here, we review evidence on the incidence and mechanisms of pulmonary fibrosis and thromboembolic disease after COVID-19, and discuss potential preventive and therapeutic treatment options. We also evaluate the effects of pre-existing respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), on post-COVID-19 outcomes.

Pulmonary fibrosis

Evidence of long-term pulmonary disease following coronavirus disease in previous pandemics[38,39] and following ARDS,[40] as well as mechanistic similarities between COVID-19-related pneumonia and idiopathic pulmonary fibrosis (IPF; figure 1),[41] raise the possibility of a substantial global burden of long-term fibrosis resulting from SARS-CoV-2 infection.

Severe COVID-19 is associated with a high level of alveolar injury that can continue even after viral clearance.[42] Such pathological changes might be caused by direct viral infection or, more commonly, by immune-mediated injury to alveolar cells,[43] causing a pattern of diffuse alveolar damage.[44,45] Augmented molecular signalling from epithelial to immune cells further perpetuates tissue damage, lung injury, and disease progression.[46,47] IPF also results from alveolar injury,[48] and shares genetic, molecular, and epidemiological risk factors with severe COVID-19 disease. Of the 19 genes known to increase the risk of IPF, several have been associated with more severe COVID-19, including *DPP9*, although *MUC5B* and *ATP11A* are associated with reduced severity.[49,50] COVID-19 is caused by the binding of the SARS-CoV-2 virus to the ACE2 receptor. This leads to internalisation of the ACE2 receptor and, consequently, increased profibrotic angiotensin 1 and 2 signalling, as well as enhanced alveolar TGF-β signalling, which are known to stimulate fibrotic pathways such as fibronectin production, collagen synthesis, and fibroblast proliferation.[51,52] Furthermore, high levels of collagen-secreting CTRHC1^{+} fibroblasts are associated with severe acute fibrosis and fatal outcomes in COVID-19.[53]

The role of immune cells is also likely to be important. Raised concentrations of eosinophils, mast cells, and lymphocytes, particularly CD8^{+} cells, have been correlated with poorer lung function and increased

	Aims	Study design	Population and target n	Setting of acute COVID-19 and follow-up
Coronavirus Post-acute Long-term Effects: Constructing an Evidence Base (CONVALESCENCE; IRAS 297578)	To define long COVID, its determinants, and health, social, and economic consequences; to assess GP adherence to NICE diagnosis and management guidelines	3-year longitudinal study using data from existing population cohorts and electronic health records; a substudy will focus on deep phenotyping; part of the COVID-19 Longitudinal Health and Wellbeing National Core Study	Participants from existing studies and health records; 300–350 participants from existing population cohorts will be recruited for the deep phenotyping substudy, including those with long COVID and controls	Follow-up of hospitalised and non-hospitalised individuals
Therapies for Long COVID in non-hospitalised individuals (TLC; ISRCTN15674970)	To evaluate symptom burden and underlying pathophysiology of long COVID syndromes in adults with a previous diagnosis of COVID-19 who were not admitted to hospital, and to assess potential therapies	1-year population-based cohort study using monthly self-reported data on symptoms, quality of life, and work capability from primary care records; statistical clustering methods will be used to identify distinct long COVID symptom clusters; a substudy will focus on immune function, proteomic and genomic profiles, and physical health measures	4000 adults with past SARS-CoV-2 infection, confirmed by PCR test, and 1000 matched controls identified using GP records and the CPRD; individuals from the four most prevalent symptom clusters and two control groups will be invited to take part in the deep phenotyping substudy	Community-based cohort; self-reported data will be collected on a digital platform; substudy samples will be collected at a clinical research facility or at the participant's home
Real-time Assessment of Community Transmission Long COVID (REACT LC; IRAS 298404)	To understand the natural history and long-term sequelae of SARS-CoV-2 infection; to characterise genetic, biological, social, and environmental factors that underpin long COVID	3-year prospective longitudinal study; part of the wider REACT programme	>120 000 participants (aged ≥5 years) from REACT-1 and REACT-2 studies; 30 000 of these participants will have past SARS-CoV-2 infection confirmed on PCR or lateral flow tests; 8000 participants with past SARS-CoV-2 infection, including 4000 with long COVID, will undergo detailed clinical phenotyping investigations	Community-based cohort
The Post-hospitalisation COVID-19 study (PHOSP-COVID; ISRCTN10980107)	To understand the long-term health outcomes for patients who have been admitted to hospital with COVID-19, including detailed recording of symptoms, and physiological and biochemical testing; to investigate the effect of rehabilitation (PHOSP-R) on long COVID symptoms	Prospective longitudinal study involving 83 NHS hospitals	10 000 adults discharged from hospital after acute COVID-19; 3000 participants will undergo detailed clinical phenotyping investigations; PHOSP-R aims to recruit 132 participants with persistent symptoms >12 weeks after hospital discharge	Follow-up of hospitalised adults, including patients admitted to the ICU
Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and Transform Existing Integrated Care Pathways (STIMULATE-ICP; ISRCTN10665760)	To evaluate the effects of current interventions, including multiorgan MRI (Coverscan) and a rehabilitation app (Living with COVID Recovery), on their own and in combination with drug therapies (anticoagulant, anti-inflammatory, and antihistamine agents) on long COVID symptoms and outcomes	2-year pragmatic, cluster-randomised trial; the effect of drug therapies *vs* usual care will be assessed in a nested adaptive platform phase 3 trial	>4500 adults with persistent COVID-19 symptoms for >4 weeks after acute SARS-CoV-2 infection; participants will be recruited on their first visit to a long COVID clinic	Community-based cohort; follow-up assessment visits will take place at 12 and 24 weeks after the baseline visit

CPRD=Clinical Practice Research Datalink. GP=general practitioner. ICU=intensive care unit. NHS=National Health Service. NICE=National Institute for Health and Care Excellence.

Table: **Summary of major funded studies investigating post-COVID-19 condition in the UK**

radiological abnormalities after COVID-19.[54] Neutrophil responses are also likely to be involved in fibrosis: increased neutrophil extracellular traps (NETs) have been identified in the serum of patients in the early post-acute phase,[55] and exogenous NETs promoted fibrogenesis in epithelial cells, even though direct infection with SARS-CoV-2 did not promote fibrogenesis in an epithelial cell model.[56]

Severe COVID-19 and IPF are more common in men and older individuals, and both conditions are associated with a range of comorbidities including obesity, type 2 diabetes, hypertension, and ischaemic heart disease.[57–59] Similarly, biomarkers that have been associated with progressive IPF, such as MMP7,[60] have also been found to be elevated in people with post-COVID-19 condition who have poorer lung function.[61] Notably, patients with IPF who contract COVID-19 are more likely to have poor clinical outcomes.[62]

Organising pneumonia is the radiological pattern that is most commonly seen in COVID-19, with subsequent fibrotic remodelling occurring in some cases.[63,64] Persistent radiological abnormalities 1 year after COVID-19 pneumonia can range from limited ground-glass opacity and subpleural reticulation to more extensive ground-glass opacity, traction bronchiectasis, and honeycombing.[65] This pattern is more prevalent among patients who are admitted to hospital, and current evidence suggests that up to 55% of these patients have persistent changes in the months following infection, although estimates vary widely.[64,66–69] A multicentre cohort study is underway to determine the prevalence of post-COVID-19 fibrosis and to identify risk factors over a longer time span in patients admitted to hospital and in those managed in the community.[70] Preliminary analysis suggests that around 7% of patients admitted to hospital with COVID-19 will have residual lung abnormalities on

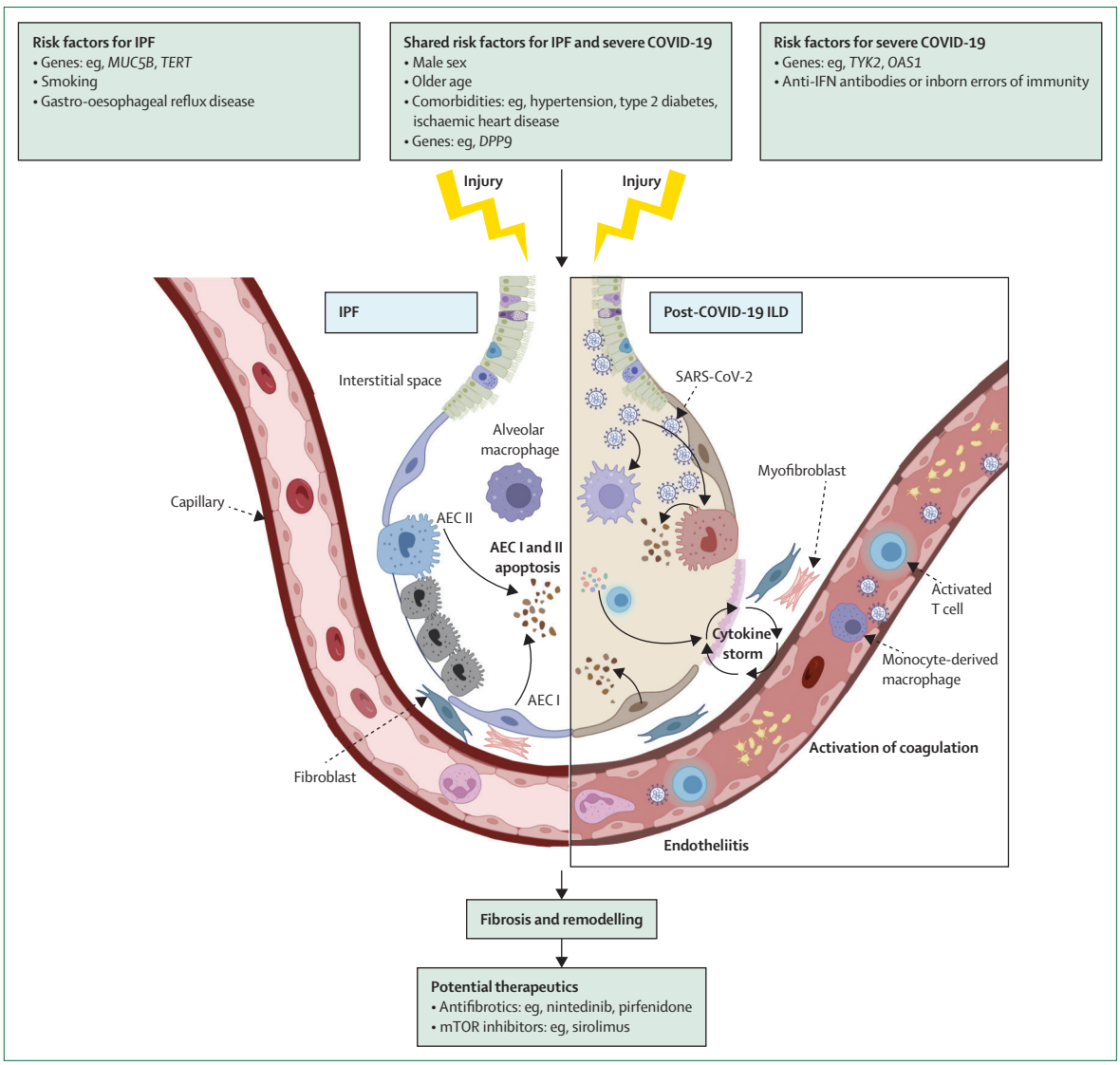

Figure 1: **Shared risk factors and mechanisms in IPF and post-COVID-19 ILD**
COVID-19 and IPF share several risk factors, including demographic and genetic factors and comorbidities. Furthermore, severe COVID-19 causes alveolar injury and activates profibrotic pathways similar to those observed in IPF. In IPF, resident cell populations are changed, with loss of AEC type I and development of a new subpopulation of aberrant transitional cells. In both IPF and post-COVID-19 ILD, apoptosis of AEC type I and type II occurs. In post-COVID-19 ILD, SARS-CoV-2 can directly infect AEC type II, leading to macrophage activation and recruitment of immune cells, causing sustained production of proinflammatory cytokines (ie, a cytokine storm). This proinflammatory response causes AEC and endothelial cell damage, resulting in fibroblast activation and the incorporation of collagen-rich extracellular matrix in the interstitial space. In genetically susceptible individuals, COVID-19 induction of profibrotic pathways has the potential to lead to pulmonary fibrosis. Treatments that reduce COVID-19-induced lung injury are likely to mitigate these effects, but long-term outcomes are yet to be determined. AEC=alveolar epithelial cells. *DPP9*=dipeptidyl peptidase 9. IFN=interferon. ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. mTOR=mammalian target of rapamycin. *MUC5B*=mucin 5B, oligomeric mucus/gel-forming. *OAS1*=2′-5′-oligoadenylate synthetase 1. *TERT*=telomerase reverse transcriptase. *TYK2*=tyrosine kinase 2. Adapted from Mehta and colleagues,[41] by permission of Springer-Verlag. Figure originally created using BioRender.com.

CT within the first 12 months, with some, albeit limited, evidence of a slow resolution during the first year.[35] Thoracic CT changes over time following hospital admission for COVID-19 in three patients are shown in figure 2.

Considerable progress has been made in the treatment of severe COVID-19-related pneumonia, which might reduce the risk of long-term fibrosis. Most treatments that are proven to reduce COVID-19 severity target the immune system. Corticosteroids (dexamethasone and methylprednisolone) are often used to treat organising pneumonia and ARDS,[71,72] and have been shown to reduce mortality in severe COVID-19.[64,73,74] Dexamethasone might limit the development of lung fibrosis by mitigating the development of severe lung injury. The mechanisms by which dexamethasone prevents lung injury are proposed to involve inhibition of neutrophil-derived type 1 interferon signalling,[75] which has been

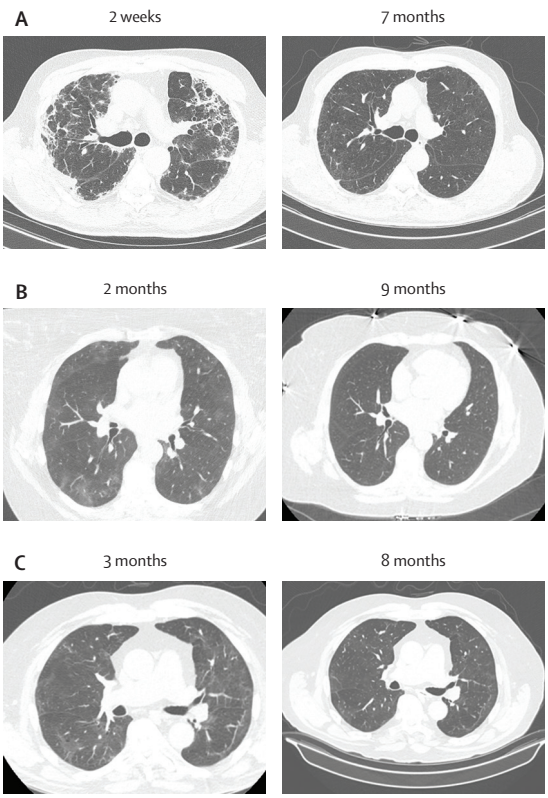

Figure 2: **Thoracic CT changes following hospital admission for acute COVID-19**

COVID-19 is associated with a range of changes on acute and follow-up thoracic CT scans. Thoracic CT scans shown here were acquired after discharge from three patients who had been admitted to hospital with COVID-19 (WHO Clinical Progression Scale ≥5). (A) CT scan from a 66-year-old man acquired 2 weeks after discharge shows initially diffuse ground-glass opacification with consolidation and interlobular septal thickening (left panel), with resolution of changes on CT imaging 7 months after discharge (right panel). (B) CT scan from a 55-year-old woman acquired 2 months after discharge shows predominantly peripheral bilateral ground-glass opacification (left panel), with resolution of changes on CT imaging 9 months after discharge (right panel). (C) CT scan from a 71-year-old man acquired 3 months after discharge shows initially diffuse ground-glass opacification and fibrosis (left panel), with partial resolution of changes and persistent fibrosis on CT imaging 8 months after discharge (right panel).

proposed to drive the development of profibrotic macrophages.[76] There are no placebo-controlled trials of steroids in post-COVID-19 interstitial lung disease (ILD), although an open-label study of high-dose (40 mg reducing to 10 mg) versus low-dose (10 mg stable dose) steroids showed that only 16 of 65 (24·6%) patients responded to the high-dose regimen, which was not significantly different from the response rate for the low-dose regimen (12 of 65 patients; 18·5%).[77] The use of steroids in COVID-19 ILD is extrapolated from the management of other inflammatory ILDs, and high bronchoalveolar lavage fluid lymphocyte counts might be a marker of corticosteroid responsiveness.[78–80] Raised bronchoalveolar lavage fluid lymphocyte counts have been found in 74·7% of patients with acute COVID-19 and are linked to increased disease severity.[81] The timing of steroid administration might be important, with the greatest reduction in mortality seen when dexamethasone is given after the first week of illness.[73,82,83] There is no proven benefit of administration in mild COVID-19.[73]

Anti-IL-6 agents, such as tocilizumab and sarilumab, appear to offer a survival benefit compared with usual care in critically ill patients with severe COVID-19.[84–86] Use of the JAK inhibitor baricitinib reduces mortality compared with usual care (with or without remdesivir and corticosteroids) and improves recovery time in patients admitted to hospital.[87,88] Experimental models suggest that anti-IL-6 and JAK inhibition therapies might also be beneficial in IPF.[89,90] Bioinformatic analysis has suggested that drugs with antifibrotic activity, including mTOR inhibitors and nintedanib, might be of value in treating COVID-19[91] and are currently being investigated in clinical trials (NCT04948203, NCT04856111, NCT04607928, NCT04541680, and NCT04619680).

Pulmonary emboli and microvascular thrombi

The causal association between COVID-19 and acute thromboembolic disease is well established. In the acute phase, vascular endothelial dysfunction, a hyperinflammatory immune response, and a hypercoagulant state predispose patients to developing venous thromboses.[92] COVID-19-associated coagulopathy potentially involves multiple pathways and mechanisms, including NETs, complement activation, platelet dysfunction, an imbalance of fibrinolysis, protein C, and antiphospholipid antibodies.[93] Remaining gaps in understanding of the pathogenesis of COVID-19-associated coagulopathy must be addressed to inform improvements in diagnostics and potential therapeutics.

The incidence of pulmonary embolism varies considerably between COVID-19 cohorts in different settings and correlates with disease severity. In patients admitted to hospital but not requiring ICU support, the incidence of pulmonary embolism is estimated to be between 0·9% and 3·4%.[94,95] In patients admitted to the ICU, the incidence of pulmonary embolism ranges from about 8%[96] to 59% in those with severe COVID-19 requiring extracorporeal membrane oxygenation.[97] Rates in people not admitted to hospital are lower but still significant.[98] Pulmonary embolism risk continues in the non-acute stage: the pooled cumulative incidence across studies is 1·5% during short-term follow-up[99] and is still elevated at 8 weeks or more from diagnosis.[100]

Significant risk factors for the development of venous thromboembolic complications in the context of acute COVID-19 include male sex, older age, receipt of mechanical ventilation, raised C-reactive protein, and raised D-dimer.[101,102] The development of thromboembolic disease, in turn, is a risk factor for increased adverse outcomes, including ICU admission, mechanical ventilation, and longer median hospital admissions.[102] In the longer term, there is evidence of incomplete

thrombus resolution despite anticoagulant treatment, with 30% estimated to be unresolved at 105 days.[103]

In the non-pandemic setting, chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially life-limiting complication of pulmonary embolism that occurs in about 4% of patients who survive an episode of acute pulmonary embolism. Despite the high numbers of patients with COVID-19-related pulmonary emboli globally, an increase in CTEPH has not been reported. A UK study of referrals to a national specialist centre did not find an increase in the incidence of CTEPH over 12 months or detect a single case that was clearly associated with COVID-19.[104] Given that the median lag time from index pulmonary embolism to CTEPH diagnosis has historically been 12·5 months,[105] it is possible that this chronic disease is yet to manifest at scale.

The apparent lack of COVID-19-related CTEPH might be due to the clot burden affecting more distal segmental anatomical locations within the pulmonary vasculature, which has been reported in several studies.[101–103] There is evidence that subsegmental disease could represent in-situ thrombosis (immunothrombosis) due to local inflammation.[106,107] Immunothrombosis, as opposed to thromboembolism arising from distal deep-vein thromboses, is suggested as a likely mechanism because most COVID-19-related pulmonary emboli do not present with concurrent deep-vein thromboses.[108] The prognostic and treatment implications of this phenotypically distinct process, compared with classic thromboembolus, are unclear. Moreover, the balance of future risk of re-thrombosis has not been defined.

Even in the absence of demonstrable CTEPH, patients might have chronic symptoms and clinically relevant biomarkers that meet the definition of persistent pulmonary embolism impairment.[109] This emerging syndrome has a 2-year cumulative incidence of 16% after pulmonary embolism in a non-COVID-19 context.[110] The incidence and relevance of persistent pulmonary embolism impairment following COVID-19-related pulmonary embolism are unknown at present.

Some evidence implicates the involvement of microvascular thrombi in post-acute COVID-19 morbidity. In-situ thrombi or microthrombi are more frequently reported than are pulmonary emboli in autopsy studies.[111] Endothelial damage in the form of inflammation or necrosis are commonly reported pathological[111,112] and electron microscopy findings in autopsy studies of patients with COVID-19.[113] Alveolar gas transfer abnormalities on hyperpolarised ^{129}Xe MRI have been demonstrated in chronically symptomatic patients with normal CT imaging months after the acute illness.[114] Dual-energy CT has also been used to quantify perfusion abnormalities that were not apparent on visual assessment of contrast-enhanced CT.[115] Imaging studies have shown evidence of concurrent pathological processes including embolic disease in the macrovasculature alongside smaller vessel disease.[97] Fibrinolysis-resistant, anomalous amyloid microclots have been identified in the plasma of patients with persistent post-COVID-19 symptoms but with normal routine coagulation profiles.[116]

There is a pressing need to clarify the extent of vascular involvement, especially in the post-acute phase of COVID-19, specifically because this could inform therapeutic options for ongoing and prospective clinical trials. Further research is also needed to define the incidence, mechanisms, diagnostics, and treatment of chronic pulmonary vascular disease following COVID-19. With regard to treatment, the HEAL-COVID trial (Helping Alleviate the Longer-term Consequences of COVID-19; NCT04801940) recently reported that 2 weeks of anticoagulant therapy with apixaban initiated at hospital discharge for COVID-19 is not an advantageous addition to the standard of care in terms of hospital re-admissions or mortality.[117] However, the therapy in this study was prescribed to individuals with clinical equipoise and not specifically to those with an established clinical indication for anticoagulation. An active multicentre trial, STIMULATE-ICP (Symptoms, Trajectory, Inequalities and Management: Understanding Long COVID to Address and Transform Existing Integrated Care Pathways; ISRCTN10665760), which is comparing the efficacy of 12 weeks of anticoagulant, anti-inflammatory, and antihistamine therapy in post-COVID-19 condition, will provide further insight into therapeutic options in this population.

For more on **HEAL-COVID** see https://heal-covid.net/

For more on **STIMULATE-ICP** see https://www.stimulate-icp.org/

Obstructive lung disease and COVID-19

With respect to airways disease in 2020–21, many countries saw a reduction in asthma and COPD exacerbations, possibly due to reduced exposure to respiratory infections as a consequence of public health measures introduced to stop the spread of COVID-19. In people with well controlled mild-to-moderate asthma, systematic reviews have not shown an increased risk of severe COVID-19[37] and, overall, people with well controlled asthma are not at increased risk of COVID-19-related death.[14,37] However, the risk of COVID-19-related death was increased in people with asthma who had recently needed oral corticosteroids for their asthma[14] or had been admitted to hospital with severe asthma,[118] and in people with other chronic respiratory diseases (this disease grouping included individuals with COPD, fibrosing lung disease, bronchiectasis, or cystic fibrosis).[14] After hospital admission for COVID-19, individuals with pre-existing conditions have an increased risk of adverse respiratory sequelae,[119] including an increased risk of death from lower respiratory tract infection and other respiratory complications.[120] Among people admitted to hospital or managed in the community for COVID-19, increased respiratory symptoms and increased inhaler use after COVID-19 have been reported in those with asthma or COPD, but whether this is due to a worsening of asthma or COPD control or to post-COVID-19-related symptoms is unclear.[121]

Several studies have included serial lung function testing up to 1 year after COVID-19.[24,122–127] The group mean data from these studies consistently show a normal ratio of FEV_1 to forced vital capacity, with a normal forced expiratory flow rate between 25% and 75% of maximum when reported. The largest of these studies reported that 10% of participants had evidence of airflow obstruction, but this was in keeping with the proportion that had pre-existing obstructive lung disease.[125] By contrast, most of these studies reported abnormal lung diffusion in approximately a third of patients. Similarly, imaging studies have identified abnormalities in thoracic CT in up to 25% of cases after 1-year follow-up.[69] In people with persistent dyspnoea at 6 months after COVID-19 with normal thoracic CT and lung function, exploratory hyperpolarised ^{129}Xe MRI has shown damage to the alveolar–capillary interface, possibly contributing to their breathlessness,[114] but again suggesting that this is not due to new obstructive lung disease.

Post-infective bronchiectasis might be predicted following COVID-19. In contrast to the 2009 H7N9 influenza A pandemic, when bronchiectasis was reported in 24% of survivors,[128] bronchiectasis was rarely observed after SARS-CoV infection and was present in about 1% of cases 1 year after COVID-19 in a study from Wuhan, China.[126] Intriguingly, SARS-CoV-2 viral entry and replication is impaired in cystic fibrosis airways owing to ACE2 downregulation mediated by dysfunctional cystic fibrosis transmembrane conductance regulator.[129] This is consistent with the observation that having cystic fibrosis is not a risk factor for acute severe COVID-19 disease and that lung function is stable after infection compared with pre-existing disease.[130,131]

Extrapulmonary sequelae of COVID-19

Extrapulmonary sequelae of COVID-19 are wide-ranging, affecting multiple organ systems. We highlight extrapulmonary features of long COVID that might contribute to breathlessness and breathing pattern disorders and could be targeted as part of comprehensive therapeutic and rehabilitative strategies.

Reduced exercise tolerance

As for many other long-term conditions, reduced exercise tolerance is an important factor in the symptoms and functional limitations seen after COVID-19. The mechanisms that contribute to this reduction in exercise tolerance are not known, but bed rest in otherwise healthy individuals results in rapid-onset muscle wasting,[132] reduced muscle endurance, and denervation.[133,134] Even more profound muscle loss is seen in the inpatient hospital setting, particularly in ICUs, where the additional mechanisms of inflammation, hypoxia, and nutritional imbalance might be involved.[135,136] Thus, it is likely that deconditioning contributes to the reduction in exercise tolerance seen after COVID-19. The potential role of deconditioning has been explored using cardiopulmonary exercise testing, which shows response patterns that are consistent with the presence of reduced muscle aerobic capacity.[137,138] In a Norwegian cohort, 12 months after hospital discharge for COVID-19, the most prevalent exercise limitation was deconditioning, defined as a percentage of predicted peak oxygen uptake of less than 80% in the absence of a ventilatory limitation and with no evidence of cardiocirculatory pathology. Reductions in the capacity for aerobic ATP generation usually occur with a reduction in the gas-exchange threshold, meaning that aerobic mechanisms of energy provision are supplemented with less efficient anaerobic mechanisms at a lower level of oxygen uptake. When the gas-exchange threshold is exceeded, the oxygen cost of exercise is increased, causing an increase in ventilation and consequently the sensation of breathlessness. Prolonged symptoms of fatigue and breathlessness commonly continue into the post-acute phase of COVID-19, and propagate a downward spiral of further inactivity, decreasing exercise tolerance, increasing sedentary behaviour, and further worsening of deconditioning and symptoms.[24]

Frailty

Physical deconditioning leads to associated loss of muscle mass and strength, which could have profound consequences, especially in elderly individuals, predisposing them to physical frailty. Frailty refers to an increased risk of adverse health outcomes due to reduced resistance to stressor events.[139] COVID-19, as with other acute infectious diseases, provides a stressor that has been both severe and extremely widespread among individuals who were frail before their illness or who are at risk of becoming frail. Early studies indicate that 20% of COVID-19 survivors will have or will be at risk of frailty[140] and, as in chronic respiratory diseases, frailty is closely associated with the degree of dyspnoea.[141]

The clinical management of frailty relies on the identification of individuals living with frailty and, more widely, those at risk of developing frailty. The comprehensive geriatric assessment[142] provides a well established framework from which assessments can be made, although modifications in focus might be important given the younger age demographic and more specific stressor event for COVID-19 survivors living with frailty.[143] Key domains that should be assessed include physical inactivity, weakness, polypharmacy, low mood, and social isolation, with clear pathways and management strategies available for onward referral.[140] Wider recognition of social inequality is also crucial in the review of people after COVID-19, because it is a major risk factor for both infection[144] and the presence of physical frailty.[143]

Recent evidence has indicated that unintentional weight loss is the most common contributor to the physical frailty phenotype in the first 6 months after hospital admission for COVID-19, highlighting the need for nutritional assessment and intervention.[143] However, this should be

considered in the context of a raised BMI in many people who are admitted to hospital with COVID-19,[24] so simply increasing nutritional intake is not the solution. Other drivers of frailty in this cohort include dyspnoea, low physical activity, and muscle weakness.[112,143] These findings combined with other data highlighting the high frequency of persistent breathlessness, muscle weakness, and fatigue,[69] as well as low mood and cognitive impairment,[24] indicate that a comprehensive assessment with provision for interventions addressing these areas would be optimal.

The potential contribution of pulmonary and extrapulmonary sequelae described in this Series paper to breathlessness in COVID-19 survivors is shown in figure 3. Non-pharmacological interventions might help to attenuate the disabling sensations of breathlessness in people with post-COVID-19 condition.

Assessment of breathlessness and altered breathing patterns

Breathlessness is a complex symptom that is inconsistently predicted from measures of lung function. In cases with a pathologically driven deficit, treatment with bronchodilators, for example, does not necessarily ameliorate breathlessness. The complexity of breathlessness has been described in the Breathing, Thinking, Functioning clinical model,[145] which acknowledges that this debilitating symptom can be influenced by physiology (including pre-existing respiratory conditions), anxiety, previous experiences of breathlessness, and the level of function (including deconditioning). Importantly, the relative contribution of all these factors can vary between individuals. This model was developed for chronic respiratory disease but resonates for those with breathlessness after COVID-19.

The treatment of breathlessness should be guided by a detailed assessment that includes routine spirometry; however, there has been a paucity of data on lung function after COVID-19 owing to pandemic restrictions and the need for personalised protective equipment in health-care settings. Even one of the largest cohort studies of patients admitted to hospital performed lung function tests in only 349 (20·1%) of 1733 participants at 6 months after discharge,[27] and testing is likely to be biased towards adults with a clinical indication, including those with pre-existing

For more on the **Breathing, Thinking, Functioning model** see https://www.btf.phpc.cam.ac.uk/

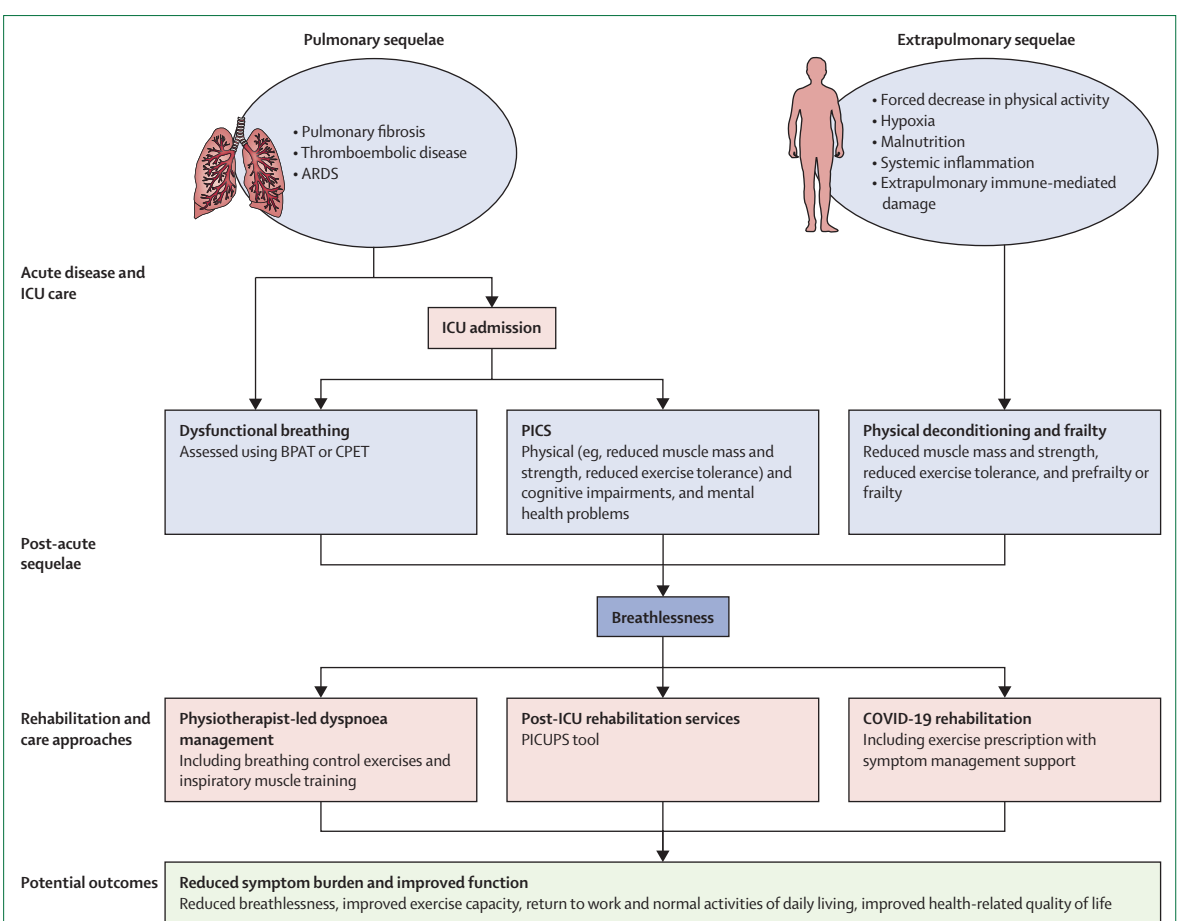

Figure 3: **Potential origins of persistent breathlessness and proposed rehabilitation and care approaches**
ARDS=acute respiratory distress syndrome. BPAT=Breathing Pattern Assessment Tool. CPET=cardiopulmonary exercise test. ICU=intensive care unit. PICS=post-intensive care syndrome. PICUPS=Post-ICU Presentation Screen.

respiratory disease. The assessment should also include validated questionnaires; the Borg Breathlessness Scale or MRC Dyspnoea Scale are commonly used, but do not capture the sensations of breathlessness such as muscle work or effort, mental effort, air hunger, chest tightness, and hyperventilation. By contrast, questionnaires such as Dyspnoea-12 or the Multi-Dimensional Dyspnoea Profile explore the multidimensional components of breathlessness.[146,147] Cardiopulmonary exercise testing might also be indicated in cases of diagnostic uncertainty relating to breathlessness, and more complex investigations such as MRI and electromyography might be considered. Hyperpolarised ^{129}Xe MRI can be used to identify changes in gas transfer and tissue plasma abnormalities that might contribute to the breathlessness presentation,[148] whereas electromyography has been used to demonstrate increased inspiratory muscle activation after COVID-19, which might indicate underlying interstitial pathology, myopathy, deconditioning, or anxiety.[149]

Acute COVID-19 can lead to altered breathing patterns, with small cohort studies reporting altered breathing patterns in almost 20% of people admitted to hospital with COVID-19 and a slightly greater proportion of people not admitted to hospital being referred to specialist follow-up clinics.[150,151] Breathing pattern abnormalities can be attributed to changes in lung function, effects of sedation on respiratory centres, effects of mechanical ventilation, health-related anxiety, and the wearing of masks or personal protective equipment.[150] Tools to assess altered breathing patterns include the Nijmegen Questionnaire (specifically for hyperventilation syndrome) and the Breathing Pattern Assessment Tool (BPAT).[152,153] The BPAT has a sensitivity and specificity of 90% and 78%, respectively, in diagnosing breathing pattern disorder in COVID-19.[154] Cardiopulmonary exercise testing can be used to support the diagnosis of a breathing pattern disorder, including hyperventilation, where a submaximal test result might be noted alongside an abnormal breathing pattern.[155] Specifically, in post-COVID-19 condition, cardiopulmonary exercise testing has been used to identify dysfunctional breathing in 30% of patients when it is defined as hyperventilation (an elevated minute ventilation to CO_2 output ratio) or an erratic breathing pattern (high variability in tidal volume, breathing frequency, or both) in the absence of a respiratory limitation or impairment in oxygen delivery or use.[156] A systematic review of cardiopulmonary exercise testing in post-COVID-19 condition reported a lower peak oxygen uptake in individuals with persistent breathlessness compared with those who had a full recovery after COVID-19; although deconditioning was the most common pattern, breathing pattern disorder was also commonly reported.[157]

For more on **PICUPS** see https://ics.ac.uk/guidance/rehabilitation.html

Rehabilitation and care approaches

The management of respiratory symptoms in the population with post-COVID-19 condition falls broadly into two categories: supervised group exercise rehabilitation programmes (adapted pulmonary rehabilitation) or individual, largely physiotherapy-based, approaches to dyspnoea management that focus on breathing control. There is a paucity of data describing effective management strategies for post-COVID-19 condition, particularly from low-income and middle-income countries. In this section, we explore post-ICU rehabilitation and rehabilitation for chronic respiratory disease that might inform long COVID services, before discussing approaches to attenuate breathlessness, including physiotherapy-based strategies, in patients recovering from COVID-19.

Post-ICU rehabilitation

Literature on the wider experience of critical illness can inform recovery services for the minority of patients with COVID-19 who require critical care. In 2009, the UK National Institute for Health and Care Excellence published the first clinical guideline detailing rehabilitation strategies for patients who survive an episode of critical illness.[158] The Faculty of Intensive Care Medicine has issued further guidance on the delivery of post-ICU services, incorporating learning from the COVID-19 pandemic.[159] A recent survey of UK hospitals reported that more than 70% had inpatient multidisciplinary post-ICU recovery services and outpatient services, demonstrating a substantial expansion of service provision compared with a previous national survey in 2013.[160] Despite these guidelines, there is wide variability in models of care for the organisation of post-intensive care services.

The evidence base for rehabilitation outcomes after critical illness interventions is weak. A wide range of interventions and follow-up services that aim to improve recovery after critical illness across the three domains of post-intensive care syndrome (physical, psychosocial, and cognitive) has been studied. For example, interventions targeting the physical health domain have included outpatient physical therapy, nutritional support, provision of a rehabilitation manual, and home-based rehabilitation.[161] However, two Cochrane systematic reviews evaluating interventions demonstrated insufficient evidence of effectiveness for a range of post-ICU outcomes.[162,163]

For this reason, post-ICU recovery guidelines largely focus recommendations on processes of care, such as tailored clinical assessment, systematic screening for rehabilitation needs, and information sharing, rather than on specific interventions.[158] One recently published screening tool, the Post-ICU Presentation Screen (PICUPS), was developed by the UK National Post-ICU Rehabilitation Collaborative, which combined experts in critical care and rehabilitation medicine to address the needs of the greater number of patients seen in ICUs due to COVID-19.[164] The 14-item PICUPS checklist supports the handover of rehabilitation needs between health-care teams, facilitates the identification of

problems that warrant more detailed assessment or referral for specialist support, and informs the development of a rehabilitation prescription.

Chronic respiratory disease rehabilitation

A large body of evidence supports the use of pulmonary rehabilitation as a key intervention to reduce breathlessness in COPD. The main outcomes are a reduction in breathlessness, psychological stress (anxiety and depression), and fatigue, and improved health-related quality of life and exercise capacity.[165] Evidence is emerging for a similarly structured rehabilitation programme for individuals with ILD. The data identify a significant and meaningful improvement in exercise capacity (measured using the 6-min walk test) and health-related quality of life.[166] An updated Cochrane review highlighted the longer-term benefits of this intervention with gains extending to 12 months in patients with ILD compared with a control (usual care) group.[166] Several studies have described rehabilitation in the management of pulmonary hypertension, most of which have focused on highly supervised rehabilitation; along with safety, benefits have been reported for important outcomes such as functional capacity and breathlessness.[167] Finally, for people with a pre-existing respiratory disease and frailty, evidence suggests that a pulmonary rehabilitation programme can positively shift the categorisation of frailty from frail to prefrail;[168] however, the acceptability of this format might be limited owing to a higher dropout rate in the frail compared with the non-frail group.

The management of exercise-induced oxygen desaturation, which can be profound in some individuals, has been a safety concern in ILD and similar concerns have been reported in post-COVID-19 condition.[169] However, the prevalence of desaturation at follow-up after COVID-19 appears to be low and is not necessarily associated with impaired functional capacity.[170] The American Thoracic Society clinical practice guideline on home oxygen therapy for individuals with exertional hypoxaemia (pulse-oximetric oxygen saturation ≤88%) includes a conditional recommendation for treatment with ambulatory oxygen, but this is based on low-quality evidence.[171] The management of exertional desaturation in post-COVID-19 condition has not been widely studied yet, but a pragmatic approach would be to use ambulatory oxygen in patients who benefit once underlying causes have been managed.

Post-COVID-19 condition rehabilitation

The use of exercise-based rehabilitation programmes (adapted pulmonary rehabilitation) for people with post-COVID-19 condition might be beneficial for symptoms of breathlessness in those with no contraindications to exercise therapy. Rehabilitation was recommended early in the pandemic, particularly for individuals with breathlessness, including those managed in primary care.[172–174] To date, few evidence-based therapeutic options for breathlessness have been developed and tested for the population with post-COVID-19 condition.[175] However, this has been identified as a research priority by all key stakeholders.[176] Within the limited body of research, there is evidence of the feasibility and safety of rehabilitation for people with post-COVID-19 condition, including face-to-face and digital modes of delivery.[177–179] The advantages and disadvantages of these rehabilitation modes need to be addressed in the context of health-care systems, but transport, social circumstances, and digital literacy are also important considerations. At present, great heterogeneity exists between rehabilitation programmes, but common components include aerobic exercise, resistance exercise, and education on symptom management. A recent systematic review on the effects of pulmonary rehabilitation including exercise programmes showed improvements in dyspnoea, physical function, and quality of life after the programme in patients with post-COVID-19 condition;[175,180] however, patients should be selected carefully according to their symptom profiles and monitored while undergoing exercise-based rehabilitation. Moreover, there is a need for further research with high-quality evidence, particularly including people who were not admitted to hospital for COVID-19.

Studies of other strategies for the management of breathlessness in post-COVID-19 condition have included an online singing-based programme delivered by the English National Opera that targeted people with breathlessness,[181] and an inspiratory muscle training programme,[182] both of which were home-based. In the former study,[181] participants' mental health showed improvements on the 36-item Short-Form Survey, but there was no change in the physical component of this scale. Importantly, the sensation of breathlessness was reduced. Inspiratory muscle training led to a reduction in the breathlessness component of the King's Brief Interstitial Lung Disease Questionnaire, a health-related quality-of-life questionnaire, but the overall questionnaire score was unchanged.[182] The mean predicted maximum inspiratory pressure improved from 92% to 109% after the intervention.

To date, the effectiveness of breathing exercises and retraining after acute COVID-19 has not been established. Breathing exercises are widely used for breathing pattern disorder in people with and without respiratory disease. A review broadly supported the use of breathing exercises in COPD, leading to improved exercise capacity but with no effect on breathlessness.[183] A Cochrane review of breathing exercises,[184] including brief physiotherapy interventions,[185] for the management of asthma showed favourable outcomes. However, another Cochrane review found no clear evidence to support the use of breathing exercises in people with breathing pattern disorder (dysfunctional breathing).[186] While evidence is being accumulated, it should be recognised that breathing

exercises are generally deemed to be low risk for people with non-COVID-19-related breathlessness, might be valuable for people with breathlessness after COVID-19, and have been proposed by WHO for the management of post-COVID-19 condition.[187]

Conclusion

The consequences of SARS-CoV-2 infection and COVID-19 are far-reaching, and the effects on the respiratory system have been an important focus in the post-COVID-19 landscape. Respiratory symptoms, including breathlessness and breathing pattern disorders, are a common feature of post-COVID-19 condition; cough, which is highly prevalent during acute illness, is less prevalent in post-COVID-19 condition. Specific pulmonary sequelae of COVID-19 (pulmonary fibrosis and thromboembolic disease) need careful assessment and might require specific investigations and treatments. A combination of pulmonary and extrapulmonary sequelae (eg, reduced exercise tolerance and frailty) might contribute to persistent and disabling breathlessness in people with post-COVID-19 condition; rehabilitation strategies for post-ICU syndrome and chronic respiratory conditions are informing services for people with this condition.

Further research is needed to understand pulmonary sequelae and extrapulmonary disruption leading to breathlessness; studies should aim to characterise long-term complications in more detail, and to determine the incidence, mechanisms of injury, and optimum diagnostic and management approaches specifically for post-COVID-19 condition to improve outcomes in this population. Key questions for future research are presented in the panel. To date, non-pharmacological options modified from those used in other respiratory conditions have focused on breathing control, respiratory pattern training, inspiratory muscle training, and exercise-based rehabilitation delivered in various formats. While research into the effectiveness of non-pharmacological interventions is ongoing, patients with post-COVID-19 condition can best be supported by an integrated multidisciplinary team. Respiratory and rehabilitation specialists should be at the core of this team, using therapeutic and rehabilitative strategies tailored to the symptom profiles and needs of individual patients, ensuring that culturally appropriate, equitable access is provided to accommodate diverse populations.

Panel: Research priorities

- What are the underlying mechanisms of post-COVID-19 condition that drive the symptom of breathlessness?
- What is the optimal treatment for acute COVID-19 to mitigate, or even prevent, the development of pulmonary fibrosis?
- Is thrombosis that is associated with COVID-19 phenotypically distinct from classic thromboembolic disease? If so, what are the treatment and prognostic implications of phenotypic clinical and biological differences?
- What is the optimal diagnostic or imaging modality for detection of post-COVID-19 pulmonary vascular disease?
- What are the mechanisms that underpin reduced asthma and COPD control after COVID-19?
- What is the incidence of extrapulmonary complications (eg, frailty, sarcopenia) that contribute to breathlessness after COVID-19?
- Are rehabilitation or breathing exercises effective strategies for reducing breathlessness in people with post-COVID-19 condition?

Search strategy and selection criteria

We searched PubMed (MEDLINE) and CINAHL for articles published in English from database inception to March 15, 2023. Combinations of the following terms were used in the searches: "COVID-19", "COVID", "SARS-CoV-2", "thromboembolic disease", "pulmonary embolism", "venous thrombosis", "microvascular", "immunothrombosis", "pulmonary vascular", "CTEPH", "pulmonary fibrosis", "acute respiratory distress syndrome", "ARDS", "rehabilitation", "frailty", "dysfunctional breathing", and "disordered breathing". The abstracts of original investigations and review articles and the references of selected studies were screened and included on the basis of relevance to the topics covered in this Series paper. We searched ClinicalTrials.gov for active and planned clinical trials of investigational medicinal products that might have antifibrotic effects in COVID-19 populations using the following terms: "COVID-19", "COVID", "pulmonary fibrosis", "fibrotic", "fibrotic lung disease", and "post-COVID fibrosis".

Contributors

The manuscript was initially developed by SJS; contributions were drafted by all authors and further developed by SJS, MMB, CEB, and RAE. All authors contributed to critical review and revision of the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

SJS has received project funding from the UK National Institute for Health Research (NIHR), UK Research and Innovation, the Department of Health and Social Care, and Actegy. She has received funding for a doctoral training programme from the Wellcome Trust, and reports funding for presentations from GSK, the UK Ministry of Justice, Cipla, and Sherbourne Gibbs. SJS is the American Thoracic Society Pulmonary Rehabilitation Assembly Chair, clinical lead for the Royal College of Physicians Pulmonary Rehabilitation Accreditation Scheme, clinical lead for the National Asthma and COPD Audit Programme for Pulmonary Rehabilitation, and is on the National Institute for Health and Care Excellence expert advisory panel for long COVID. CEB has received funding to his institution for consultancy and investigator roles from GSK, AstraZeneca, Genentech, Roche, Sanofi, Regeneron, Boehringer Ingelheim, Chiesi, Mologic, and 4DPharma. RAE reports research funding from the NIHR, UKRI, and the Wolfson Foundation. She has received payment for a consultancy role from AstraZeneca, for invited lectures from Boehringer Ingelheim, and for conference attendance from Chiesi. RAE is secretary of the European Respiratory Society Group 01.02 Rehabilitation and Chronic Care. RGJ has received grants to his institution from AstraZeneca, Biogen, Galecto, GSK, Nordic Biosciences, RedX, and Pilant. He reports consultancy fees from AstraZeneca, Brainomix, Bristol Myers Squibb, Chiesi, Cohbar, Daewoong, GSK, Pliant,

Resolution Therapeutics, Roche, and Veracyte, and lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Roche, and PatientMPower. RGJ is on data safety monitoring boards for Boehringer Ingelheim, Galapagos, and Vicore, and is on the advisory board of NuMedii. RGJ is the current president of Action for Pulmonary Fibrosis. MT has received funding from MorphogenIX and Jansen for taking part in advisory boards and has received support from GSK and Jansen to travel and attend meetings. All other authors declare no competing interests.

Acknowledgments

SJS and CEB are UK National Institute for Health Research (NIHR) Senior Investigators. SJS, MMB, ED, RAE, NJG, and HM are supported by the NIHR Leicester Biomedical Research Centre. MT and JN are supported by the Cambridge NIHR Biomedical Research Centre. The views expressed in this article are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. PM is a Medical Research Council–GSK EMINENT (Experimental Medicine Initiative to Explore New Therapies) clinical training fellow with project funding unrelated to this manuscript.

References

1 John Hopkins University & Medicine. John Hopkins Coronavirus Resource Centre – COVID-19 Dashboard. https://coronavirus.jhu.edu/map.html (accessed May 5, 2023).

2 Office for National Statistics. Coronavirus (COVID-19) latest insights: hospitals. March 28, 2023. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/hospitals (accessed May 5, 2023).

3 Huang YZ, Kuan CC. Vaccination to reduce severe COVID-19 and mortality in COVID-19 patients: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2022; **26:** 1770–76.

4 National Institute of Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19. NICE Guideline (NG191). March 23, 2021. https://www.nice.org.uk/guidance/NG191 (accessed May 5, 2023).

5 Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome. *N Engl J Med* 2003; **349:** 2431–41.

6 Huntley CC, Patel K, Bil Bushra S-E-S, et al. Pulmonary function test and computed tomography features during follow-up after SARS, MERS and COVID-19: a systematic review and meta-analysis. *ERJ Open Res* 2022; **8:** 00056–2022.

7 World Health Organisation. Post COVID-19 condition (long COVID). Dec 7, 2022. https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition (accessed May 5, 2023).

8 Office for National Statistics. Self-reported long COVID after infection with the omicron variant in the UK: 18 July 2022. Jul 18, 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidafterinfectionwiththeomicronvariant/18july2022 (accessed Oct 30, 2022).

9 The PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022; **10:** 761–75.

10 Whitaker M, Elliott J, Chadeau-Hyam M, et al. Persistent COVID-19 symptoms in a community study of 606,434 people in England. *Nat Commun* 2022; **13:** 1957.

11 Subramanian A, Nirantharakumar K, Hughes S, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med* 2022; **28:** 1706–14.

12 Dryden M, Mudara C, Vika C, et al. Post-COVID-19 condition 3 months after hospitalisation with SARS-CoV-2 in South Africa: a prospective cohort study. *Lancet Glob Health* 2022; **10:** e1247–56.

13 Mahmud R, Rahman MM, Rassel MA, et al. Post-COVID-19 syndrome among symptomatic COVID-19 patients: a prospective cohort study in a tertiary care center of Bangladesh. *PLoS One* 2021; **16:** e0249644.

14 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.

15 Drake TM, Docherty AB, Harrison EM, et al. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. *Am J Respir Crit Care Med* 2020; **202:** 1656–65.

16 Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022; **23:** 210–16.

17 Castanares-Zapatero D, Chalon P, Kohn L, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. *Ann Med* 2022; **54:** 1473–87.

18 Kachroo P, Stewart ID, Kelly RS, et al. Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma. *Nat Med* 2022; **28:** 814–22.

19 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023; **21:** 133–46.

20 Klein S, Cortese M, Winter SL, et al. SARS-CoV-2 structure and replication characterized by in situ cryo-electron tomography. *Nat Commun* 2020; **11:** 5885.

21 Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022; **185:** 881–95.e20.

22 Wulf Hanson S, Abbafati C, Aerts JG, et al. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA* 2022; **328:** 1604–15.

23 O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of long covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. *EClinicalMedicine* 2022; **55:** 101762.

24 Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021; **9:** 1275–87.

25 Florencio LL, Fernández-de-Las-Peñas C. Long COVID: systemic inflammation and obesity as therapeutic targets. *Lancet Respir Med* 2022; **10:** 726–27.

26 Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369:** m1985.

27 Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med* 2022; **10:** 863–76.

28 Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307:** 2526–33.

29 Chiumello D, Taccone P, Berto V, et al. Long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position. *Intensive Care Med* 2012; **38:** 221–29.

30 Parry SM, Nalamalapu SR, Nunna K, et al. Six-minute walk distance after critical illness: a systematic review and meta-analysis. *J Intensive Care Med* 2021; **36:** 343–51.

31 Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med* 2008; **70:** 512–19.

32 Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA* 1999; **281:** 354–60.

33 Kamdar BB, Suri R, Suchyta MR, et al. Return to work after critical illness: a systematic review and meta-analysis. *Thorax* 2020; **75:** 17–27.

34 Cameron JI, Chu LM, Matte A, et al. One-year outcomes in caregivers of critically ill patients. *N Engl J Med* 2016; **374:** 1831–41.

35 Stewart I, Jacob J, George PM, et al. Residual lung abnormalities following COVID-19 hospitalization: interim analysis of the UKILD post-COVID study. *Am J Respir Crit Care Med* 2022; **207:** 693–703.

36 Burgel P-R, Goss C. COVID-19 outcomes in people with cystic fibrosis. *Curr Opin Pulm Med* 2021; **27:** 538–43.

37 Liu S, Cao Y, Du T, Zhi Y. Prevalence of comorbid asthma and related outcomes in COVID-19: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2021; **9:** 693–701.

38 Ng CK, Chan JW, Kwan TL, et al. Six month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. *Thorax* 2004; **59:** 889–91.

39 Das KM, Lee EY, Al Jawder SE, et al. Acute Middle East respiratory syndrome coronavirus: temporal lung changes observed on the chest radiographs of 55 patients. *AJR Am J Roentgenol* 2015; **205:** W267–74.

40 Orme J Jr, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003; **167:** 690–94.

41 Mehta P, Rosas IO, Singer M. Understanding post-COVID-19 interstitial lung disease (ILD): a new fibroinflammatory disease entity. *Intensive Care Med* 2022; **48:** 1803–06.

42 Shao H, Qin Z, Geng B, et al. Impaired lung regeneration after SARS-CoV-2 infection. *Cell Prolif* 2020; **53:** e12927.

43 Schurink B, Roos E, Radonic T, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 2020; **1:** e290–99.

44 Filbin MR, Mehta A, Schneider AM, et al. Longitudinal proteomic analysis of severe COVID-19 reveals survival-associated signatures, tissue-specific cell death, and cell-cell interactions. *Cell Rep Med* 2021; **2:** 100287.

45 Peiris S, Mesa H, Aysola A, et al. Pathological findings in organs and tissues of patients with COVID-19: A systematic review. *PLoS One* 2021; **16:** e0250708.

46 Leisman DE, Mehta A, Thompson BT, et al. Alveolar, endothelial, and organ injury marker dynamics in severe COVID-19. *Am J Respir Crit Care Med* 2022; **205:** 507–19.

47 Chua RL, Lukassen S, Trump S, et al. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol* 2020; **38:** 970–79.

48 Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. *Ther Adv Respir Dis* 2010; **4:** 367–88.

49 Allen RJ, Guillen-Guio B, Croot E, et al. Genetic overlap between idiopathic pulmonary fibrosis and COVID-19. *Eur Respir J* 2022; **60:** 2103132.

50 Allen RJ, Stockwell A, Oldham JM, et al. Genome-wide association study across five cohorts identifies five novel loci associated with idiopathic pulmonary fibrosis. *Thorax* 2022; **77:** 829–33.

51 Tatler AL, Jenkins G. TGF-β activation and lung fibrosis. *Proc Am Thorac Soc* 2012; **9:** 130–36.

52 Morganstein T, Haidar Z, Trivlidis J, et al. Involvement of the ACE2/Ang-(1-7)/MasR axis in pulmonary fibrosis: implications for COVID-19. *Int J Mol Sci* 2021; **22:** 12955.

53 Melms JC, Biermann J, Huang H, et al. A molecular single-cell lung atlas of lethal COVID-19. *Nature* 2021; **595:** 114–19.

54 Cheon IS, Li C, Son YM, et al. Immune signatures underlying post-acute COVID-19 lung sequelae. *Sci Immunol* 2021; **6**: eabk1741.

55 George PM, Reed A, Desai SR, et al. A persistent neutrophil-associated immune signature characterizes post-COVID-19 pulmonary sequelae. *Sci Transl Med* 2022; **14:** eabo5795.

56 Pandolfi L, Bozzini S, Frangipane V, et al. Neutrophil extracellular traps induce the epithelial-mesenchymal transition: implications in post-COVID-19 fibrosis. *Front Immunol* 2021; **12:** 663303.

57 Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J* 2017; **49:** 1601592.

58 García-Sancho Figueroa MC, Carrillo G, Pérez-Padilla R, et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. *Respir Med* 2010; **104:** 305–09.

59 Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* 2015; **46:** 1113–30.

60 Khan FA, Stewart I, Saini G, Robinson KA, Jenkins RG. A systematic review of blood biomarkers with individual participant data meta-analysis of matrix metalloproteinase-7 in idiopathic pulmonary fibrosis. *Eur Respir J* 2021; **59:** 2101612.

61 Chun HJ, Coutavas E, Pine AB, et al. Immunofibrotic drivers of impaired lung function in postacute sequelae of SARS-CoV-2 infection. *JCI Insight* 2021; **6:** e148476.

62 Naqvi SF, Lakhani DA, Sohail AH, et al. Patients with idiopathic pulmonary fibrosis have poor clinical outcomes with COVID-19 disease: a propensity matched multicentre research network analysis. *BMJ Open Respir Res* 2021; **8:** e000969.

63 Vadász I, Husain-Syed F, Dorfmüller P, et al. Severe organising pneumonia following COVID-19. *Thorax* 2021; **76:** 201–04.

64 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:** 799–806.

65 Luger AK, Sonnweber T, Gruber L, et al. Chest CT of lung injury 1 year after COVID-19 pneumonia: The CovILD study. *Radiology* 2022; **304:** 462–70.

66 Aul DR, Gates DJ, Draper DA, et al. Complications after discharge with COVID-19 infection and risk factors associated with development of post-COVID pulmonary fibrosis. *Respir Med* 2021; **188:** 106602.

67 Valenzuela C, Waterer G, Raghu G. Interstitial lung disease before and after COVID-19: a double threat? *Eur Respir J* 2021; **58:** 2101956.

68 Li X, Shen C, Wang L, et al. Pulmonary fibrosis and its related factors in discharged patients with new coronavirus pneumonia: a cohort study. *Respir Res* 2021; **22:** 203.

69 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:** 220–32.

70 Wild JM, Porter JC, Molyneaux PL, et al. Understanding the burden of interstitial lung disease post-COVID-19: the UK Interstitial Lung Disease-Long COVID Study (UKILD-Long COVID). *BMJ Open Respir Res* 2021; **8:** e001049.

71 Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; **131:** 954–63.

72 Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; **63** (suppl 5)**:** v1–58.

73 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; **384:** 693–704.

74 Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020; **56:** 2002808.

75 Sinha S, Rosin NL, Arora R, et al. Dexamethasone modulates immature neutrophils and interferon programming in severe COVID-19. *Nat Med* 2022; **28:** 201–11.

76 Fraser E, Denney L, Blirando K, et al. Type-1 IFN primed monocytes in pathogenesis of idiopathic pulmonary fibrosis. *bioRxiv* 2020; published online Jan 17. https://doi.org/10.1101/2020.01.16.908749 (preprint).

77 Dhooria S, Chaudhary S, Sehgal IS, et al. High-dose *versus* low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial). *Eur Respir J* 2022; **59:** 2102930.

78 De Sadeleer LJ, Hermans F, De Dycker E, et al. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. *Eur Respir J* 2020; **55:** 1901983.

79 Vacchi C, Sebastiani M, Cassone G, et al. Therapeutic options for the treatment of interstitial lung disease related to connective tissue diseases. A narrative review. *J Clin Med* 2020; **9:** 407.

80 Yamagata A, Arita M, Tachibana H, et al. Impact of bronchoalveolar lavage lymphocytosis on the effects of anti-inflammatory therapy in idiopathic non-specific interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis, and unclassifiable idiopathic interstitial pneumonia. *Respir Res* 2021; **22:** 115.

81 Gelarden I, Nguyen J, Gao J, et al. Comprehensive evaluation of bronchoalveolar lavage from patients with severe COVID-19 and correlation with clinical outcomes. *Hum Pathol* 2021; **113:** 92–103.

82 Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med* 2018; **197:** 757–67.

83 Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004; **31:** 304–09.

84 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.

85 Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; **384:** 1491–502.

86 Khan FA, Stewart I, Fabbri L, et al. Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. *Thorax* 2021; **76:** 907–19.

87 Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021; **9:** 1407–18.

88 Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021; **384:** 795–807.

89 Milara J, Hernandez G, Ballester B, et al. The JAK2 pathway is activated in idiopathic pulmonary fibrosis. *Respir Res* 2018; **19:** 24.

90 Le TT, Karmouty-Quintana H, Melicoff E, et al. Blockade of IL-6 trans signaling attenuates pulmonary fibrosis. *J Immunol* 2014; **193:** 3755–68.

91 Karam BS, Morris RS, Bramante CT, et al. mTOR inhibition in COVID-19: a commentary and review of efficacy in RNA viruses. *J Med Virol* 2021; **93:** 1843–46.

92 Vincent JL, Levi M, Hunt BJ. Prevention and management of thrombosis in hospitalised patients with COVID-19 pneumonia. *Lancet Respir Med* 2022; **10:** 214–20.

93 Conway EM, Mackman N, Warren RQ, et al. Understanding COVID-19-associated coagulopathy. *Nat Rev Immunol* 2022; **22:** 639–49.

94 Aktaa S, Wu J, Nadarajah R, et al. Incidence and mortality due to thromboembolic events during the COVID-19 pandemic: multi-sourced population-based health records cohort study. *Thromb Res* 2021; **202:** 17–23.

95 Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021; **9:** 251–59.

96 COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021; **47:** 60–73.

97 Weir-McCall JR, Galea G, Mun Mak S, et al. Vascular thrombosis in severe COVID-19 requiring extracorporeal membrane oxygenation: a multicenter study. *Crit Care Med* 2022; **50:** 624–32.

98 Miró Ò, Llorens P, Jiménez S, et al. Frequency of five cardiovascular/hemostatic entities as primary manifestations of SARS-CoV-2 infection: results of the UMC-19-S$_2$. *Int J Cardiol* 2021; **330:** 268–72.

99 Zuin M, Engelen MM, Barco S, et al. Incidence of venous thromboembolic events in COVID-19 patients after hospital discharge: a systematic review and meta-analysis. *Thromb Res* 2022; **209:** 94–98.

100 Ho FK, Man KKC, Toshner M, et al. Thromboembolic risk in hospitalized and nonhospitalized COVID-19 patients: a self-controlled case series analysis of a nationwide cohort. *Mayo Clin Proc* 2021; **96:** 2587–97.

101 Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 pneumonia detected with pulmonary CT angiography. *Radiology* 2020; **296:** E186–88.

102 Benito N, Filella D, Mateo J, et al. Pulmonary thrombosis or embolism in a large cohort of hospitalized patients with Covid-19. *Front Med (Lausanne)* 2020; **7:** 557.

103 Whyte MB, Barker R, Kelly PA, et al. Three-month follow-up of pulmonary embolism in patients with COVID-19. *Thromb Res* 2021; **201:** 113–15.

104 Newman J, Boubriak I, Jenkins D, et al. Rising COVID-19 related acute pulmonary emboli but falling national chronic thromboembolic pulmonary hypertension referrals from a large national dataset. *ERJ Open Res* 2021; **7:** 00431–2021.

105 Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; **124:** 1973–81.

106 Desborough MJR, Doyle AJ, Griffiths A, Retter A, Breen KA, Hunt BJ. Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. *Thromb Res* 2020; **193:** 1–4.

107 van Dam LF, Kroft LJM, van der Wal LI, et al. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: a different phenotype of thrombotic disease? *Thromb Res* 2020; **193:** 86–89.

108 Gul MH, Htun ZM, de Jesus Perez V, et al. Predictors and outcomes of acute pulmonary embolism in COVID-19; insights from US National COVID cohort collaborative. *Respir Res* 2023; **24:** 59.

109 Konstantinides SV, Barco S, Rosenkranz S, et al. Late outcomes after acute pulmonary embolism: rationale and design of FOCUS, a prospective observational multicenter cohort study. *J Thromb Thrombolysis* 2016; **42:** 600–09.

110 Valerio L, Mavromanoli AC, Barco S, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. *Eur Heart J* 2022; **43:** 3387–98.

111 Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. *Mod Pathol* 2020; **33:** 2156–68.

112 Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020; **20:** 1135–40.

113 Prieto-Pérez L, Fortes J, Soto C, et al. Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. *Mod Pathol* 2020; **33:** 2139–46.

114 Grist JT, Collier GJ, Walters H, et al. Lung abnormalities detected with hyperpolarized ^{129}Xe MRI in patients with long COVID. *Radiology* 2022; **305:** 709–17.

115 Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020; **202:** 690–99.

116 Pretorius E, Vlok M, Venter C, et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc Diabetol* 2021; **20:** 172.

117 Toshner MR, Gamble C, Baillie JK, et al. Apixaban following discharge in hospitalised adults with COVID-19: Preliminary results from a multicentre, open-label, randomised controlled platform clinical trial. *medRxiv* 2022; published online Dec 7. https://doi.org/10.1101/2022.12.07.22283175 (preprint).

118 Bloom CI, Drake TM, Docherty AB, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK. *Lancet Respir Med* 2021; **9:** 699–711.

119 Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ* 2021; **372:** n693.

120 Bhaskaran K, Rentsch CT, Hickman G, et al. Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: a cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLoS Med* 2022; **19:** e1003871.

121 Philip KEJ, Buttery S, Williams P, et al. Impact of COVID-19 on people with asthma: a mixed methods analysis from a UK wide survey. *BMJ Open Respir Res* 2022; **9:** e001056.

122 Morin L, Savale L, Pham T, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021; **325:** 1525–34.

123 Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. *Respir Physiol Neurobiol* 2021; **288:** 103644.

124 Froidure A, Mahsouli A, Liistro G, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. *Respir Med* 2021; **181:** 106383.

125 Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021; **9:** 747–54.

126 Siddiqui S, Brightling CE. Pathological disease in the lung periphery after acute COVID-19. *Lancet Respir Med* 2021; **9:** 1089–90.

127 Cassar MP, Tunnicliffe EM, Petousi N, et al. Symptom persistence despite improvement in cardiopulmonary health — insights from longitudinal CMR, CPET and lung function testing post-COVID-19. *EClinicalMedicine* 2021; **41:** 101159.

128 Chen J, Wu J, Hao S, et al. Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection. *Sci Rep* 2017; **7:** 17275.

129 Bezzerri V, Gentili V, Api M, et al. SARS-CoV-2 viral entry and replication is impaired in cystic fibrosis airways due to ACE2 downregulation. *Nat Commun* 2023; **14:** 132.

130 Medino P, Alicandro G, Rosazza C, et al. Impact of COVID-19 on lung disease in people with cystic fibrosis: a 6-month follow-up study on respiratory outcomes. *Biomedicines* 2022; **10:** 2771.

131 Jaudszus A, Pavlova M, Rasche M, Baier M, Moeser A, Lorenz M. One year monitoring of SARS-CoV-2 prevalence in a German cohort of patients with cystic fibrosis. *BMC Pulm Med* 2022; **22:** 101.

132 Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007; **297:** 1772–74.

133 Manganotti P, Buoite Stella A, Ajcevic M, et al. Peripheral nerve adaptations to 10 days of horizontal bed rest in healthy young adult males. *Am J Physiol Regul Integr Comp Physiol* 2021; **321:** R495–503.

134 Narici M, Vito G, Franchi M, et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. *Eur J Sport Sci* 2021; **21:** 614–35.

135 Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013; **310:** 1591–600.

136 McAuley HJC, Harvey-Dunstan TC, Craner M, et al. Longitudinal changes to quadriceps thickness demonstrate acute sarcopenia following admission to hospital for an exacerbation of chronic respiratory disease. *Thorax* 2021; **76:** 726–28.

137 Skjørten I, Ankerstjerne OAW, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J* 2021; **58:** 2100996.

138 Mohr A, Dannerbeck L, Lange TJ, et al. Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. *Multidiscip Respir Med* 2021; **16:** 732.

139 Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci* 2013; **68:** 62–67.

140 Müller I, Mancinetti M, Renner A, et al. Frailty assessment for COVID-19 follow-up: a prospective cohort study. *BMJ Open Respir Res* 2022; **9:** e001227.

141 Milne KM, Kwan JM, Guler S, et al. Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease. *Respirology* 2017; **22:** 728–34.

142 Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993; **342:** 1032–36.

143 McAuley HJC, Evans RA, Bolton CE, et al. Prevalence of physical frailty, including risk factors, up to 1 year after hospitalisation for COVID-19 in the UK: a multicentre, longitudinal cohort study. *EClinicalMedicine* 2023; **57:** 101896.

144 Vandentorren S, Smaïli S, Chatignoux E, et al. The effect of social deprivation on the dynamic of SARS-CoV-2 infection in France: a population-based analysis. *Lancet Public Health* 2022; **7:** e240–49.

145 Spathis A, Booth S, Moffat C, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *NPJ Prim Care Respir Med* 2017; **27:** 27.

146 Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. *Thorax* 2010; **65:** 21–26.

147 Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. *Eur Respir J* 2015; **45:** 1681–91.

148 Grist JT, Collier GJ, Walters H, et al. Lung abnormalities detected with hyperpolarized ^{129}Xe MRI in patients with long COVID. *Radiology* 2022; **305:** 709–17.

149 Hameed S, Khan AF, Khan S. Electrodiagnostic findings in COVID-19 patients: a single center experience. *Clin Neurophysiol* 2021; **132:** 3019–24.

150 Stockley JA, Alhuthail EA, Coney AM, et al. Lung function and breathing patterns in hospitalised COVID-19 survivors: a review of post-COVID-19 Clinics. *Respir Res* 2021; **22:** 255.

151 Heightman M, Prashar J, Hillman TE, et al. Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. *BMJ Open Respir Res* 2021; **8:** e001041.

152 Grammatopoulou EP, Skordilis EK, Georgoudis G, et al. Hyperventilation in asthma: a validation study of the Nijmegen Questionnaire—NQ. *J Asthma* 2014; **51:** 839–46.

153 Todd S, Walsted ES, Grillo L, Livingston R, Menzies-Gow A, Hull JH. Novel assessment tool to detect breathing pattern disorder in patients with refractory asthma. *Respirology* 2018; **23:** 284–90.

154 Hylton H, Long A, Francis C, et al. Real-world use of the Breathing Pattern Assessment Tool in assessment of breathlessness post-COVID-19. *Clin Med (Lond)* 2022; **22:** 376–79.

155 Ionescu MF, Mani-Babu S, Degani-Costa LH, et al. Cardiopulmonary exercise testing in the assessment of dysfunctional breathing. *Front Physiol* 2021; **11:** 620955.

156 Frésard I, Genecand L, Altarelli M, et al. Dysfunctional breathing diagnosed by cardiopulmonary exercise testing in 'long COVID' patients with persistent dyspnoea. *BMJ Open Respir Res* 2022; **9:** e001126.

157 Durstenfeld MS, Sun K, Tahir P, et al. Use of cardiopulmonary exercise testing to evaluate long COVID-19 symptoms in adults: a systematic review and meta-analysis. *JAMA Netw Open* 2022; **5:** e2236057.

158 Tan T, Brett SJ, Stokes T. Rehabilitation after critical illness: summary of NICE guidance. *BMJ* 2009; **338:** b822.

159 The Faculty of Intensive Care Medicine. FICM position statement and provisional guidance: recovery and rehabilitation for patients following the pandemic. May 2020. https://www.cc3n.org.uk/uploads/9/8/4/2/98425184/ficm_rehab_provisional_guidance.pdf (accessed May 5, 2023).

160 Connolly B, Milton-Cole R, Adams C, et al. Recovery, rehabilitation and follow-up services following critical illness: an updated UK national cross-sectional survey and progress report. *BMJ Open* 2021; **11:** e052214.

161 Brown SM, Bose S, Banner-Goodspeed V, et al. Approaches to addressing post-intensive care syndrome among intensive care unit survivors. A narrative review. *Ann Am Thorac Soc* 2019; **16:** 947–56.

162 Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. *Cochrane Database Syst Rev* 2018; **11:** CD012701.

163 Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. *Cochrane Database Syst Rev* 2015; **2015:** CD008632.

164 Turner-Stokes L, Corner EJ, Siegert RJ, et al. The post-ICU presentation screen (PICUPS) and rehabilitation prescription (RP) for intensive care survivors part I: development and preliminary clinimetric evaluation. *J Intensive Care Soc* 2022; **23:** 253–63.

165 McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; **2015:** CD003793.

166 Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2021; **2:** CD006322.

167 Grünig E, MacKenzie A, Peacock AJ, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J* 2021; **42:** 2284–95.

168 Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax* 2016; **71:** 988–95.

169 Carlucci A, Paneroni M, Carotenuto M, et al. Prevalence of exercise-induced oxygen desaturation after recovery from SARS-CoV-2 pneumonia and use of lung ultrasound to predict need for pulmonary rehabilitation. *Pulmonology* 2021; published online Jun 4. https://doi.org/10.1016/j.pulmoe.2021.05.008.

170 González J, Benítez ID, Carmona P, et al. Pulmonary function and radiologic features in survivors of critical COVID-19: a 3-month prospective cohort. *Chest* 2021; **160:** 187–98.

171 Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020; **202:** e121–41.

172 Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020; **370:** m3026.

173 Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated international task force. *Eur Respir J* 2020; **56:** 2002197.

174 Singh SJBC, Nolan C, Harvey-Dunstan T, Connolly B, Man W, Walker P. Delivering rehabilitation to patients surviving COVID-19 using an adapted pulmonary rehabilitation approach – BTS guidance. Sept 16, 2020. https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/pulmonary-rehabilitation-for-covid-19-patients/ (accessed May 5, 2023).

175 Zheng B, Daines L, Han Q, et al. Prevalence, risk factors and treatments for post-COVID-19 breathlessness: a systematic review and meta-analysis. *Eur Respir Rev* 2022; **31:** 220071.

176 Houchen-Wolloff L, Poinasamy K, Holmes K, et al. Joint patient and clinician priority setting to identify 10 key research questions regarding the long-term sequelae of COVID-19. *Thorax* 2022; **77:** 717–20.

177 Gloeckl R, Leitl D, Jarosch I, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res* 2021; **7:** 00108–02021.

178 Li J, Xia W, Zhan C, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax* 2022; **77:** 697–706.

179 Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition — a cohort study. *Chron Respir Dis* 2021; **18:** 14799731211015691.

180 Reinert G, Müller D, Wagner P, et al. Pulmonary rehabilitation in SARS-CoV-2: a systematic review and meta-analysis of post-acute patients. *Diagnostics (Basel)* 2022; **12:** 3032.

181 Philip KEJ, Owles H, McVey S, et al. An online breathing and wellbeing programme (ENO Breathe) for people with persistent symptoms following COVID-19: a parallel-group, single-blind, randomised controlled trial. *Lancet Respir Med* 2022; **10:** 851–62.

182 McNarry MA, Berg RMG, Shelley J, et al. Inspiratory muscle training enhances recovery post-COVID-19: a randomised controlled trial. *Eur Respir J* 2022; **60:** 2103101.

183 Holland AE, Hill CJ, Jones AY, McDonald CF. Breathing exercises for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **10:** CD008250.

184 Santino TA, Chaves GS, Freitas DA, Fregonezi GA, Mendonça KM. Breathing exercises for adults with asthma. *Cochrane Database Syst Rev* 2020; **3:** CD001277.

185 Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018; **6:** 19–28.

186 Jones M, Harvey A, Marston L, O'Connell NE. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. *Cochrane Database Syst Rev* 2013; **5:** CD009041.

187 World Health Organization. COVID-19 clinical management: living guidance, 25 January 2021. Jan 25, 2021. https://apps.who.int/iris/handle/10665/338882 (accessed May 5, 2023).