**Pulmonary sequelae of COVID-19: approaches to clinical care and rehabilitation**

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**Summary**

Whilst the exact prevalence is unknown, a significant group of individuals suffer from post-COVID sequelae; defined as persistent symptoms >3 months after an acute COVID-19 infection. These sequelae are highly heterogeneous in nature and adversely affect multiple biological systems, although breathlessness is a frequently cited symptom. Specific pulmonary post-COVID-19 sequelae exist that need to be assessed and may require specific investigations and treatments. In this series paper, we provide an overview of the pulmonary sequelae of COVID-19, address the impact of COVID-19 on pre-existing respiratory conditions, and explore the extra-pulmonary disruption that may contribute to breathlessness in this patient cohort. Non-pharmaceutical therapeutic options that may attenuate breathlessness in COVID-19 survivors, including exercise-based rehabilitation and breathing control exercises, are then presented, alongside future research directions.

**Introduction**

Over the first three years of the COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) hospital admissions and mortality have reduced.1 The improvements are due to a combination of effective vaccinations reducing the severity of the acute illness2 and acute treatments such as dexamethasone, anti-interleukin-6 (IL-6) therapies, anti-virals, and Baricitinib.3 People with chronic lung disease do not appear to be at increased risk of acquiring COVID-19 unless they have co-morbid impaired immunity or are receiving treatment with immunosuppressant therapy. In contrast, having chronic lung disease increases the risk of COVID-19-related death.4,5 As with other acute respiratory viruses (SARS pandemic 2002/Middle Eastern Respiratory Syndrome [MERS] coronavirus) causing acute lung injury,6,7 longer term sequelae are described and are likely to increase in prevalence with the increase in survivorship.

At the time of writing, post-COVID sequelae are broadly defined internationally by the persistence of symptoms (originally a patient derived definition of ‘Long COVID’) usually three months, and at least two months, after acute SARS-Cov-2 infection.8 The exact prevalence of Long COVID is unknown and differs depending on how it is measured in different cohorts, between variants, and with vaccination status. Triple vaccination against COVID-19 appears to reduce the likelihood of persistent sequelae, but does not ameliorate Long COVID. In a recent report of a UK survey of private households, 4.5%, 4.2%, and 5.0%, of triple vaccinated adults experienced persistent symptoms 12-16 weeks after confirmed SARS-CoV-2 infection with Omicron BA.1, Omicron BA.2, and Delta variants, respectively.9 Risk factors for Long COVID include severe acute disease including receipt of invasive mechanical ventilation, female sex, obesity, socioeconomic deprivation, and pre-existing disease.10-12 Although these risk factors were established in high income countries, many are mirrored in middle and low income countries where access to services may be compromised.13,14 Potential underlying mechanisms associated with Long COVID to date include ongoing systemic inflammation including activation of type I and III interferons and IL-615, autoimmunity, micro-clotting, hypoadrenalism, and viral persistence.16-20 In people with chronic respiratory disease there is often worsening of respiratory symptoms post-COVID-19; whether this is due to destabilising their underlying respiratory condition or due to other COVID-19 related effects is uncertain.

Breathlessness, fatigue, muscle pain, brain fog, sleep disturbance, and headache, are the most prevalent symptoms described in Long COVID independent of the severity of the acute illness defined by hospitalised or non-hospitalised.10,11 In contrast, cough, fever, and loss of taste and smell, are highly prevalent during the acute illness but are less prevalent in Long COVID. In hospitalised cohorts, although those receiving invasive mechanical ventilation are less likely to fully recover, there is not a linear relationship between the severity of acute illness and likelihood of recovery.21 This indicates that some of the mechanisms behind Long COVID are not directly related to the acute lung injury. Clustering of individual symptoms has also not led to identification of disease-specific clusters of symptoms except for potentially a ‘respiratory cluster’ dominated by ‘shortness of breath’ and ‘chest pain’.11 Clusters in a post-hospital cohort were mostly defined by the burden of symptoms and ongoing health impairments with a positive association between severity and the total number of symptoms experienced.10 The more severe clusters were also associated with lower exercise tolerance,10 and were less likely to have returned to work at six months after hospital admission.21 There were intriguing associations between obesity and ongoing systemic inflammation with elevated blood CRP levels and IL-6 in the more severe clusters compared to mild highlighting different phenotypes and potential therapeutic targets.22

Whilst helpful to define a group of people who have not recovered by ongoing symptoms, we need to further understand the precise underlying mechanisms of symptoms, ongoing organ impairment and the relationship between symptoms and organ damage. Acute lung injury was the dominant insult requiring a hospital admission (acute severe COVID-19) for respiratory support in contrast to mild-moderate acute COVID-19 (non-hospitalised) and any post-COVID sequelae may differ requiring specific assessments and interventions.

During the first quarter of 2020, around one in six hospitalised immune-naïve patients with COVID-19 developed severe disease requiring critical care admission, with the majority requiring respiratory support (non-invasive or invasive mechanical ventilation).23 The current risk of developing severe COVID-19 in immune-naïve patients is less clear due to the increase in SARS-CoV-2 exposure and difficulty ascertaining a true immune-naïve population. Similar to any critical illness, severe COVID-19 disease can leave patients with longer term morbidity, affect any organ system, and impact on health-related quality of life and wellbeing. These consequences may be related to the underlying disease process itself, or from treatments administered within the intensive care unit (ICU) to facilitate life support therapies, or both.

Post-acute COVID-19 morbidity may be more severe for patients requiring ICU compared with other hospitalised patients. In a large multicentre follow-up study of hospitalised patients with COVID-19, patients requiring invasive mechanical ventilation were less likely to feel fully recovered at 6 months after discharge compared with those requiring supplemental oxygen only (18.8% vs 36.3%), confirmed in analyses adjusting for differences in patient characteristics.21 In unadjusted comparisons, those requiring invasive mechanical ventilation also had lower physical performance (Incremental Shuttle Walk Test distance 39.4% predicted vs 50.1%), and worse lung physiology measured by spirometry and pulmonary diffusion capacity.21 However, severity of acute COVID-19 illness was not associated with clusters representing phenotypes of patient-reported recovery.

Most critically ill patients with COVID-19 disease develop an extensive inflammatory insult 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 a variety of acute insults only one of which is viral pneumonia.24 A well-developed evidence base has described the sequelae of ARDS in the pre-pandemic era, which can be drawn on to provide insights into COVID-19-associated ARDS recovery trajectories given the current limited evidence base. Follow-up studies of ARDS demonstrate that those surviving ARDS can experience significant longer term respiratory morbidity. Those reporting detailed pulmonary evaluation have most frequently identified mild to moderate reductions in pulmonary diffusion capacity at one year follow up.25 Reduced exercise capacity, most commonly measured by six minute walk test, is evident in ARDS cohorts, improving from 60-71% of predicted distance at 12 months to 71-76% at 5 years.26

An important feature of this wider ARDS literature is the broader impact of sequelae on patients and families. Consequences of critical illness extend beyond the respiratory system, and may contribute to the increased incidence of physical and mental health sequelae,27 impaired quality of life,28 socioeconomic impacts through no longer being able to work,29 and broader impacts on the family unit, as members may have to adopt caregiver roles.30

The above highlights the multi-system nature of Long COVID,18-20 but there are specific pulmonary post-COVID sequelae which need to be assessed in clinical care and may need specific interventions. This article focuses on the post-COVID pulmonary sequelae, extra-pulmonary disruption, and interventions that may present a therapeutic option for individuals suffering from disabling dyspnoea.

**Pulmonary post-COVID sequelae**

Post-COVID there is an increased risk of thromboembolic disease and lung fibrosis, whereas there is currently insufficient evidence to suggest an increase incidence of other chronic respiratory diseases.31,32

**Pulmonary fibrosis and COVID-19**

Evidence of long-term pulmonary disease after previous coronavirus pandemics33,34 and following ARDS,35 as well as mechanistic similarities between COVID pneumonia and Idiopathic Pulmonary Fibrosis (IPF) raises the possibility of a significant global burden of long-term fibrosis resulting from SARS-CoV-2 infection.

Severe COVID-19 is associated with a high level of alveolar injury which can continue even after viral clearance.36 This may be caused by direct viral infection or, more commonly, by immune mediated injury to alveolar cells,37 causing a pattern of diffuse alveolar damage.38,39 Augmented molecular signalling from epithelial to immune cells further perpetuates tissue damage, lung injury, and disease progression.40,41 IPF also results from alveolar injury,42 and shares genetic, molecular, and epidemiological risk factors with severe COVID infection. Of the 19 genes known to increase the risk of IPF, a number have been associated with more severe COVID infection including DPP9, although MUC5B and ATP11A are associated with reduced severity.43,44 COVID infections are caused by binding of the SARS-CoV-2 virus to the ACE2 receptor. This leads to internalisation of the ACE2 receptor with consequent 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 and collagen synthesis and fibroblast proliferation.45,46 Furthermore, high levels of collagen secreting CTRHC1+ fibroblasts are associated with severe acute fibrosis and fatal outcomes in COVID-19.47 The role of immune cells is also likely to be very important. Eosinophils, mast cell and lymphocytes, particularly CD8+ cells have been correlated with poorer lung function and increased radiological abnormalities post-COVID.48 Neutrophil responses are also likely involved with increased Neutrophil Extracellular Traps (NETs) being identified in the serum of patients in the early post-acute phase, and exogenous NETs were able to promote fibrogenesis in epithelial cells, even though direct infection with SARS-CoV-2 infection could not in the same models.49

Severe COVID infection and IPF are more common in males and older individuals, and both conditions are associated with a range of comorbidities including obesity, type 2 diabetes, hypertension, and ischaemic heart disease.50-52 Similarly biomarkers that have been associated with progressive IPF such as MMP753 are also found to be elevated in patients with post-acute COVID who have poorer lung function.54 Notably, patients with IPF who contract COVID-19 are more likely to have poor clinical outcomes.55

Organizing pneumonia (OP) is the radiological pattern most commonly seen in COVID-19, with subsequent fibrotic remodelling seen in some cases.56,57 Persistent radiological abnormalities one year after COVID-19 pneumonia can range from limited ground glass opacity (GGO) and subpleural reticulation to more extensive GGO, traction bronchiectasis, and honeycombing.58 This is more prevalent amongst the cohort of patients who were hospitalised, and current evidence suggests that up to 55% of these patients have persistent changes in the months following infection, although estimates vary widely.57,59-62 A multi-centre cohort study is currently underway to determine the prevalence of post-COVID fibrosis and to identify risk factors over a longer time span in both hospitalised patients and those managed in the community.63 Preliminary analysis suggests around 7% of patients hospitalised with COVID-19 will have Residual Lung Abnormalities within the first 12 months with limited evidence of slow resolution during the first year.64 Thoracic CT changes over time following a hospitalisation for COVID-19 in three example patients is shown in Figure 1.

Considerable progress has been made in the treatment of severe COVID pneumonia that may possibly reduce the risk of long-term fibrosis. The majority of treatments proven to be effective for reducing COVID severity target the immune system. Corticosteroids (dexamethasone and methylprednisolone) are often used for OP and ARDS65,66 and have been shown to reduce mortality in severe COVID-19.57,67,68 There are no placebo controlled trials of steroids in post-COVID ILD although an open label study of high dose (40mg reducing to 10mg) versus low dose (10mg stable dose) found only 16/21 (24.6%) response in the high dose regime which was not significantly different from the low dose regime 12/60 (18.6%) response.69 Their use is extrapolated from other inflammatory ILDs, and high bronchoalveolar lavage fluid (BALF) lymphocyte counts may be a marker of corticosteroid responsiveness.70-72 Raised BALF lymphocyte counts have been found in 74.7% of acute COVID-19 patients and are linked to increased disease severity.73 Timing of administration may be important, with the greatest reduction in mortality seen when dexamethasone is given after the first week of illness.67,74,75 There is no proven benefit to administration in mild COVID-19 infection.67 Anti-IL-6 agents, such as tocilizumab and sarilumab, appear to offer a survival benefit compared with usual care in critically unwell patients with severe COVID-19 infection.76-78 Use of the JAK inhibitor, baricitinib, reduces mortality compared with usual care (+/- remdesivir and corticosteroids) and improves recovery time in hospitalised patients.79,80 Experimental models suggest that anti-IL-6 and JAK inhibition may also be beneficial in IPF.81,82 Bioinformatic analysis has suggested that drugs with anti-fibrotic activity including, mTOR inhibitors and nintedanib, may be of value in treating COVID-1983 and are currently being investigated in clinical trials (NCT04948203, NCT04856111, NCT04607928, NCT04541680, NCT04619680).

In summary, severe COVID-19 infection causes alveolar injury and induces profibrotic pathways similar to those observed in IPF. In genetically susceptible individuals, COVID-19 induction of profibrotic pathways has the potential to lead to pulmonary fibrosis. The effect of treatments that reduce COVID induced lung injury are likely to mitigate these effects, but long-term outcomes are yet to be determined.

**Pulmonary emboli and microvascular thrombi and COVID-19**

The causal association between COVID-19 and acute thromboembolic disease is well established. In the acute phase, vascular endothelial dysfunction, a hyper-inflammatory immune response, and a hyper-coagulant state predispose patients to developing venous thromboses.84 COVID-19-associated coagulopathy potentially involves multiple pathways and mechanisms including NETs, complement activation, platelet dysfunction, an imbalance of fibrinolysis, protein-C, and anti-phospholipid antibodies.85 Remaining gaps in the understanding of the pathogenesis of the coagulopathy must be addressed to inform improvements in diagnostics and potential therapeutics.

The incidence of pulmonary emboli (PE) varies considerably between COVID-19 cohorts in different settings correlating with disease severity. In hospitalised patients not requiring ICU support, the incidence of PE is estimated between 0.9%-3.4%86,87. In ICU patients’ the incidence of PE ranges from ~8%88 to as high as 59% in severe COVID-19 requiring extra corporeal membrane oxygenation.89 Non-hospitalised rates are lower but still significant.90 PE risk continues in the non-acute stage with a pooled cumulative incidence across studies of 1.5% in short term follow-up91 and is still elevated at least 8 weeks from diagnosis.92

Significant risk factors for developing venous thromboembolic complications in the context of acute COVID-19 include male sex, older age, mechanical ventilation, raised C-reactive protein, and raised D-dimer.93,94 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.94 Longer term there is evidence of incomplete thrombus resolution despite anti-coagulant treatment estimated to be 30% at 105 days.95

In the pre-pandemic setting, chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially life-limiting complication of PE that occurs in ~4% of patients. Despite the high numbers of COVID-19-related PE globally, an increase in CTEPH is yet to be reported. In the UK, national specialist centre referrals did not find an increase in the incidence of CTEPH over 12 months or detect a single case clearly associated with COVID-19.96 Given that the median lag time from index PE to CTEPH diagnosis has historically been 12.5 months,97 it is possible that this chronic disease is yet to manifest at scale.

The apparent lack of COVID-19-related CTEPH may be due to clot burden affecting more distal segmental anatomical locations within the pulmonary vasculature as reported by numerous studies.93-95 There is evidence that subsegmental disease may represent in situ thrombosis (immunothrombosis) due to local inflammation.98,99 Immunothrombosis, as opposed to thromboembolism arising from distal deep vein thromboses (DVT), is suggested as a likely mechanism as the majority of COVID-19-related PE do not have concurrent DVT.100 It is unclear what prognostic and treatment implications this phenotypically distinct process has relative to classical thromboembolus. The balance of future risk of re-thrombosis is yet to be defined.

Even with a lack of demonstrable CTEPH, patients may have chronic symptoms and clinically relevant biomarkers that meet the definition of persistent pulmonary embolism impairment (PPEI).101 This emerging syndrome has a two-year cumulative incidence of 16% post-PE in a non-COVID-19 context.102 The incidence and relevance of PPEI following COVID-19-related PE is yet to be determined.

There is some evidence implicating microvascular thrombi in post-acute COVID-19 morbidity. Autopsy studies more often report thrombosis in situ or microthrombi than PE.103 Endothelial damage in the form of inflammation or necrosis are commonly reported pathological findings103,104 and on electron microscopy.105 Abnormalities on hyperpolarised xenon MRI have been demonstrated in chronically symptomatic patients with normal CT imaging months after the acute illness.106 Dual-energy CT has also been used to quantify perfusion abnormalities not apparent on visual assessment of contract-enhanced CT.107 There is evidence from imaging studies of concurrent pathological processes including embolic disease in the macro-vasculature alongside smaller vessel disease.89 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.108

There is a pressing need to clarify the extent of vascular involvement, especially in the post-acute phase, specifically because this could inform therapy options for ongoing and prospective clinical trials. There is a clear need for further research into defining the incidence, mechanisms, diagnostics, and treatment of chronic pulmonary vascular disease following COVID-19. With regard to treatment, the HEAL-COVID trial recently reported that two weeks of anti-coagulant 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.109 However, the therapy in this study was prescribed to individuals with clinical equipoise and not those with an established clinical indication for anti-coagulation. An active multi-centre trial (STIMULATE-ICP; ISRCTN10665760) comparing the efficacy of 12 weeks of anti-coagulant, anti-inflammatory, and antihistamine therapy, in Long COVID, will provide further insight into therapeutic options in the post-COVID-19 population.

**Pre-existing respiratory diseases 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 consequent to public health measures. In people with well-controlled, mild-to-moderate asthma systematic reviews have not shown an increased risk of severe COVID-1932 and overall, people with well-controlled asthma are not at increased risk of COVID-19-related death.4,32 However, the risk of COVID-19-related death was increased in people with asthma who had recently needed oral corticosteroids for their asthma,4 were hospitalized with severe asthma110 and in those people with other chronic respiratory diseases.4 Following hospitalisation for COVID-19 there is an increased risk of adverse respiratory sequelae,111 including increased risk of death from lower respiratory tract infection and other respiratory complications.112 In those hospitalised or managed in the community for COVID-19 infection, there are increased symptoms and inhaler use in people with asthma or COPD, but whether this is worsening asthma/COPD control or Long COVID related symptoms is unclear.113 Several studies have included serial lung function testing up to 1 year following COVID-19.21,114-119 The group mean data from these studies consistently shows normal FEV1/FVC ratio with a normal FEF25-75 where reported. The largest of these studies described that 10% of the participants had evidence of airflow obstruction, but this was in keeping with the proportion that had pre-existing obstructive lung disease.117 In contrast, most of these studies report abnormal lung diffusion in approximately one-third of patients. Similarly, imaging studies have identified abnormalities in thoracic CT in up to 25% of cases after 1-year follow-up.62 In people with persistent dyspnoea 6 months post-COVID with normal thoracic CT and lung function exploratory hyper-polarised Xenon-129 MRI imaging shows damage to the alveolar-capillary possibly contributing to their breathlessness106 but again suggesting this is not due to new obstructive lung disease. Post-infective bronchiectasis could be predicted following COVID-19. In contrast to the influenza A pandemic (H7n9) where bronchiectasis was reported in 24% of survivors,120 bronchiectasis was rarely observed post SARS-CoV-1 and is present in ~1% of cases 1-year after COVID-19 in the Wuhan study.118 Intriguingly, SARS-CoV-2 viral entry and replication is impaired in cystic fibrosis airways due to ACE2 downregulation mediated by dysfunctional cystic fibrosis transmembrane conductance regulator.121 This is consistent with the observation that having cystic fibrosis is not a risk factor for acute severe COVID infection and lung function is stable post-infection compared to pre-existing disease.122,123

**Extra-pulmonary post-COVID sequelae**

**Reduced exercise tolerance**

Like many other long-term conditions, reduced exercise tolerance is a significant factor in the symptoms and functional limitation seen post COVID-19. The factors contributing to this reduction in exercise tolerance remain unknown, but bed-rest in other-wise healthy individuals results in rapid onset muscle wasting,124 reduced muscle endurance, and denervation.125,126 Even more profound muscle loss is seen in the inpatient hospital setting, particularly in intensive care units, where additional mechanisms of inflammation, hypoxia, and nutritional imbalance occur.127,128 Thus, it is likely that deconditioning is a contributing factor to the reduction in exercise tolerance seen following COVID-19. This has been explored using cardiopulmonary exercise testing (CPET) which demonstrates patterns of response consistent with the presence of reduced muscle aerobic capacity.129,130 Indeed, in a Norwegian cohort, 12 months post-hospital discharge for COVID-19, the most prevalent exercise limitation was deconditioning, defined as a peak oxygen uptake <80% predicted in the absence of a ventilatory limitation and no evidence of cardiocirculatory pathology. Reductions in the capacity for aerobic ATP generation usually occur with a reduction in the gas exchange threshold, meaning aerobic mechanisms of energy provision are supplemented with less efficient anaerobic mechanisms at a lower oxygen uptake. This results in an earlier onset of the fatigue cascade and a progressive increase in the oxygen cost of exercise, increasing 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 deconditioning and symptoms.21

**Frailty**

Physical deconditioning leads to associated loss of muscle mass and strength which may have profound consequences, especially in the elderly, predisposing to physical frailty. Frailty is a term that refers to individuals at increased risk of adverse health outcomes due to reduced resistance to stressor events.131 COVID-19, like other acute infections, provided a stressor that was both severe and extremely widespread both among individuals who were frail before their illness and those at risk of becoming frail. Early studies indicate that 20% of COVID-19 survivors will have or be at risk of frailty132 and as with frailty in chronic respiratory disease, it is closely associated with the degree of dyspnoea.133

The clinical management of frailty relies on both identifying individuals living with frailty and, more widely, those at risk of development of frailty. The comprehensive geriatric assessment134 provides a well-established framework from which these assessments can be performed though modifications in focus may be important given the younger age demographic and more specific stressor event for COVID-19 survivors living with frailty.135 Key domains to be assessed include physical inactivity, weakness, polypharmacy, low-mood, and social isolation, with clear pathways and management strategies available for onward referral.132 Wider recognition of social inequality is also crucial in the review of people following COVID-19, as it is a major risk factor for both infection136 and presence of physical frailty.135

Recent evidence has suggested that unintentional weight loss is the most common contributor to the physical frailty phenotype in the first six months following a COVID hospitalisation, highlighting the need for nutritional assessment and intervention.135 Importantly it should be recognised in the context that most people who were hospitalised with COVID-19 had a raised body mass index,21 so simply increasing nutritional intake is not the solution. Other drivers of frailty in this cohort include dyspnoea, low physical activity, and muscle weakness.104,135 Combining this with other data highlighting the high frequency of persistent breathlessness, muscle weakness, and fatigue,62 as well as low mood and cognitive impairment,21 a comprehensive assessment with provision for interventions addressing these areas may be optimal.

We postulate that the pulmonary and extra-pulmonary sequelae of COVID described in this review may contribute to breathlessness in COVID-19 survivors (Figure 2). Non pharmaceutical interventions may attenuate the disabling sensations of breathlessness in the post COVID-19 population following a comprehensive assessment.

**Assessment of breathlessness**

Breathlessness is a complex symptom that is inconsistently predicted from measures of lung function. Where a pathological driven deficit exists, treatment for example with bronchodilators does not necessarily ameliorate breathlessness. The complexity of breathlessness has been described in the Breathing, Thinking, Functioning (BTF) clinical model137 acknowledging that this debilitating symptom can be influenced by physiology (including pre-existing respiratory conditions), anxiety, previous experiences of breathlessness, and lastly the level of function (including deconditioning). Importantly the relative contribution of all these factors can vary among individuals. This model was developed for chronic respiratory disease but resonates for those with breathlessness post COVID-19.

The treatment should be guided by a detailed assessment that should include routine spirometry; however, there is a paucity of data around lung function after COVID-19 due to the pandemic restrictions and need for personalised protective equipment. Even the largest hospitalised cohorts report pulmonary function tests in 230/806 (28.5%) of participants and testing is likely to be biased towards adults with a clinical indication and include those with pre-existing disease. The assessment should also include validated questionnaires; the Borg breathlessness scale or MRC dyspnoea scale are commonly used but do not themselves explore the sensations of breathlessness such as muscle work/effort, mental effort, air hunger, chest tightness, and hyperventilation. In contrast, questionnaires, such as the Dyspnoea-12 or the Multi-Dimensional Dyspnoea Profile, explore the multidimensional components of breathlessness.138,139 Depending on the breathlessness presentation, the assessment may warrant tools for assessing altered breathing patterns, such as the Nijmegen questionnaire (specifically for hyperventilation-syndrome) and the Breathing Pattern Assessment Tool (BPAT).140,141 The BPAT has a sensitivity and specificity of 90% and 78% respectively in diagnosing breathing pattern disorder in COVID-19.142 A CPET may also be indicated where there is diagnostic uncertainty relating to breathlessness, with more complex investigations such as MRI and electromyography possible. Hyperpolarised MRI can identify changes in gas transfer and tissue plasma abnormalities that may contribute to breathlessness presentation,143 whereas, electromyography has been used to demonstrate increased inspiratory muscle activation post-COVID-19 that may indicate underlying interstitial pathology, myopathy, deconditioning or anxiety.144

**Rehabilitation and care approaches**

The management of respiratory symptoms in the post COVID-19 population broadly falls into two categories: a formal rehabilitation programme or a largely physiotherapy-based approach to dyspnoea management. There is a paucity of data describing effective management strategies for the post COVID-19 population, particularly from the low- and middle-income countries. The following section will explore post-ITU rehabilitation and rehabilitation for chronic respiratory disease that may inform long COVID services, before discussing physiotherapy based strategies to attenuate breathlessness.

**Post ICU rehabilitation**

There is a broad literature to draw on from the wider experience of critical illness to inform recovery services for the minority of patients with COVID-19 who require critical care. The National Institute for Health and Care Excellence (NICE) published the first clinical guideline detailing rehabilitation strategies for patients who survive an episode of critical illness in 2009.145 The Faculty of Intensive Care Medicine has issued further guidance on delivery of post-ICU services incorporating learning from the COVID-19 pandemic.146 A recent survey of UK hospitals reported that over 70% had inpatient multi-disciplinary post-ICU recovery services and out-patient services, demonstrating a substantial expansion of service provision compared with a previous national survey in 2013.147 Despite these guidelines, there is wide variety in models of care for the organisation of post-intensive care services.

The evidence base for rehabilitation after critical illness interventions remains weak. A wide range of interventions and follow-up services has been evaluated, which aim to improve recovery after critical illness across the three domains of post intensive care syndrome (physical, psychosocial, cognitive). For example, interventions targeting the physical health domain have included outpatient physical therapy, nutritional support, provision of a rehabilitation manual, and home-based rehabilitation.148 However, two Cochrane systematic reviews evaluating interventions demonstrated insufficient evidence of effectiveness for a range of post-ICU outcomes.149,150

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 specific interventions.145 One recently published screening tool, the Post ICU Presentation Screen (PICUPS) tool, was developed by a National Collaborative combining experts in critical care and rehabilitation medicine, in response to the greater number of post-ICU patients seen in services due to COVID-19.151 The 14-item checklist supports 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.

**Rehabilitation for chronic respiratory disease**

There is overwhelming evidence describing pulmonary rehabilitation as a key intervention to reduce breathlessness in COPD. The key outcomes are a reduction in breathlessness and psychological stress (anxiety and depression), and improved health-related quality of life, exercise capacity, and fatigue.152 There is an emerging evidence base for a similarly structured rehabilitation programme for individuals with ILD. The data identifies a significant and meaningful improvement in exercise capacity (measured by the six minute walk test) and health-related quality of life.153 An updated Cochrane review highlighted the longer term benefits of this intervention with gains extending to 12 months as compared to a control (usual care) group.153 There are several studies describing the benefits (and safety) of highly supervised rehabilitation in the management of pulmonary hypertension. Unlike COPD and ILD, most of the evidence is from highly supervised studies but benefits have been described for important outcomes such as functional capacity and breathlessness.154 Finally there is evidence suggesting that for those with a pre-existing respiratory disease and frailty that a pulmonary rehabilitation programme can positively shift the categorisation of frailty from frail to prefrail;155 currently, the acceptability of this format may be limited with a higher dropout rate in the frail compared to the non-frail group.

The management of exercise-induced desaturation, which can be profound in some individuals, has been a safety concern in ILD and similar concerns have been reported in Long COVID.156 However, the prevalence of desaturation at follow up post COVID-19 appears to be low, and not necessarily associated with impaired functional capacity.157 The American Thoracic Society (ATS) clinical practice guideline on home oxygen therapy for individuals who experience exertional hypoxemia (SpO2 ≤88%) includes a conditional recommendation for treatment with ambulatory oxygen, but this is based upon low-quality evidence.158 The management of exertional desaturation in Long COVID 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.

**COVID rehabilitation**

To utilise exercise based rehabilitation programmes modified for the Long COVID population would seem desirable. Rehabilitation was recommended early in the pandemic particularly for breathless individuals including those managed in primary care.159-161 To date there are few evidence-based therapeutic options described in the literature developed and tested for the Long COVID community with respect to breathlessness.162 However, this has been identified as a research priority by all key stakeholders.163 Within the limited body of research, there has been evidence to demonstrate the feasibility and safety of rehabilitation for those experiencing long COVID, which include face to face and digital modes of delivery.164-166 The advantages and disadvantages of these rehabilitation modes need to be addressed in the context of healthcare systems, but transport, social circumstances, and digital literacy are important to consider. 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 COVID rehabilitation demonstrated improvements in dyspnoea, physical function, and quality of life, pre- to post-programme in patients with post-acute COVID-19.167; however, there is a need for further research with high quality evidence, particularly in non-hospitalised patients.

**Breathing pattern disorders**

Acute SARS-Cov-2 infection can lead to altered breathing patterns with small cohort studies reporting altered breathing patterns in almost 20% of those hospitalised with COVID-19 and a slightly greater proportion of non-hospitalised patients referred to a specialist follow up clinics.168,169 The causes of 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 wearing masks/personal protective equipment.168 CPET can be used to support the diagnosis of breathing pattern disorder, including hyperventilation, where a submaximal test may be noted alongside an abnormal breathing pattern.170 Specifically in Long COVID, CPET has been used to identify dysfunctional breathing in 30% of patients when it is defined as hyperventilation (measured as an elevated V̇E/V̇CO2 slope) or an erratic breathing pattern (high variability in tidal volume and/or breathing frequency) in the absence of a respiratory limitation or impairment in O2 delivery/utilisation.171 A systematic review of CPETs in Long COVID reported a lower V̇O2peak in individuals with persistent breathlessness compared to those who had a full recovery post-COVID-19; although deconditioning was the most common pattern, breathing pattern disorder was also commonly reported.172

To date the effectiveness of breathing exercises and retraining following acute SARS-CoV-2 infection 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 exercise in COPD improving exercise capacity but observing no impact upon breathlessness.173 A Cochrane Review of breathing exercises for the management of asthma was favourable,174 which included brief physiotherapy interventions.175 A similar review for breathing pattern disorder (dysfunctional breathing) found no clear evidence for breathing exercises.176

In the interim whist evidence is being accumulated it should be recognised these interventions are low risk, may be valuable in Long COVID and have been proposed in the management of Long COVID by the World Health Organisation.177 Current reported studies of the management of breathlessness in Long COVID include an online singing based programme delivered by the English National Opera targeted those with breathlessness, and an inspiratory muscle training programme, both of which were home based.178,179In the former, participants’ mental health improved measured by the SF-36, but the physical component did not change. Importantly, the sensation of breathlessness was also reduced. Inspiratory muscle training secured a reduction in breathlessness as a component of a health-related quality of life score, but the overall score was unchanged. The mean predicted maximum inspiratory pressure improved from a mean of 92% to 109% post intervention.

**Conclusion**

The consequences of SARS-Cov-2 infection are far reaching, and the impact upon the respiratory system has been a focus in the post-COVID landscape. Pulmonary sequelae and extra-pulmonary disruption continue to be investigated. To date non-pharmaceutical options currently focus on breathing control, respiratory muscle retraining, and exercise-based rehabilitation delivered in a variety of formats. Whilst research is ongoing regarding the effectiveness of non-pharmacological interventions, patients can best be supported by an integrated MDT which includes respiratory and rehabilitation specialists at the core.

**Search strategy and selection criteria**

PubMed (MEDLINE) and CINAHL were used to search for articles published in English from database origin to March 1st 2023. Combinations of the following terms were included in 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, disordered breathing. The abstracts of original investigations and review articles, and the references of selected studies were screened. ClinicalTrials.gov was used to identify active and planned clinical trials of investigational medicinal products that may have anti-fibrotic effects in COVID-19 populations.

**Research priorities**

* What are the underlying mechanisms of Long COVID that drive the symptom of breathlessness?
* What is the optimal treatment for acute COIVID-19 to mitigate, or even prevent, the development of pulmonary fibrosis?
* Is thrombosis associated with COVID-19 phenotypically distinct from classical thromboembolic disease? What treatment and prognostic implications may this have?
* What is the optimal diagnostic or imaging modality for detection of post-COVID-19 pulmonary vascular disease?
* What are the mechanisms underpinning reduced asthma/COPD control post-COVID?
* What is the incidence of extra-pulmonary complications (e.g. frailty, sarcopenia) that contribute to breathlessness post COVID-19?
* Are rehabilitation and/or breathing exercises effective strategies for reducing breathlessness in the post-COVID population?

**Contributions**

The manuscript was initially developed by SJS; contributions were drafted by all authors (MB, ED, RE, NG, GJ, NL, HM, PM, JN, DS, SS, MT, and CB) and further developed by SJS, MB, CB, and RE. All authors contributed to critical review and revision of the manuscript. All authors had final responsibility for the decision to submit for publication.

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**Figures**

Figure 1. Resolution of thoracic CT changes over time following admission for acute COVID-19 infection. Two example patients showing the changes in thoracic CT findings in 2 scans acquired following discharge. Patient 1 with a CT scan acquired a) 2 weeks and b) 7 months post-discharge showing initially diffuse ground-glass opacification with consolidation and interlobular septal thickening and patient 2 with a CT scan acquired c) 2 months and b) 9 months post-discharge showing initially predominantly peripheral bilateral ground-glass opacification with later resolution on thoracic CT scans in both patients.

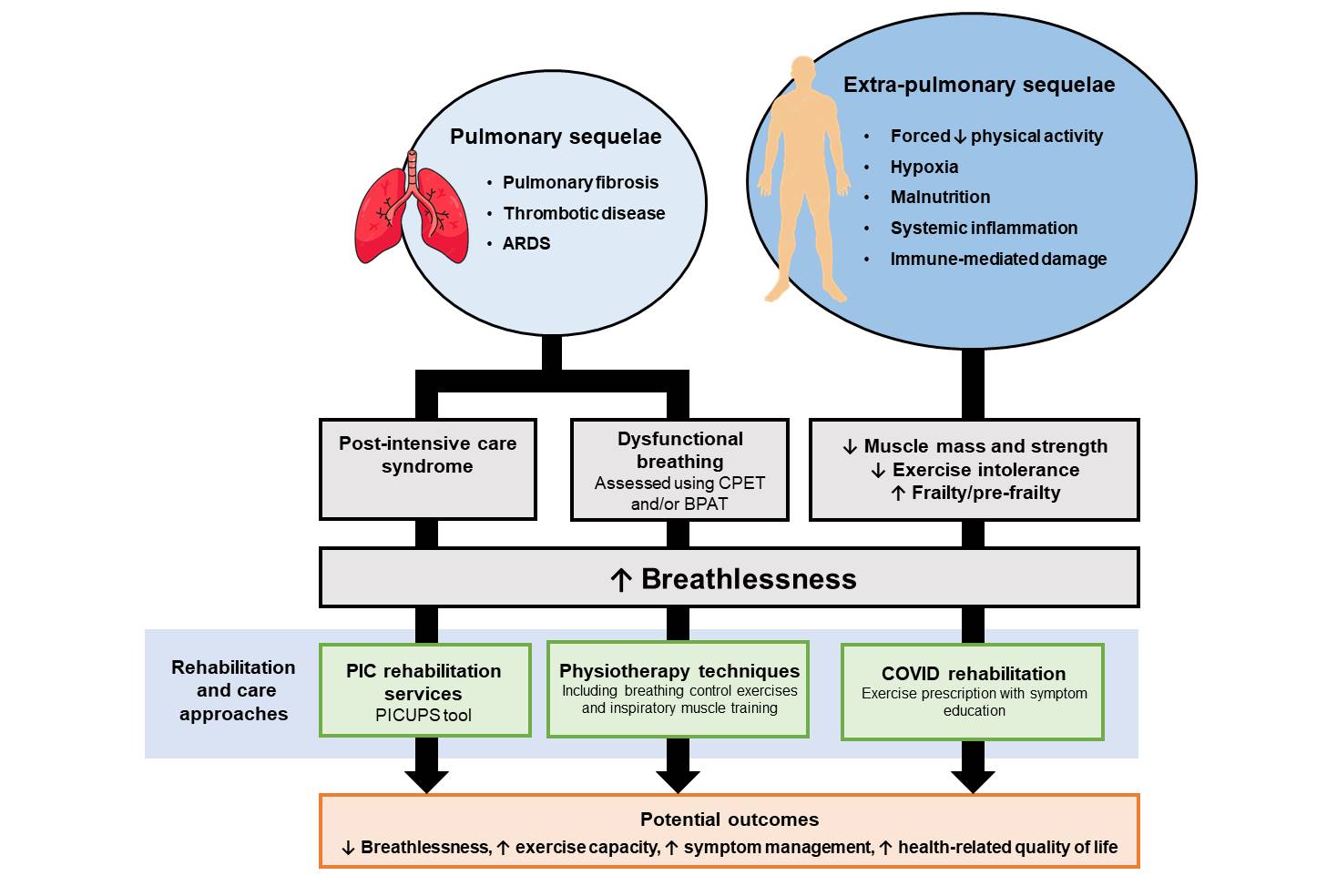
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Figure 2. Pulmonary and extra-pulmonary sequelae of COVID-19 that may contribute to breathlessness, with suggested rehabilitation and care approaches. ARDS: Acute respiratory distress syndrome, BPAT: Breathing Pattern Assessment Tool, CPET: Cardiopulmonary exercise testing, PIC: Post-intensive care, PICUPS: Post-intensive Care Unit Presentation Screen.

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