The Feasibility of Pulmonary Rehabilitation in Patients with Interstitial Lung Diseases Including Patients with Combined Pulmonary Fibrosis and Emphysema

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Abstract

Introduction: Interstitial lung diseases (ILD) are characterized by interstitial inflammation or fibrosis, leading to impaired gas exchange, shortness of breath, decreased exercise tolerance, and reduced quality of life. Combined pulmonary fibrosis and emphysema (CPFE) is the co-existing presence of pulmonary fibrosis and emphysema. Data describing the experience of tailored pulmonary rehabilitation program (PRP) in people with ILD is rare and in particular in patients with CPFE are lacking. This PhD aimed to determine the characteristics and prognosis of patients with CPFE in a United Kingdom cohort, and to assess the feasibility of inspiratory muscle training (IMT) as part of a PRP for patients with ILD including patients with CPFE.

Methods: A five-year retrospective single centre study was conducted at the regional ILD clinic. Then a feasibility study with a randomized controlled trial design was conducted Patients were randomized into intervention group IMT + PRP and a control group PRP only. The IMT was performed using POWERBreathe® twice daily. The PRP consisted of one session a week for 6-8 weeks.

Results: Retrospective study showed that 203 patients with CPFE were diagnosed. Mean age and Body Mass Index (BMI) for patients with CPFE were 72 years (*SD* = 8.7), and 28.1 kg/m² (SD = 4.4) respectively. Median survival time for patients with idiopathic pulmonary fibrosis (IPF) subtype CPFE n= 93 was 3.2 years (2.1-4.2).. Kaplan Meier analysis showed statistically significant differences between Gender at birth-Age-Physiology (GAP) stages with a p-value of 0.012 in patients with IPF subtype CPFE. PRP had an attendance and completion rates of mean of 87% and 64% respectively. No side effects were reported during the study. The maximum inspiratory pressure (MIP) improved in all participants.

Conclusion: Patients with CPFE were relatively old, majority male, with a history of smoking, and had poor prognosis. The GAP index and staging system demonstrated prognostic capability in patients with IPF subtype CPFE. At least half the patients with CPFE were not referred to PRP, indicating low referral rates. A tailored PRP program was feasible and well received in patients with CPFE, indicating that this was a viable and beneficial treatment option for patients with CPFE where therapeutic options are limited.

Declaration

I confirm that the work presented in this thesis is my own. I confirm that the thesis has stated when information has been taken from other sources.

Francesca Chambers and Laura McNeillie performed the exercise training.

Claire Donaldson and Lyndsey Langlands performed blood collection.

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List of Abbreviations

ILDs: Interstitial lung diseases

IPF: Idiopathic pulmonary fibrosis

CTD-ILD: connective tissue associated ILD

CT: Computed tomography

HRCT: High-resolution chest tomography

HP: Hypersensitivity pneumonitis

FVC: forced vital capacity

DLCO: diffusion capacity for carbon monoxide

MMF: mycophenolate mofetil

RA-ILD: rheumatoid arthritis-associated ILD

UIP: usual interstitial pneumonia

COPD: chronic obstructive pulmonary disease

CPFE: combined pulmonary fibrosis and emphysema

PFT: pulmonary function test

TLCO: transfer factor for carbon monoxide

FEV1: forced expiratory volume in one second

KCO: carbon monoxide transfer coefficient

6MWT: six-minute walk test

FIO2: fraction of inspired oxygen

NICE: National Institute for Health and Care Excellence

ATS: American Thoracic society

ERS: European Respiratory Society

HRQoL: health-related quality of life

PRPs: pulmonary rehabilitation programmes

6MWD: six-minute walk distance

IMT: inspiratory muscle training

PaO2: partial pressure of oxygen in arterial blood

PaCO2: partial pressure of carbon dioxide in arterial blood

SpO2: oxygen saturation

BMI: body mass index

GAP: Gender at birth, Age, and physiology

RVI: Royal Victoria infirmary

MDT: Multidisciplinary team

FVC%: FVC percentage predicted

TLCO%: TLCO percentage predicted

DLCO%: DLCO percentage predicted

mGAP: modified GAP score

dGAP: Diffusion GAP score

CPI: Composite physiologic index

PROMS: Patients reported outcome measures

MIP: Maximum inspiratory pressure

MCID: Minimal clinically important difference

K-BILD: King's brief interstitial lung disease questionnaire

FSS: Fatigue severity scale

HADS: Hospital anxiety and depression scale

MID: Minimal important difference

1MSTS: One-minute sit-to-stand test

MMP-7: Matrix Metalloproteinase 7

ELISA: Enzyme-linked immunosorbent assays

PA: Physical activity

MVA: Moderate and vigorous activity

EWGSOP: European Working Group on Sarcopenia in Older People's

BIA: Bioelectrical impedance analysis

ASM: Appendicular skeletal muscle mass

Chapter 1: Introduction

1.1 Interstitial Lung Diseases (ILD)

There are over 200 different interstitial lung diseases (ILDs). ILDs ranges from disorders that are extremely rare, such as lymphangioleimymatosis, to multisystem diseases like systemic sclerosis or rheumatoid arthritis, to more common diseases like idiopathic pulmonary fibrosis (IPF) (Wijsenbeek et al., 2022).

The interstitial space is attached to the alveolar epithelium on one side and the capillary endothelium by the other side. In the interstitial space, there are lymphatic vessels, few fibroblasts, and extracellular matrix proteins like collagen. In healthy individuals, the interstitium structure offers structural support to the alveolus and is only a few micrometres thick, thereby enabling effective gas exchange. Interstitial lung diseases cause either fibrosis or inflammation within the interstitial space, which leads to impaired gas exchange and the eventual consequence of breathlessness, and in many respiratory failure, and mortality (Wijsenbeek et al., 2022).

1.1.1 Classification of interstitial lung diseases

ILDs can be broadly classified idiopathic, autoimmune-related ILD, exposure-related, cysts or airspace filling ILD, sarcoidosis, and other orphan diseases (see Figure 1). With this broad classification of ILD, the onset of the disease can be slow and progressive or can be acute and life-threatening (Wijsenbeek et al., 2022).

In order to diagnose and classify ILD, a combination of clinical, imaging, and in certain cases pathological information is utilized.

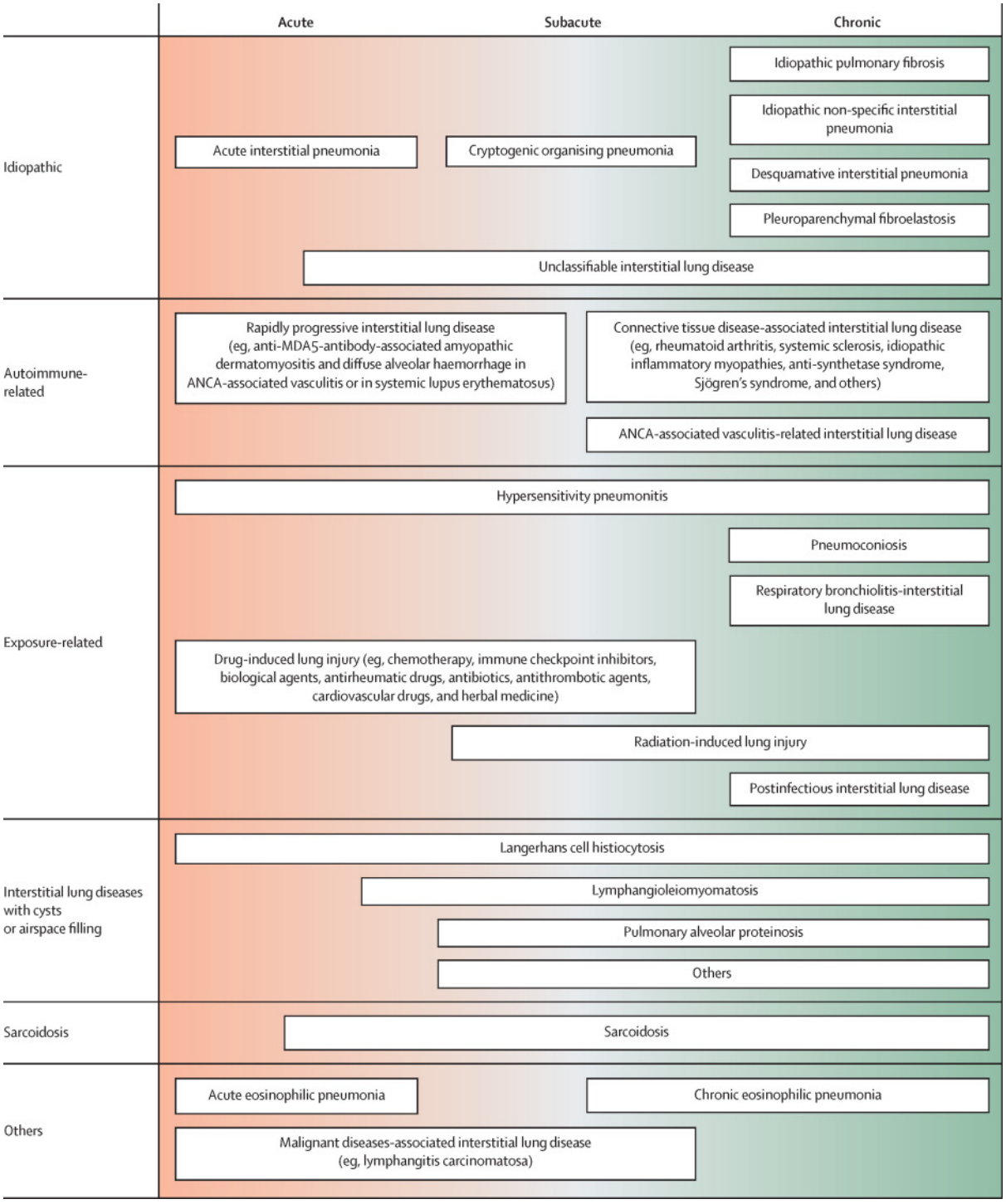

Figure 1 Classification of interstitial lung diseases (Wijsenbeek et al., 2022)

1.1.2 Epidemiology

Epidemiological data indicate that the incidence of ILD varies widely by age, gender, race, and geographical area. Idiopathic pulmonary fibrosis is more common in those aged over 60 years, male, with an estimated incidence of 0.9-9.3 cases per 100,000 people/year in Europe and North America and 3.5-13.0 cases per 100,000 people/year in South America and Asia (Natsuizaka et al., 2014, Duchemann et al., 2017, Maher et al., 2021). In contrast IPF, half the cases of idiopathic non-specific interstitial pneumonia and connective tissue disease associated ILD (CTD-ILD) occur in those aged 40-60 years and in older women (Belloli et al., 2016, Raimundo et al., 2019, Li et al., 2021). There are fewer reported instances of other ILDs, with available data suggesting that they are less common than IPF (Raimundo et al., 2019, Li et al., 2021, Fernández Pérez et al., 2018). The overall general prevalence of ILD is 6.3-76.0 cases per 100 000 people (Olson et al., 2021).

1.1.3 Diagnosis

1.1.3.1 Clinical presentation

ILDs have a non-specific clinical presentation, with dyspnoea, coughing, and fatigue being the most common symptoms (Behr et al., 2015, Guenther et al., 2018, Singh et al., 2017). Some people may have symptoms for many months or years before being diagnosed (Hewson et al., 2017, Spagnolo et al., 2021). A physical examination of ILD reveals bibasilar crackles in 60%-79% of the patients. Clubbing is also common,but is not specific to ILD as it occurs in patients with other lung or heart diseases (Behr et al., 2015).The presence of extrapulmonary symptoms increase the possibility of ILDs related to systemic disorders. Joint, skin, hand, or muscle-related abnormalities can indicate a connective tissue disease (Fischer et al., 2015). In certain cases, early asymptomatic ILDs can be detected incidentally when computed tomography (CT) imaging or chest radiographs are conducted for other indications (Sverzellati et al., 2011).

1.1.3.2 Diagnosis

For ILD diagnosis a multidimensional approach is needed where clinical, radiological, physiological, and when needed histological data are used. Taking a through clinical history and performing a thorough examination are critical first steps in confirming the presence of ILD (Wijsenbeek et al., 2022). Work-related exposure to organic antigens such as moulds or from birds, certain drugs (like amiodarone, bleomycin, or nitrofurantoin), dust inducing pneumoconiosis (like asbestos, coal, or silica dust) all indicate external causes for ILD (Fernández Pérez et al., 2013). In addition, pulmonary function test results in patients with ILD commonly show a restrictive pattern and decreased diffusion capacity, although there can be normal lung function or an obstructive lung pattern in certain cases (Wijsenbeek et al., 2022). Although a chest x-ray might detect signs of ILD, subtle changes may be missed. High-resolution chest tomography (HRCT) of the lungs is the main key diagnostic test for ILD. HRCT paired with clinical findings is efficient in providing a diagnosis in as over two-thirds of patients with ILD (Wijsenbeek et al., 2022). Moreover, serum autoantibodies can aid in the diagnosis of the presence of a connective tissue disease (Suzuki et al., 2017). Cellular analysis of bronchoalveolar lavage fluid can be helpful when non-idiopathic pulmonary fibrosis ILDs are suspected. Further, Lymphocytosis from bronchoalveolar lavage is an indicator of hypersensitivity pneumonitis. The presence of eosinophilia from bronchoalveolar lavage supports the diagnosis of drug-induced lung injury or eosinophilic pneumonia. Bronchoalveolar lavage results can also be helpful in diagnosing certain conditions, such as Langerhans cell histiocytosis and pulmonary alveolar proteinosis, and also help exclude infections and malignancy (Meyer et al., 2012).

In certain patients in whom clinical, radiological, and bronchoscopic results fail to support a specific diagnosis after a multidisciplinary meeting, histopathological evaluation might be considered. Surgical lung biopsy performed using a video-assisted thoracic surgery is the gold standard histopathological procedure in ILD. Nevertheless, surgical lung biopsy procedure is associated with risks for complications of 30-day post procedure mortality of 1.5%-2.4%. Therefore,

surgical lung biopsy is not preferred and the risks and benefits of performing it should be weighted and discussed in multidisciplinary meetings and with the patient (Durheim et al., 2017, Hutchinson et al., 2016). Transbronchial lung cryobiopsy is a less invasive approach for acquiring biopsy samples compared to surgical lung biopsy. Further, transbronchial lung cryobiopsy has been indicated to have the same diagnostic accuracy with less incidence of complication than surgical lung biopsy, thereby providing a good alternative (Troy et al., 2020, Tomassetti et al., 2020, Maldonado et al., 2020).

1.1.4 Management

Few ILDs have evidence-based therapy guidelines, and off-label use of medications is frequent. Therefore, patients' education and shared decision-making that weigh the benefits and risks of treatment are of utmost importance. Multidisciplinary management is recommended and important in patients with progressive ILDs such as IPF (Wijsenbeek et al., 2022).

In the last decade, there have been major advances in the treatment of ILDs. In patients with IPF, randomised controlled trials have shown that antifibrotic medications were effective and revealed that immunosuppressive therapy is harmful (Richeldi et al., 2014, Dale et al., 2014, Raghu et al., 2012, Farrand et al., 2020).

For patients with IPF, antifibrotic medication with either pirfenidone or nintedanib is recommended by international guidelines (Raghu et al., 2015b). Both antifibrotic medications pirfenidone and nintedanib have shown to slow down decline in lung function, protect against acute exacerbations, and improve survival (Richeldi et al., 2014, King et al., 2014, Dempsey et al., 2019, Petnak et al., 2021). The most common adverse events for antifibrotic medication are nausea with pirfenidone and diarrhoea with nintedanib. Pirfenidone can also possibly cause phototoxicity. In drug trials, 7% of participants in the pirfenidone and nintedanib trials had liver toxicity (King et al., 2014, Richeldi et al., 2014). Regular follow-up is recommended when antifibrotic medication are prescribed (Wijsenbeek et al., 2022). Recently, in

addition to its use in IPF, nintedanib has been approved to treat patients with other forms of progressive pulmonary fibrosis. Nintedanib has also been shown to be effective in patients with progressive pulmonary fibrosis by reducing the rate of decline in lung function by half over a period of 52 weeks (Flaherty et al., 2019, Wells et al., 2020).

Hypersensitivity pneumonitis (HP) is the most prevalent exposure associated with ILDs. The identification and removal of the triggering antigen are crucial for enhancing outcome in patients with HP (Fernández Pérez et al., 2013), which can occasionally be challenging to achieve. No standard algorithm exists for the pharmacological therapy of HP (Hamblin et al., 2022). There is limited evidence that corticosteroids slow the rate of progression of fibrotic HP or even result in long-term benefits (De Sadeleer et al., 2020, Mönkäre and Haahtela, 1987, De Sadeleer et al., 2018). Immunosuppressants are commonly prescribed to patients with HP (Wijsenbeek et al., 2019), but the evidence supporting their use is limited. There have been concerns over the chronic use of immunosuppression due to the harmful effects of azathioprine and prednisone seen in patients with IPF (Raghu et al., 2012). An improvement has been seen in forced vital capacity (FVC) and the diffusion capacity for carbon monoxide (DLCO) after one year of therapy with azathioprine or mycophenolate mofetil (MMF) (Morisset et al., 2017a, Fiddler et al., 2019, Terras Alexandre et al., 2020). Moreover, nintedanib which is an antifibrotic medication, has recently shown benefit in treating patients with progressive fibrotic ILDs including HP (Flaherty et al., 2019).

In patients with rheumatoid arthritis-associated ILD (RA-ILD), various immunosuppressive drugs—such as cyclophosphamide, methotrexate, azathioprine, and rituximab—have been shown to decrease the loss in lung function (McDermott et al., 2021). Immunosuppression should be used with caution in patients with RA-ILD, as usual interstitial pneumonia (UIP) is the most common pattern of fibrosis and—based on data from patients with IPF—immunosuppression in this situation may be harmful (Raghu et al., 2012). Contrary to previous data suggesting that methotrexate is associated with ILD in patients

with rheumatoid arthritis, data from studies in the general rheumatoid arthritis population demonstrated that methotrexate does not increase the risk of RA-ILD (Roubille and Haraoui, 2014, Juge et al., 2021). For patients with other CTD-ILD —such as Sjögren's syndrome, systemic lupus erythematosus, mixed connective tissue disease, and those with undifferentiated connective tissue disease—there is a lack of evidence-based therapy (Jee et al., 2021).

1.2 Combined Pulmonary Fibrosis and Emphysema (CPFE)

IPF and pulmonary emphysema are two different pathophysiological conditions that have long been recognized (Wiggins et al., 1990, Cottin et al., 2005). IPF is a chronic ILD characterised by fibrosis of an unknown aetiology. This typically affects adults and is characterised by a usual interstitial pneumonia histopathological pattern (Raghu et al., 2011). It is the most common type of the presenting ILDs and, specifically, the most common of the idiopathic interstitial pneumonias specifically. IPF has an estimated prevalence approximately 50 per 100,000. Its prevalence increases markedly with age; in patients younger than 50 it is almost absent but in those older than 75 it is estimated to be present in 0.2% of people (Raghu et al., 2006). IPF has a poor prognosis, with a median survival rate of only three years (Kim et al., 2006).

Chronic obstructive pulmonary disease (COPD) is a very common condition that is preventable and treatable. It is characterized by airflow limitation and presence of respiratory symptoms. The airflow limitation is caused by a combination of small airways, obstructive disease, and destruction of parenchyma (emphysema); the contribution of the two mechanisms differs from patient to patient. COPD is most commonly caused by tobacco smoking, indoor and outdoor air pollution, and occupational exposures. Other contributions like genetics, poor lung growth during childhood, and airway hyper-reactivity (Eisner et al., 2010, Salvi and Barnes, 2009, Tashkin et al., 1992) are also believed to be potentially important contributors. Recently, the presence of both IPF and COPD in the same patient has been increasingly recognized, presenting as a particularly aggressive ‘overlap’ pathophysiology (Dias et al., 2014).

Co-existing pulmonary fibrosis and emphysema was formally described for the first time in 1990 by Wiggins et al., who identified eight heavy smokers complaining of severe breathlessness, with upper lobe emphysema and fibrosis, preserved lung volumes, and low DLCO (Wiggins et al., 1990).

In 2005, the term combined pulmonary fibrosis and emphysema (CPFE) was first defined by Cottin et al. who described the CT results of 61 patients with pulmonary

fibrosis in the lower lobes and emphysema in the upper lobes (Cottin et al., 2005). Ever since this report, there has been an increased interest in this newly defined condition. Patients with CPFE typically present with a complaint of severe breathlessness and cough, are mainly male, and commonly have a history of heavy smoking. On physical examination, digital clubbing is seen and crackles are heard in the lower lung lobes. Patients with CPFE also commonly have pulmonary hypertension, which usually indicates a poor prognosis (Dias et al., 2014).

Patients with combined pulmonary fibrosis and emphysema have different pulmonary function test (PFT) results than patients with either pulmonary fibrosis or emphysema alone. In fact, their PFTs show relatively preserved dynamic lung volumes as a result of the counteracting effect of pulmonary fibrosis and emphysema. In addition their transfer factor for carbon monoxide (TLCO) is decreased (Ciccarese et al., 2016). Therefore, TLCO needs to be measured in order to indicate the physiological impact of the disease pathology that might be underestimated by dynamic lung volume measurements, such as FVC, which are used to indicate disease activity in ILD. The median survival in reported series of people with CPFE has ranged between 2.1 to 8.5 years (Malli et al., 2019, Sugino et al., 2014, Todd et al., 2011, Zhang et al., 2016b). Patients with CPFE may therefore have a particular poor prognosis but the scarce literature is variable and contradictory.

1.2.1 Epidemiology

Patients with fibrotic interstitial lung diseases who are current smokers or former smokers commonly have emphysema as well. The prevalence of CPFE varies according to the population examined and the definition criteria applied, ranging from 8%–67% of patients with IPF (Cottin et al., 2022a). The prevalence of CPFE in the general population is uncertain because most of the data originates from patients who have an indication for CT imaging (Cottin et al., 2022b).

1.2.2 Aetiology

Exposures, ageing, and genetic predisposition

CPFE has been consistently linked to cigarette smoking and being male. CPFE occurs in males nine time more than that in females, and this difference is not entirely explained by the longer history of smoking in males (Jankowich and Rounds, 2012). History of smoking is reported by almost all patients with CPFE, with an average exposure of 40 pack-years, except for patients with HP or connective tissue disease (Jacob et al., 2018b, Raghu et al., 2020). Despite its most common association with cigarette smoking, CPFE can also occur in non-smokers, but most commonly in patients with CTD. Occupation-related inhalational exposures, such as asbestosis and silicosis, have also been found to be associated with CPFE (Akira et al., 2003, Copley et al., 2007, Huuskonen et al., 2004). In addition, genetic predisposition when combined with other risk factors like cigarettes smoking, exposures, and/or ageing may increase the likelihood of developing CPFE (Cottin and Cordier, 2009).

1.2.3 Diagnosis

1.2.3.1 Clinical presentation

Patients with CPFE are usually male, with an average age of 65–70 years. They present with symptoms of exertional dyspnoea and cough (Cottin et al., 2022a). Pulmonary hypertension and lung cancer are the most prevalent comorbidities in CPFE (Cottin et al., 2022a). Peripheral vascular disease, coronary artery disease, and diabetes are also common comorbidities in CPFE (Zhang et al., 2016b, Girard et al., 2014).

1.2.3.2 Imaging in combined pulmonary fibrosis and emphysema

Imaging studies play a major role in the diagnosis of CPFE. Even though chest X-rays are less sensitive than HRCT scans, they can still indicate hyperlucency in the upper lung fields and an interstitial pattern in the basal lung fields and subpleural region (Cottin et al., 2005, Dias et al., 2014).

Emphysema appears as areas of low attenuation (Hansell et al., 2008) and can be classified as centrilobular, paraseptal, or panacinar emphysema (Lynch et al., 2015). Interstitial fibrosis appears as areas of high attenuation with a reticulation, ground-glass opacities, honeycombing, and/or traction bronchiectasis (Cottin et al., 2022a). In patients with CPFE centrilobular or paraseptal emphysema is seen in the upper lung fields, and septal thickening, reticular opacities, honeycombing, and ground glass appearance are seen in lower lung fields (Cottin et al., 2005). An example of CPFE HRCT imaging is shown in (see Figure 2) and (see Figure 3), which is a HRCT of one our clinic patients here at the Royal Victoria Infirmary (RVI), Newcastle upon Tyne, United Kingdom.

Matsuoka et al. conducted a study to assess the correlation between quantitative objectively computed HRCT scans and PFT results in patients with CPFE (Matsuoka et al., 2015). The percentage of low attenuation area represented areas with emphysema, while a high attenuation area represented areas with interstitial fibrotic lesion. They found a significant correlation between indicators of restrictive

pattern, which is indicated as decrease in FVC, TLC, and FRC with percentage of high attenuation area. They also found a correlation between DLCO and percentage of high attenuation area. Therefore, it has been shown that percentage of high attenuation area may be beneficial in the evaluation of the degree of fibrosis, and also that pulmonary function is of importance in CPFE (Matsuoka et al., 2015).

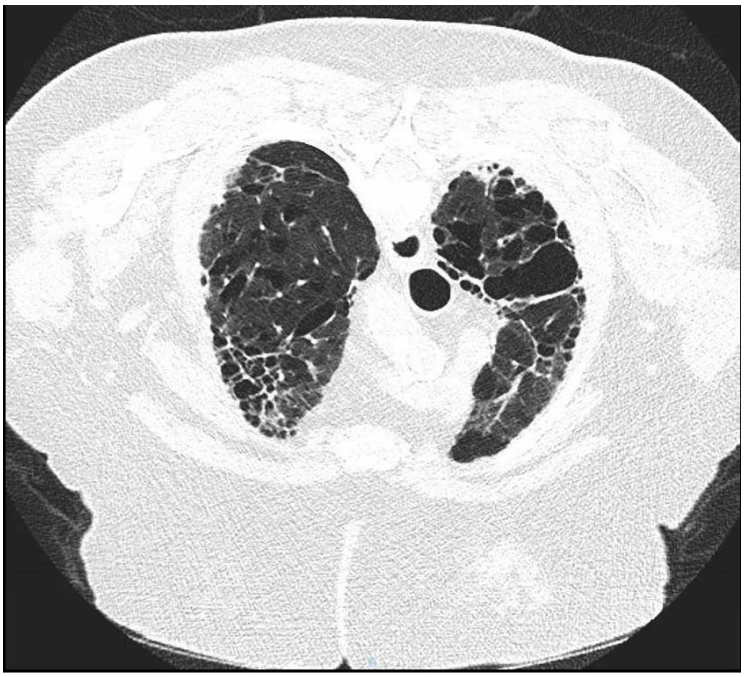

Figure 2 Typical CPFE feature indicating emphysema in the upper lung field in one of our patients

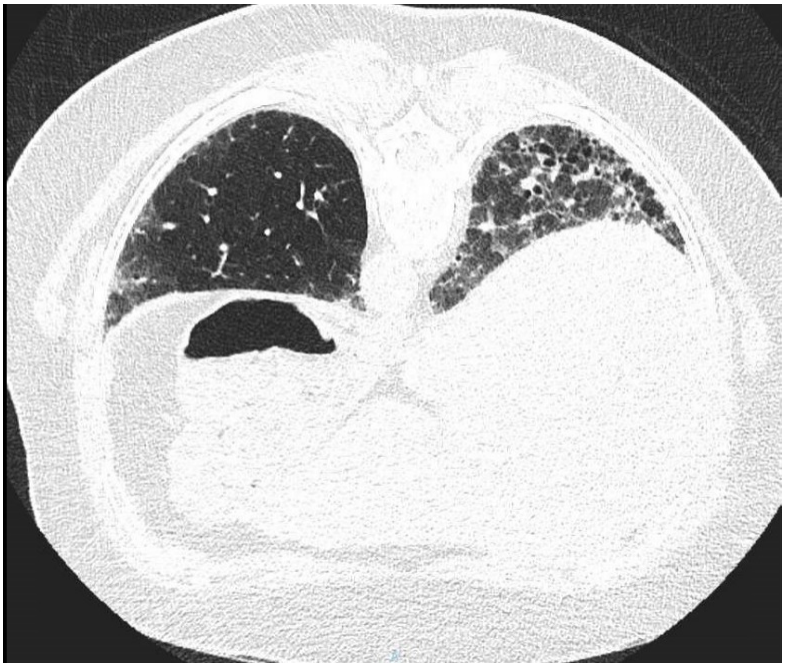

Figure 3 Typical CPFE feature showing lower lung field honeycombing that indicates the usual interstitial pneumonia (UIP) pattern in one of our patients.

Interestingly, a unilateral pattern is displayed here, although this is not always the case.

1.2.3.3 Pulmonary function tests

Patients with combined pulmonary fibrosis and emphysema have different PFT results than patients with either pulmonary fibrosis or emphysema alone. This has important implications for treatment, which is discussed subsequently. The PFTs of CPFE patients show preserved lung volumes and airflow rates. This is because pathologically pulmonary fibrosis can cause a traction that supports the small airway, which prevents them from collapsing on expiration—something that is observed in emphysema. Physiologically, this tends to preserve the forced expiratory volume in one second (FEV_1) and FVC (Jankowich & Rounds, 2012). Although preservation of spirometry values is seen in patients with CPFE, some patients do have airflow obstruction that is observed as post bronchodilation FEV_1/FVC ≤70% depending on the degree of the fibrotic and emphysematous aspects of the disease (Kitaguchi et al., 2014).

In contrast, TLCO can be rather significantly decreased in CPFE (Cottin, 2013, Kitaguchi et al., 2014, Mura et al., 2006). The reduction in diffusing capacity of carbon monoxide seen in CPFE is caused by a reduction in pulmonary capillary blood volume and vascular surface area due to pulmonary fibrosis and emphysema. In addition, thickening of the alveolar membrane caused by pulmonary fibrosis leads to less efficient gas exchange (Jankowich and Rounds, 2012).

When compared to IPF, patients with CPFE have larger lung volumes FVC and TLC, similar FEV_1, and lower TLCO and carbon monoxide transfer coefficient (KCO) (Cottin et al., 2022a). Compared to COPD, patients with CPFE have lower hyperinflation, preserved FEV_1, and FEV_1/FVC, and lower TLCO (Kitaguchi et al., 2013). Therefore the degree of pulmonary fibrosis and emphysema correlates better with the decrease in DLCO and the extent of pulmonary hypertension (Kitaguchi et al., 2014). Annual changes in PFT results can also show a significantly more rapid reduction in FEV_1/FVC values in patients with CPFE when compared to patients with IPF alone (Kim et al., 2014); moreover, a significantly larger decrease in FVC and VC is seen when compared to patients with

emphysema alone (Kitaguchi et al., 2013). Further, when compared to patients with emphysema only, the annual decrease in FEV_1/FVC is lower in patients with CPFE (Kitaguchi et al., 2013). Thus, it is recommended to use a combination of clinical presentation, imaging, and lung function results and there must be less reliance on FVC trends, as employed in other ILDs (Cottin et al., 2022a).

1.2.4 Management

1.2.4.1 General management

There are no clinical practice guidelines on the treatment of patients with CPFE. Management of CPFE is drawn from approaches applied in isolated COPD and from IPF studies that have subgroups of patients with CPFE (Cottin et al., 2022a). Smoking cessation should be provided to patients with CPFE along with oxygen therapy for those with respiratory failure. Patients with CPFE that continue to smoke have been found to have a worse prognosis than those who stopped smoking (Chae et al., 2015). In addition, it is reasonable to provide vaccinations for influenza and S. pneumonia (Papiris et al., 2013). Inhaled bronchodilators can be given to patients with airflow obstruction (Cottin, 2013). Even though more studies evaluating the effect of pulmonary hypertension therapy on patients with CPFE are still needed, the abovementioned therapies may improve hemodynamics (Mercurio et al., 2012, Sato et al., 2013).

1.2.4.2 Oxygen therapy

Oxygen therapy is provided for patients with resting hypoxaemia, exercise-induced hypoxaemia, and/or nocturnal hypoxaemia (Zhang et al., 2016a). For patients with IPF, clinical practice guidelines highly recommend oxygen therapy. (Raghu et al., 2011) An oxygen saturation of ≤ 88% at rest, during exertion, or at sleep it is an indication for home oxygen therapy. Prescribing home oxygen therapy should be based on results of six-minute walk test (6MWT) or treadmill tests, along with polysomnography or nocturnal oximetry (Lederer and Martinez, 2018).

In patients with IPF with resting hypoxemia, there are no data for evaluating the use of long-term oxygen therapy (Raghu et al., 2011). Indirect evidence was derived from patients with obstructive lung diseases from two large randomized clinical trials, which have shown survival benefits from long-term oxygen therapy. Therefore, current guidelines recommend the use of long-term oxygen therapy in patients with IPF with resting hypoxemia, even though there is a low quality of evidence of its effectiveness (Raghu et al., 2011). Dowman et al. have found that

the use of oxygen in IPF during exercise relieves exercise-induced hypoxemia, decreases dyspnoea, and improves exercise tolerance. The use of oxygen at rest at fraction of inspired oxygen (FiO2) of 0.50 is regarded as safe (Dowman et al., 2017a). More studies are needed in patients with ILDs when it comes to the use of ambulatory oxygen and its effect on exercise, quality of life, and breathlessness (Sharp et al., 2016).

1.2.4.3 Treatment for fibrosis: anti-fibrotic drugs

Pirfenidone and nintedanib are two novel antifibrotic treatments that slow the progression of mild to moderate IPF disease and other types of progressive pulmonary fibrosis by approximately 50% at one-year follow up (Richeldi et al., 2014, King et al., 2014). The National Institute for Health and Care Excellence (NICE) previous guidelines that recommend pirfenidone and nintedanib for treating patients with IPF with a predicted FVC of between 50% and 80%. Therefore, NICE guidelines did not recommend pirfenidone and nintedanib to patients with a predicted FVC of above 80% (Landells et al., 2013, Laurenson et al., 2016). Since patients with CPFE have preserved lung volumes with preserved FVC, these patients were excluded and were not prescribed antifibrotic medications despite the fact that they have significant and progressing lung disease. Others have been reporting that antifibrotic medications might be tolerated by patients with CPFE and help stabilize the progression of the disease (Oltmanns et al., 2014). A subgroup analysis of the INPULSIS trials for IPF with nintedanib showed no difference in the effect of treatment when mild to moderate emphysema was present (Flaherty et al., 2019). But it was not until recently that the (INBUILD trial of nintedanib) study has shown that in progressive fibrotic lung diseases other than IPF, the effect of treatment by nintedanib was the same across different types of ILD diseases (Flaherty et al., 2019). This has led to a change in clinical practice and allows patients with CPFE to be prescribed nintedanib. In patients with CPFE with HP or CTD-ILD, immunosuppressive and/or glucocorticoids might be beneficial (Wijsenbeek and Cottin, 2020).

1.2.4.4 Treatment for emphysema

Inhaled bronchodilators might be considered for patients with CPFE with significant airflow limitation (Dong et al., 2015). Surgical/bronchoscopic reduction of lung volume procedure removes emphysematous areas of the lungs, thereby enabling normal lung tissue to expand. Most patients with CPFE tend to be excluded from these procedures due their severely low DLCO (Fishman et al., 2001).

1.2.4.5 Lung transplantation

Lung transplantation should be considered for patients with CPFE at an advanced disease condition (Jankowich and Rounds, 2012). Age is a relative contraindication for lung transplantation and diagnostic uncertainty leads to diagnostic misclassification. Combined with the aggressive nature of the pathophysiology, this implies that lung transplantation is unlikely to be available for CFPE patients.

1.2.4.6 Pulmonary rehabilitation

Pulmonary rehabilitation and exercise are provided to patients with CPFE (Tomioka et al., 2016). Although there is a lack of studies that evaluate pulmonary rehabilitation in patients with CPFE, exercise and pulmonary rehabilitation are considered foundational management for patients with COPD and are increasingly recognized in Fibrotic ILDs (Cottin et al., 2022a).

1.3 Pulmonary Rehabilitation

The American Thoracic society (ATS) and the European Respiratory Society (ERS) have defined pulmonary rehabilitation in a 2013 statement as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies—which include, but are not limited to, exercise training,

education, and behaviour change—designed to improve the physical and psychological conditions of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviours" (Spruit et al., 2013).

Pulmonary rehabilitation is conducted by an interdisciplinary team comprising of physicians and other health care professionals, such as physiotherapists, respiratory therapists, nurses, behavioural specialists, psychologists, Dietitians exercise physiologists, social workers, and occupational therapists. Pulmonary rehabilitation should be personalised to specific needs of individual patients, based on initial and follow up assessments depending on disease severity and comorbidities. Pulmonary rehabilitation can be initiated at any stage of the disease, whether clinically stable or during or immediately after the exacerbation of the disease. The goals of pulmonary rehabilitation include reducing symptom burden, optimising exercise capacity, encouraging autonomy, increasing patient's involvement in daily life activities, improving health related quality of life, and inducing long-term health-promoting behaviour change (Spruit et al., 2013).

1.3.1 Exercise training

The main concepts of exercise training for patients with chronic respiratory disease are the same as those for healthy people or even athletes. For exercise training to be effective, the total training load should represent the individual's unique requirements, should exceed loads experienced in daily life activities in order to enhance aerobic capacity and muscle strength (namely, the training threshold), and should progress with improvement (Spruit et al., 2013).

1.3.1.1 Endurance training

The aim of endurance training is to enhance cardiorespiratory fitness and condition ambulatory muscles in order to increase exercise tolerance and decrease shortness of breath and leg discomfort (Armstrong and Vogiatzis, 2019).

Continuous moderately intensive exercise is recommended to enhance exercise capacity (Spruit et al., 2013). However, patients with severe ventilatory limitations cannot tolerate such intensities for a sufficient duration (Maltais et al., 1996). An alternative for these patients is high-intensity interval exercise training, which consists of repeated short periods of maximal/high intensity exercise, followed by periods of rest or low-intensity exercise (Vogiatzis et al., 2002). It has been shown that with interval training there was a decrease in symptoms of dyspnoea and leg discomfort, which permitted significantly higher amounts of work to be accomplished than continuous exercise (Vogiatzis et al., 2004).

Cycling on a cycle ergometer and/or walking on either a treadmill or flat surface are considered optimal exercises for endurance training (Spruit et al., 2013). The prescription of endurance training must be tailored to the individual needs of patients with chronic pulmonary disease. Stationary cycling has the advantage of providing an accurate implementation of exercise intensity and a higher load on locomotor muscles, and thereby causing lower oxygen desaturation when compared to walking (Man et al., 2003). Although for certain patients walking training on either a treadmill or a flat surface might be more beneficial and can result in improved walking capacity (Leung et al., 2010). Alternative endurance exercises include stair climbing, water-based workouts, and Nordic walking (Armstrong and Vogiatzis, 2019).

1.3.1.2 Strength (resistance) training

Resistance training is preformed through repetitive lifting or pushing of relatively heavy weights to train peripheral muscle groups. Resistance strength training is believed to be important for both healthy people and patients with chronic lung diseases (Garber et al., 2011, Spruit et al., 2013). In patients with chronic lung diseases, peripheral muscle dysfunction and muscle weakness are common extrapulmonary features encountered, and resistance training has shown to partially reverse such features and, therefore, diminish the impairment from the chronic disease (Troosters et al., 2005). In extant literature, the prescription of

resistance training varies widely, in terms of the number of repetitions, intensities, and methods of resistance strength training described (O'Shea et al., 2009). The ATS/ERS pulmonary rehabilitation guidelines recommend performing 6-12 repetitions in two to four sets with an intensity of between 50% and 85% up to a maximum of two to three times per week (Spruit et al., 2013).

1.3.1.3 Flexibility and stretching training

A typical component of many pulmonary rehabilitation programmes (is flexibility and stretching training, which is performed through exercises for the upper and lower body. It includes stretching of the major muscle groups like the calves, quadriceps, hamstrings, and biceps, and also motion exercises for the neck and shoulders (Armstrong and Vogiatzis, 2019).

1.3.2 Pulmonary rehabilitation in ILD

The symptoms experienced by patients with ILD include dyspnoea, fatigue, cough, anxiety, and depression. Health-related quality of life (HRQoL) is reduced in patients with ILD and it tends to deteriorate with disease progression. Evidence supporting pulmonary rehabilitation in ILD is still under development when compared to the strong evidence base available in support of the use of pulmonary rehabilitation in other chronic respiratory disease like COPD (Nakazawa et al., 2017).

A recent Cochrane review was published in 2021 by Dowman et al. reviewing pulmonary rehabilitation in patients with ILD. This included 21 studies with a total of 909 patients with ILD (Dowman et al., 2021). They have reported improvements in 6MWT by average of 40 meters. Improvements in quality of life and shortness of breath were also reported. Patients with IPF when compared to other ILD conditions have shown to have comparable benefits in exercise capacity, quality of life, and shortness of breath after pulmonary rehabilitation programme (PRP). Benefits have been maintained at 6 to 12 months post PRP patients when compared to those who did not attend PRP (Dowman et al., 2021).

Exercise training has been associated with short-term gains in patients with ILD. Aerobic exercises or both aerobic and resistance training have also been used. Nevertheless, the most efficient exercise training strategy has not yet been determined in patients with ILD. There have been a variety of exercise durations and frequencies of pulmonary rehabilitation session per week in reported studies, but it appears that longer programs with greater number of sessions results in greater benefits (Dowman et al., 2021).

1.3.2.1 Exercise limitation in ILD

Decreased exercise capacity is a key finding in ILD, and exercise limitation has been shown to be a better predictor of prognosis than lung function. It has been found that the six-minute walk distance (6MWD) in patients with IPF is an independent predictor of mortality (du Bois et al., 2014). Therefore, therapies that could potentially increase exercise performance have garnered increased interest due to their potential to positively impact ILD outcomes (Nakazawa et al., 2017). Multiple factors lead to exercise limitation in ILD including impairment of gas exchange and pulmonary circulation, muscle dysfunction, and ventilator dysfunction.

1.3.2.1.1 Impairments to gas exchange and pulmonary circulation

Gas exchange impairment occurs because of membrane thickening and/or pulmonary capillary destruction, thereby leading to reduced diffusion capacity and resulting in ventilation perfusion mismatch (Agusti et al., 1991, Nakazawa et al., 2017). Circulatory limitations due to pulmonary capillary destruction and pulmonary vasoconstriction due to hypoxemia results in cardiac dysfunction and, possibly, pulmonary hypertension. It has been shown that ILD patients with pulmonary hypertension (related to their pulmonary disorder) had shorter 6MWD, reduced oxyhaemoglobin saturation, and a decreased transfer factor when compared to patients without pulmonary hypertension (Raghu et al., 2015a).

1.3.2.1.2 Ventilation limitation

Patients with ILD may have an abnormal respiratory pattern, which may present as a high respiratory rate and low tidal volume, particularly during exercise. Nevertheless, an abnormal respiratory pattern may not cause a major limitation in exercise performance due to the capability of increasing minute ventilation and having a large ventilator reserve. Therefore, it is believed that factors other than reduced ventilation play a greater role in the reduced exercise performance in ILD than ventilation (Hansen and Wasserman, 1996, Harris-Eze et al., 1996).

1.3.2.1.3 Muscle dysfunction

Patients with ILD may have received glucocorticoids and immunosuppressive therapy, which can cause myopathy (Nakazawa et al., 2017). In patients with chronic respiratory disease, it has been found that corticosteroids used daily for over a year significantly reduced muscle function (Levin et al., 2014). In patients with COPD, an accelerated aging process and deficient nutritional status have an effect on muscle mass (AJRCCM., 1999). This relationship is still unknown in patients with ILD (Nakazawa et al., 2017).

1.3.3 Pulmonary rehabilitation in CPFE

Unlike in COPD, studies evaluating the effectiveness of pulmonary rehabilitation in patients with CPFE are rather limited. To my knowledge, there are only two published articles evaluating pulmonary rehabilitation in patients with CPFE; one is a case report and the other is a retrospective study. In 2015 a case report by De Simone et al. was the first to explore the effect of an aerobic physical retraining program for a patient with CPFE. They presented a case of a 65-year-old Caucasian man with CPFE and respiratory failure who was a previous smoker of 40 pack-years. The patient was receiving long-term oxygen therapy at a flow of 2.5L/min 24 hours a day (De Simone et al., 2015). Their patient underwent an intervention of four weeks of physical rehabilitation with moderate intensity aerobic and breathing exercises. The exercise program consisted of two 30-minutes sessions per day for five days a week. The program consisted of a session of aerobic exercise, followed by a breathing exercise session. At the end of the rehabilitation programme, arterial blood gas analysis showed an improvement in oxygenation which enabled to drop the patient's long-term oxygen therapy from 2.5 L/min to 1.5 L/min oxygen flow. The reduction seen in oxygen requirement was explained by De Simone et al. to be possibly due to the strengthening of respiratory muscles leading to improvements in exercise capacity. There were also improvements in quality of life, physical performance, and levels of depression and dyspnoea, but none in respiratory parameters. De Simone et al. concluded that even though studies with a large patient population evaluating long-term effects are necessary for conclusive results, PRP with aerobic and breathing exercises appeared to be beneficial for patients with CPFE and might be considered for their management (De Simone et al., 2015).

Tomioka et al. conducted a retrospective analysis study to evaluate the effect of pulmonary rehabilitation in patients with CPFE as compared to with patients with COPD. The study was conducted in an inpatient pulmonary ward where a three-week long PRP was performed. (Tomioka et al., 2016). Between March 2007 and February 2015, 17 participants with CPFE and 49 participants with COPD were included and completed the PRP. In participants with CPFE, improvements were

seen in FEV_1; nevertheless, there was no significant improvement seen in the 6MWT, Borg scale, oxygen saturation (SpO2), and distance. Regarding HRQL, significant improvements were seen in physical function; however, there was a significant worsening in social functioning. In participants with COPD, improvements were seen in FEV_1, six min walk test, and in four of the eight SF-36 subscales. Tomioka et al. concluded that patients with COPD obtained greater benefit from the short-term pulmonary rehabilitation than patients with CPFE. They recommended that future research should concentrate on developing a PRP specifically tailored to patients with CPFE (Tomioka et al., 2016).

1.4 Inspiratory Muscle Training

1.4.1 Background

While breathing, respiratory muscles are responsible for producing airflow to the lungs by lifting the ribs and expanding the chest wall during inspiration as well as reducing intrathoracic pressure and airway resistance (Gransee et al., 2012). According to a literature review conducted by Powers et al., endurance respiratory training increases the number of fibres and mitochondrial activity in the respiratory muscles. This review demonstrated the beneficial effects of training, indicating a decrease in oxidative stress and a delay in respiratory muscle exhaustion (Powers and Criswell, 1996).

1.4.2 IMT and chronic respiratory diseases

The ATS and ERS have recommended the addition of inspiratory IMT to PRPs for the treatment of patients with chronic lung diseases, particularly when inspiratory muscle weakness is present (Nici et al., 2006, Spruit et al., 2013).

A systematic review and meta-analysis in patients with COPD that evaluates the effect of IMT has shown that IMT in isolation was an effective therapeutic technique for enhancing inspiratory muscle strength, functional capacity, and lung function in patients with COPD, with no change in quality of life and dyspnoea (Figueiredo et al., 2020). Although IMT has been extensively evaluated in patients with COPD and asthma, studies evaluating IMT patients with ILD are limited and more data needed. A recent systematic scoping review by Hoffman et al. evaluating IMT in patients with ILD have shown that the addition of IMT in the treatment of patients with ILD requires further investigation, as only few studies currently confirm its efficacy. They have concluded stating that there is a gap in the literature about the effects of IMT on patients with ILD, despite the fact that published limited research tend to reveal advantages in terms of improvement in quality of life, activities of daily living, and exercise ability (Hoffman, 2021).

1.5 Summary

There are over 200 different ILDs, with IPF being the most prevalent. Patients with ILD present with symptoms of dyspnoea, coughing, and fatigue. CPFE is the co-existence of IPF and emphysema in the same patient. Patients with CPFE also present with symptoms of exertional dyspnoea and cough. Compared to other chronic respiratory diseases, such as COPD, evidence supporting pulmonary rehabilitation in patients with ILD is limited and still developing. In particular there is a need to evaluate the effect of pulmonary rehabilitation in patients with CPFE. Although the ATS and ERS have recommended the addition of IMT to PRPs for the treatment of patients with chronic lung diseases, there is a gap in the literature regarding the effects of IMT on patients with ILD. Future research should focus on evaluating PRP, the role of IMT, and the most effective exercise training strategy for patients with ILD. Future work to develop PRP tailored specifically to patients with CPFE is also needed.

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Chapter 2: Early Diagnosis of Idiopathic Pulmonary Fibrosis: A Narrative Review

2.1 Introduction

2.1.1 What is idiopathic pulmonary fibrosis?

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease of unknown cause (Raghu et al., 2022). It is characterised by irreversible loss of lung function due to lung fibrosis and typically presents with symptoms of chronic exertional dyspnoea and dry cough over a period of months to years (Lederer and Martinez, 2018, Raghu et al., 2022).

IPF remains a rare disease with worldwide incidence recently reported as 0.09-1.3 and prevalence of 0.33–4.51 per 10,000 (Maher et al., 2021). The prevalence of IPF appears to be increasing though it is unclear whether this reflects increased recognition or a true increase in incidence (Lederer and Martinez, 2018).

The prognosis for people living with IPF remains poor with a median life expectancy of three to five years from diagnosis if left untreated. Despite the development of antifibrotic medications to slow disease progression, IPF remains an incurable and an ultimately fatal interstitial lung disease. Early diagnosis is crucial to ensure timely treatment selection such as consideration of antifibrotic medications, supportive and palliative therapies, and, if appropriate, referral for lung transplantation (Aiello et al., 2017, Mori and Kondoh, 2021).

2.2 Early-Stage Diagnosis in IPF

2.2.1 Clinical presentation

IPF is usually diagnosed in the sixth or seventh decade of life and is uncommon below the age of 50 years (Raghu et al., 2014, Raghu et al., 2006). Risk factors for IPF include older age, male sex and a history of cigarette smoking (Cottin et al., 2022b). Typically, IPF presents with chronic exertional dyspnoea, chronic dry cough, fatigue and a gradual decline in ability to undertake activities of daily living. Symptoms can be present for many months to years. Bilbasal 'velcro-like' mid to end inspiratory crackles on chest auscultation, nail clubbing and resting hypoxaemia or exertional desaturation are common physical examination findings. Patients with early IPF may be asymptomatic with typical radiological features identified incidentally on cross-sectional imaging performed for other reasons (Yamazaki et al., 2022).

2.2.2 Pulmonary function tests

Pulmonary function tests provide a non-invasive quantitative measure of the severity of IPF and repeated testing to monitor disease course has become the cornerstone of current practice (Kirtland and Winterbauer, 1997). In patients with suspected IPF, lung function studies typically identify a reduced forced vital capacity (FVC), reduced total lung capacity (TLC) and a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) (Lederer and Martinez, 2018).

Patients with early IPF may have normal or only mildly impaired lung function parameters (Jo et al., 2018). Moreover, the course of IPF can be highly unpredictable with significant variation across individuals ranging from patients who have gradual worsening of lung function over years to those who decline rapidly from disease onset (Albera et al., 2016, Ley et al., 2011). Baseline lung function alone is therefore a poor predictor of mortality in IPF (King et al., 2001)

and composite scoring systems such as the Gender at birth-Age-Physiology (GAP) index may offer better prognostic accuracy (Barratt et al., 2018) (see section 2.3).

A recent analysis from the Australian IPF registry found that patients with IPF with mild physiological impairment (FVC ≥ 80%) had better survival than patients with moderate to severe disease (FVC <80%). However, the overall rate of disease progression was comparable thus suggesting that better survival in early disease simply reflects an earlier point on the natural history of IPF (Jo et al., 2018). Similarly, post-hoc analyses of major clinical drug trials in IPF have found that the rate of FVC decline is similar between patients with more preserved FVC (≥ 80%) and those with less preserved FVC (< 80%) (Albera et al., 2016, Kolb et al., 2017).

Research also indicates that patients with early IPF (based on pulmonary function test results) have fewer episodes of acute exacerbation than those with advanced disease (Kolb et al., 2017, Kondoh et al., 2010, Song et al., 2011). Artificial intelligence (AI) software capable of interpreting spirometry has been developed and validated and has demonstrated superiority in accurate interpretation over pulmonologists, whose interpretations are prone to variability and error (Topalovic et al., 2019). Ray et al. drew upon United Kingdom Biobank data to investigate whether AI software can detect ILD based on a spirometry measurement obtained before patients received an ILD diagnosis. Data from subjects who had ILD as a documented cause of death, had performed an acceptable spirometry measurement up to 7 years prior to their death and had not received an ILD diagnosis on the date of their spirometry measurement were analysed. Spirometry data and subject demographic information were used as inputs into an AI software system. In 27% of cases, AI software identified patients with ILD up to 6.8 years before a clinician's diagnosis. Most of these cases had normal lung function (using standard interpretation guidelines), indicating that artificial intelligence software may be able to identify ILD before standard spirometry interpretation (Ray et al., 2022). These studies show that AI interpretation of spirometry in the primary care setting has the potential to improve diagnosis of ILD leading to earlier referrals to specialist ILD centres.

2.2.3 High resolution computed tomography (HRCT)

IPF is restricted to the lungs and is characterised by the radiographic pattern of usual interstitial pneumonia (UIP) on high resolution computed tomography (HRCT) imaging of the chest (Raghu et al., 2018a).

2.2.3.1 The ATS/ERS/JRS/ALAT's 2018 clinical practice guidelines for diagnosis of IPF

2.2.3.2 Features of the UIP pattern on HRCT

UIP pattern interstitial lung disease on radiology is typically subpleural in distribution and with an apicobasal gradient (Raghu et al., 2018a) Characteristic HRCT features of UIP include honeycombing, traction bronchiectasis, and traction bronchiolectasis with the possible presence of ground glass opacification and fine reticulation (Raghu et al., 2018a). Honeycombing is characterised by clustered cystic airspaces with thick, well-defined walls of normally uniform diameter of 3-10 mm with some occasionally larger cysts. Typically, with honeycombing there is also a reticular pattern of traction bronchiectasis and bronchiolectasis present (Hansell et al., 2008). Traction bronchiectasis and bronchiolectasis is a key characteristic indicating pulmonary fibrosis, ranging from minor irregularity and non-tapering of the bronchial and/or bronchiolar wall to severe airway distortion (Sumikawa et al., 2008, Edey et al., 2011).

2.2.3.3 HRCT patterns of IPF

The ATS/ERS/JRS/ALAT's 2018 clinical practice guidelines for diagnosis of IPF recommend using four diagnostic classifications to describe HRCT features: UIP pattern, probable UIP pattern, indeterminate UIP pattern, and alternative diagnosis (Raghu et al., 2018a). The UIP pattern is the hallmark HRCT feature of IPF. Honeycombing—with or without traction bronchiectasis or bronchiolectasis—must be present in the HRCT for a definite UIP pattern diagnosis. Sometimes, mild ground-glass opacification may also be present, usually superimposed on a

reticular pattern. To justify a probable UIP pattern diagnosis, a basal predominant subpleural reticular pattern with peripheral traction bronchiectasis or bronchiolectasis must be present. Ground-glass opacification may also be present in patients with probable UIP, but it is not the main abnormality. An indeterminate UIP pattern diagnosis is considered when the HRCT scan captures features of fibrosis that do not meet the criteria for definite UIP or probable UIP pattern and when no signs point to an alternative diagnosis. An alternative diagnosis is made when the HRCT pattern suggests another diagnosis. In some cases, the HRCT pattern may suggest a definite UIP, probable UIP, or indeterminate UIP while additional results indicate an alternative diagnosis. In these cases, an alternative diagnosis should be taken into account (Raghu et al., 2018a). This guideline was updated in 2022, but the four diagnostic classifications of HRCT features remained unchanged (Raghu et al., 2022).

2.2.3.4 Early IPF based on HRCT

In patients with IPF, the degree of fibrosis on HRCT imaging can be determined by two components: the extent of the fibrosis (% fibrosis) and the radiological features of the fibrosis. While a small percentage of fibrosis on HRCT imaging probably indicates early IPF, there are no standardised cut-off points that define the extent of fibrosis for characterising early IPF. Several studies have found that the extent of fibrosis on HRCT scans in patients with IPF is associated with mortality. Among patients whose scans showed idiopathic interstitial pneumonias (IIPs) with a UIP pattern, an HRCT fibrosis score of >30% predicted a worse prognosis (Romei et al., 2015). Ley et al. modified the GAP model (which considers gender at birth, age, and physiology with FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) by replacing the DLCO with the HRCT scan's extent of fibrosis score. This was divided into three categories (≤10%, 11%–30%, >30%), with more fibrosis being associated with an increased risk of mortality (Ley et al., 2014). These studies suggest a fibrosis score of either ≤30% or ≤10% as a cut-off point for defining early IPF.

Looking at the features of fibrosis, the presence of honeycombing and traction bronchiectasis may indicate advanced features of IPF, as some patients with an inconsistent or possible UIP pattern on their HRCT eventually develop a definite UIP pattern over months or years (De Giacomi et al., 2018, Yamauchi et al., 2016). Several studies have identified a poor prognosis for patients with fibrotic lung disease that shows features of honeycombing on HRCT(Flaherty et al., 2003, Akira et al., 2011, Edey et al., 2011). In an observational study using data from five hospitals in the United States, Adegunsoye et al. evaluated the prognostic value of the presence of honeycombing among various ILD subtypes. Honeycombing was prevalent in various ILD subtypes and was associated with a higher mortality rate than among those without honeycombing. It is proposed that the honeycombing seen in the HRCT of patients with ILD indicates a progressive fibrotic ILD. In patients with IPF, no difference in mortality was found on the basis of the presence of honeycombing, probably because IPF is already a progressive fibrotic ILD phenotype (Adegunsoye et al., 2019). One study found that patients with IPF and a possible UIP pattern on their HRCT had better survival than those with a definite UIP pattern (Salisbury et al., 2017), while others found no differences in survival between patients with possible UIP and those with definite UIP-pattern IPF (Lee et al., 2015). Using data drawn from the INPULSIS trials, Raghu et al. evaluated differences in prognosis between the diagnostic subgroups of IPF as well as their responses to the antifibrotic medication nintedanib. They found that patients with a possible UIP pattern with traction bronchiectasis on their HRCTs had a similar disease progression and responded similarly to nintedanib as patients whose IPF showed a definite UIP pattern (Raghu et al., 2017).

In diagnosing and evaluating patients with IPF, HRCT plays a crucial rule. The current standard of visually assessing HRCT scans to determine IPF disease extent is hindered by interobserver variation with poor reproducibility. This has led to research evaluating objective automated computed tomography analysis. Several systems have been developed for the automated analysis of HRCT scans (Wu et al., 2019). CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) is a novel tool that can be used for the analysis and

quantification of lung abnormalities on HRCT imaging. Jacob et al. have shown that in patients with IPF, automated quantitative computed tomography using CALIPER had superior performance compared to visual scoring (Jacob et al., 2016). Several studies have demonstrated the value of automated quantification of computed tomography in predicting survival (Maldonado et al., 2014, Humphries et al., 2022)and FVC decline (Romei et al., 2020, Jacob et al., 2018a).

2.2.4 Index systems

Several composite scoring systems have been developed in aiming to accurately prognosticate in patients with IPF (see Table 1). These include the Composite Physiologic Index (CPI) (Wells et al., 2003), du Boise score (du Bois et al., 2011) (see Table 2), and the Gender at birth-Age - Physiology (GAP) index and staging system (Ley et al., 2012) Table 3.

Table 1 Different composite scoring systems in IPF and their predictor components

Composite scoring systems in IPF	**Predictors**
Composite physiologic index (CPI)	Extent of disease on CT= 91.0 – (0.65 X percent predicted DLCO - (0.53 X percent predicted FVC) + (0.34 X percentage predicted FEV1)
Du Boise score	Age 24-week history of respiratory hospitalization FVC % predicted 24-week change in FVC %predicted
GAP index and staging system	Gender at birth Age (years) Physiology FVC %predicted DLCO %predicted

Table 2 Du Boise mortality risk scoring system for patients with IPF.

First, Individual scores are summed for each risk factor		Second, expected 1-year probability of death is identified corresponding to total risk score	
Risk factors	Score	Total risk score	Expected 1-year risk of death
Age			
≥70	8		
60-69	4	0-4	<2%
<60	0	8-14	2-5%
Recent respiratory hospitalization		16-21	5-10%
		22-29	10-20%
Yes	14	30-33	20-30%
No	0	34-37	30-40%
Baseline FVC %predicted		38-40	40-50%
≤50	18	41-43	50-60%
51-65	13	44-45	60-70%
66-79	8	47-49	70-80%
≥80	0	>50	>80%
24-week change in FVC % predicted			
≤ -10	21		
-5 to -9.9	10		
> -4.9	0		

The GAP index is the most widely used for assessing patients with IPF. This simple tool uses commonly available clinical and physiological variables to predict prognosis in patients with IPF. The GAP index is derived from data on patients' gender at birth, age and respiratory physiology (which includes the percentage predicted of forced vital capacity (FVC %) and percentage predicted of diffusing capacity for carbon monoxide (DLCO %) **(see** Table 3**.**). The GAP index and staging system classifies patients with IPF into three stages: stage I (0-3 points), stage II (4-5 points), and stage III (6-8 points), with a higher GAP stage signifying more progressed IPF. The GAP index and staging system is an easy and quick screening approach in evaluating risk in patients with IPF (Ley et al., 2012).

Composite scoring systems capture various aspects of the disease's pathophysiology and offer a broader range of prognostic information. The optimal composite scoring system for staging IPF has not yet been determined, as all the published systems have limitations in either methodology, design, population, sample size or follow-up period (Rozanski and Mura, 2014). Patients in early stages as determined by composite scoring systems may be considered as having early IPF.

Table 3 The GAP index and staging system.

	Predictor	Points
Gender at birth	Female	0
	Male	1
Age (years)	≤60	0
	61-65	1
	>65	2
Physiology	FVC % predicted	
	>75	0
	50-75	1
	<50	2
	DLCO % predicted	
	>55	0
	36-55	1
	≤35	2
	Cannot perform	3

2.3 Awareness among primary care physicians

IPF can be difficult to diagnose in its early stages due to overlap of symptoms with other more common conditions. As patients with IPF usually present with symptoms of cough and shortness of breath, their symptoms are often attributed to ageing, smoking or more prevalent respiratory or cardiovascular conditions (Hoyer et al., 2019). Moreover, patients with early disease may have minimal symptoms or subtle clinical signs and as such, diagnosis necessitates a high index of clinical suspicion among primary care physicians. Patients with IPF frequently endure significant delays before diagnosis, with a recent study finding an average delay of 2.1 years from the onset of symptoms to diagnosis (Hoyer et al., 2019). Furthermore, ratifying a diagnosis of IPF requires a specialised, multidisciplinary team with expertise in interstitial lung disease (Martinez et al., 2017, Raghu et al., 2018a), which is typically only available in specialist centres (Furini et al., 2019).

Primary care physicians are often the first to consult with patients with suspected IPF and are responsible for referral to specialised ILD centres for confirmation of diagnosis and management. Recently, Silva et al. evaluated primary care physicians' awareness of the main ILD subtypes, including IPF. Their questionnaire assessed the respondents' degree of awareness of the basic diagnosis and management of the main ILD conditions, including IPF, in five health care centres in Portugal. The participants performed acceptably in the sections related to hypersensitivity pneumonitis, connective tissue disease ILD, sarcoidosis, and drug-induced ILD, but, unfortunately, their level of awareness of IPF was deemed to be poor (Silva et al., 2022). The critical role that primary care physicians play in the early diagnosis of IPF highlights the need for educational intervention to raise awareness of interstitial lung disease in this setting. This in turn could result in rapid referral of patients to specialist centres and ongoing dialogue between pulmonologists and primary care physicians during patient follow up (Silva et al., 2022).

2.4 Lung Cancer Screening and Early IPF Detection

In several studies, patients who underwent computed tomography (CT) for lung cancer screening were found to have interstitial lung abnormalities (ILAs) (Jin et al., 2013, Hewitt et al., 2022, Mackintosh et al., 2019), and some reported ILD (Sverzellati et al., 2011). ILAs are identified when a CT scan finding indicates a potential diagnosis of ILD in patients without clinical suspicion of ILD or in patients with an abdominal CT scan showing only the lower lung lobes. ILA is solely a radiological term that refers to the incidental finding of a CT abnormality (Hatabu et al., 2020).

In Hewitt et al.'s recently published analysis of people who ever-smoked aged 55–75 years who were invited for lug health check through low-dose CT (LDCT) lung cancer screening, ILA was found in 78 of 1,853 (4.2%) in the cohort. 59 participants (3.2%) of the ILA group met the criteria for ILD specialist evaluation, and a diagnosis of ILD was made in 28 patients (1.51%) who underwent LDCT screening, with IPF being present in half those cases. In the same population, lung cancer was found in 2.5% of patients, and the incidence of ILD in this study was comparable to that of lung cancer (Hewitt et al., 2022). Therefore, lung cancer screening provides an opportunity for early ILD detection and treatment, potentially leading to better patient outcomes. This strategy's resource efficiency and cost-effectiveness in the context of international healthcare settings merits additional analysis (Hewitt et al., 2022).

2.5 When to Treat IPF: The Importance of Early Diagnosis

Antifibrotic medication with pirfenidone or nintedanib is recommended for patients with IPF by international guidelines. Randomised clinical trials have shown that the antifibrotic medications pirfenidone and nintedanib slow lung function decline as reflected by FVC (Richeldi et al., 2014, King et al., 2014).

Pirfenidone is a synthetic compound that has antifibrotic, anti-inflammatory, and antioxidant characteristics. It accomplishes this by inhibiting pro-fibrotic growth factors like transforming growth factor beta, inhibition of the production of

inflammatory cytokines (e.g. tumour necrosis factor- a) and decreasing lipid peroxidation and oxidative stress (Iyer et al., 1999). Pirfenidone was evaluated in both the CAPACITY (Noble et al., 2011) and the ASCEND (King et al., 2014) trials and demonstrated reduction in the progression of IPF as indicated by changes in FVC, exercise tolerance (6-minute walk test), and progression free survival (King et al., 2014).

Nintedanib is an intracellular inhibitor that targets several tyrosine kinases like fibroblast growth factors, vascular endothelial growth factors and platelet-derived growth factor receptors (Hilberg et al., 2008). In the INPULSIS trials, nintedanib slowed the decline in FVC over a 52-week treatment period in patients with IPF (Richeldi et al., 2014).

Albera et al. evaluated data pooled from the ASCEND (King et al., 2014) and CAPACITY (Noble et al., 2011) studies to assess the effect of pirfenidone in patients with IPF with preserved baseline lung volume versus patients with impaired lung volume (FVC ≥80% vs. FVC <80% predicted) or by GAP index stage (stage I vs. stage II–III). They concluded that the efficacy of pirfenidone was similar regardless of FVC or GAP stage (Albera et al., 2016).

In a post hoc analysis using data from the ASCEND (King et al., 2014) and CAPACITY (Noble et al., 2011) studies, Nathan et al. assessed the efficacy of pirfenidone in patients with IPF with advanced lung function impairment (FVC <50% predicted and/or DLCO <35% predicted). They found that pirfenidone significantly mitigates the decline in FVC, risk of all-cause mortality and respiratory-related hospitalisation. These results indicate that pirfenidone is beneficial in patients with IPF and advanced lung function impairment with no increased risk of adverse treatment events (Nathan et al., 2019).

Kolb et al. analysed pooled data from the INPULSIS trials (Richeldi et al., 2014) and found that patients with IPF who have preserved lung volume experience a similar rate of FVC decline and a similar benefit from nintedanib as patients with more impaired lung volume. Their post hoc subgroup analyses compared participants with FVC ≤90% predicted with those having FVC >90% predicted. In

patients with FVC >90% predicted, the annual rates of FVC decline in the nintedanib group vs. the placebo group were -91.5 ml/year and -224.6 ml/year, respectively, a difference of 133.1 ml/year. In the group of patients with FVC ≤90% predicted, the annual FVC decline in the nintedanib group vs. the placebo group were -121.5 ml/year and -223.6 ml/year, respectively, a difference of 102.1 ml/year (Kolb et al., 2017). Costabel et al. report similar findings, with nintedanib having a similar effect of slowing disease progression in patients with IPF with a baseline FVC ≤70% predicted compared to those with a baseline FVC >70% predicted (Costabel et al., 2016). Nintedanib has shown acceptable long-term safety and tolerability, allowing patients with IPF to use it for long periods to slow disease progression (Crestani et al., 2019). The results of these studies encourage the prompt initiation of the antifibrotic medications pirfenidone and nintedanib in patients with IPF, regardless of the severity of disease.

IPF is commonly diagnosed late, as its symptoms are often misdiagnosed as those of more common diseases, such as asthma, chronic obstructive pulmonary disease (COPD) or heart disease, resulting in delayed referrals to specialist centres (Schoenheit et al., 2011). An early diagnosis of IPF may lead to earlier treatment with antifibrotic medications and even though individual clinical trials were not sufficiently powered to demonstrate significant effects on acute exacerbations and mortality, evidence is growing supporting the effects of pirfenidone and nintedanib in decreasing the risk of acute decline in lung function and improving life expectancy by slowing the progression rate of IPF. Antifibrotic medications have demonstrated efficacy in slowing the rate of FVC decline and in improving outcomes in patients with IPF. Given that the progress of a patient’s condition cannot be anticipated at diagnosis and considering the poor overall prognosis of untreated IPF, antifibrotic medications should be considered for all patients with IPF (Maher and Strek, 2019)

Chapter 3: A Retrospective Cohort Study of Characteristics of Patients with Combined Pulmonary Fibrosis and Emphysema and the role of GAP staging

3.1 Introduction

The simultaneous presence of both emphysema and pulmonary fibrosis was first reported in 1990 by Wiggins et al., who described eight patients with a history of heavy smoking who presented with severe breathlessness. These patients had concurrent upper lobe emphysema and fibrosis, and their lung function tests showed preserved dynamic lung volumes and markedly reduced lungs diffusion capacity. The authors note that the use of HRCT was valuable in determining the severity of breathlessness and gas transfer impairment in the patients (Wiggins et al., 1990). The term *combined pulmonary fibrosis and emphysema* was first introduced by Cottin et al. in 2005. In their study, the HRCT results of 61 patients showed upper lobe emphysema and lower lobe fibrosis. The patients were mainly men with a history of heavy smoking and usually presented with severe breathlessness and cough. On physical examination, basal lung crackles were heard, and digital clubbing was observed in the patients (Cottin et al., 2005). Pulmonary hypertension is also frequently observed in patients with CPFE and commonly signals a poor prognosis (Cottin and Cordier, 2009, Cottin et al., 2010). Since Cottin et al. 2005 report, the newly identified condition has drawn increased interest and international recognition.

The ATS and ERS update on the classification of idiopathic interstitial pneumonias describes CPFE as a coexisting pattern of pulmonary fibrosis and emphysema and does not consider it a distinct idiopathic interstitial pneumonia. This demonstrates the need for further research (Travis et al., 2013).

3.1.1 Studies describing patients with CPFE

A single centre retrospective cohort study was conducted by Kishaba et al. in a Japanese cohort to evaluate the characteristics and predictors of mortality in patients with CPFE, identifying 93 patients with CPFE via HRCT scans and a multidisciplinary meeting. In their study, patients were excluded who had occupation-related ILD, such as asbestosis, silicosis, drug-associated ILD and CTD-ILD. The authors found that, in their cohort, patients with CPFE had poor survival. The presence of finger clubbing was independent predictors of mortality in this group of patients. The researchers also found that patients with CPFE frequently developed acute exacerbations. Levels of Kerbs von Lungren 6 antigen (KL-6) (a mucinous glycoprotein of high molecular weight) was found to be a valuable predictor of acute exacerbations (Kishaba et al., 2012). Recently, Malli et al. (2019) published a study evaluating the characteristics of patients with CPFE and examining prognostic factors in a Greek cohort. This nationwide retrospective study included 97 patients with CPFE. The authors found that the lung function tests of CPFE patients revealed preserved dynamic lung volume and reduced DLCO. They also found that decreased DLCO and increased extent of ILD as determined by HRCT were associated with a poor prognosis (Malli et al., 2019).

As CPFE is a recently recognized, uncommon lung condition that has only lately drawn interest from researchers and clinicians, the above-mentioned studies of Kishaba et al. and Malli et al. represent the only published research describing the characteristics of patients with CPFE. This indicates the need for an audit describing the characteristics of patients with CPFE in a large United Kingdom cohort.

3.1.2 GAP score

The multidimensional GAP index and staging system was developed to assess patients with IPF. This simple tool uses commonly available clinical and physiological variables to predict prognosis in patients with IPF (Ley et al., 2012). The score is derived from data on patients' **g**ender at birth, **a**ge and respiratory **p**hysiology (GAP).

3.1.3 Contradictory findings for CPFE prognosis in the literature

The literature has yielded contradictory findings in terms of the prognosis of patients with CPFE compared to patients with IPF (Mejía et al., 2009, Todd et al., 2011). Some studies report a worse prognosis for CPFE than for IPF, while others report a better prognosis for patients with CPFE (Malli et al., 2019, Todd et al., 2011), so more research is needed to determine prognostic variables that can predict the clinical course and guide management in patients with CPFE.

The main aim of this PhD research is to evaluate the effect of pulmonary rehabilitation in patients with CPFE. Thus, an audit would contribute to locating and determining the number of patients with CPFE in the regional clinic, information which would then inform my plan to approach patients for the pulmonary rehabilitation research. The aim of this specific chapter, therefore, was to describe the characteristics of patients with CPFE in a UK cohort through the Northeast regional ILD clinical service, evaluate CPFE patients' survival time, the role of the GAP score and staging system and the modified GAP (mGAP) score in patients with CPFE and compare the results with published data.

3.2 Methodology

3.2.1 Audit

This five-year retrospective single-centre study was conducted at the regional ILD clinic at the RVI hospital, Newcastle upon Tyne, UK. The ILD clinic at RVI is considered to be a centre of expertise in ILDs and receives general practitioners' referrals from the whole Northwest and Northeast of England. (see Figure 4).

Figure 4 Regions of the UK with the Northeast and Northwest regions circled in red (Image: UK website of the European Parliament Liaison Office)

An ILD multidisciplinary team (MDT) comprising members of both the pulmonary and radiology departments meets twice monthly at the RVI to consider referrals. When a patient with an ILD is identified, an appointment is made for the patient to be seen by the ILD team. Excel sheet was used to develop a data abstraction instrument for the researcher to record required data.

The ILD multidisciplinary team file records of all patients discussed by the team were used to obtain patients' medical record numbers. Then, patients' records were accessed by the researcher through the RVI hospital electronic record system. All patients discussed by the ILD team from January 2014 through December 2018 (a five-year period) were reviewed. Due to time constraints, we

considered five years period for the retrospective study to be appropriate. Only patients with a diagnosis of CPFE were included in this study.

Patient data in this study were obtained from the electronic medical record system at the RVI hospital. Demographic, clinical, and physiological data were collected, including age, sex, weight, body mass index (BMI), type of fibrosis, dyspnoea scores, smoking status, oxygen use, anti-fibrotic medications, environmental exposures and point-of-diagnosis pulmonary function. Data were collected from the initial diagnosis of CPFE point and no follow up data collection was performed. In the event there were missing data, they were identified as such.

3.2.2 Study population

Participants were included in this study who had a final diagnosis of CPFE as determined by the ILD multidisciplinary team meeting, which reviewed both patient history and HRCT to reach a diagnosis.

3.2.3 Survival analysis

The survival time of patients with CPFE was analysed in this study using Kaplan-Meier survival analysis. Survival was calculated from diagnosis by the ILD MDT until either death or the end of study.

3.2.4 GAP score analysis

3.2.4.1 GAP score

The collected GAP score data included gender at birth, age, and physiological variables of FVC% and DLCO percentage predicted (DLCO%) (see Figure 5) (Ley et al., 2012). In this study the GAP score was calculated by the researcher and was not extracted from the medical records.

	Predictor	Points
	Gender	
G	Female	0
	Male	1
	Age years	
A	⩽60	0
	61–65	1
	>65	2
	Physiology	
	FVC % predicted	
	>75	0
	50–75	1
	<50	2
P	*D*LCO % predicted	
	>55	0
	36–55	1
	⩽35	2
	Cannot perform	3

Maximum possible points=8. FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide.

Figure 5 Method for calculating GAP index (Ley et al., 2012)

3.2.4.2 mGAP index

This study also collected scores on the mGAP index, a modification of (Kobayashi et al., 2017) original GAP score that consists of gender at birth, age and FVC%. The mGAP index score ranges from 0 through 5 and is calculated as follows: gender at birth (female = 0, male = 1), age in years (≤ 60 = 0, 61–65 = 1, > 65 = 2) and FVC% (> 75% = 0, 50%–75% = 1, < 50% = 2). The mGAP index has two stages, stage I (0–3 score) and stage II (4–5 score).

3.2.4.3 dGAP score

This study also modified the GAP score by removing the FVC% and keeping the DLCO%. The resulting diffusion GAP score (dGAP) consists of gender at birth, age, and DLCO%.

3.2.5 Statistical analysis

Descriptive statistics and frequencies were calculated. Descriptive data were expressed as means ± standard deviation for continuous variables, and as percentages for categorical variables. Unpaired t-test and Mann-Whitney U tests were utilised to compare the results for continuous variables, and chi-square and Fisher's exact tests were utilised for categorical variables. The primary outcome was mortality, which was defined as the time from the initial diagnosis of CPFE till either death or censoring at the last data patients were known to be alive, The Kaplan-Meier method was used to produce survival curves, and the log-rank test was used to analyse statistical significance difference between the three GAP stage groups. The multivariate cox regression analysis was used to assess predictors of mortality in patients with CPFE. A p-value of < 0.05 was defined as statistically significant. Statistical analysis was conducted with IBM SPSS software version 25.

3.3 Results

3.3.1 Demographics

From a total reviewed clinic population of 3,063 patients, this study identified 203 patients with CPFE, or around 6.6% of the ILD clinic population. Of the 203 patients with CPFE, 149 (73%) were referred to and treated at RVI's ILD clinic (see Figure 6), while the rest were only discussed at the ILD team meeting. The CPFE group as a whole were relatively old and overweight, with a mean and standard deviation (SD) of age and BMI of 72 years (8.7) and 28.1kg/m² (4.4), respectively (see Table 4). Based on their BMIs, 33 (23.4%) patients were of normal weight, 65 (46.1%) were overweight and 43 (30.5%) were obese; none were underweight, and BMI data were missing for 8 (5.4%) participants. In terms of the classification of those who were obese, 34 (79.1%) were in class 1, 8 (18.6%) in class 2 and 1 (2.3%) in class 3. The majority of the patients were male (81.9%). At the time of the study's completion, around half (50.3%) of the patients had passed away. Most of the sample (86%) were former smokers, 11% were current smokers, 2.7% had never smoked and 0.7% lacked data. Forty-seven percent of the population used oxygen, while 51.7% did not use oxygen and two patients (1.3%) were missing data (see Table 4)..

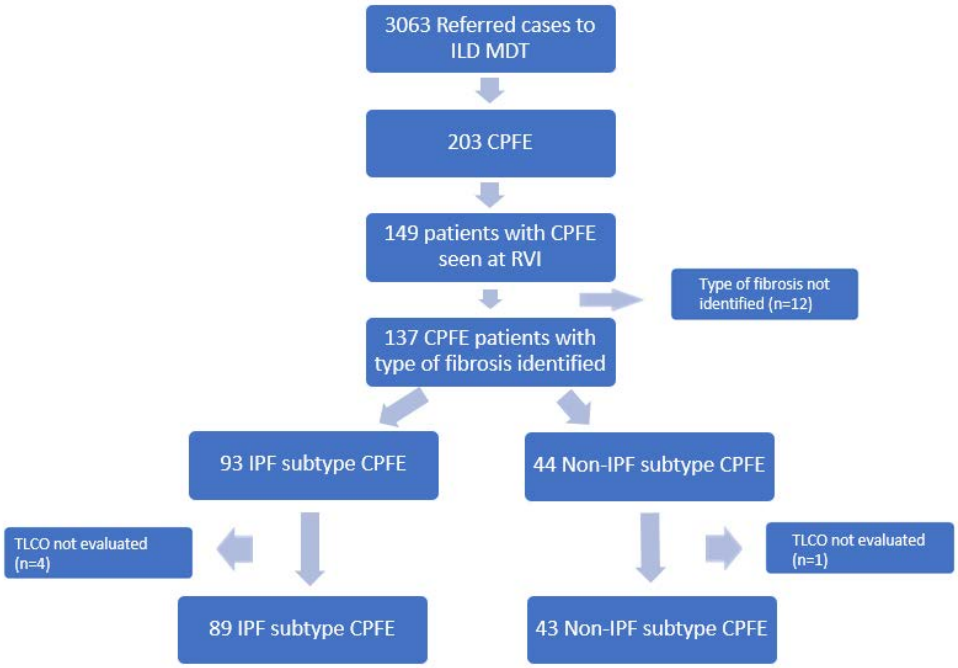


Figure 6 Flowchart diagram of study

Abbreviations: ILD MDT, interstitial lung diseases multidisciplinary meeting team; CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; RVI, royal Victoria infirmary hospital; TLCO, transfer factor for carbon monoxide.

Table 4 Clinical characteristics of all patients with CPFE.

Variables	Patients with CPFE diagnosis N = 149 Mean (SD)
Age years	72.0 (8.7)
Male gender	122 (81.9%)
Race White British Other, not stated Black or Black British, African	 86 (57.7%) 62 (41.6%) 1 (0.7%)
Mortality	75 (50.3%)
Weight kg	81.8 (14.9)
BMI kg/m^2	28.1 (4.4)
PFT data FEV_1 litres FVC litres FEV_1/FVC (%) FVC% predicted TLCO%	 2.2 litres (0.5) 2.9 litres (0.8) 76.7% (11.9) 83.9% (18.2) 43.7% (13.9)
Smoking status Current smoker Ex-smoker Never smoker Missing data	 16 (10.7%) 128 (85.9%) 4 (2.7%) 1 (0.7%)
Oxygen use	70 (47%)

BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, FEV1/FVC (%): FEV1/FVC ratio, FVC% predicted: forced vital capacity percentage predicted, TLCO%: transfer factor for carbon monoxide percentage predicted.

Table 5 Clinical characteristics of patients with CPFE based on IPF subtype.

Variables	IPF subtype CPFE (n=89) Mean (SD)	Non-IPF subtype CPFE (n=43) Mean (SD)	p-value
Age, years	72.9 (7.9)	70.7 (9.4)	0.493
Male gender	75 (84.3%)	32 (74.4%)	0.176
Mortality	46 (51.7%)	18 (41.9%)	0.290
Weight kg	79.5 kg (14.5)	85.4 kg (14.1)	0.668
BMI kg/m^2	27.8 kg/m^2 (4.6)	29.1 kg/m^2 (4.1)	0.582
FEV_1 litres	2.1 litres (0.5)	2.3 litres (0.6)	0.279
FVC litres	2.8 litres (0.7)	3.0 litres (0.8)	0.322
FEV/FVC (%)	77.5% (13.3)	75.9% (8.8)	0.815
FVC% predicted	83.5% (16.9)	86.6% (19.6)	0.400
TLCO%	41.1% (12.2)	48.3% (15.9)	*0.011
Smoking status			0.414
Current smoker	10 (11.2 %)	4 (9.3 %)	
Ex-smoker	74 (83.1 %)	39 (90.7 %)	
Never smoker	4 (4.5%)	0 (0%)	
Missing data	1 (1.1%)	0 (0%)	
Oxygen use	49 (55.1%)	13 (30.2%)	*0.010

BMI: body mass index, FEV1/FVC (%): FEV1/FVC ratio, FVC% predicted: forced vital capacity percentage predicted, TLCO%: transfer factor for carbon monoxide percentage predicted, *: P-value ≤0.05.

3.3.2 Type of fibrosis in patients with CPFE

Regarding type of fibrosis, 93 patients (62.4%) had an IPF subtype of CPFE, 44 (29.5%) had other types of ILD (non-IPF subtype CPFE) (see Table 5) and 12 CPFE patients (8.1%) had no data on lung fibrosis type.

The whole sample had CPFE, with usual interstitial pneumonia (UIP) and IPF being the predominant types of fibrosis at 36.9% and 25.5%, respectively, followed by asbestosis (6%), rheumatoid arthritis (4.7%), NSIP (4%) and unclassifiable (2.7%) (see Table 6).

A review of HRCT scans found that, in 41.6% of the sample, emphysema was judged to be more dominant than fibrosis, while fibrosis was more dominant than emphysema in 16.8%, both were severe in 3.4% and both were minor 2%; 1.3% had a 50/50 distribution with no mention of severity, and 34.9% had missing data (see Table 7).

Table 6 Type of fibrosis in patients with CPFE.

Type of fibrosis	Number (%)
Idiopathic pulmonary fibrosis (IPF)	38 (25.5%)
Usual interstitial pneumonia (UIP)	55 (36.9%)
Chronic hypersensitivity pneumonitis (CHP)	3 (2.0%)
Asbestosis	9 (6.0%)
Rheumatoid arthritis (RA)	7 (4.7%)
Nonspecific interstitial pneumonia (NSIP)	6 (4.0%)
Unclassifiable	4 (2.7%)
Smoking related interstitial fibrosis (SRIF)	1 (0.7%)
Connective tissue disease-associated ILD (CTD-ILD)	2 (1.3%)
Polydermatomyositis related ILD	1 (0.7%)
Usual interstitial pneumonia (UIP) and smoking-related interstitial fibrosis (SRIF)	4 (2.7%)
Nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP)	2 (1.3%)
IPF or asbestosis	3 (2.0%)
Rheumatoid arthritis (RA) and nonspecific interstitial pneumonia (NSIP)	1 (0.7%)
Rheumatoid arthritis (RA) and usual interstitial pneumonia (UIP)	1 (0.7%)
Missing data	12 (8.1%)

Table 7 Predominant pattern seen on HRCT of patients with CPFE.

Predominant pattern	**N (%)**
Emphysema > fibrosis	62 (41.6%)
Fibrosis > emphysema	25 (16.8%)
Both severe	5 (3.4%)
Both minor	3 (2.0%)
50% distribution (no mention of severity)	2 (1.3%)
Missing data	52 (34.9%)

3.3.3 Pulmonary function test results

Point-of-diagnosis PFT results were collected. The measured FEV1 and FVC were obtained with means and standard deviations of 2.2 litres (SD = 0.54) and 2.9 litres (SD = 0.76), respectively. The mean and standard deviation of the FEV1/FVC (%) ratio were 76.7% (SD = 11.9). FVC percentage predicted (FVC%) had a mean of 83.9% (SD = 18.2). The TLCO percentage predicted was also measured and yielded a mean and standard deviation of 43.7% (SD = 13.9) (see Table 4).

3.3.4 Anti-fibrotic medications

Almost one-third of the sample were on anti-fibrotic medications, either nintedanib (35 patients; 23.5%) or pirfenidone (13 patients; 8.7%), while the rest were not on anti-fibrotic medications.

3.3.5 Pulmonary rehabilitation referral

Of the patients with CPFE, about 23% were referred for a pulmonary rehabilitation programme, around 26% were recommended for a pulmonary rehabilitation programme and approximately 50% did not receive pulmonary rehabilitation (see Table 8). Sixty-five percent of the sample had not been exposed to any environmental factors.

Table 8 Referral for pulmonary rehabilitation programme

Pulmonary rehabilitation referral	**N (%)**
Referred for pulmonary rehabilitation	34 (22.8%)
Not referred for pulmonary rehabilitation	74 (49.7%)
Pulmonary rehabilitation was recommended	39 (26.2%)
Missing data	2 (1.3%)

3.3.6 Survival time analysis

A five-year follow-up of patients was conducted at the time of the study's analysis (March 2018). Among the 149 patients with CPFE, there were 75 fatalities (50.3%), with a median survival time of 40.1 months (3.3 y). In the IPF subtype CPFE group, 50 of the 93 patients (53.8%) had died, with a median survival time of 34.1 months (2.8 y). In the non-IPF subtype CPFE group, 19 of 44 patients (43.2%) were deceased at the time of the study. The median survival time of the non-IPF subtype CPFE group was 55.6 months (4.6 y) (see Table **9**). The Kaplan-Meier survival time curve is shown in (see Figure 7). A log-rank test showed no significance difference associated with median survival time (p = 0.113).

Table 9 Median survival time of patients with IPF subtype CPFE and non-IPF subtype CPFE

	IPF subtype CPFE	Non-IPF subtype CPFE	p-value
Mortality	46 (51.7%)	18 (41.9%)	0.290
Median survival time	38 months	55.6 months	0.113

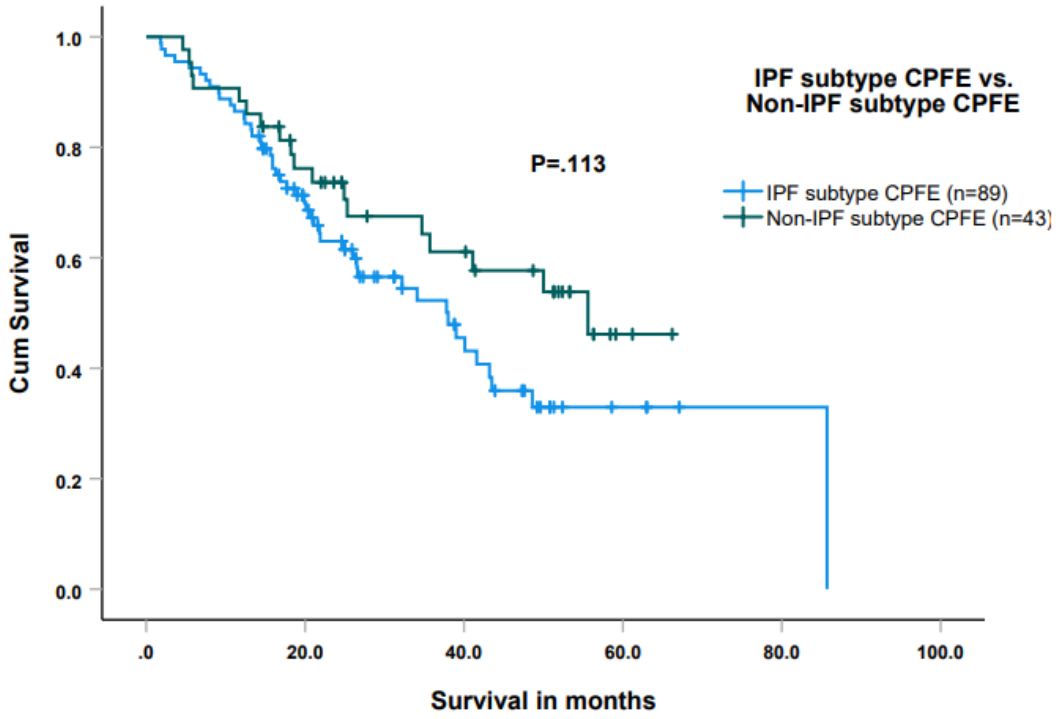


Figure 7 Kaplan-Meier survival analysis of IPF subtype CPFE and non-IPF subtype CPFE

Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema.

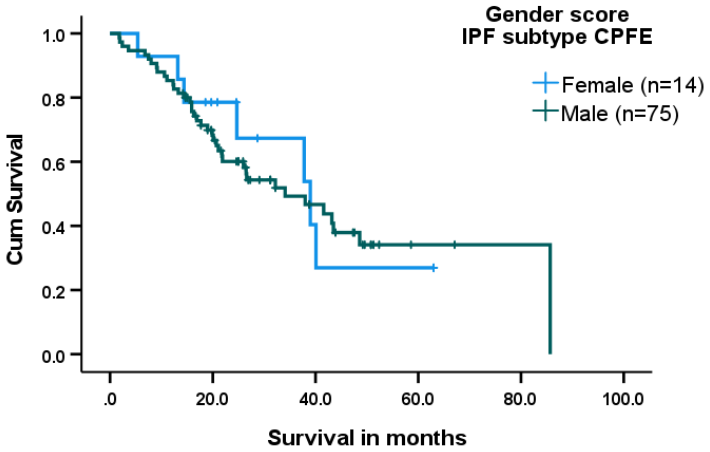
3.3.7 GAP score

3.3.7.1 Gender at birth score

In the IPF subtype CPFE group, 43 of 79 male patients (54.4%) were dead at the time of the analysis compared to 7 of 14 (50%) females. Male patients had a median survival time of 32.2 months (2.7 y), while females had a median survival time of 39 months (3.3 y) (see Figure 8). A log-rank test showed no significance difference associated with gender at birth score (p = .705).

In the non-IPF subtype CPFE group, 15 of 33 male patients (45.5%) were dead at the time of the study compared to 4 of 11 females (36.4%). Male patients had a median survival time of 55.6 months (4.6 y) (see Figure 8). Among female patients, the median survival time could not be calculated with the Kaplan-Meier test, as the Kaplan-Meier curve did not cross the 50% threshold. The log-rank test showed no significance difference associated with gender at birth (p = .660).

IPF subtype CPFE



Non-IPF subtype CPFE

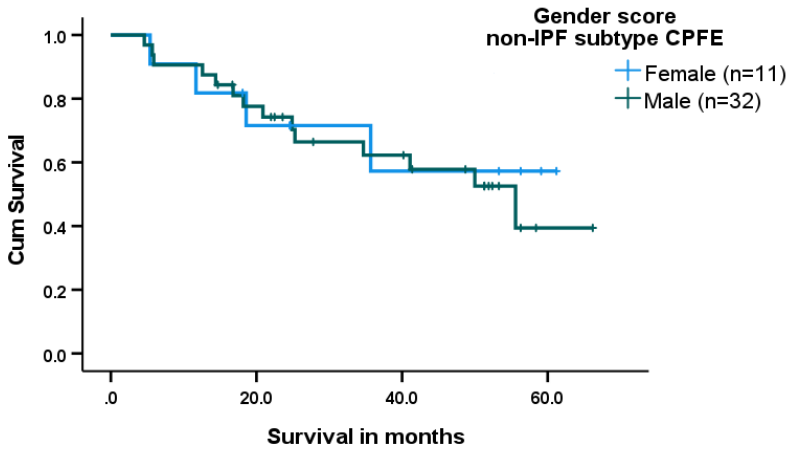


Figure 8 Kaplan-Meier analysis of gender at birth score in patients with IPF subtype and non-IPF subtype CPFE

Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema.

3.3.7.2 Age score

In patients with IPF subtype CPFE, 5 of 7 patients ≤ 60 years of age (71.4%) were dead at the time of this study compared to 5 of 10 patients aged 61–65 years (50%) and 40 of 76 patients aged > 65 years (52.6%). Patients aged ≤ 60 years had a median survival time of 19.9 months (1.7 y), those aged 61–65 had a median survival time of 32.2 months (2.7 y) and patients aged > 65 had a median survival time of 38 months (3.2 y) (see Figure 9). The log-rank test showed no statistically significant difference (p = 0.193).

In patients with non-IPF subtype CPFE, 4 of 7 patients ≤ 60 years (57.1%) were dead by the time of the study compared to 0 of 2 patients aged 61–65 (0%) and 15 of 35 aged > 65 (42.9%). In the non-IPF subtype of CPFE, median survival times by age score could not be calculated, as the Kaplan-Meier curve did not cross the 50% threshold (see Figure 9). The log-rank test showed no statistically significant difference (p = 0.463).

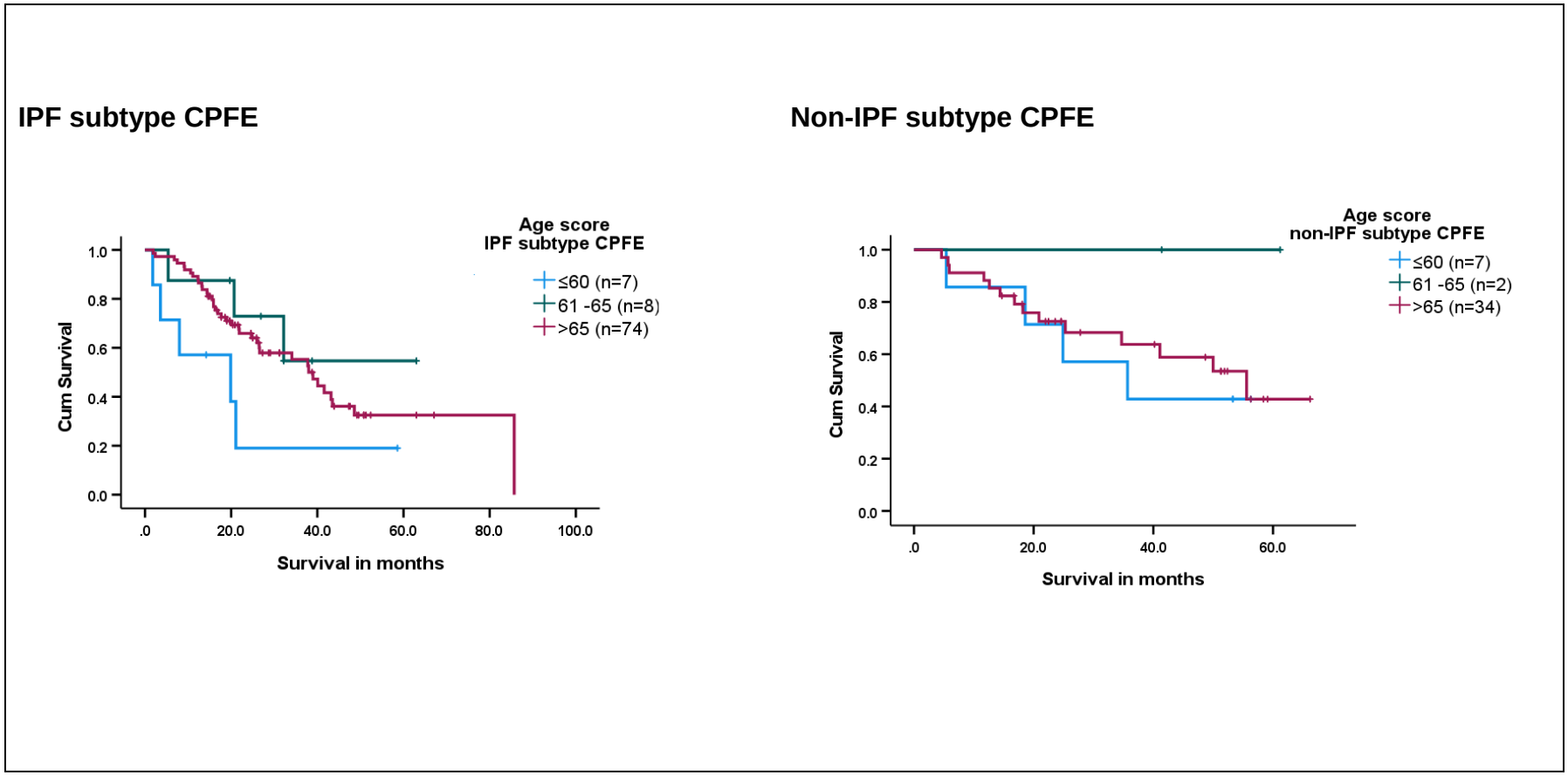


Figure 9 Kaplan-Meier analysis of age score in patients with IPF and non-IPF subtypes of CPFE

Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema.

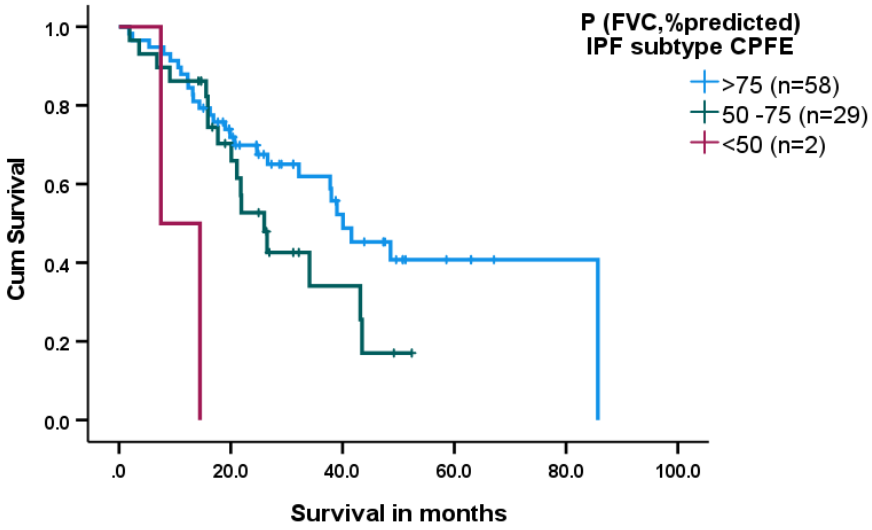
3.3.7.3 PFVC score

Among IPF subtype CPFE patients, the analysis of the physiological value of physiological variable forced vital capacity (PFVC) in the GAP score showed that 27 of 58 patients with a PFVC of > 75% (46.6%) were dead by the time of the study, while 18 of 30 patients with a PFVC of 50%–75% were dead (60%) and 3 of 3 patients with a PFVC of < 50% were dead (100%).

Patients with a PFVC of > 75% had a median survival time of 40.1 months (3.3 y), while patients with a PFVC of 50%–75% had a median survival time of 26 months (2.2 y) and patients with a PFVC of < 50% had a median survival time of 14.5 months (1.2 y) (see Figure 10). The log-rank test showed a statistically significant difference for this trend of earlier death associated with lower levels of FVC ($p = 0.002$).

In patients with non-IPF subtype CPFE, the analysis of PFVC in the GAP score showed that 11 of 29 patients with a PFVC of > 75% were dead by the time of the study (38%), while 7 of 13 (53.8%) patients with a PFVC of 50%–75% were dead and 0 of 1 patient with a PFVC of < 50% was dead (0%). The median survival time by PFVC score could not be calculated, because the Kaplan-Meier curve did not cross the 50% threshold (see Figure 10). The log-rank test showed no statistically significant difference ($p = 0.295$).

IPF subtype CPFE



Non-IPF subtype CPFE

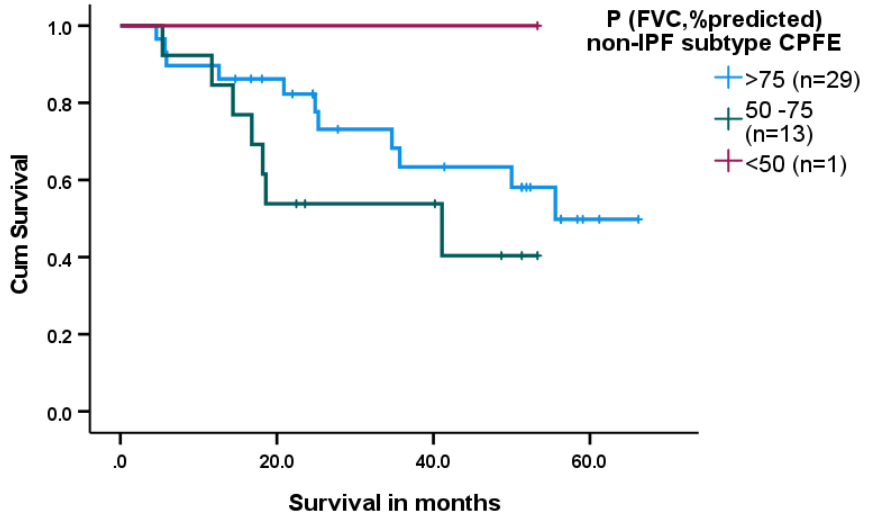


Figure 10 Kaplan-Meier analysis of PFVC scores in patients with IPF and non-IPF subtype CPFE.

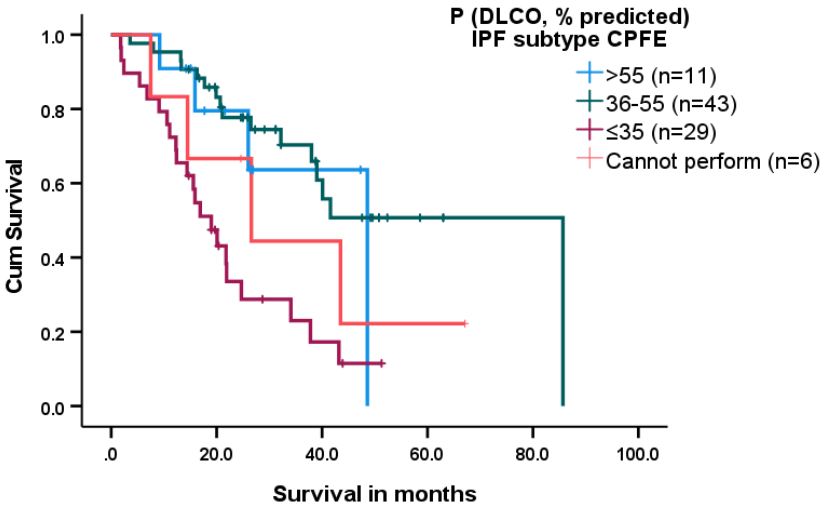
Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; FVC, %predicted, forced vital capacity percentage predicted.

3.3.7.4 PDLCO% score

Among patients with IPF subtype CPFE, analysis of the physiological value of percentage predicted diffusion capacity of lung for carbon monoxide (PDLCO%) in the GAP score showed that 4 of 11 patients with a PDLCO% of > 55% were dead by the time of this study (36.4%), while 16 of 43 with a PDLCO% of 36%–55% were dead (37.2%) and 22 of 29 (75.9%) with a PDLCO% of ≤ 35% were dead. Four of six patients who could not perform the test were dead (66.7%). Patients with a PDLCO% of > 55% had a median survival time of 48.6 months (4.1 y), those with a PDLCO% of 36%–55% had a median survival time of 85.7 months (7.1 y), those with a PDLCO% ≤ 35% had a median survival time of 19 months (1.6 y) and patients who could not perform the test had a median survival time of 26.6 months (2.2 y) (see Figure 11). The log-rank test showed a statistically significant difference (p = .000).

In patients with non-IPF subtype CPFE, the analysis of PDLCO% in the GAP score showed that 3 of 13 patients with a PDLCO% of > 55% were dead by the time of this study (23.1%), while 10 of 23 patients with a PDLCO% of 36%–55% were dead (43.5%) and 4 of 5 patients with a PDLCO% ≤ 35% were dead (80%). Two of three patients who could not perform the test were dead (66.7%). The median survival time of patients with a PDLCO% of > 55% could not be calculated, as the Kaplan-Meier curve did not cross the 50% threshold. The patients with a PDLCO% of 36%–55% had a median survival time of 50 months (4.2 y), those with a PDLCO% of ≤ 35% had a median survival time of 12.6 months (1.1 y) and patients who could not perform the test had a median survival time of 55.6 months (4.6 y) (see Figure 11). The log-rank test showed a trend for decreased survival in patients with reduced PDLCO%, which was close to being statistically significant, with a p-value of p = 0.057.

IPF subtype CPFE



Non-IPF subtype CPFE

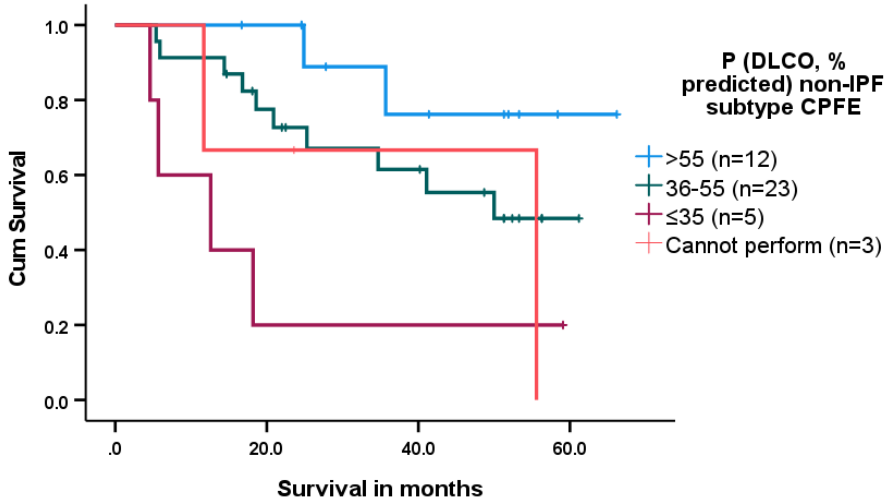


Figure 11 Kaplan-Meier analysis of PDLCO% score in patients with IPF and non-IPF subtype of CPFE.

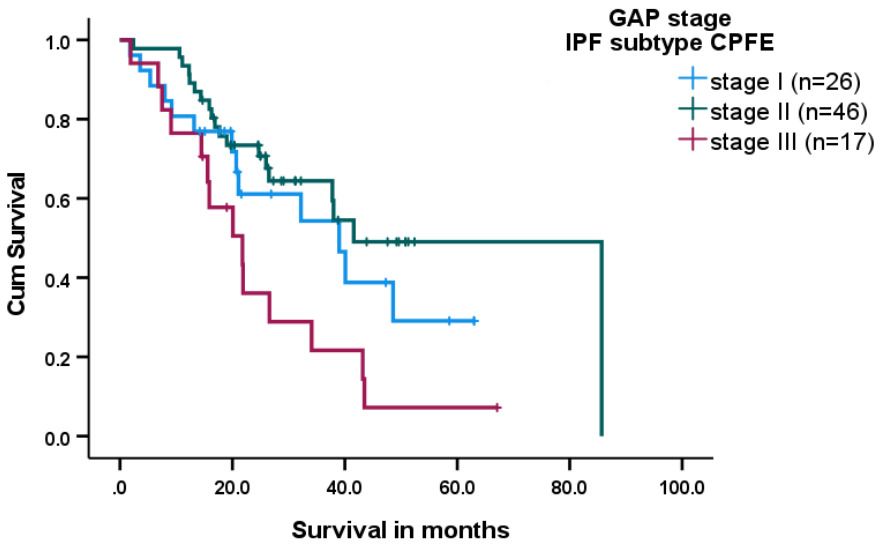
Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; DLCO, %predicted, diffusion capacity of the lungs for carbon monoxide percentage predicted.

3.3.7.5 GAP stage

Among patients with IPF subtype CPFE, the analysis of GAP stage showed that 13 of 26 patients (50%) at GAP stage I (score 0–3), 19 of 46 (41.3%) at GAP stage II (score 4–5) and 14 of 17 (82.3%) at GAP stage III (score 6–8) were dead by the time of this study. The median survival time was 39 months (3.3 y) for patients at GAP stage I, 41.6 months (3.5 y) for patients at GAP stage II and 21.8 months (1.8 y) for patients at GAP stage III (see Figure 12). The log-rank test showed a statistically significant difference between the GAP stages ($p = 0.012$).

In patients with non-IPF subtype CPFE, the analysis of GAP stage showed that 4 of 18 patients at GAP stage I (22.2%), 11 of 21 (52.4%) patients at GAP stage II and 3 of 4 (75%) patients at GAP stage III were dead at the time of the study. The median survival time for patients at GAP stage I could not be calculated, because the Kaplan-Meier curve did not cross the 50% threshold. The median survival time was 41.1 months (3.4 y) for patients at GAP stage II and 18.2 months (1.5 y) for patients at GAP stage III (see Figure 12). The data showed a trend for decreased survival in patients with higher gap score, which was close to statistical significance log-rank test, p-value of (0.073).

IPF subtype CPFE



Non-IPF subtype CPFE

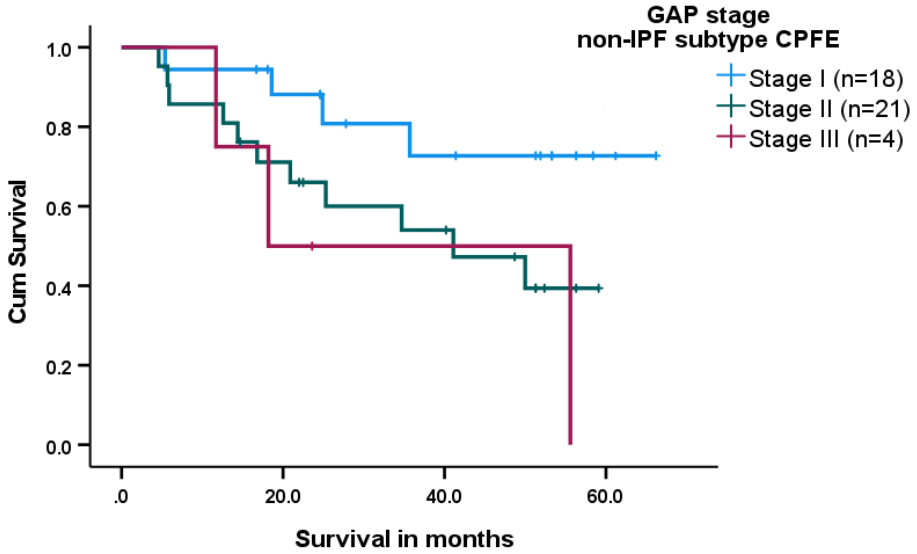


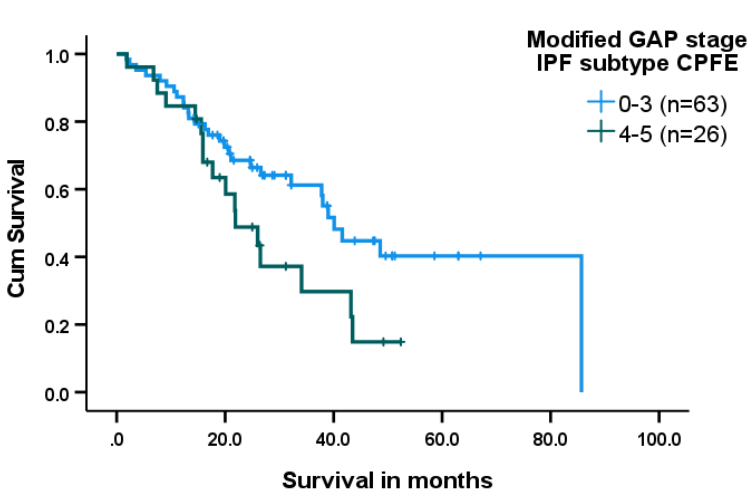
Figure 12 Kaplan-Meier analysis of GAP stages in patients with IPF and non-IPF subtype CPFE.

Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; GAP, gender at birth-age-physiology.

3.3.8 mGAP stage

Among IPF subtype CPFE patients, the analysis of mGAP showed that 29 of 63 patients (46%) at mGAP stage I were dead by the time of this study compared to 19 of 28 (67.9%) patients at mGAP stage II. The median survival time was 40.1 months (3.3 y) for patients at mGAP stage I and 21.8 months (1.8 y) for those at mGAP stage II (see Figure 13). The log-rank test showed a statistically significant difference between the mGAP stages ($p = .027$). In the non-IPF subtype CPFE group, the analysis of mGAP showed that 14 of 34 patients (41.2%) at mGAP stage I were dead by the time of this study compared to 4 of 9 (44.4%) at mGAP stage II. The median survival time was 55.6 months (4.6 y) for patients at mGAP stage I and 41.1 months (3.4 y) for those at stage II (see Figure 13). The log-rank test showed no statistically significant difference between the mGAP stages in terms of survival in patients with non-IPF subtype CPFE ($p = 0.71$).

IPF subtype CPFE



Non-IPF subtype CPFE

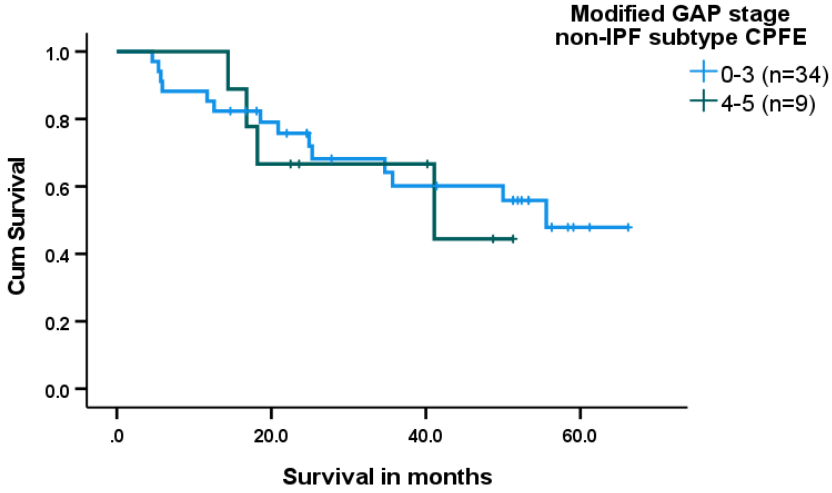


Figure 13 Kaplan-Meier analysis of mGAP stage in patients with IPF and non-IPF subtype CPFE.

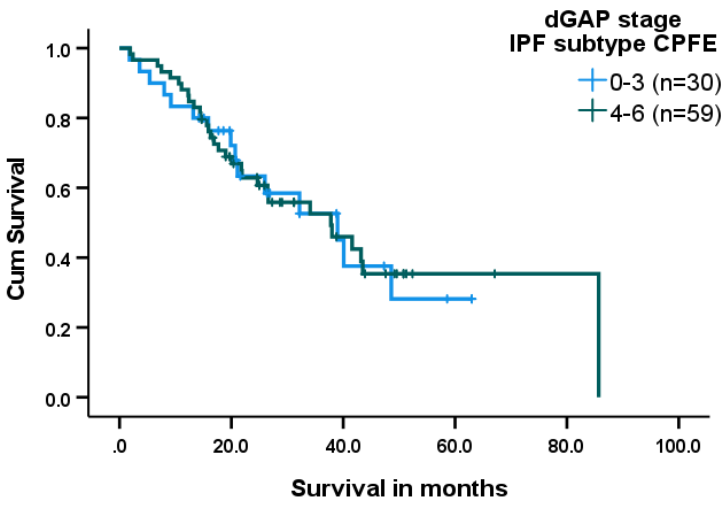
Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; GAP, gender at birth-age-physiology.

3.3.9 Diffusion GAP stage

Among IPF subtype CPFE patients, the analysis of dGAP stage showed that 15 of 30 patients (50%) at dGAP stage I were dead by the time of this study compared to 31 of 59 (52.5%) patients at dGAP stage II. The median survival time was 39 months (3.3 y) for patients at dGAP stage I and 37.8 months (3.2 y) for those at stage II (see Figure 14). The log-rank test showed no statistically significant difference between the dGAP stages (p = .906).

In the non-IPF CPFE group, the analysis of dGAP showed that 5 of 19 patients (26.3%) at dGAP stage I were dead by the time of this study compared to 14 of 25 (56%) patients at stage II. The median survival time of patients at dGAP stage I could not be calculated, as the Kaplan-Meier curve did not cross the 50% threshold. The median survival time was 41.1 months (3.4 y) for patients at dGAP stage II (see Figure 14). The data showed a trend for decreased survival in patients with higher dGAP score that was close to statistical significance, log-rank test p-value of (0.07).

IPF subtype CPFE



Non-IPF subtype CPFE

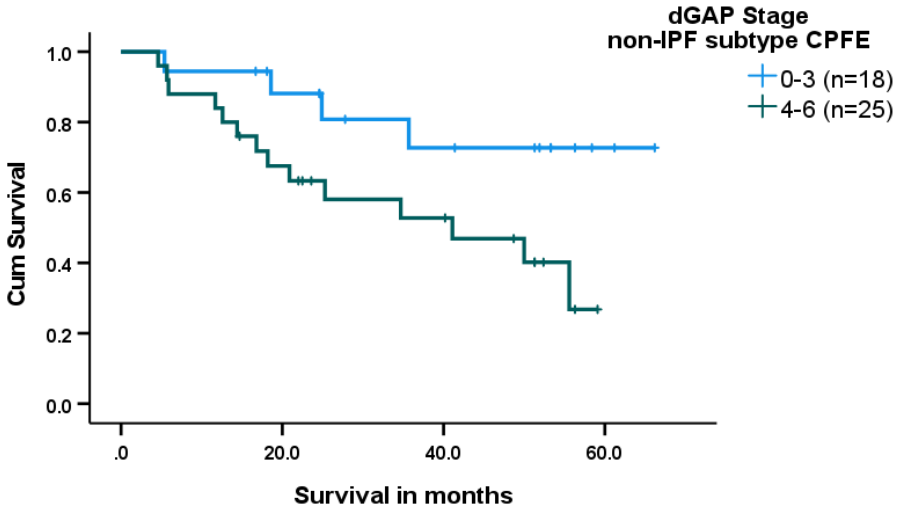


Figure 14 Kaplan-Meier analysis of dGAP stage in patients with IPF and non-IPF subtype of CPFE.

Abbreviations: IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; dGAP, diffusion GAP score.

3.3.10 Predictors of mortality in patients with CPFE:

The multivariate cox regression analysis model showed that the transfer factor for carbon monoxide percentage predicted (TLCO%) was a predictor factor of mortality (see Table 10), with lower TLCO% being associated with higher mortality.

Table 10 Mortality predictors in patients with CPFE

	Multivariate Cox analysis		
Variables	Hazard ratio	(95%CI)	P-value
GAP stage			
	1.859	0.66-5.27	0.244
	0.773	0.34-1.75	0.538
Oxygen use	0.456	0.22-0.96	0.039
FVC% predicted	1.004	0.98-1.03	0.687
FEV1/FVC%	1.009	0.98-1.04	0.506
TLCO%	0.931	0.89-0.97	***<0.001

GAP: gender at birth-age-physiology; FVC% predicted: forced vital capacity percentage predicted; FEV_1/FVC (%): FEV_1/FVC ratio; TLCO%: transfer factor for carbon monoxide percentage predicted; ***: P-value ≤0.001.

3.4 Discussion

Currently, nearly 700 patients with ILDs are discussed at RVI's regional multidisciplinary ILD team meeting yearly. Because CPFE is a very rare lung condition with high mortality, our aim was to perform a retrospective audit to determine the number of those patients with CPFE and locate them. The audit provided valuable information on the number of patients with ILD and CPFE in the Northeast and Northwest regions of the UK as well as information on the characteristics of patients with CPFE. In this audit of five years from January 2014 through December 2018, 203 patients with a diagnosis of CPFE were identified at the ILD meeting from a total clinic population of 3,063 patients, indicating that CPFE patients make up around 6.6% of the ILD clinic population. While this is a small minority of total patients, it represents a considerable number of individual patients who had not previously been formally documented. This may be an important finding for the ILD clinic at RVI, as the optimal management of CPFE may require resource planning tailored to an accurate number of patients and an awareness of likely disease progression.

As expected, patients with CPFE were older, with ages ranging from 45 to 90 years, and 82% of the patients were male, consistent with the pattern in other ILDs, such as IPF, which are less common in women. Most patients had a history of smoking, with around 86% being former smokers, 11% being current smokers and only 3% having never smoked (see Table 4). For current smokers, smoking cessation was a highly recommended therapeutic option by the ILD physicians at RVI, where patients were referred to a smoking cessation programme. Our data, which to our knowledge are the first of their kind in the UK, align with the limited published data of Dias et al. (Dias et al., 2014). In Japanese and French populations, patients with CPFE were mainly male, presented with severe shortness of breath and had a history of smoking (Cottin et al., 2005, Dias et al., 2014, Kishaba et al., 2012). A review by Jankowich and Rounds describes similar findings. In that review, the subgroup of patients with coexistent emphysema and pulmonary fibrosis usually presented with dyspnoea, a history of smoking, physiological abnormalities as seen in lung function results and, often, pulmonary hypertension. Jankowich et al. also note that patients with CPFE are predominantly male, which may be attributed to more exposure to smoking in men than in woman. Nevertheless, a greater prevalence of smoking in men does not fully explain the male predominance. Jankowich and Rounds speculate that men are more prone to smoking-induced coexistence of emphysema and pulmonary fibrosis due to greater

susceptibility to abnormal lung aging in males (Jankowich and Rounds, 2012). It is of interest that the commonly used GAP index and staging prognostic tool for ILD prognosis includes male gender as a contributor to risk.

Of the 203 patients with CPFE referred to the RVI's ILD meeting, 74% were treated at the RVI's ILD clinic, while 26% were only discussed at the ILD meeting. This study has identified the number of patients with ILD (and specifically with CPFE) who are being seen and treated by the ILD team at RVI. The patients with CPFE who were referred to the RVI's ILD team in the five years of this audit showed a poor prognosis, as 100 (49.3%) had died by the time of the study.

3.4.1 Type of fibrosis in patients with CPFE

All the patients in this audit had CPFE, that is, coexistent pulmonary fibrosis and emphysema. UIP and IPF were the predominant types of fibrosis at 36.9% and 25.5%, respectively, followed by asbestosis (6%), rheumatoid arthritis (4.7%), NSIP (4%) and unclassifiable (2.7%) (see Table 6). Around two-thirds of the patients (62%) had either IPF or UIP as the fibrotic component. Emphysema was more dominant than fibrosis in this sample (see Table 7). This information is valuable in better understanding the characteristic of this disease and possible treatment choices. (Malli et al., 2019) found in their study that patients with CPFE with fibrosis as the predominant component had a worse prognosis. Other studies have contradicted that result, finding no influence of the fibrotic component on survival results (Zhang et al., 2016a).

3.4.2 PFT results

PFT results were collected at the point of diagnosis. The patients with CPFE had mildly abnormal or normal PFT results but with a severely impaired diffusion capacity TLCO. In comparison to patients with non-IPF subtype emphysema, patients with IPF-subtype CPFE had significantly more impaired TLCO. This may have caused substantially more patients with IPF subtype CPFE to require oxygen supplementation (see Table 5). Our findings complement the few other published studies showing that patients with CPFE present with normal or mildly impaired lung volumes (Jankowich and Rounds, 2010). Other groups have reported a restrictive pattern (Kishaba et al., 2012, Malli et al., 2019). Todd et al. address the divergent findings in the literature by noting that lung volumes differ in patients with CPFE depending on the degree of emphysema,

which may explain the inconsistency among the studies (Todd et al., 2011). In our study, the majority of patients were deemed to have emphysema as the predominant disease as determined by HRCT scan. A potential physiological explanation of our finding—normal or mildly subnormal lung function results despite a more severe impairment in lung diffusion capacity TLCO—is that the emphysema component of the disease causes hyperinflation and increased lung compliance due to a decrease in elasticity. This is counterbalanced by the decrease in lung compliance caused by the fibrotic component of the overall CPFE pathophysiology. It is also possible that the fibrotic component of CPFE stops the early closure of small airways due to emphysema (Dias et al., 2014).

3.4.3 Anti-fibrotic medications

Only one-third of the patients with CPFE were on anti-fibrotic medications (23.5% on nintedanib; 8.7% on pirfenidone), while the rest were not on anti-fibrotic medications. During the data-collection period of this retrospective study (January 2014–December 2018), the National Institute for Health and Care Excellence (NICE) guidelines for anti-fibrotic medications stated that pirfenidone or nintedanib could be given to patients with IPF with a FVC between 50% and 80% predicted (Landells et al., 2013, Laurenson et al., 2016). Patients with CPFE are known to have preserved spirometry lung volumes and preserved FVC because the two diseases counteract each other; therefore, many patients with CPFE do not get anti-fibrotic medications based on the guidelines. Our data show that only a third of patients with CPFE were prescribed anti-fibrotic medications during 2014–2018. Fortunately, nintedanib has recently been shown to benefit patients with progressive fibrosing ILD (Flaherty et al., 2019). With the newly updated NICE guidelines on the use of nintedanib in patients with progressive fibrotic ILD, we expect an increase in the use of anti-fibrotic medications in patients with CPFE.

3.4.4 Pulmonary rehabilitation referral

This audit found that only around half the patients with CPFE had either participated in a pulmonary rehabilitation programme or were referred by their clinician to attend such a programme at their local health care facility. Two previous studies have shown that pulmonary rehabilitation programmes with both aerobic and breathing exercises can improve the condition of patients with CPFE (De Simone et al., 2015, Tomioka et al.,

2016). Despite these data, at least half the patients with CPFE were not being referred to pulmonary rehabilitation program. Also, the clinical team at the RVI had the impression that patients with CPFE may be too weak to complete a pulmonary rehabilitation programme. This showed that there is a clear need to develop and evaluate a pulmonary rehabilitation programme specifically for patients with CPFE (Tomioka et al., 2016), which encourages the further work of this PhD.

3.4.5 Survival prognosis

This study evaluated patients with CPFE who were referred to the ILD MDT at RVI from 1 January 2014 through 31 December 2018. The patients were divided into two groups (those with IPF subtype CPFE and those with non-IPF subtype CPFE. The result shows that patients with CPFE have a poor prognosis whether in the general CPFE population or the IPF subtype CPFE group, with median survival times of 40.1 months (3.3 y) and 34.1 months (2.8 y), respectively. Although, patients with non-IPF subtype CPFE showed a slightly better survival, with a median survival time of 55.6 months (4.6 y), but this difference did not reach statistical significance.

The scarce available literature offers contradictory results regarding mortality in patients with CPFE compared to those with IPF. Ryerson et al. found no differences in survival between CPFE and IPF (Ryerson et al., 2013). A previous study by Todd et al. assessed the amount of emphysema in CT images using a modification of the National Emphysema Treatment Trial scoring system and found that patients with pulmonary fibrosis and an advanced emphysema score of > 2 (marked emphysema ≥ 51%) had a better prognosis than patients with pulmonary fibrosis alone as well as better than those with pulmonary fibrosis and a lesser emphysema score of ≤ 2 (mild emphysema ≤ 25%). The authors note that the survival advantage in advanced emphysema was observed in patients with a substantial centrilobular emphysema or mixed emphysema. Patients with advanced paraseptal emphysema had a similar survival time to patients with fibrosis alone. The authors report a median survival time of 63 months for patients with pulmonary fibrosis and emphysema vs. 29 months for those with pulmonary fibrosis alone and 32 months for those with pulmonary fibrosis and a minor extent of emphysema (score ≤ 2) (Todd et al., 2011). In a Greek cohort, Malli et al. report a mean survival time of 84 months (7 years) after diagnosis in patients with CPFE (Malli et al., 2019).

In contrast other studies suggest that patients with CPFE have a worse prognosis than those with IPF (Sugino et al., 2014, Zhang et al., 2016a). Sugino et al. report that

patients with CPFE had a significantly worse survival than patients with IPF, with median survival times of 22 and 50 months, respectively. CPFE patients with paraseptal-type emphysema and a high estimated pulmonary arterial pressure measurement had the worst prognosis (Sugino et al., 2014). Further, Zhang et al. found that patients with CPFE had a worse prognosis than patients with IPF in a Chinese cohort. Both pulmonary arterial hypertension (PAH) and a ≥ 5-point rise in composite physiologic index (CPI) score per year were associated with higher mortality in patients with CPFE (Zhang et al., 2016a).

These contradictory results may reflect the heterogeneity of patients with CPFE. Additionally, this rare condition was only recently recognised and deemed worthy of study. The contradictory findings in the literature may also result from the use of different inclusion criteria for CPFE in various studies. For example, some studies have included patients with any ILD component in their CPFE patient groups, while others have specifically included only patients with IPF subtype CPFE. The extent of the fibrotic and emphysematous components in patients with CPFE can differ significantly, and the prevalence of ILD is known to vary by geographical location.

3.4.6 GAP score

The rare CPFE-specific physiological data in this study may have implications for the prognostic scoring systems that are increasingly used in IPF research and clinical practice. The widely used GAP, based on weighted scores for the patient's gender at birth, age, FVC% and DLCO% (Ley et al., 2012), is easy to use with commonly measured variables and could potentially be relevant in CPFE. Male gender, for example is associated with an increased risk of mortality, so the predominance of male patients in our CPFE cohort may have significant implications for our patients' outcome. Thus, we evaluated the GAP score in the specific context of CPFE. Conceivably, the standard GAP approach might be modified in patients with CPFE, among whom the deficit in DLCO%, for example, may be a more accurate assessment of functional status. The original GAP scoring system in IPF was derived from the data of 228 IPF patients at the University of California–San Francisco and then validated in 330 IPF patients at the Mayo Clinic and Morgagni-Pierantoni Hospital (Ley et al., 2012). In this five-year single centre, retrospective study, data on 149 patients with CPFE were collected. The ILD clinic at the RVI is regarded a centre of expertise in ILD. Even though they receive referrals from the entire Northeast and Northwest of the UK, we

were only able to identify 149 patients with CPFE in this five years retrospective study. This might be attributed to CPFE disease's rarity. Therefore, future studies might consider using a multicentre design which could help in obtaining a larger sample size. Such studies would need to carefully consider issues of standardisation so that the benefits of increased sample sizes are not undermined by variation between centres.

In patients with IPF, the GAP score has shown significant predictive ability for mortality (Lee et al., 2016). A retrospective study in a Japanese cohort of 65 patients with IPF found that a higher GAP stage (≥ II) predicted the onset of acute exacerbation (AE) (Kakugawa et al., 2016). The usefulness of the GAP stage as a prognostic tool was also demonstrated in another Japanese retrospective single-centre study of 54 IPF patients (Kishaba et al., 2015). In their review of disease severity assessment and staging systems in ILD, Tomassetti et al. confirm the promising potential of the GAP index and call for further research to expand the GAP index with more biomarkers (Tomassetti et al., 2015). A large Australian IPF registry study with 647 IPF patients found that the baseline GAP index, along with lung function data and patient-reported outcome measures (PROMs), was a significant predictor of mortality (Jo et al., 2017).

When patients with IPF were evaluated for lung transplant, the IPF-specific GAP index was a superior predictor of mortality than single variables (Fisher et al., 2017), performing similarly to the lung allocation score. This could contribute to decision-making and to determining the time of referral for lung transplantation in people with IPF (Fisher et al., 2017).

The literature on CPFE is generally sparse, and there appears to be only one study on the GAP score in people with CPFE. In this study, conducted by Jee Youn Oh and colleagues (2018), 12 years of medical record data were analysed retrospectively, and 227 CPFE patient records were studied. The authors confirmed the GAP score as a predictor of AE in patients with CPFE (Oh et al., 2018). In the present study, the GAP staging system was a significant predictor of mortality. In the IPF subtype of CPFE, the GAP stage was a significant predictor of mortality, with stage III being associated with poor prognosis and stages I and II associated with better outcomes. Both FVC% and DLCO% were significant predictors of prognosis. In the non-IPF CPFE group, GAP stage, DLCO% and FVC% were not significant predictors of mortality, with p-values of .073, .057 and .295, respectively. The lower number of patients (n = 44) in the non-IPF CPFE group may explain why the result did not quite reach the level of significance.

A review by Kolb and Collard highlights the importance of developing a standardised, evidence-based IPF prognosis staging system. Doing so will require that (1) accurate predictors of IPF prognosis be identified and (2) a clinically practical method of combining those predictor variables be found (Kolb and Collard, 2014). A Korean nationwide five-year retrospective study compared the predictive accuracy of the CPI and the GAP index in 832 patients with IPF, with the following formula used to calculate CPI: 91.0 – (0.65 × DLCO%) – [0.53 × FVC%] + [0.34 × FEV1%]. In that study, both CPI and the GAP index were significant predictors of mortality, but CPI proved more accurate in predicting one-, two-, and three-year mortality (Lee et al., 2018).

Several attempts have been made to modify the GAP index to improve its prognostic capability and/or evaluate its applicability for predicting prognosis in ILD conditions other than IPF. For example, the original GAP index for patients with IPF was shown to predict prognosis with similar accuracy in patients with rheumatoid arthritis–associated ILD (Morisset et al., 2017b). Kobayashi et al. used the mGAP in patients with both IPF and non–small cell lung cancer (NSCLC). They note that DLCO% is not routinely tested in patients with NSCLC and IPF, as the procedure is exhausting for them. The simpler mGAP index uses gender at birth, age and only FVC% to generate a score. The authors conclude that the mGAP index and staging system predicts acute exacerbations of IPF in patients with NSCLC and IPF (Kobayashi et al., 2017). Singh and colleagues verified the utility of mGAP as a survival predictor in patients with ILD in an Indian population (Singh et al., 2021).

Originally developed by Ryerson et al., the ILD-GAP was modified by Kobayashi et al. as the ILD-NSCLC-GAP index and staging system, which includes ILD subtype, gender at birth, age and FVC% (without DLCO%). The authors report that the modified index is a useful tool to evaluate prognosis and the incidence of acute exacerbations in patients with NSCLC and ILD (Kobayashi et al., 2018). The ILD-GAP has also been proven effective in predicting prognosis in patients with surgically resected lung cancer (Ueno et al., 2020). A large, multicentre, international cohort study found that both resting and exertional hypoxemia had prognostic capability in patients with ILD (Khor et al., 2021). The authors further modified and validated the ILD-GAP-O^2 model, which was derived from the ILD-GAP, and found that addition of oxygenation status improved the performance of the ILD-GAP (Khor et al., 2021).

Ley et al. further modified the GAP to create the CT-GAP model, in which a CT fibrosis score component replaces DLCO% due the difficulty of measuring diffusion capacity

in some patients. CT is routinely performed in those patients, and the authors conclude that the CT-GAP score performs comparably to the original GAP score and offers an interesting, simpler option (Ley et al., 2014). Because of the growing evidence that the degree of fibrosis observed in CT is related to poor prognosis in patients with IPF, Chahal et al. combined the fibrotic score from CT with the GAP score in a thin-section CT-GAP index, which demonstrated a better prognostic ability for survival analysis than the GAP score alone in patients with IPF, particularly those with a mild disease as shown by a GAP score of ≤ 3 (Chahal et al., 2019). A study by Suzuki et al. assessed the GAP index as a prognostic variable at the time of anti-fibrotic medication initiation, and their results support the prognostic value of GAP and BMI in patients with IPF. They also found that a lower BMI was associated with a poor prognosis independent of the GAP index (Suzuki et al., 2021).

Further, Zinellu et al. compared the prognostic capability of the original GAP to an mGAP-derived index (IC4) that included FVC%, DLCO%, BMI and six-minute walk distance (6MWD). Ninety patients with IPF were recruited in two cohorts in France and Italy. The IC4 proved superior to its individual components and to the original GAP index in predicting mortality (Zinellu et al., 2021).

Recently, Torrisi et al. developed and validated the TORVAN model and index, which includes age, FVC%, DLCO% and comorbidity variables. In two independent multinational cohorts, the TORVAN prediction index was shown to be superior to the GAP in predicting survival in patients with IPF. The authors note that, in survival prediction in IPF, the key comorbidities are gastro-oesophageal reflux disease (GORD), lung cancer, pulmonary hypertension, atrial arrhythmias and valvular heart disease (Torrisi et al., 2019).

In the present study, the mGAP index was also a significant predictor of mortality, specifically in patients with IPF subtype CPFE. Although lung function tests in patients with CPFE commonly show mildly abnormal or normal dynamic lung volumes with significantly reduced diffusion capacity, the mGAP index (which includes gender at birth, age and FVC% without DLCO%) still showed prognostic predictive capability. This finding is potentially valuable, as some patients with CPFE cannot perform technically satisfactory diffusion capacity tests due to their breathlessness or low vital capacity (VC) but can complete spirometry. In the non-IPF CPFE group, mGAP was not a significant predictor of mortality. Considering the small size of this group (n = 44),

lack of power could explain why significant results did not emerge. A larger sample size may be needed to investigate this further.

Because lung volumes in patients with CPFE are usually mildly abnormal or normal and their diffusion capacity is markedly reduced, this study modified the GAP index by removing the PFVC term, including only gender at birth, age and PDLCO%. This new modification of GAP, the dGAP stage system, showed prognostic capability in the general CPFE group but not in the IPF subtype CPFE group. Additionally, dGAP approached the threshold of statistical significance ($p = .070$) in the non-IPF CPFE group, with stage I having a better prognosis than stage II on the Kaplan-Meier curve. Additionally, multivariate cox analysis of mortality predictors in patients with CPFE has identified TLCO% to be associated with mortality (see Table 10). This further shows the potential prognostic value of TLCO% in patients with CPFE and its consideration when developing/evaluating prognostic indices.

3.5 Limitations

The 149 patients identified in this study are consistent with the sample sizes in other published studies, but our conclusions would be strengthened by studies involving greater numbers of patients and by replication in independent cohorts. Due to the rarity of CPFE, future studies should consider employing a multicentre design, which could help in collecting a larger sample size. Calculation of statistical power would be useful for future research. Long-term follow up studies of 1 to 3 years are needed in patients with CPFE. This study included and evaluated patients with CPFE, and no comparison was made with an IPF group of patients. Therefore, future research studies should consider including a comparison cohort of IPF patients.

3.6 Conclusion

This study provided valuable data on the prevalence of ILD and CPFE in the Northeast and Northwest regions of the United Kingdom, as well as CPFE patient characteristics. The ILD MDT meeting diagnosed 203 patients with CPFE out of 3,063 patients with ILD over a five-year period. Indicating that approximately 6.6% of ILD clinic patients are CPFE patients. Prior to this study, the number of patients with CPFE had not been formally documented in the United Kingdom. This may be a crucial finding for the ILD clinic at RVI, as the optimal management of CPFE may necessitate patient-specific resource planning. Patients with CPFE were relatively old, majority male, with a history of smoking. The predominant type of fibrosis was IPF in 62% of patients with CPFE. Lung function test results showed normal or mildly impaired lung volumes with decreases lungs diffusion capacity. At least half the patients diagnosed with CPFE were not referred for a pulmonary rehabilitation programme. This is despite the recommendations that patients with chronic lung disease should attend such a programme. This clearly identified the need to develop a tailored pulmonary rehabilitation programme for patients with CPFE. Almost half, 100 (49.3%) of patients with CPFE had died by the time of this study. Our data add to the very few and contradictory studies published to date and support the conclusion that CPFE has a worse prognosis than other ILDs. In particular, IPF variant CPFE has poor prognosis.. In our study, the median survival time for people with IPF subtype CPFE was 34.1 months (2.8 y), while the life expectancy at age 65 in the UK is 18.5 years for males and 21 years for females (Ons.gov.uk., 2021).

Recently, the GAP model developed for IPF has been effectively applied to various subgroups of fibrotic ILD (ILD-GAP). This study is one of the few studies that evaluated the role of the GAP index and staging system in patients with CPFE. In this study, the GAP index and staging system as well as the mGAP index proved their prognostic capability in patients with IPF subtype CPFE. This shows the potential role of the GAP staging system in patients with CPFE, providing a simple tool for assessing disease severity. In the future, it would be interesting to attempt to replicate our findings in an independent, larger group of patients, e.g. drawn from British Thoracic Society ILD registry data. If confirmed, the findings of this study may have important implications for patient stratification in situations such as pulmonary rehabilitation, transplant waiting lists and palliative care referrals.

Chapter 4: The Feasibility of Respiratory Muscle Training as Part of a Pulmonary Rehabilitation Programme for Patients with Interstitial Lung Diseases

4.1 Introduction

ILDs are a group of disabling chronic lung conditions that include idiopathic IPF, hypersensitivity pneumonitis, acute and chronic interstitial pneumonias, asbestosis, sarcoidosis, silicosis, as well as connective tissue diseases related to ILD such as rheumatoid arthritis and scleroderma. There are over 200 different types of ILD conditions; these cause interstitial inflammation and fibrosis and also provoke wound-healing responses, which further progresses the disease. Patients with ILD present with dyspnoea, fatigue, persistent cough, and decreased exercise tolerance, which leads to decreased health-related quality of life (Holland et al., 2015, Dowman et al., 2021).

Currently, there is no cure for patients with ILD and therapeutic options are limited. Further, in patients with IPF, anti-fibrotic medications pirfenidone and nintedanib can slow the progression of the disease, as reflected by slowing down the decline in FVC (King et al., 2014, Richeldi et al., 2014). In other progressive fibrosing ILDs, it has been revealed that nintedanib also slows disease progression (Flaherty et al., 2019). The effect of anti-fibrotic medications on health-related quality of life is not clearly known and limited data is available on the subject (Graney and Lee, 2018, Kreuter et al., 2020).

Pulmonary rehabilitation programmes (PRPs) are a multidisciplinary intervention for patients with chronic lung disease. They typically include exercise training (endurance and/or strength) and respiratory muscle training as well as education sessions, nutritional guidance, psychosocial support, and self-management. In patients with COPD, there is well established evidence that supports pulmonary rehabilitation and its benefits in improving health-related quality of life, exercise capacity, reducing dyspnoea, and healthcare costs (McCarthy et al., 2015). However, there is limited evidence of the influence of pulmonary rehabilitation on these outcomes in patients with ILD. Moreover, the role and efficacy of inspiratory muscle training (IMT) in combination with PRPs in patients with ILD remains unknown, as limited studies have examined this, despite the fact IMT has been widely examined in patients with COPD

(Geddes et al., 2008). In particular, there are very little data available on patient with CPFE.

The aim of this chapter is to evaluate the feasibility of IMT as part of a PRP for patients with ILDs, which included a few people with CPFE.

4.2 Methods

4.2.1 Study design and participants

The current study is a feasibility pilot study with a randomized controlled trial design. Patients diagnosed with CPFE, IPF, or ILD by an ILD multidisciplinary team were recruited from the Royal Victoria Infirmary hospital, Newcastle upon Tyne. This study was approved by the UK health and research authority (HRA) (REC reference 18/NE/0037) (see Appendix 1). The patients included in this study were randomized into two groups. Randomization was performed using a website (sealedenvelope.com) that provides a high-quality, accessible platform for randomizing patients in clinical trials. Patients randomized into the intervention group received PRP and IMT (PRP + IMT), while those randomized to the control group received only PRP.

4.2.2 Inclusion criteria

Patients with CPFE, IPF, or ILD diagnosed by an ILD multidisciplinary team. Patients who are able to perform the exercises and follow instructions. Other comorbidities that could have affected the results of the study were excluded.

- Age ≥ 40 years old.
- Working diagnosis of IPF, CPFE, or ILD made by an ILD multidisciplinary team.
- Patient is able to follow instructions and perform exercises.

4.2.3 Exclusion criteria

- Uncontrolled heart disease.
- Uncontrolled hypertension.
- Patient unable to follow instructions (e.g. learning difficulty).
- Patient unable to perform exercises (e.g. orthopaedic or neuromuscular diseases).
- Patient attended pulmonary rehabilitation in the past six months.
- Patients with other lung diseases related to occupational exposures or drugs.
- Patients with severe asthma who suffer from frequent severe exacerbations and have low symptom/dyspnoea perception.
- History of syncope during exercises.
- Patients with ruptured eardrum or any other diseases of the ear that may affect balance.
- Patients with worsening heart failure symptoms after RMT/IMT.
- Patients with raised left ventricular end diastolic volume and pressure.

4.2.4 Intervention

Patients were randomized into either the intervention group that received PRP + IMT or to the control group that received only the PRP; the randomization was conducted via sealed envelope™ (sealedenvelope, 2023). Transportation support with taxies was offered to participants who needed them. The PRP consisted of supervised sessions (120 minutes) conducted once a week for a total duration of eight weeks or six weeks as a modification made in response to the COVID-19 pandemic in March 2020. The programme consisted of exercise training, education sessions, and relaxation. The exercise training included warming up, aerobic exercises, strength training, and cooling down. Patients first underwent 5–10 minutes of warm-up exercises. Then, aerobic exercises were conducted using a cycle ergometer for 20 minutes with a target BORG scale of 5 (Borg, 1982, Bausewein et al., 2007). Heart rate and blood oxygen saturation were monitored during the exercises. Oxygen therapy was provided/increased when the pulse oximetry oxygen saturation SpO2 fell below 80%, with the aim of maintaining a saturation level ≥90%. Further, strength training was performed with two sets of six repetitions for the following muscles/area: biceps, triceps, pectorals, back, abdomen, deltoid, quadriceps, calf, and hamstrings. At the end of the regimen, patients were instructed on how to perform cool down exercises for five minutes. Thereafter, patients attended a relaxation session, which included listening to relaxing music, low light, and comfortable chairs. As a modification made in response to the COVID-19 pandemic in March 2020, patients participated in a relaxation session once in the programme instead of every week (see Table 15). The ATS and the ERS have made a shared statement regarding the key concepts of pulmonary rehabilitation and its advances, providing guidelines for PRPs (Spruit et al., 2013).

All patients in both groups were also instructed to perform 40 minutes of home exercises twice a week. The home exercise programme consisted of five minutes of warming up, stretching for all muscle groups, 20 minutes on the cycle ergometer (NRS Healthcare Pedal Exerciser with Digital Display, ©2022 NRS Healthcare), and strength training with Thera-band® exercise bands (©2016 Performance Health;). Patients used Thera-band® exercise bands (see Figure 15) to perform nine exercises with two sets of six repetitions.

Patients were also instructed to walk on four days a week on the days they were not exercising. A pedometer (OMRON HEALTHCARE Co., Ltd.;) (see Figure 16) was provided to all patients to count daily steps with a memory of seven days. Participants

were also provided with a walking distance and steps log to record and track their walking. This log was assessed by the researcher on a weekly basis to track the participants' progress and to provide encouragement when needed. Every week, the average step count of patients was calculated; patients were instructed to increase their walking steps by 10% each week (New steps target = average steps count + 10%).

Figure 15 Thera-band® exercise bands (©2016 Performance Health.).

Figure 16 A pedometer (OMRON HEALTHCARE Co., Ltd.)

Further, patients randomized to the intervention group received IMT through the POWERbreathe® Medic plus device (POWERbreathe®, International Ltd, UK). The POWERbreathe® device (see Figure 17) is a variable resistance device that can be adjusted with a calibrated spring. The resistance training level was initially adjusted at 40% of the patient's baseline maximal inspiratory muscle pressure (PImax). Patients were instructed to use the device twice daily (for seven days a week), once in the morning and once in the afternoon, as tolerable, for 30 breaths in each session with periods of rests, as needed, between every three to five breaths, and particularly if tired or dizzy. To perform IMT training with POWERbreathe®, patients were instructed to sit down in an upright sitting position, hold the POWERbreathe® device in their hand, and place their mouth on the device with their lips around the mouthpiece. Then, they were instructed to breathe out all the air from their lungs as much as they could. Thereafter, patients were asked to inhale as fast and as deep as possible, with an obvious expansion of their chest. Moreover, patients were instructed to keep their shoulders levelled and not hunch them upwards toward their ears while inhaling through the device. Finally, patients were instructed to exhale slowly and passively. Depending on patients' progress, the resistance training level of POWERbreathe® was increased in a range of 0.5–1 each week.

Figure 17 POWERBreathe® Medic plus device (POWERbreathe®, International Ltd, UK).

4.2.5 Outcomes

4.2.5.1 Primary outcomes

4.2.5.1.1 Attendance, completion, and dropouts

The data regarding participants' attendance and completion and dropout of the programme was collected.

4.2.5.1.2 Side effects

Any complication or side effect of the participating in the program were observed.

4.2.5.2 Secondary outcomes

The following outcomes were collected at baseline and after eight weeks:

1. Maximum inspiratory pressure (MIP) measured using the POWERbreathe® KH2 (POWERbreathe® International Ltd, UK) (see Figure 18). The POWERbreathe® KH2 is an electronic handheld IMT device. It also provides an MIP Test Mode that was utilized in this study before PR and after eight weeks. During the MIP Test Mode, participants were instructed to breathe out slowly and completely until their lungs felt emptied of air. Then, participants were instructed to take in a deep inhalation and hold their breath for approximately two seconds. Thereafter, they were instructed to relax and take their mouth off the mouthpiece. The test was repeated until three tests varying by less than 20% were achieved. The minimal clinically important difference (MCID) for inspiratory muscle strength has yet not been established for ILD. Iwakura et al. recently identified an MCID of 17.2 cmH2O for outpatients with COPD who attended a pulmonary rehabilitation programme (Iwakura et al., 2021).

Figure 18 POWERbreathe® KH2 (POWERbreathe® International Ltd, UK).

2. The King's Brief Interstitial Lung Disease Questionnaire (K-BILD) (Patel et al., 2012) was used to evaluate the impact of ILD on different aspects of the patient's life. The K-BILD questionnaire comprises three domains with 15 items each, with a seven-point response range: breathlessness and activities (items 1, 4, 11, and 13), chest symptoms (items 2, 7, and 9), and psychological (items 3, 5, 6, 8, 10, 12, and 14). The total score ranged from 0 to 100, with higher scores indicating better quality of life. Further, the internal consistency for the K-BILD total score was (Cronbach's $\alpha = 0.94$). The MCID of K-BILD in patients with ILD was 5 for the mean K-BILD total score. For the K-BILD domains, the MCIDs were 7 for breathlessness and activities, 11 for chest symptoms, and 6 for psychological (Sinha et al., 2019).
3. Fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp et al., 1989). This scale consists of nine statements regarding the frequency, severity, and impact of fatigue on activities of daily life. Participants were asked to rate their agreement on a scale ranging from 1 to 7 on these statements. A total score on the FSS of less than 36 is considered normal. A score above 36 up to a maximum of 81 is indicative of significant impact of fatigue on activities of daily life. Furthermore, the MCID of the FSS ranges between 0.45 and 0.88, which implies a difference of 6.4% to 12.6% in the overall FSS score (Rooney et al., 2019).

4. Anxiety and depression was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). It consists of 14 multiple-choice items—7 items for anxiety and 7 items for depression. The total score ranges from 0 to 21. A score of less than 8 implies that there is no anxiety or depression, a score ranging from 8 to 10 is indicative of borderline anxiety or depression, and a score 11 or more suggests a clinically significant anxiety or depression.
5. Pulmonary function test: Lung volumes and capacities were measured using spirometry FEV1, FVC, and FEV1/FVC ratio. TLCO was measured by the single-breath technique. A spirometer was used with participants in the seated position following standard guidelines from the ATS/ERS (Graham et al., 2017, Graham et al., 2019).
6. Six-minute walking tests (6MWT) were performed based on guidelines from the ATS (2002) in order to calculate the six-minute walking distance (6MWD). The 6MWD has a Minimal Important Difference (MID) in patients with ILD of 30 meters–33 meters, and for patients with IPF 29 meters–34 meters (Holland et al., 2014b).
7. The one-minute sit-to-stand test (1MSTS) was assessed to evaluate exercise capability (Bohannon et al., 1995, Ozalevli et al., 2007). A chair with a height of 46 cm with no arm rests was used. Patients were asked to sit in the chair with knees and hips at an angle of 90°, with feet apart and flat on the ground. Patients were asked to sit and stand repeatedly as many times as possible at their own pace and in a comfortable and safe manner for the duration of one minute. In addition, patients were instructed to not use their arms for support while standing or sitting. They were allowed to rest if needed during the one-minute test period. The number of repetitions were documented for each patient. Dyspnoea was assessed before and immediately after 1MSTS using the modified Borg scale. Throughout the duration of the test, a pulse oximeter was placed on the patients' fingers for continuous monitoring of SpO2 and heart rate (HR). A drop of SpO2 ≥4% was considered a significant desaturation. Furthermore, an MCID after pulmonary rehabilitation of 2.03–3.45 repetitions was identified for patients with COPD (Schneeberger et al., 2018).

8. The strength of major body muscles (quadriceps, deltoid, and biceps) was measured using a handheld dynamometer microFET2™ (HOGGAN SCIENTIFIC, LLC) (see Figure 19) at baseline and after eight weeks. The same assessor performed the assessment on all patients. MicroFET2™ provides a simple and affordable tool for evaluating muscle strength. It is designed to fit into the palm of the hand, which enables the user to apply resistance directly to the movement of an extremity and determine the force output of the muscle movement in the extremity.

Figure 19 The MicroFET device

9. Blood biomarker Matrix Metalloproteinase 7 (MMP-7) was assessed in this study. Blood samples were collected pre and post eight weeks of the PRP. The blood samples were then taken to Newcastle University, centrifuged, and then stored at -80°C. Enzyme-linked immunosorbent assays (ELISA) are used to evaluate the presence of proteins in samples. An R&D Systems DuoSet Kit (R and D Systems, Minneapolis, MN, USA) was used for performing Sandwich ELISA according to the manufacturer's instructions

4.2.6 Statistical analysis

For the statistical analysis, GraphPad Prism 9 (GraphPad Software, Inc.) was used to obtain descriptive statistics. Means, medians, standard deviation, and interquartile ranges were used to describe numeric variables, and absolute and relative frequencies (%) were used for categorical variables. Due to this study being a feasibility pilot study of a randomised controlled trial, no statistical testing of hypotheses was performed. A quote from Leon et al. supports this "A pilot study is not a hypothesis testing study. Therefore, no inferential statistical tests should be proposed in a pilot study protocol. With no inferential statistical tests, a pilot study will not provide p-value" (Leon et al., 2011).

4.3 Results

4.3.1 Characteristics of participants

Fourteen patients with the diagnosis ILD including nine with CPFE referred to pulmonary rehabilitation by their ILD consultant at the RVI, Newcastle upon Tyne, United Kingdom were enrolled into this study. 12 study participants attended the full PRP with only 2 dropouts. Pre and post data of 14 participants baseline characteristics is provided in (see Table 11 and Table 13), which shows patients mean age was 68 years, 64% were male, and the mean FVC was 2.42 litres. Patients' characteristics by study group intervention versus control group is provided in (see Table 12).

Table 11 Baseline characteristics of all study participants. Data are presented as mean ± standard deviation.

Variable	**Number of participants = 14** **Mean (SD)**
Age (years)	68 (9.4)
Male	9 (64%)
Female	5 (36%)
ILD Disease	
CPFE	9 (64%)
IPF	2 (14%)
HP	2 (14%)
CTD-ILD	1 (7%)
Weight (kg)	79.1 (13.7)
Height (cm)	168.7 (8.0)
BMI (kg/m^2)	28.0 (4.3)
FVC (L)	2.4 (1.0)
FVC (%pred)	73.1 (26.7)
FEV1 (L)	1.9 (0.8)
FEV1/FVC (ratio %)	105 (9.3)
TLCO (% pred)	43.5 (13.5)

Abbreviations: ILD, interstitial lung diseases; CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; HP, hypersensitivity pneumonitis; CTD-ILD, connective tissue disease associated-ILD; BMI, body mass index; FVC, forced vital capacity, FVC (%pred), FVC percentage predicted; FEV1, forced expiratory volume in one second; TLCO (% pred), transfer factor for carbon monoxide percentage predicted.

Table 12 Baseline characteristics of participants by study group. Data are presented as mean ± standard deviation.

	Intervention group	**Control Group**
	Mean (SD)	**Mean (SD)**
Age (years)	68 (4.6)	68 (11.5)
Male	4 (80%)	5 (56%)
Female	1 (20%)	4 (44%)
ILD	CPFE 4 (80%)	CPFE 5 (56%)
	CTD-ILD 1 (20%)	IPF 2 (22%)
		HP 2 (22%)
Weight (kg)	80.1 (14.5)	78.6 (14.1)
Height (cm)	171 (11.2)	167.3 (6.0)
BMI (kg/m^2)	27.4 (4.2)	28.3 (4.6)
FVC (L)	2.5 (1.0)	2.4 (1.0)
FVC (% pred)	69.6 (25.8)	75.1 (28.6)
FEV1 (L)	2.1 (1.0)	1.8 (0.8)
FEV1/FVC (ratio %)	110.4 (11.2)	102 (7.0)
TLCO (% pred)	44 (8.5)	43.3 (15.9)

Abbreviations: ILD, interstitial lung diseases, BMI, body mass index; FVC, forced vital capacity, FVC (%pred), FVC percentage predicted; FEV1, forced expiratory volume in one second; TLCO (% pred), transfer factor for carbon monoxide percentage predicted.

Table 13 Baseline characteristics of all the participants in the study.

Participant	ILD disease	Sex	Study group	Age	BMI	FVC (L)	FVC (% pred)	FEV1 (L)	FEV1/FVC (ratio %)	TLCO (% pred)
101	CPFE	Male	Control	83	23.4	4.4	134	3.5	110	56
102	CPFE	Male	Intervention	72	26.1	3.6	88	3.1	114	41
103	CPFE	Female	Control	56	29.8	2.3	80	1.8	99	38
104	CPFE	Male	Intervention	61	23.9	3.4	85	3.1	120	43
105	CPFE	Female	Control	70	35.1	2.6	89	1.8	92	51
106	CPFE	Female	Intervention	72	26.0	1.9	89	1.4	99	56
107	CPFE	Male	Control	83	31.2	2.1	86	1.5	96	71
108	CPFE	Male	Control	81	24.6	3.3	86	2.2	95	26
109	CPFE	Male	Intervention	69	26.2	2.4	55	2.2	121	36
110	HP	Female	Control	56	32.1	1.4	47	1.1	104	47
111	HP	Female	Control	62	22.9	1.1	46	0.9	102	-
112	IPF	Male	Control	60	32.0	2.4	60	2.0	109	27
113	CTD-ILD	Male	Intervention	66	34.6	1.1	31	0.9	98	-
114	IPF	Male	Control	61	23.8	2.0	48	1.7	111	30

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; HP, hypersensitivity pneumonitis; CTD-ILD, connective tissue disease associated-ILD; BMI, body mass index; FVC, forced vital capacity, FVC (%pred), FVC percentage predicted; FEV1, forced expiratory volume in one second; TLCO (% pred), transfer factor for carbon monoxide percentage predicted.

Table 14 Descriptive statistics of outcome variables pre and post the pulmonary rehabilitation programme. Data are presented as medians (IQR)

	Intervention group N = 5		**Control group N = 9**	
Median (IQR)	**Pre**	**Post**	**Pre**	**Post**
MIP (cmH2O)	48.5 (33-67)	85.7 (45-102)	47 (38-60)	67.4 (49-89)
KBILD Total score	74 (47-81)	68 (54-86)	57 (49-74)	57.5 (46-88)
FSS score	4.8 (3.2-5.8)	4.9 (4.89-5.22)	5.2 (2.6-6.7)	4.9 (3.6-5.6)
HADS-D	6.5 (3.8-7.8)	7 (2.0-8.0)	5 (3.0-8.0)	5.5 (1.0-11.0)
HADS-A	6 (4.0-9.5)	5 (2.0-7.0)	9 (2.5-12.0)	11 (4.5-11.3)
FVC (litres)	2.4 (1.5-3.5)	2.2 (1.1-3.7)	2.3 (1.7-2.9)	2.1 (1.7-2.9)
FVC%	85 (43-88.5)	50 (31-91)	80 (47.5-87.5)	60 (46.3-96)
TLCO%	42 (37.3-52.8)	46 (44-48)	42.5 (27.8-54.8)	38 (33-49)
1MSTS (number of repetitions)	14 (11-17.5)	17 (13-21)	13 (10.5-17.5)	17 (15.5-27)
Rt quadriceps strength (lbs)	129.5 (91-168)	128 (82-185)	116 (82-157.5)	112.5 (83-154)

Lt quadriceps strength (lbs)	127.5 (95-163)	117 (102-181)	109 (78-149)	98 (79-143)
Rt deltoid strength (lbs)	126 (90-143)	134 (67-208)	97 (66-164)	121.5 (83-142.5)
Lt deltoid strength (lbs)	124.5 (88-152)	140 (76-144)	106 (64-156)	125.5 (98-144)
Rt biceps strength (lbs)	164 (130-205)	117 (113-222)	132 (87-186)	129 (101-149)
Lt biceps strength (lbs)	163 (118-201)	113 (94-253)	132 (114-176)	132.5 (96-152)

Abbreviations: MIP, maximum inspiratory pressure; KBILD, The king's brief interstitial lung disease questionnaire; FSS, fatigue severity scale, HADS, The hospital anxiety and depression scale; FVC, forced vital capacity; FVC%, FVC percentage predicted; TLCO%, transfer factor for carbon monoxide percentage predicted, 1MSTS, one minute sit to stand test.

Table 15 Adapted changes due to the impact of COVID-19 disruption

	Pre COVID-19	**Post COVID 19**	**Rational**
Location	Marie Curie Hospice	Freeman hospital and RVI, Newcastle upon Tyne.	Marie curie hospice with the critical patients they have were still limiting access to the facility
Duration of programme	8-week PRP	6 weeks PRP	This was a modification made by the physiotherapy department on the program
Target participants	CPFE	CPFE + ILD	We have decided to include patients with ILD as well in the time remaining for data collection
Outcomes collected	6 MWT	1MSTS	This was to follow social distance COVID-19 guidelines at RVI and was adapted by the physiotherapy department
Education session	Weekly face to face provided from various allied health professionals	Recorded educational videos developed by various allied health professionals	Due to COVID-19, social distance guidelines were still in place. The goal was to have as few contacts to patients as possible.
Relaxation session	Weekly	Once at the end of PRP	The weekly relaxation session before COVID-19 used to be conducted in a room designated for relaxation at Marie curie hospice.

4.3.2 Attendance

Table 16 Attendance of the participants in the pulmonary rehabilitation programme

	Pre measurements	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Post measurements**	**Attendance %**
101	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
102	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
103	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	87.5%
104	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	100%, lost to follow up.
105	✓	✓	X	✓	✓	✓	X	✓	X	X	62.5%, lost to follow up.
106	✓	✓	✓	✓	✓	X	✓	✓	X	X	75%, lost to follow up.
107	✓	✓	X	X	X	X	X			X	Dropout chest infection
108	✓	✓	X	X	X	X	X			X	Dropout time not convenient
109	✓	✓	✓	✓	✓	✓	✓			✓	100%
110	✓	✓	✓	✓	✓	✓	X			✓	83.33%
111	✓	✓	✓	✓	✓	✓	✓			✓	100%
112	✓	✓	X	✓	X	✓	X			✓	50%

113	✓	✓	✓	✓	✓	✓	X			✓	83.33%
114	✓	✓	✓	✓	✓	✓	✓			✓	100%
											Mean 86.81% Dropout 14.29%

Note: From participant 107, the duration of the pulmonary rehabilitation program was changed from 8 weeks to 6 weeks by the physiotherapy department post COVID 19.

The PRP had a good attendance rate, with a mean attendance of 87%. In this study, 64% participants completed the study. There were only two dropouts (14%)—one dropped out due to a chest infection at the time of the study, while the timing of the PRP patient was inappropriate for another patient. Due to the March 2020 COVID-19 pandemic restriction, post measurements data of three participants were not collected, and they were lost to follow-up.

4.3.3 Side effects

No side effects or complications with participants' health or safety were observed during the study. The PRP with or without inspiratory muscle training was safe to conduct in patients with ILD, including (n=9) patients with CPFE.

4.3.4 Maximum inspiratory pressure (MIP)

In this study, the MIP tended to increase in all the participants in this study, irrespective of whether they were in the intervention or control groups (see Figure 20). Moreover, the number of participants in this study was low: only three in the intervention group (see Figure 20) graph (A) and six in the control group (see Figure 20) graph (B). The improvement in the intervention group was expected, as these participants received eight weeks of daily IMT. The improvement in IMT, as evident from an increase in MIP of the control group, might be due to an indirect effect of the other exercises performed as part of the PRP and regular spirometry measurements.

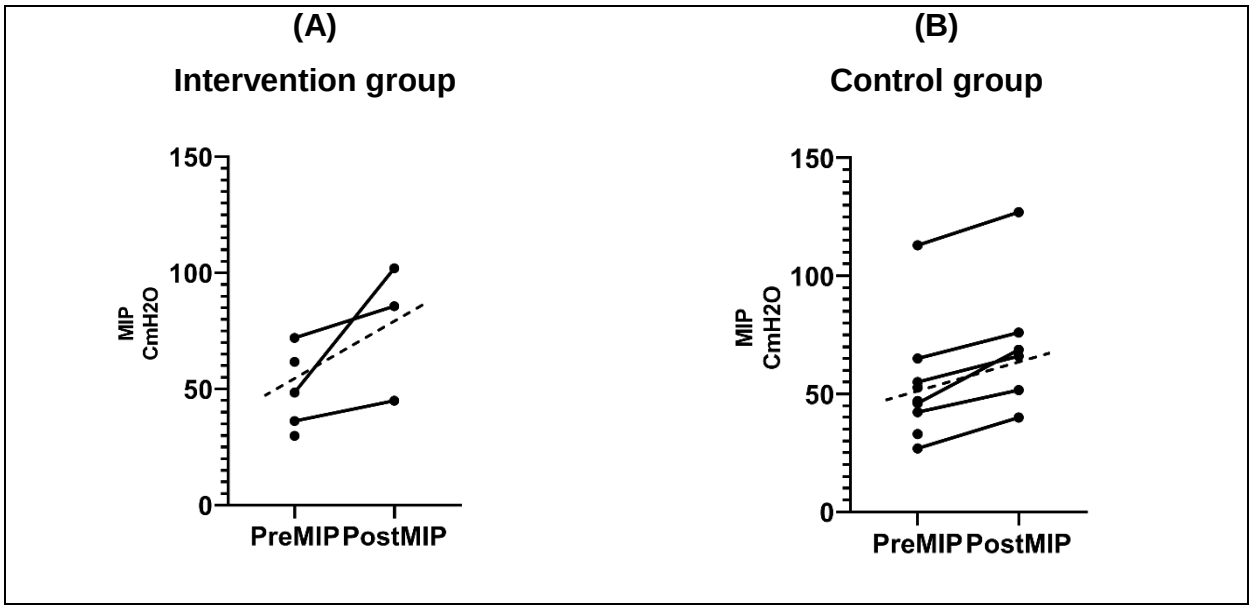


Figure 20 Change in maximum inspiratory pressure (MIP) Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. MIP = Maximum Inspiratory Pressure.

4.3.5 Patient-reported outcome measures

4.3.5.1 The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)

4.3.5.1.1 K-BILD breathlessness domain score

The K-BILD comprises 15 items divided into 3 domains: breathlessness and activities (items 1, 4, 11, and 13), chest symptoms (items 2, 7, 9), and psychological (items 3, 5, 6, 8, 10, 12, and 14). The K-BILD breathlessness and activities (items 1, 4, 11, and 13) revealed a trend of remaining constant or improving slightly in this study. In the intervention group, K-BILD breathlessness and activities improved in one out of three patients, while it remained the same for the other two participants. In the control group,

four out of six participants showed an improvement in the K-BILD breathlessness and activities domain (see Figure 21).

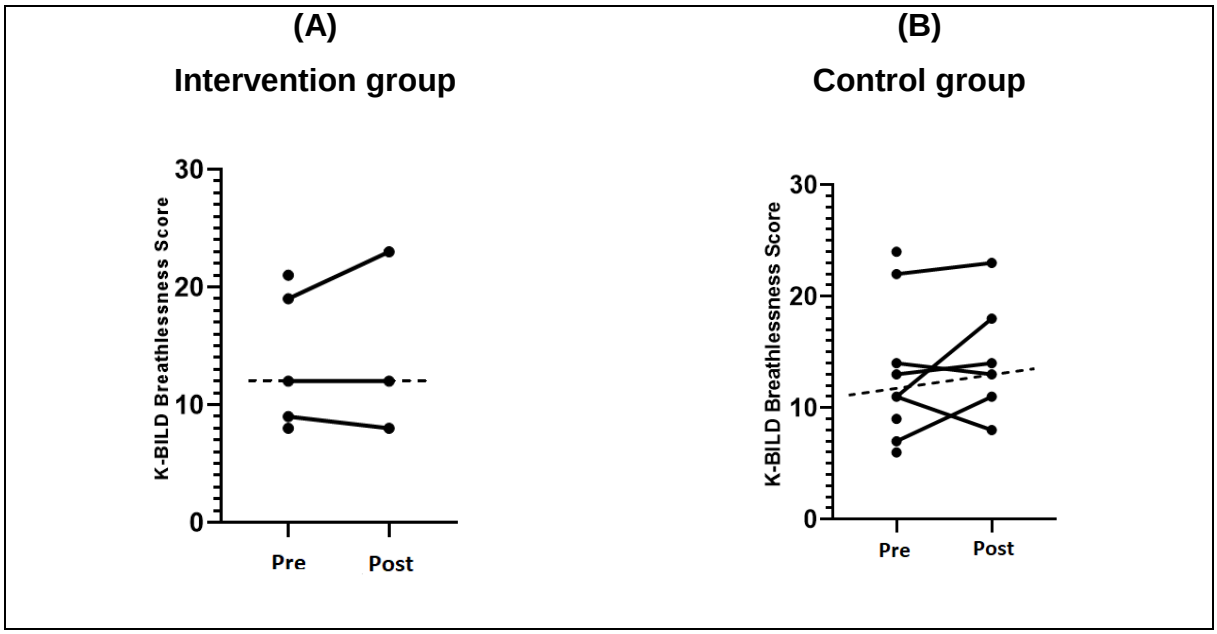


Figure 21 Change in the K-BILD breathlessness domain score. Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. K-BILD = The King's Brief Interstitial Lung Diseases Questionnaire

4.3.5.1.2 The K-BILD psychological domain score

The K-BILD psychological domain score (items 3, 5, 6, 8, 10, 12, and 14) showed a trend of improving slightly or remaining the same in most of the participants in this study. In the intervention group, the K-BILD psychological domain score improved in one out of three participants. In the control group, the K-BILD psychological domain score improved for four out of six participants *(see* Figure 22*)*.

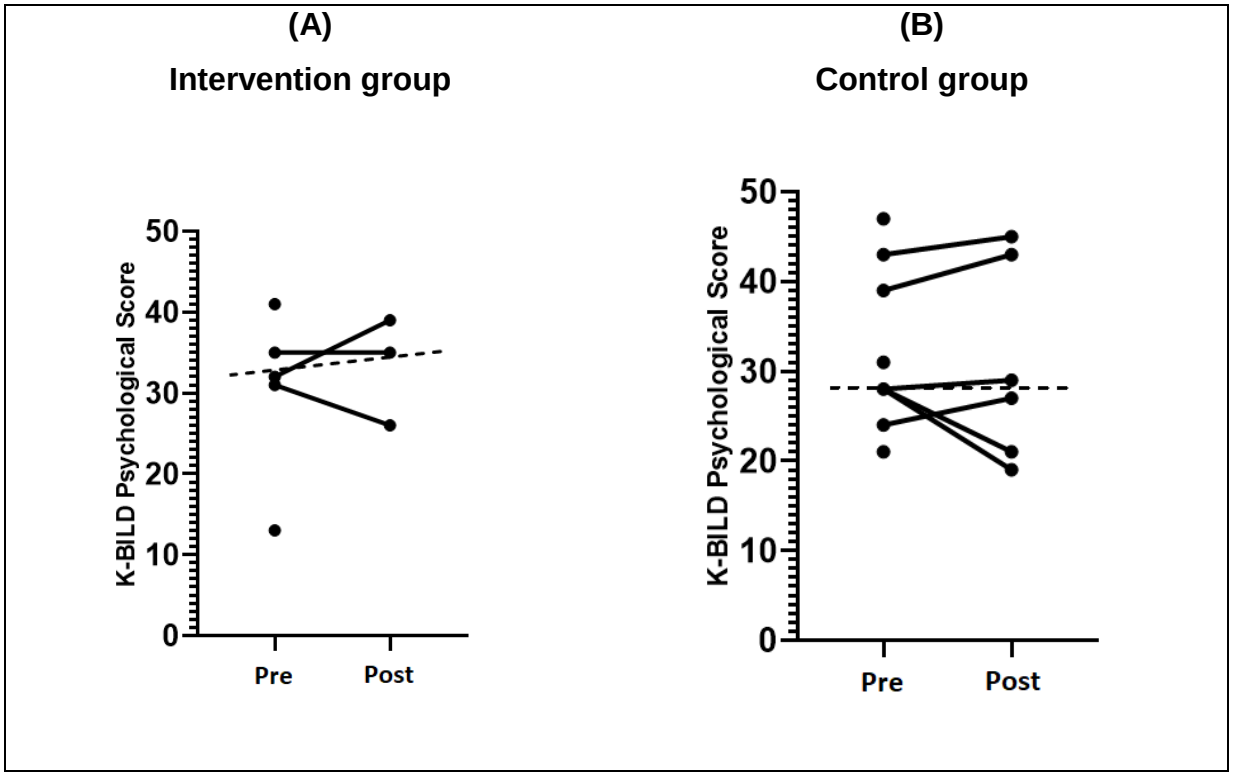


Figure 22 Change in the K-BILD psychological domain score.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. K-BILD = The King's Brief Interstitial Lung Diseases Questionnaire.

4.3.5.1.3 The K-BILD chest symptoms domain score

The K-BILD chest symptoms domain score (items 2, 7, and 9) showed a trend of decreasing in the intervention group, and slightly improving in the control group. In the intervention group, the score for the K-BILD chest symptoms domain improved in one out of three participants. In the control group, this score improved for four out of six participants (see Figure 23).

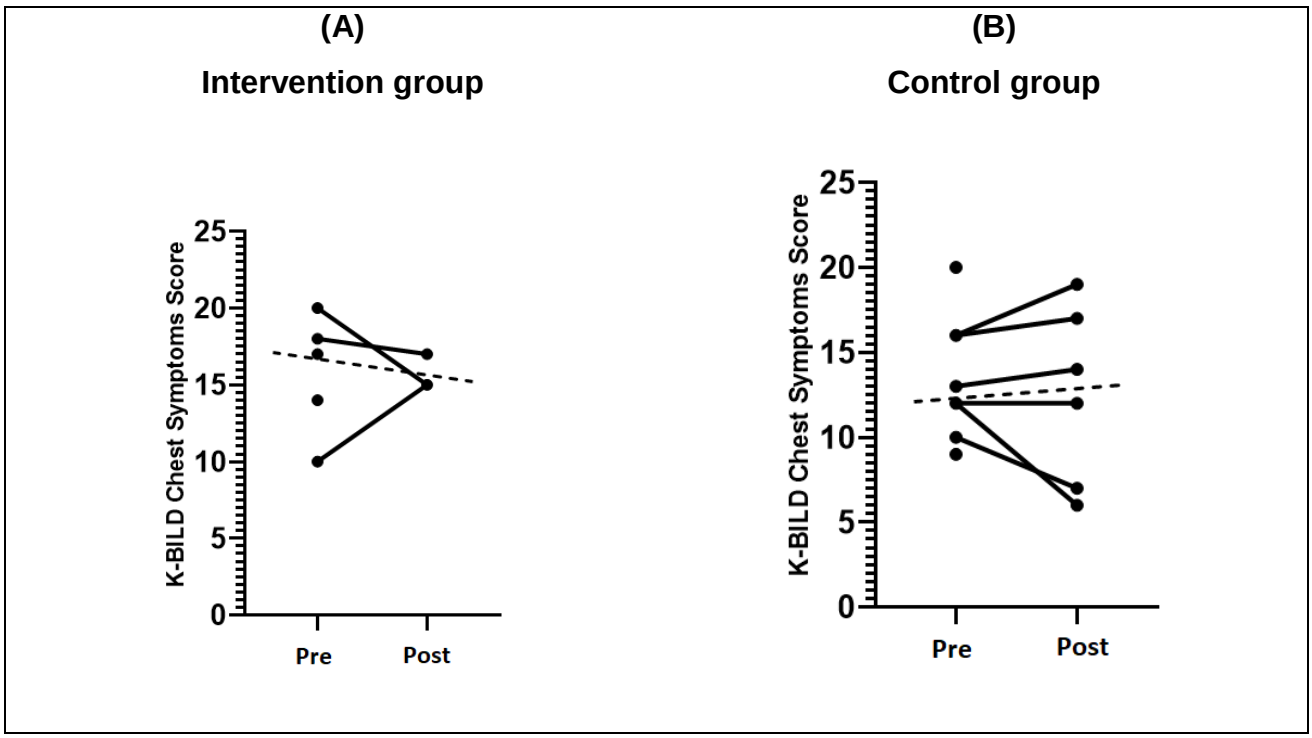


Figure 23 Change in the K-BILD chest symptoms domain score. Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. K-BILD = The King's Brief Interstitial Lung Diseases Questionnaire

The score for the K-BILD chest symptoms domain (items 2, 7, and 9).

4.3.5.1.4 Overall K-BILD score

The K-BILD total score ranges from 0 to 100, with higher score indicating better quality of life. The K-BILD total score showed a trend toward being slightly improved or maintained in most of the participants in this study (see Figure 24). In the intervention group, K-BILD total score was either improved or maintained in two out of 3 study participants. In the control group four out of 6 had improvement in K-BILD total score.

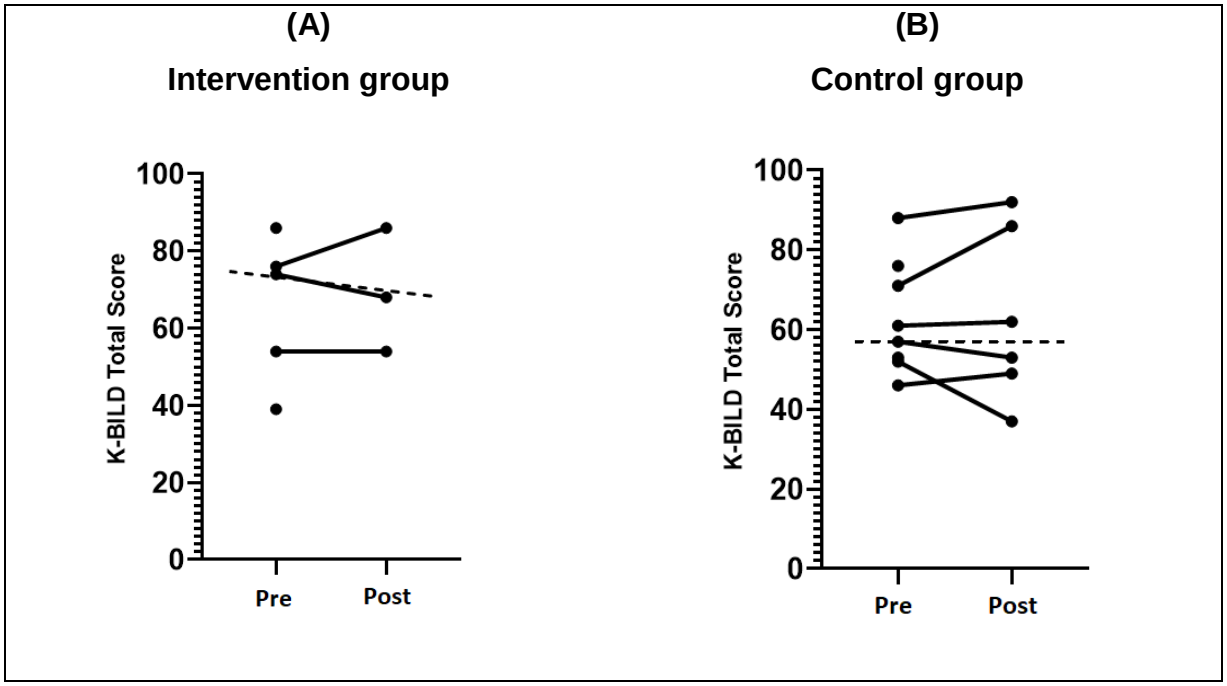


Figure 24 Change in the overall K-BILD score. Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. K-BILD = The King's Brief Interstitial Lung Diseases Questionnaire.

4.3.5.2 Fatigue severity scale (FSS)

The fatigue severity scale (FSS) comprises nine statements regarding the frequency, severity, and impact of fatigue on activities of daily life. Participants were asked to rate their agreement with each statement on a scale ranging from 1 to 7. In this study, as depicted in (see Figure 25), the FSS score for two out of three participants either decreased or remained the same in the intervention group. In the control group, the FSS score for four out of six participants indicated an improvement in fatigue level, while the FSS score for the other two participants increased.

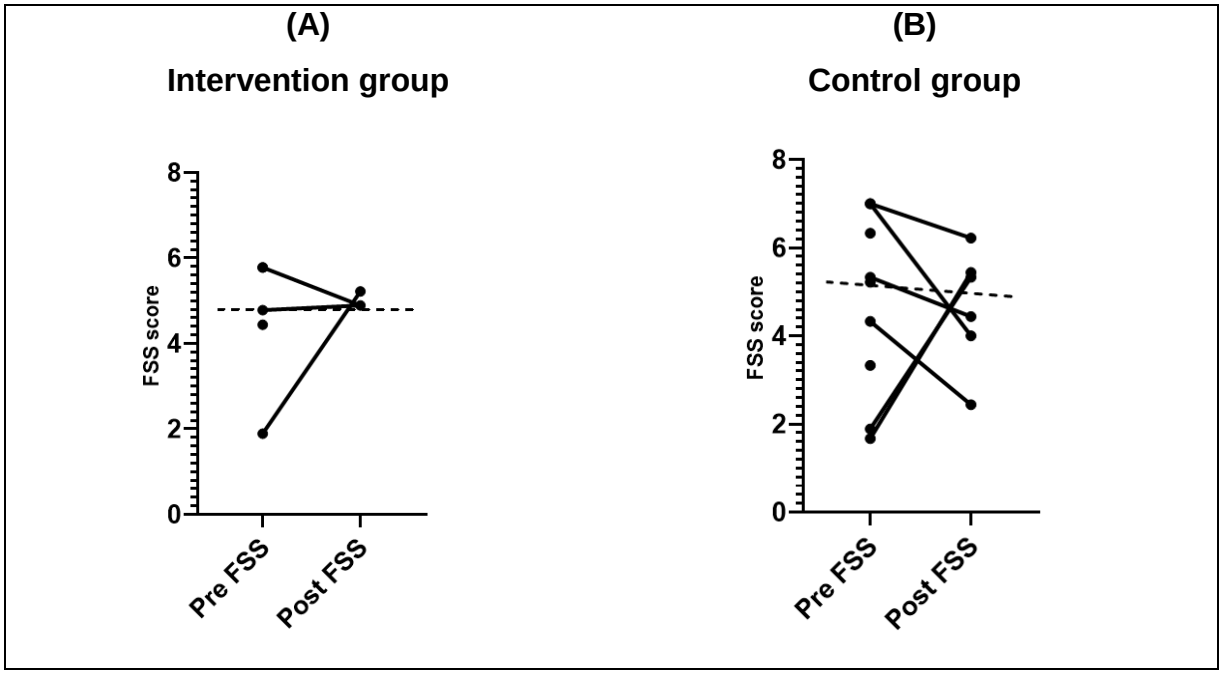


Figure 25 Change in the fatigue severity scale (FSS). Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. FSS = Fatigue Severity Scale.

4.3.5.3 The Hospital anxiety and depression scale (HADS)

4.3.5.3.1 Hospital anxiety and depression scale—Depression

The Hospital Anxiety and Depression Scale (HADS) comprises 14 multiple-choice items—7 items for anxiety and 7 items for depression. The total score ranges from 0 to 21. A score of less than 8 implies the absence of anxiety or depression, a score from 8 to 10 is indicative of borderline anxiety or depression, and a score 11 or over suggests a clinically significant anxiety or depression. In this study, participants in the intervention group had a normal baseline HADS-Depression score (less than 8) and maintained this normal score post the PRP and IMT. In the control group, three participants had normal baseline HADS-Depression score (less than 8) and maintained this normal score post the PRP. One participant in the control group had an abnormal high HADS-Depression score, with only a slight improvement in score from 19 to 17 post PRP. Two participants in the control group had a normal HADS-Depression score before the PRP, which changed to a borderline score after the PRP (see Figure 26).

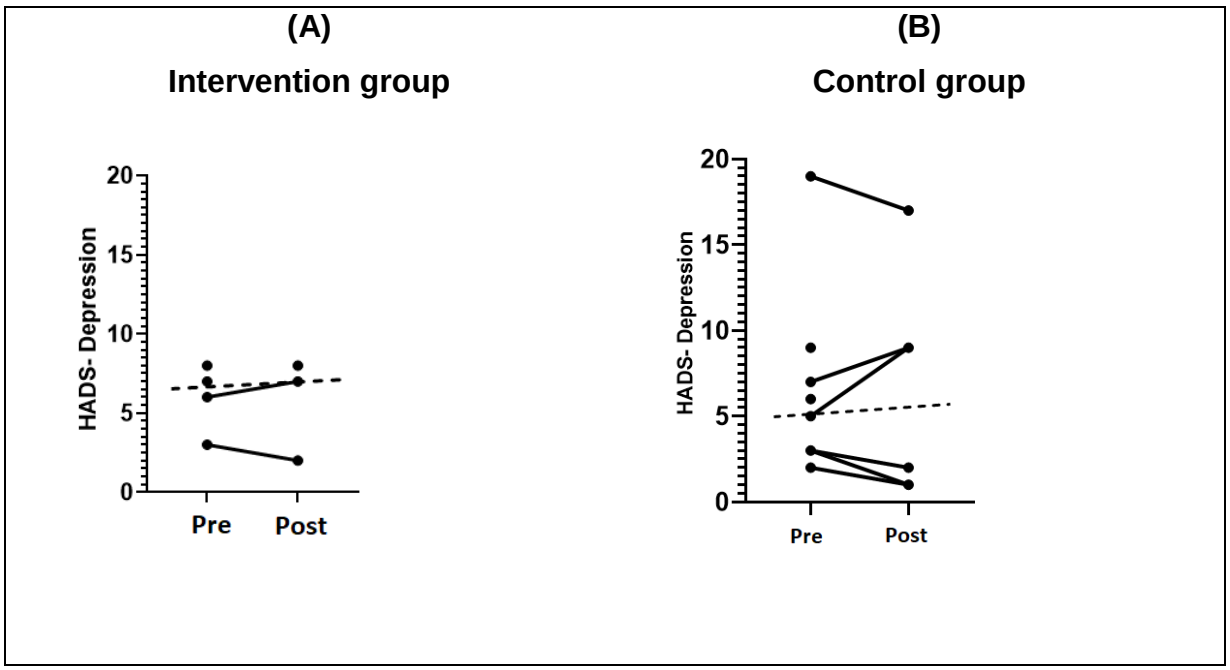


Figure 26 Change in the Hospital Anxiety and Depression Scale (HADS)—Depression scores.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. HADS= Hospital Anxiety and Depression Scale.

4.3.5.3.2 Hospital anxiety and depression scale—Anxiety

In this study, participants in the intervention group had normal baseline HADS—Anxiety score, except for one participant with a borderline score that improved post pulmonary rehabilitation and IMT. In the control group, the score for two participants changed after the pulmonary rehabilitation from borderline to abnormal. The remainder of the participants (n = 4) in the control group maintained either normal or abnormal scores, with trends towards increased anxiety (see Figure 27).

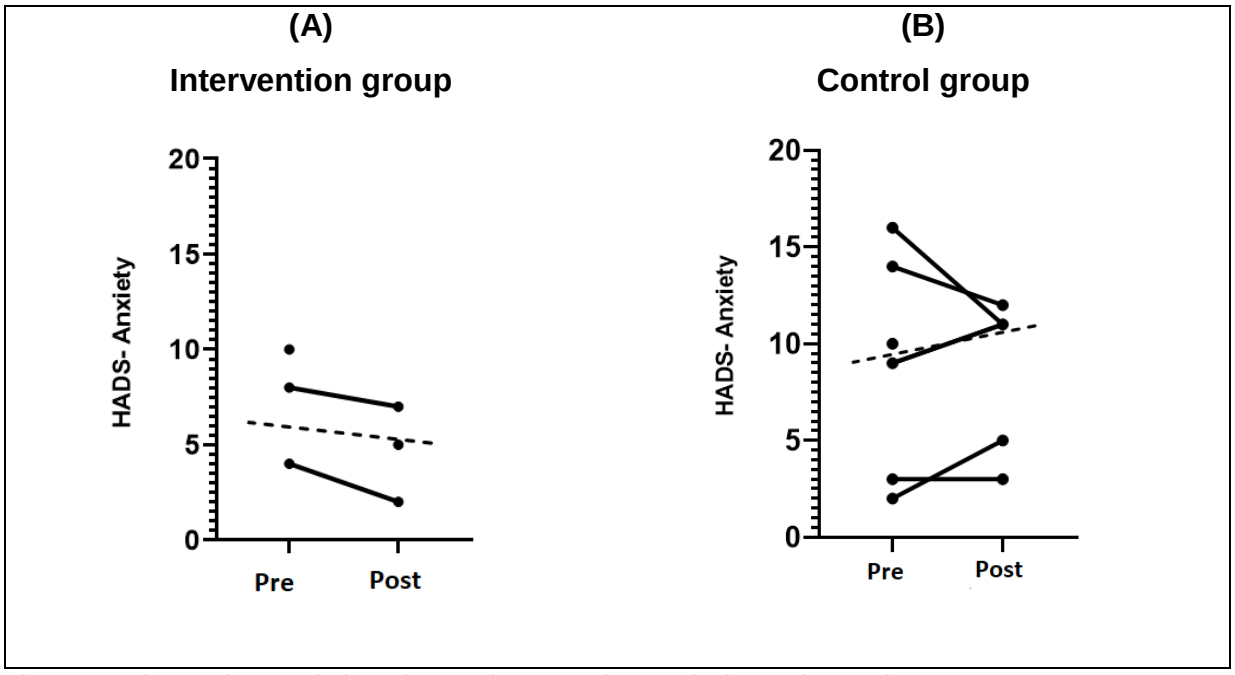


Figure 27 Change in Hospital Anxiety and Depression Scale (HADS)—Anxiety scores.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. HADS= Hospital Anxiety and Depression Scale.

4.3.6 Minimal clinically important difference (MCID) of outcomes

The MCID represents the smallest changes in an outcome after an intervention, which is considered clinically meaningful improvement. The amount of change in outcomes (post data – pre data) of all participants in this study is shown in (see Table 17). The MCID of MIP was found for two out of nine participants (22%), while the MCID of the 1MSTS repetitions was found for seven out of nine participants (78%). The K-BILD breathlessness score achieved MCID for one out of nine participants (11%). The K-BILD psychological score achieved the MCID for one out of nine participants (11%). The K-BILD chest symptoms score achieved MCID in none of the participants (0%). The K-BILD overall score achieved MCID for three out of nine participants (33%), and the FSS score achieved MCID for five out of nine participants (56%)

Table 17 Change in outcomes (post data-pre data) for all participants in the study assessing achievement of minimal clinically important difference (MCID).

	Change in outcome= (post measurement – pre measurement)							
Participants	**Study group**	**MIP**	**1MSTS Repetitions**	**K-BILD Breathlessness and activities**	**K-BILD Psychological**	**K-BILD Chest symptoms**	**K-BILD Total**	**FSS**
MCID		**17.2 cmH2O**	**2.03–3.45 repetitions**	**7 (6–8) score**	**6 (5–7) score**	**11 (7–14) score**	**5 (4–7)**	**(0.45–0.88)**
101	Control	13.14	**5**	1	2	1	**4**	**-1.89**
102	Intervention	**53.5**	**12**	4	**7**	-1	**10**	0.11
103	Control	11	**4**	1	-7	0	-4	**-3**
104	Intervention	Excluded						
105	Control	Excluded						
106	Intervention	Excluded						
107	Control	Dropout						
108	Control	Dropout						
109	Intervention	8.76	**3**	0	0	-5	-6	3.33
110	Control	9.3	**3**	-3	-9	-6	-15	3.77
111	Control	10	**3**	4	3	-3	3	**-0.78**

112	Control	14	2	-1	1	1	1	3.44
113	Intervention	13	-4	-1	-5	5	0	**-0.89**
114	Control	**22.7**	**7**	**7**	4	3	**15**	**-0.89**
Mean (SD)		**17.34** (14.19)	**3.89** (4.26)	1.33 (3.12)	-0.44 (5.39)	-0.56 (3.6)	0.89 (8.81)	0.36 (2.52)

MCID, minimal clinical important difference; MIP, maximum inspiratory pressure; 1MSTS, one minute sit to stand test; K-BILD, The king's brief interstitial lung diseases questionnaire; FSS, fatigue severity scale. Bolded and underlined mean MCID was achieved. MCID for 1MSTS after pulmonary rehabilitation of 2.03–3.45 repetitions was identified for patients with COPD.

4.3.7 Pulmonary function test

4.3.7.1 Forced vital capacity (FVC)

The FVC (in litres) was measured pre- and post- the PRP in both the intervention and control groups (see Figure 28). In the intervention group, one participant showed an improvement in FVC, one maintained their score, and one participant had a decrease in FVC post the PRP and IMT. In the control group, there was a decrease in median FVC after the PRP. There was an improvement in FVC for two participants, a maintenance of the same score for two, and a decrease in the FVC for two participants after the PRP. In this cohort of patients, the FVC showed a stable trend in this study It is difficult to make definite conclusions regarding the FVC due to the low number of participants.

With regard to the FVC% (see Figure 29), an FVC% <80% is required for antifibrotic prescription. In this study, two out of five participants in the intervention group and four out of nine in the control group had an FVC% <80%, with a trend toward no change or decrease in FVC% in both groups.

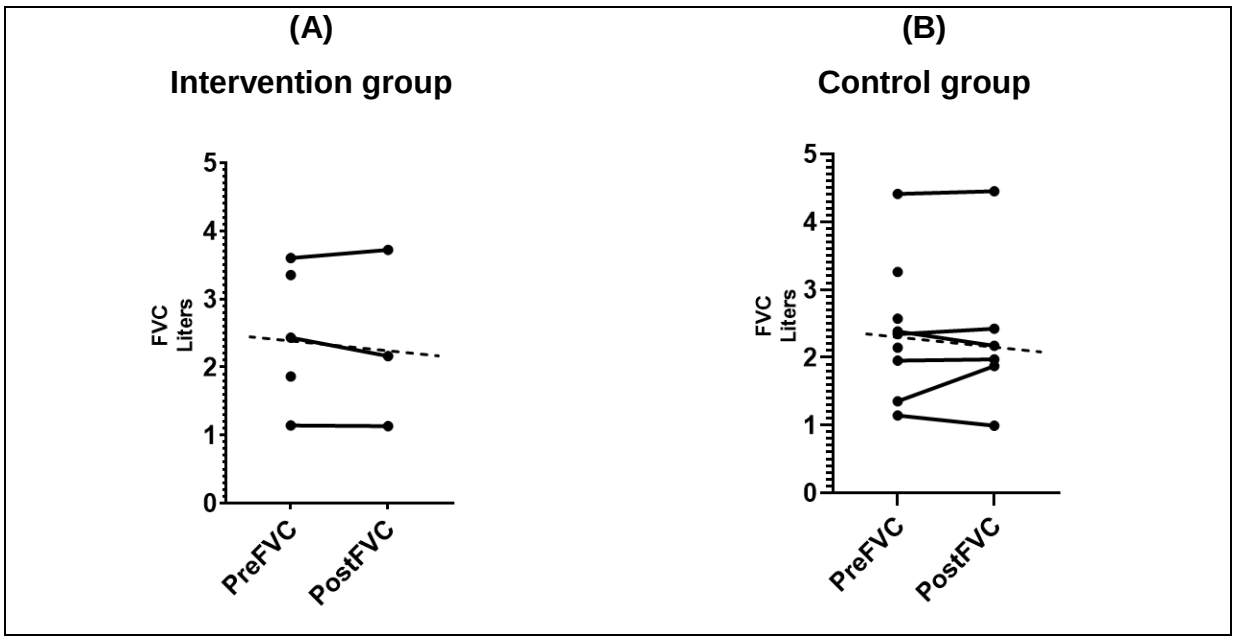


Figure 28 Change in forced vital capacity (FVC) in litres. Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. FVC = Forced Vital Capacity.

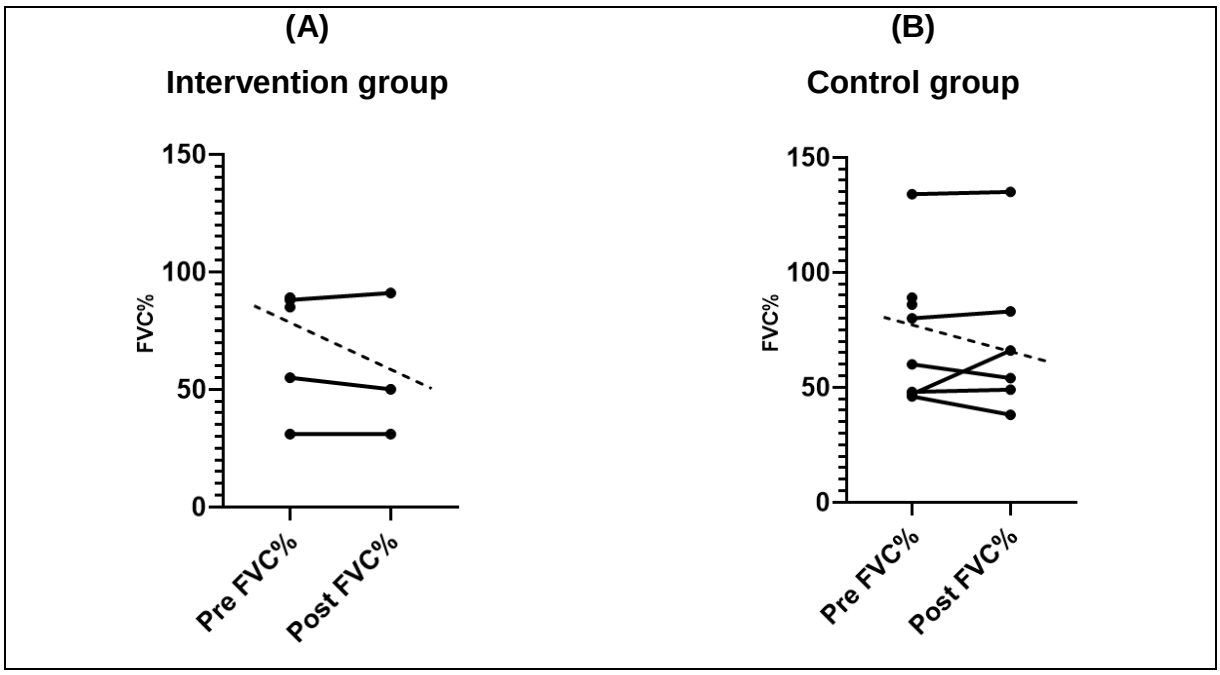


Figure 29 Change in in percentage of predicted forced vital capacity (FVC%) Data are given as individual values.

The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

4.3.7.2 The transfer capacity of the lungs for carbon monoxide (TLCO)

The TLCO% was measured for both the intervention and control groups, pre- and post-PRP (see Figure 30). Two participants in the intervention group showed an improvement in TLCO% post pulmonary rehabilitation and IMT. In the control group, the median of TLCO% decreased slightly. In the control group, the score for two participants improved, that for one participant was maintained, and that for two participants decreased post-PRP. In this cohort of patients, the TLCO% showed a stable trend in this study; however, it is difficult to draw definite conclusions with a small sample size.

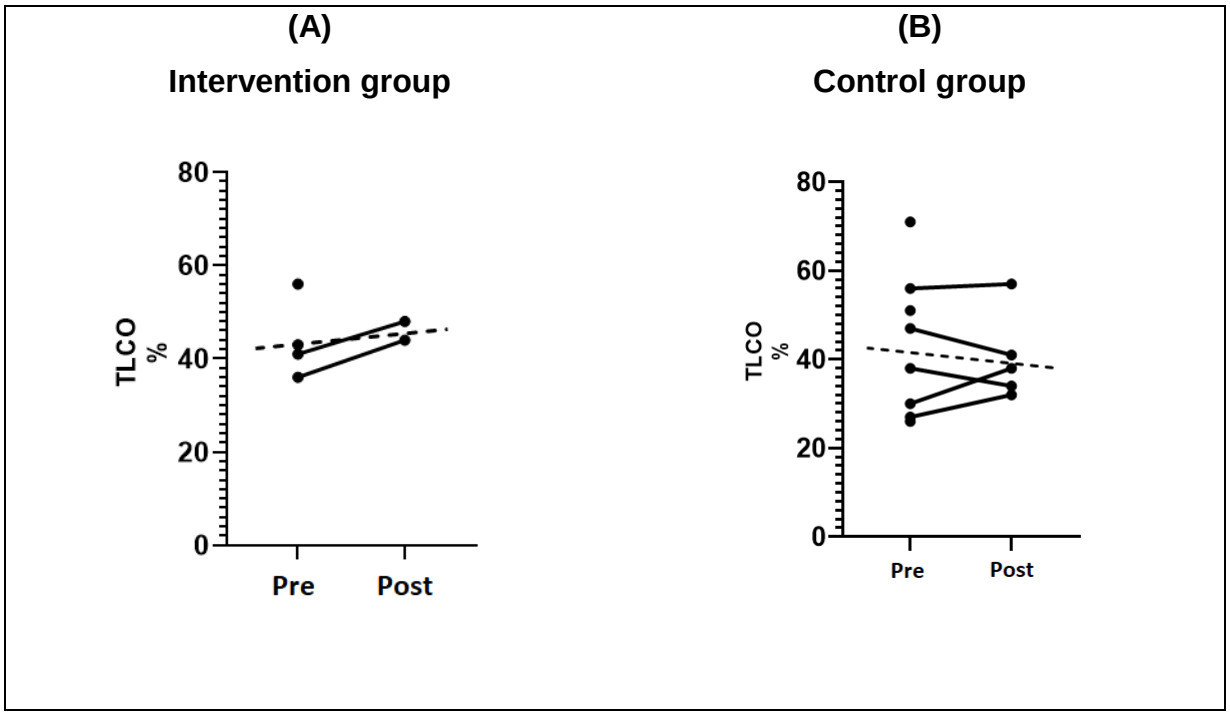


Figure 30 Change in percentage of predicted transfer capacity of the lungs for carbon monoxide (TLCO%).

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

4.3.7.3 TLCO Z-scores

There were two participants in the intervention group for whom the TLCO z-score data was collected; they both improved after the PRP and IMT. In the control group, three participants showed little improvement in their TLCO z-score, while for two participants, the TLCO z-score decreased slightly after PRP. There was either no change or a slight decrease in the TLCO z-score median of the control group after the PRP (see Figure 31).

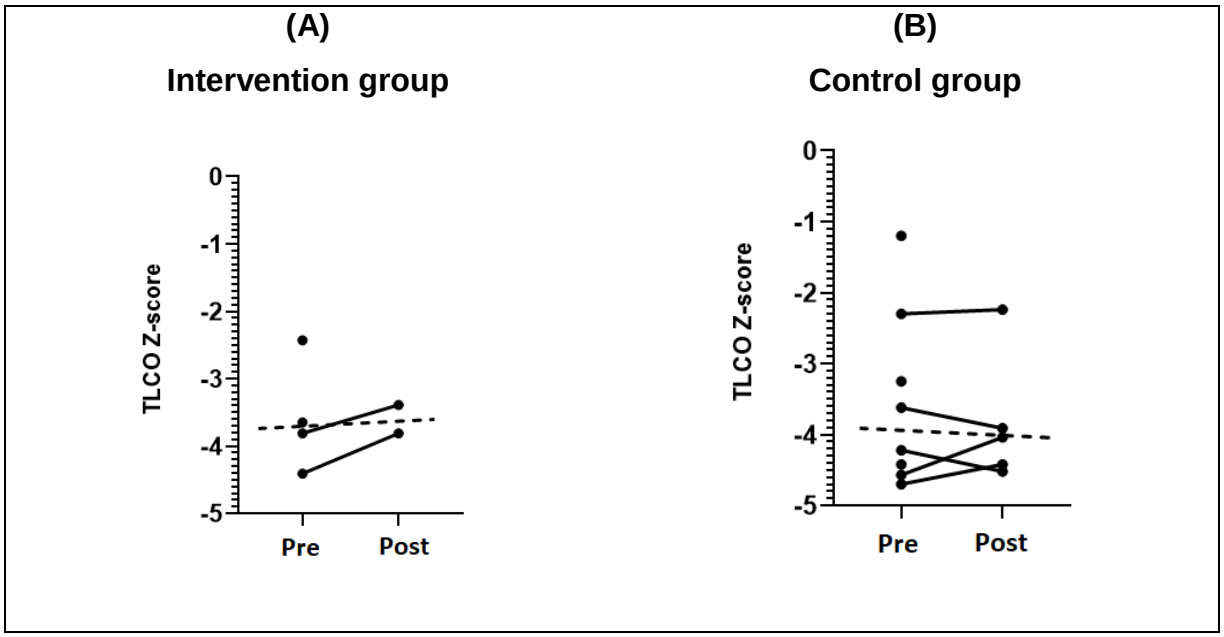


Figure 31 Change in Transfer Capacity of The Lungs for Carbon Monoxide z-score.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. TLCO = transfer capacity of the lungs for carbon monoxide.

4.3.8 One Minute sit-to-stand test (1MSTS)

The 1MSTS was assessed in this study to evaluate exercise capability for both the intervention and control groups (see Figure 32). Two out of three participants in the intervention group showed an improvement in their 1MSTS score after the PRP and IMT. In one of the three participants in the intervention group, whose disease condition was exacerbated during the study, there was a reduction in the 1MSTS score. All the participants in the control group showed an improvement in their 1MSTS scores after the PRP. All the participants both in the intervention and control groups showed an improvement in their 1MSTS scores after the PRP, except for one participant from the intervention group, as mentioned above.

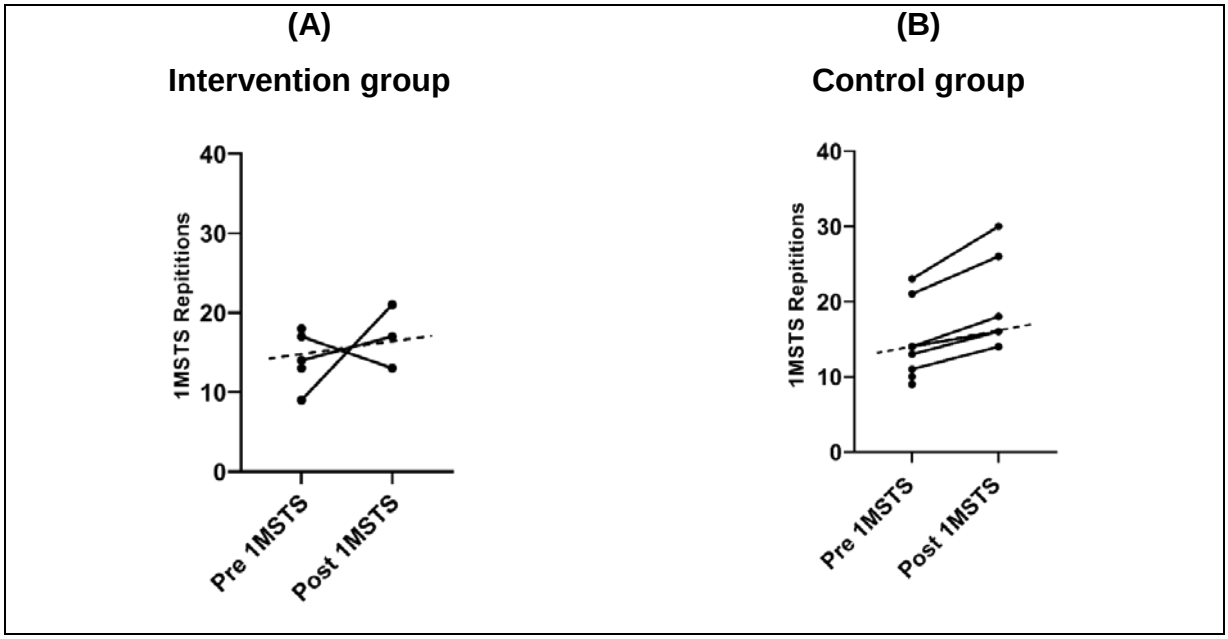


Figure 32 Change in the one minute sit-to-stand test scores.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. 1MSTS= One Minute Sit-to-Stand Test

4.3.9 Strength of major body muscles

4.3.9.1 Strength of the right biceps

The right biceps muscle strength was measured using a handheld dynamometer (microFET) by the same assessor pre- and post- PRP. As depicted in (see Figure 33), in the intervention group, the right biceps muscle strength for one participant was maintained, while that for the other reduced after the PRP and IMT. In the control group, there was no change in the median scores, with the right biceps muscle strength improving for one participant, being maintained for another, and reducing for four participants after PRP and IMT.

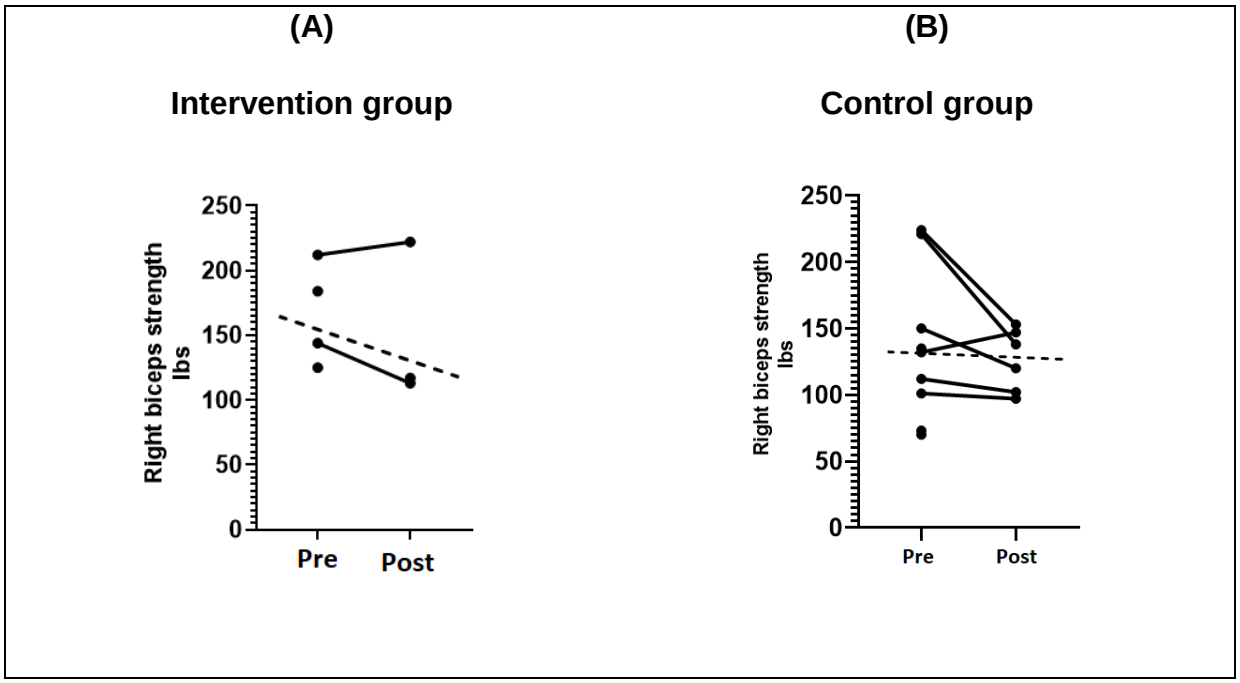


Figure 33 Change in strength of the right biceps.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.9.2 Strength of the left biceps

The strength of the left biceps was measured in a similar manner as that for the right quadriceps—using a handheld microFET device. As depicted in (see Figure 34), there was an improvement in the strength of the left biceps for one participant in the intervention group after PRP and IMT, while there was a decrease in the strength of the left biceps for another participant in the same group. In the control group, there was no change in median after the PRP, with an improvement in the strength of the left biceps for one participant, a maintenance of the same level of strength for another, and a decrease in the strength of the left biceps for four participants after the PRP.

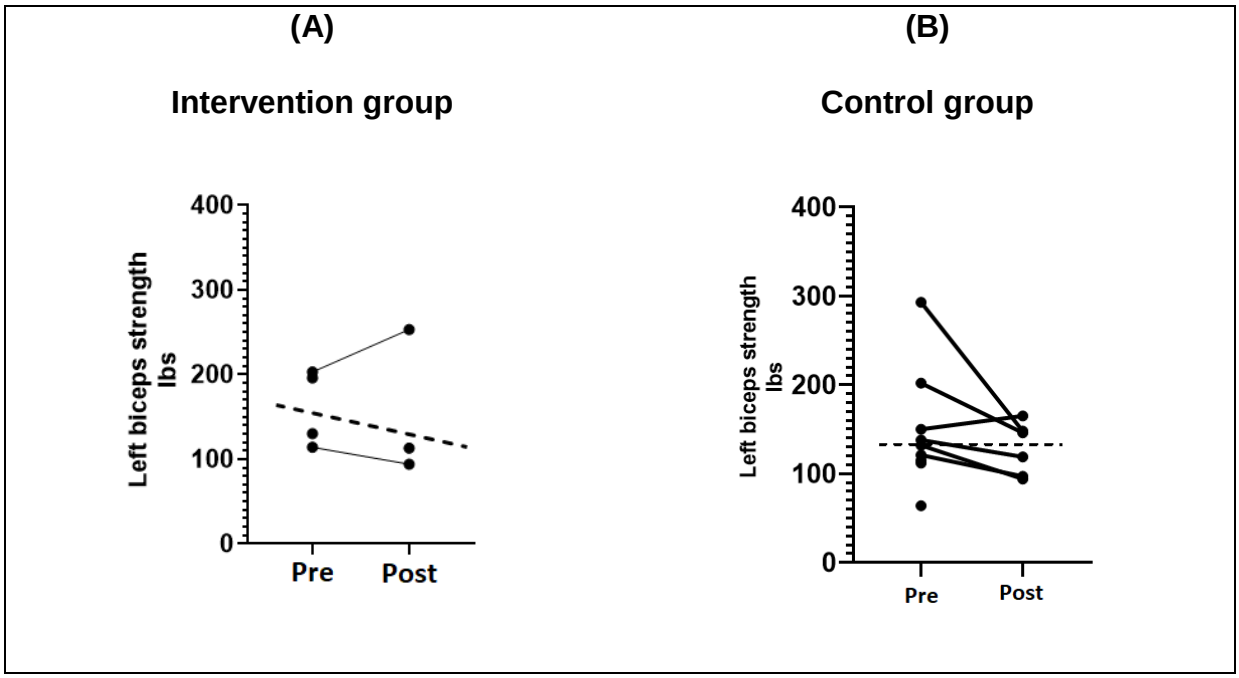


Figure 34 Change in the strength of the left biceps.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.9.3 Strength of the right deltoid

The strength of the right deltoid was measured using a handheld dynamometer microFET as well. As depicted in (see Figure 35), there was an improvement in the strength of the right deltoid for one participant in the intervention group, and a reduction in the strength of the right deltoid for one participant in the same group after the PRP and IMT. In the control group, there was an improvement in the median of the strength of the right deltoid after the PRP. There was an improvement in the strength of the right deltoid for two participants and a reduction in the strength of the right deltoid for four participants in the control group after the PRP.

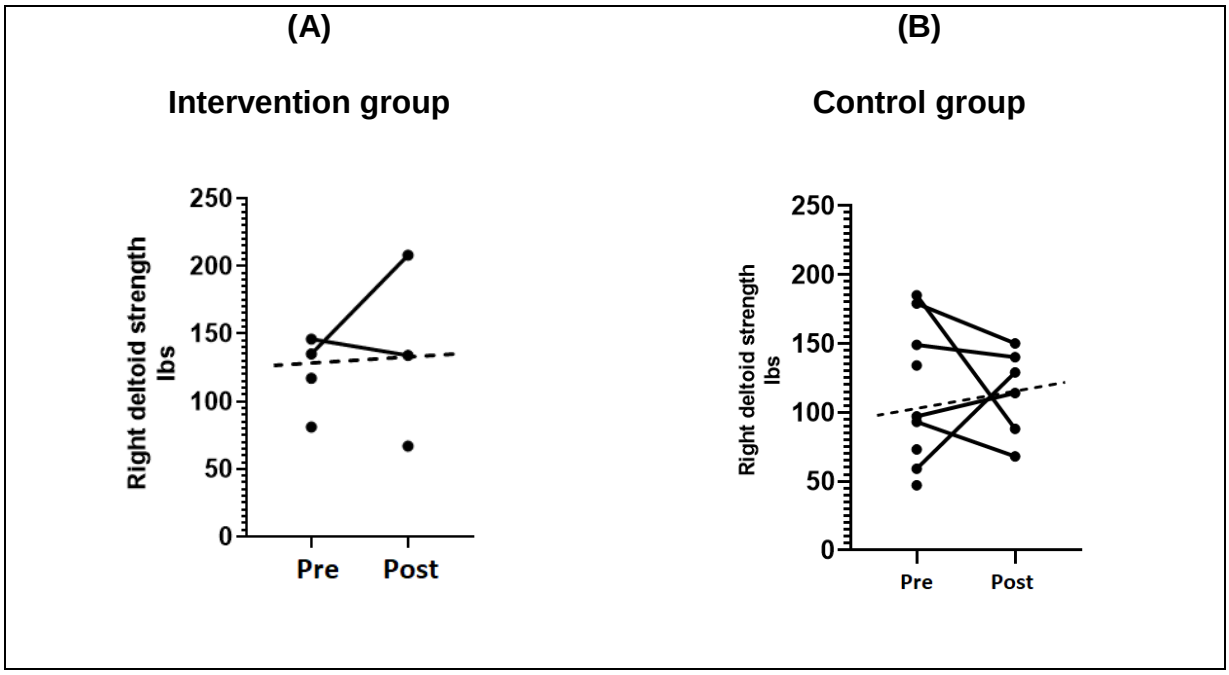


Figure 35 Change in the strength of the right deltoid.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.9.4 Strength of the left deltoid

A handheld dynamometer microFET device was used to assess the strength of the left deltoid. As evident from (see Figure 36), in the intervention group, there was an improvement in the strength of the left deltoid for one participant after the PRP and IMT, while there was a decrease in the strength of the left deltoid for another participant. In the control group, there was an improvement in the median score after the PRP. Moreover, the strength of the left deltoid improved for two participants, remained the same for one, and decreased for three participants in the control group.

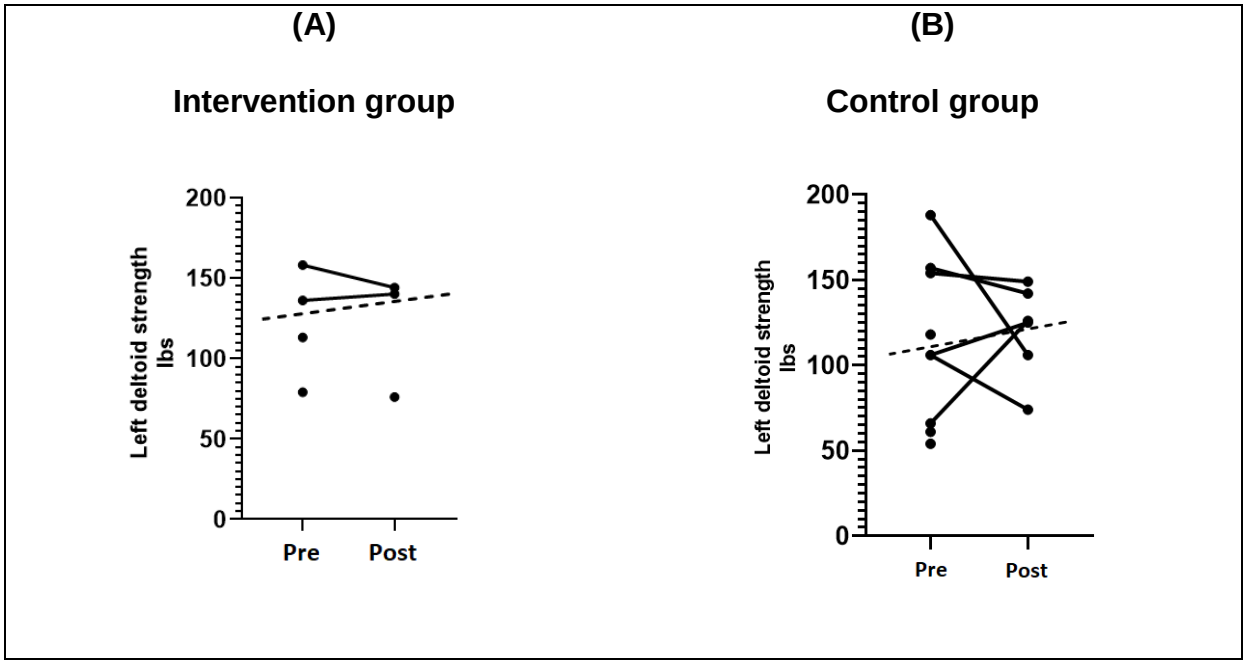


Figure 36 Change in the strength of the left deltoid.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.9.5 Strength of the right biceps

The strength of the right biceps among participants in both groups was assessed using a handheld dynamometer microFET. As depicted in (see Figure 37), there was an improvement in the strength of the right biceps for one participant in the intervention group, while there was a decrease in the in the strength of the right biceps for another participant in the same group. In the control group, the strength of the right biceps improved for one participant, remained the same for another, and decreased for four participants. Moreover, there was a decrease in the median score of the strength of the right biceps for the control group after the PRP.

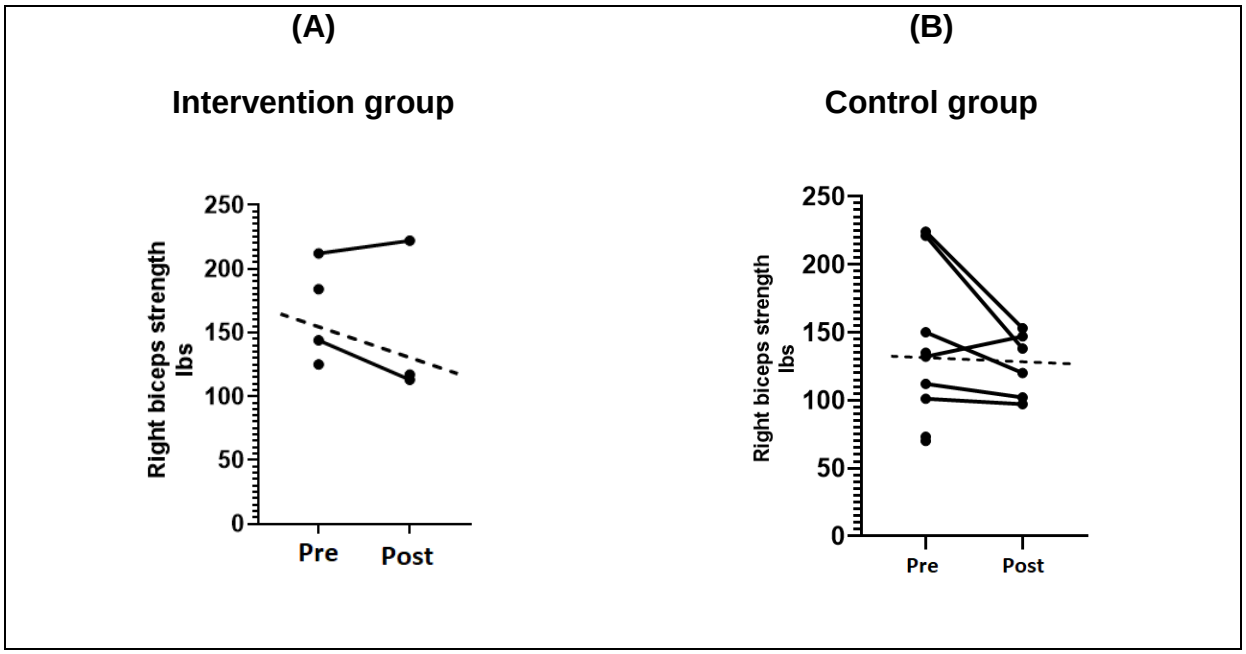


Figure 37 Change in the strength of the right biceps.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.9.6 Strength of the left biceps

The strength of the left biceps was measured using a microFET handheld dynamometer. As evident in (see Figure 38), the left biceps muscle strength improved for one participant, but worsened for another participant in the intervention group. In the control group, there was no change in the median score of the strength of the left biceps after the PRP. Moreover, there was an improvement in the strength of the left biceps for one participant and a reduction in the strength for five participants in the control group.

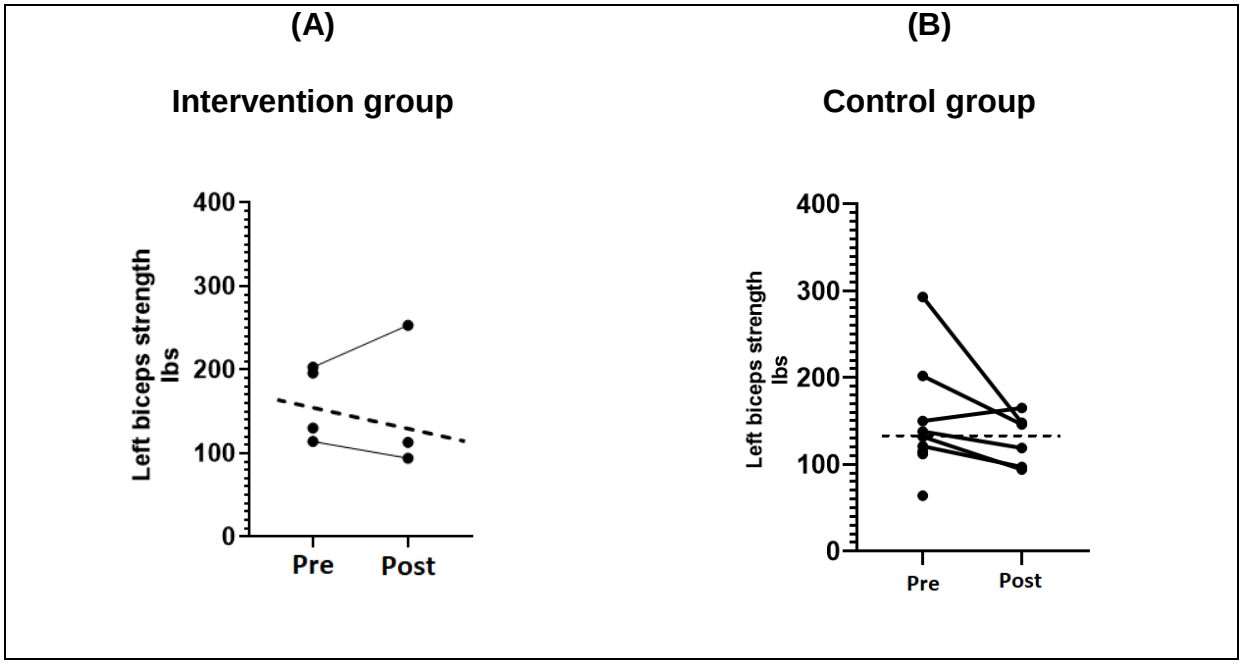


Figure 38 Change in the left biceps strength.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. lbs = pound.

4.3.10 Blood biomarker matrix metalloproteinase 7 (MMP-7)

The blood biomarker MMP-7 was measured in this study. Data of three participants was available for the intervention group. There was trend toward maintenance in the intervention group with a slight increase in medians from 2.081 to 2.380 nanograms/milliliter (ng/mL) post pulmonary rehabilitation + IMT. The control group. MMP-7 data of 6 participants was available and showed maintained median with only a slight decrease 3.318 to 3.187 ng/mL (see Figure 39).

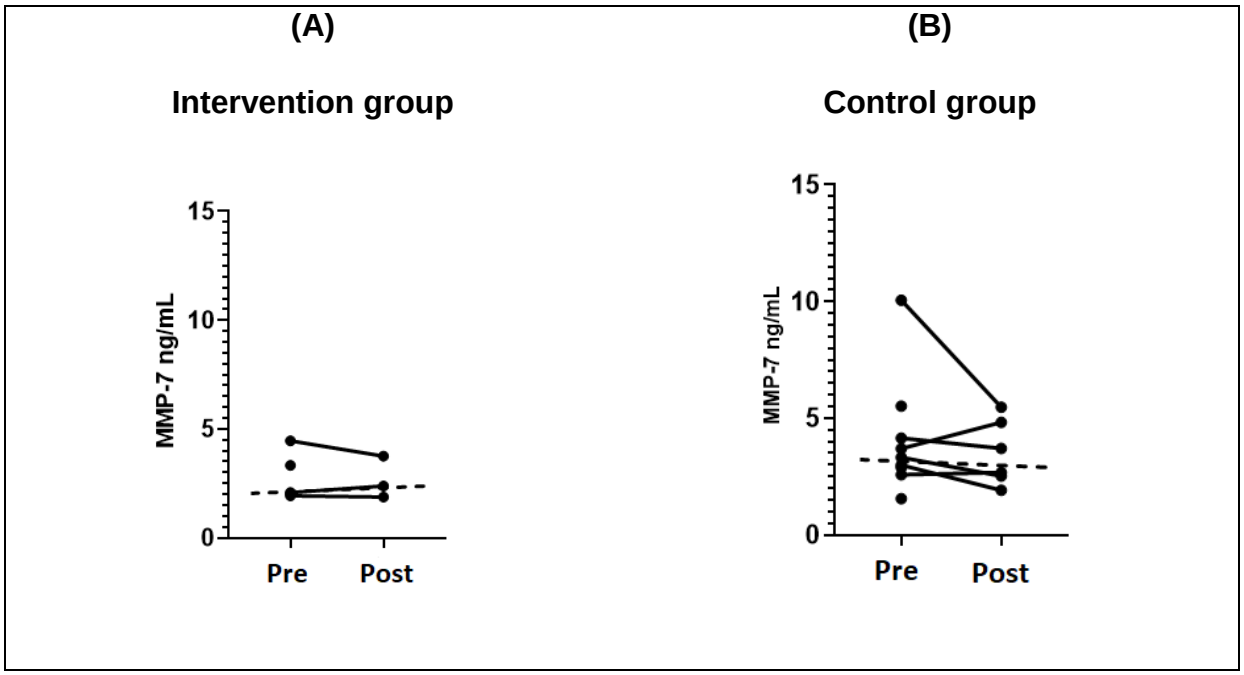


Figure 39 Change in MMP-7 biomarker.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group. MMP-7= Matrix Metalloproteinase 7.

Table 18 Change in MMP-7 level in all participant

Participants	Group	Diagnosis	Pre MMP-7 ng/mL	Post MMP-7 ng/mL	Change in MMP-7
101	Control	CPFE	2.57	2.67	No change
102	Intervention	CPFE	2.11	2.38	↑
103	Control	CPFE	4.15	3.70	↓
104	Intervention	CPFE	3.33	Dropout	-
105	Control	CPFE	2.89	Dropout	-
106	Intervention	CPFE	2.02	Dropout	-
107	Control	CPFE	1.55	Dropout	-
108	Control	CPFE	5.52	Dropout	-
109	Intervention	CPFE	4.55	3.75	↓
110	Control	HP	2.99	1.91	↓
111	Control	HP	10.06	5.47	↓
112	Control	IPF	3.70	4.82	↑ Increased >> patient condition progressed and died.
113	Intervention	CTD-ILD	1.93	1.87	No change
114	Control	IPF	3.32	2.52	↓

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; CTD ILD, connective tissue disease associated interstitial lung diseases; MMP-7, Matrix Metalloproteinase 7, ng/ml, nanograms/milliliter.

4.4 Discussion

The aim of this chapter was to evaluate the feasibility of IMT as a part of the PRP in patients with ILDs. In this study, we were able to demonstrate that IMT as part of the PRP is feasible in a group of ILD patients, which included a few people with CPFE, with good attendance and completion rates. The programme was safe, with no adverse events recorded during the study. Further, in this study, no changes were seen in health-related quality of life, fatigue, anxiety and depression, pulmonary function test results, and strength of major body muscles. However, the low number of participants in this study might be an important consideration in interpreting these data.

4.4.1 Attendance

In this study, the PRP had a good attendance rate, with a mean of 87% and a low dropout rate of only 2 (14%) (see Table 16). The two dropouts were both from the control group; one had a chest infection at the time of the study, and the other had time scheduling conflicts.. Further, three participants were lost to follow-up as their post measurements data were not collected due COVID-19 pandemic restrictions in March 2020. The participant that dropped out due to inconvenient timing, as well as the three participants who were lost to follow-up, are missing at random. There was nothing to suggest that this was not by random, with the exception for the one participant that dropped out due to chest infection. The percentage of participants who completed the study was 64%. In addition, the participants (which included 9 (64%) of participants with CPFE) were mainly keen to attend the PRP and provided positive feedback.

Our completion rate of 64% is consistent with that reported from a large, randomised control trial conducted by Dowman et al., which included 142 patients with ILD, where 66% of the participants in their intervention group completed the study. They also found that adherence to the PRP and progression of exercise intensity maximized the benefits of the PRP (Dowman et al., 2017b). Other studies have reported that when compared to COPD, patients with IPF obtained similar benefits from the PRP and similar completion rates of the programme as well. The PRP improved exercise capacity, health-related quality of life, and dyspnoea in patients with IPF (Nolan et al., 2022, Arizono et al., 2017). Nolan et al. also found that no completion and non-response were associated with increased one-year mortality in patients with IPF (Nolan

et al., 2022). Others reported that completion of the PRP in patients with IPF prior to receiving unilateral lung transplantation was associated with risk of death being decreased by half in patients with IPF as well, reduced duration of life support on a mechanical ventilator, stay at intensive care unit, and overall duration of stay in hospital (Florian et al., 2019).

4.4.2 Side effects

The PRP was safe to implement for patients with ILD, even though the participants were elderly with some signs of frailty, in a group that included people with CPFE. There were no adverse events registered during exercise training. This is consistent with the work of Dowman et al. in their large, randomized control trial involving 142 patients with ILD, in which there were no adverse events either (Dowman et al., 2017b).

4.4.3 IMT and ILD

This study has shown that six to eight weeks of the PRP and IMT in patients with ILD was effective in improving the strength of the patient's inspiratory muscles, as measured by the MIP. An interesting finding was that the improvement in the inspiratory muscle pressure was observed in all participants, both in the intervention and control groups, as depicted in (see Figure 20). This indicates that participants' inspiratory muscle strength increased merely by attending a PRP, regardless of receiving IMT; however, higher improvement were observed in those in the intervention group who received inspiratory muscle training using POWERbreathe®.

Although IMT has been extensively studied in patients with COPD, studies that evaluate its role and effectiveness in patients with ILD are scarce. The ERS and ATS recommended IMT as an additional therapy to PRPs in patients with chronic lung diseases (Nici et al., 2006, Spruit et al., 2013). One of the first studies to describe IMT was Leith and Bradley (1976). They showed that the inspiratory muscles could be trained, thereby leading to an increase in strength and endurance (Leith and Bradley, 1976).

Further, there have been a limited number of studies evaluating IMT in patients with ILD. There is only one recently published randomized controlled single-blinded trial study with parallel groups that evaluated IMT during a PRP in patients with ILD

conducted by Zaki et al. in 2022; they aimed to evaluate the effect of adding IMT to the PRP in patients with ILD. Fifty-one participants with ILD were randomly assigned to either PR with IMT (Intervention group = 26) or to PR only (Control group = 25) for a duration of eight weeks. The PR programme was conducted three sessions/week for eight weeks and consisted of aerobic exercises, strength training, dyspnoea coping strategies, psychological counselling, and nutritional information. In addition, the PR with IMT intervention group underwent 21 minutes of IMT after the PR sessions using POWERbreathe® Medic, a threshold inspiratory muscle trainer. POWERbreathe® was initially set at 30% of the patient's baseline (PImax). The results obtained by Zaki et al. were consistent with our findings in that the inclusion of IMT to PRPs in patients with ILD showed better improvement in inspiratory muscle strength and functional capacity, even though Zaki et al. observed further improvements in health-related quality of life, as measured by SGRQ and dyspnoea (Zaki et al., 2022).

In accordance with increased inspiratory muscle strength observed in this study, other studies have demonstrated that a PRP with IMT in patients with IPF has resulted in improvements in inspiratory muscle pressure and exercise capacity as well as improvements in dyspnoea, thereby improving the effectiveness of the PRP compared to a control group that received only general body exercises but no IMT (Vivek et al., 2017).

Kaushal et al. also recently evaluated the effect of IMT combined with pulmonary rehabilitation in 25 patients with ILD. The pulmonary rehabilitation program consisted of 60 minutes of exercise training (endurance training with cycle ergometry, strength training, flexibility training, and respiratory muscle training with a threshold IMT) in 3 supervised sessions a week for a duration of 8 weeks. The programme also included education on lung health, breathing exercises, stress management, and medication. Significant improvement in functional capacity 6MWT was seen in patients with ILD at the end of the programme. Moreover, the dyspnoea scale, as measured by the modified Medical Research Council scale, improved from severe to mild at the end of the programme. The inspiratory muscle pressure increased significantly at the end of the eight weeks. A negative correlation was found between inspiratory muscle pressure and dyspnoea, which implied that an increase in inspiratory muscle pressure was associated with a decrease in dyspnoea. At the six-month follow up, these improvements were not maintained and were reversed (Kaushal et al., 2019).

Another study examined the effects of an IMT as a standalone programme in 22 Advanced Lung Disease patients (IPF n = 5, hypersensitivity pneumonitis n = 1, COPD n = 11, bronchiectasis n = 4, and asthma n = 1). Patients performed eight weeks of IMT as a high-intensity interval training programme with a flow resistive tapered loading device. Improvements in quality of life, dyspnoea during daily life activities, respiratory muscle strength, and endurance were observed and maintained at the three-month follow up (Hoffman et al., 2021a). In a previous study in 2018, the same group evaluated the same IMT programme and its effect based on the perception of the patients. Interviews with patients with advanced lung disease (IPF = 2) revealed improvements in breathlessness and mobility after the IMT programme, which led to improvements in daily life activities and communication (Hoffman et al., 2018). Further, Koulopoulou et al. also conducted a pilot study in which 17 patients with ILD were randomized into high-intensity IMT (intervention group n = 9) or low-intensity IMT programmes (control group n = 8) for eight weeks. Inspiratory muscle strength improved significantly in the intervention group, with no difference between the groups in terms of dyspnoea, quality of life, or exercise capacity (Koulopoulou et al., 2016).

According to these data, we can infer that inspiratory muscle training as an addition to PRP in patients with ILD will likely result in increased inspiratory muscle strength as measured by maximum inspiratory pressure, which is demonstrated in this chapter as well. In addition, it is also possible that IMT training could also result in further improvements in functional exercise capacity. Other studies have reported improvements in dyspnoea and health-related quality of life, but these findings were not observed in this study.

4.4.4 Functional exercise capacity: One minute sit-to-stand test

Another aim of this study was to evaluate the effect of a PRP in patients with ILD on exercise tolerance and functional exercise capacity. The 1MSTS was used as a measure of exercise tolerance. Consistent with extant literature, this study revealed that exercise tolerance increased 6–8 weeks after the PRP in all participants (see Figure 32).An MCID of three repetitions was achieved in all participants who attended the PRP, with a mean (SD) of 3.89 repetitions (4.26), (see Table 17). The 1MSTS is logistically a more easily deliverable test in busy clinics compared to the six-minute walk test and this experience of the 1MST indicates that it provides useful information in the context of pulmonary rehabilitation.

In accordance with the present results, several randomized controlled trials conducted in patients with ILD (see Table 19) randomized to either the PRP or to a control group have shown improvements in exercise capacity, as measured by the 6MWT (Dale et al., 2014, Dowman et al., 2017b, Holland et al., 2008, Wallaert et al., 2020, Xiao et al., 2019, Behnke et al., 2003, Menon et al., 2011, Vivek et al., 2017). In patients with IPF, several randomized controlled trials (see Table 20)have also shown improvement in 6MWT after pulmonary rehabilitation (Jarosch et al., 2020, Nishiyama et al., 2008, Shen et al., 2016, Shen et al., 2021). Unlike these studies, in the present study, we used the 1MSTS as a measure of exercise tolerance due to its simplicity and ease of use. While the 6MWT requires a 30-meter long hallway and is usually time consuming for routine outpatient clinic consultation, the 1MSTS is quick and simple, which makes it a valuable possible measure of functional status. Further, during the COVID-19 lockdown, the RVI local NHS guidelines were to not perform 6MWT, as it would mean having patients in corridors and making it difficult to maintain distance. In their randomized controlled trial, Lanza et al. used the 30-second chair stand test and the 6MWT to evaluate the effect of pulmonary rehabilitation in patients with IPF, both of which significantly improved post the PRP compared to a control group (Lanza et al., 2019). There is only one randomized control trial conducted by Jackson et al. that reported no improvements in functional exercise capacity post pulmonary rehabilitation. It is unclear what the reasons were for such a lack of improvement in Jackson et al.'s study, but it could be due to a small number of participants or how the 6MWT was conducted (Jackson et al., 2014).

The largest randomized control trial evaluating the efficacy of exercise training in 142 patients with ILD was conducted by Dowman et al. in 2017. This was a multicentre

assessor-blinded randomized controlled study that was conducted in three specialist hospitals in Melbourne, Australia. In their study, 142 patients with ILD were randomized to either receive 8 weeks of exercise training or receive usual medical care. Patients in the pulmonary rehabilitation intervention group received two sessions a week of outpatient supervised exercise training. The PRP consisted of 30 minutes of aerobic exercises—either walking or cycling and resistance training. The intensity for the cycling was set at 70% of the maximum work rate as calculated from 6MWT, and that for the walking was set at 80% of peak speed from 6MWT. Exercise intensity was increased on a weekly basis. Moreover, supplemental oxygen was provided to patients during exercises, if needed, in order to maintain an oxygen saturation of above 88%. Patients also received home exercise and education. The control group received telephone calls once per week for general care. From November 2011 till June 2014, 142 patients with ILD participated in this study. Of these, 61 patients had IPF, 23 had CTD-ILD, 22 had asbestosis, and 36 had other ILD aetiologies. Dowman et al. have showed the efficacy of exercise training in patients with ILD, which further supported the rationale of recommending pulmonary rehabilitation in this group of patients. Patients with asbestosis showed greater improvements than patients with IPF, with both asbestosis and IPF patients showing clinically meaningful improvements. Their study also revealed that improvements were maintained for longer durations in patients with milder disease. Moreover, patients who increased the intensity of their exercise training throughout the programme were more likely to maintain their improvements (Dowman et al., 2017b).

Several recent large multi-centre and international retrospective studies have been conducted to evaluate the effect of PRPs in patients with ILD and concluded that improvements in functional exercise capacity, dyspnoea, and health-related quality of life were achieved post PRPs (Brunetti et al., 2021, Guler et al., 2021, Matsuo et al., 2021). In their large international retrospective study, Guler et al. found that improvements in 6MWD after a PRP in patients with fibrotic ILD resulted in improved survival for up to three years (Guler et al., 2021). Others have recommended early intervention in the form of pulmonary rehabilitation before disease progresses in fibrotic ILD (Matsuo et al., 2021). Holland et al. found that pulmonary rehabilitation was most effective, as it maintained benefits in patients with IPF when disease is mild, thereby supporting early referral to pulmonary rehabilitation in patients with IPF (Holland et al., 2012). On the other hand, in patients with ILD, pulmonary rehabilitation was shown to

be beneficial regardless of disease severity. In their prospective study on ILD patients, Ryerson et al. (n = 54) assessed the effect of pulmonary rehabilitation and reported that patients with worse symptoms and lower 6MWD at baseline were associated with higher improvements in symptoms and 6MWD after pulmonary rehabilitation (Ryerson et al., 2014a). Ferreira et al. also reported similar findings in their retrospective study which showed that patients with lower baseline 6MWT had the most improvements in their 6MWT after pulmonary rehabilitation, thereby suggesting the importance of pulmonary rehabilitation even in patients with severe ILD disease (Ferreira et al., 2009).

In a recent Cochrane review conducted by Dowman et al. that reviewed pulmonary rehabilitation in patients with ILD, it was concluded that better designed randomized controlled trials are required to identify the best exercise programme and determine how to increase long-term benefits (Dowman et al., 2021).

Thus, the present study provides valuable information, which has been identified as an international research priority. The findings of this study suggest that a tailored rehabilitation programme with or without IMT is feasible in frail elderly people with ILD/IPF and those with CPFE. This study also indicated that the 1MSTST could be used in a post-COVID-19 clinical setting to provide useful functional information on patients. Further, the findings indicate that a rehabilitation programme could improve the functional exercise capacity of patients with ILD and the results could be used to help design additional larger studies to inform clinical guidelines.

Table 19 Randomized control trials on interstitial lung diseases (ILD).

	Study	Participants	Design	Intervention	Results	Long-term Maintenance
1	Holland et al. (2008) (Holland et al., 2008)	57 ILD (34 IPF)	Randomized controlled trial (RCT)	Intervention eight weeks PRP twice a week. 30 minutes of endurance with walking and cycling. Strength training for lower limbs and upper limbs, endurance training, and home exercises was prescribed with target of a total of five sessions a week.	Improvement in: - Exercise capacity - Dyspnoea and fatigue symptoms	Changes not maintained at six months.
2	Dale et al. 2014 (Dale et al., 2014)	35 dust-related respiratory diseases, including asbestosis and asbestoses-	RCT multi-centre, parallel group, assessor blinded RCT in Australia (Jan	Patients randomized to either the exercise or control groups. Patients in the intervention exercise group received a supervised aerobic	Improvement in: - Exercise capacity - HRQoL	At 6.5 months improvement maintained.

		related pleural disease (Behnke et al., 2003)	2009–July 2011)	exercise training that included walking and cycling three times a week for a duration of eight weeks. There was no strength training or education included in this programme. At the end of the programme, patients did not receive any maintenance of exercise information. The control group received usual medical care.		
3	Dowman et al. 2017 (Dowman et al., 2017b)	142 ILD (61 IPF)	RCT Multi-centre assessor blinded RCT At three specialist hospitals in	The pulmonary rehabilitation programme consisted of 30 minutes of aerobic exercises either walking or cycling and resistance training. Exercise intensity was	Improvement in: - Exercise capacity - HRQoL - Worse symptoms and lower 6MWD at baseline were associated with	At six months Maintained improvements were seen in patients with milder disease.

			Melbourne, Australia (Nov 2011–June 2014)	increased on a weekly basis. Patients also received home exercise instructions and pertinent education. The control group received telephone calls once every week for general care.	larger improvements. - Adherence to exercise training progression results in greater maintained benefits.	
4	Ku et al. 2017 (Vivek et al., 2017)	40 ILD attending Government Medical College Hospital, India (Sept. 2012–Sept. 2014)	RCT randomized for standard treatment + PR (intervention group) or conventional treatment (Control group)	Patients in the intervention group received the PRP for eight weeks. The PRP consisted of exercise training, patient assessment, nutrition, education, and psychosocial support. Exercise training was conducted four times a week, with two of them being supervised and lasting for two hours each.	Improvement in: - Exercise capacity - HRQoL	Not assessed.

				Endurance training and upper/lower limbs strength training, and IMT. The education component included medications used, disease information, non-pharmacological techniques, and behavioural change.		
5	Wallaert et al. 2020 (Wallaert et al., 2020)	38 patients Stage IV Sarcoidosis	RCT Multi-centre in France (Between 2012 and 2016) Patients randomized to two-month PRP (n = 20) or to counselling (n = 18)	Patients assigned to the intervention group attended an outpatient PRP 3 times a week for 8 weeks, with each session lasting for at least 30 minutes. The PRP included endurance training, strength training, and upper and lower limb exercises. Patients also	Improvement in: - Exercise tolerance - HRQoL - Dyspnoea None of the daily life physical activity measures improved after PRP.	At 6 months and 12 months. - Exercise tolerance - Fatigue - Dyspnoea

				received therapeutic patient education. Patients in the control group received oral counselling to improve their physical activity at home.		
6	Baradzina et al. 2013 (Baradzina, 2013)	Abstract only 140 Sarcoidosis	RCT patients randomized to a PRP (n = 70) or control group (n = 70)	The PRP consisted of exercise training five times a week, each session being for a duration of 40 min, education, physiotherapeutic procedures, stress management, and nutritional advice.	Improvement in: - Dyspnoea - HRQoL - Walking test - disappearance of weakness.	After five years intervention group showed: - Improved lung function - Normalized radiological picture - Absence of relapses
7	Menon et al. 2011 (Menon et al., 2011)	Abstract only 28 ILD	RCT	Patients were randomized to either a control group who received standard medication or to the	Improvement in: - Exercise capacity. - DLCO	Not measured

				intervention group who received supervised eight weeks of PR with standard medication.	- Mid-Thigh Cross Sectional Area on CT (MTCSAct)	
8	Wewel et al. 2005(Behnke et al., 2003)	Abstract only 99 ILD	RCT	Intervention (PR) group (n = 49), control group (n = 50). The intervention group: 6 months home-based walking twice daily, for 15 minutes each day. Control group: no specified walking.	Improvement in: - Exercise capacity - HRQoL - Cardiopulmonary exercise testing (CPET) - Walking distance pedometer - Dyspnoea	Not measured
9	Xiao et al. 2019 (Xiao et al., 2019)	Abstract only. 80 coal workers' pneumoconiosis	RCT	Patients were randomized to either comprehensive rehabilitation treatment or an individualized exercise programme (n = 40) and control group (n = 40).	Improvement in: - Exercise capacity - HRQoL - Lung function indexes	Not measured

Table 20 Randomized controlled trials in idiopathic pulmonary fibrosis (IPF).

	Study	Participants	Design	Design	Results	Long-term Maintenance
1	Nishiyama et al. (2008) (Nishiyama et al., 2008)	30 IPF	RCT	Patients attended a 10-week pulmonary rehabilitation programme. They were randomly assigned to either pulmonary rehabilitation (n = 13) or to a cohort group (n = 15). Two sessions a week of exercise training and strength training. Education lectures were provided.	Improvement in: - HRQoL - Exercise capacity No improvement in PFT; no improvement in arterial blood gas analysis values.	Not measured
2	Gaunaurd et al. 2014 (Gaunaurd et al., 2014)	21 IPF	RCT	The PRP comprised two sessions a week, each lasting 90 minutes for 12 weeks, thereby resulting in a total of 24 sessions. The control group did not receive any exercise programme. The rehabilitation programme included cardiopulmonary endurance training (30 min), flexibility exercises (20 min), strength training (25 min), and educational lectures. Patients were	Improvement in: - The International Physical Activity Questionnaire (IPAQ). - HRQoL	After three months Improvements in IPAQ were not maintained

				also asked to perform home exercises with therapeutic bands twice a week.		
3	Jackson et al. 2014 (Jackson et al., 2014)	21 IPF (Miami, USA)	RCT non blinded	A total of 24 sessions twice a week, with each session lasting two hours over a three-month period. Patients in the control group did not receive pulmonary rehabilitation. The PRP consisted of endurance training (treadmill, cycling), flexibility exercises, strength training, and education lectures. Patients were required to do home exercises as well.	Improvement in: - MIP increased. - Maintained exercise oxygen consumption (VO_2). - Constant load exercise time lengthened. No significant change in 6MWT, dyspnoea.	Not measured
4	Jarosch et al. 2020 (Jarosch et al., 2020)	54 IPF UIP pattern	RCT multi-centre (three study centres) in Germany.	Patients in the PR group received psychological support, breathing therapy, medical care (e.g. initiation/adjustment of long-term oxygen therapy, non-invasive ventilation), education, and exercise training. The exercise training	Improvement in: - Exercise capacity - HRQoL	At three months: - Change in HRQoL was maintained.

				consisted of three-week inpatient training, 5–6 days/week, with total of 15 to 18 sessions. It included interval cycle training or endurance training. Resistance training for large muscle groups was performed with 3 sets of 15 to 20 repetitions.		
5	Shen et al. 2016 (Shen et al., 2016)	Abstract only 31 IPF	RCT	Pulmonary fibrosis rehabilitation exercise, designed by Professor Li Huiping of Shanghai hospital, was performed thrice a day, for a three-month period.	Improvement in: - Lung function of FVC, DLCO, and FEV1. - HRQoL - Exercise capacity	Not measured
6	Shen et al. 2021 (Shen et al., 2021)	82 IPF from Shanghai hospital (Jan 2015–May 2017)	RCT	Patients in the intervention group received training on how to perform LHP's RRPF breathing exercises; thereafter, they attended a 12-month programme. LHP's RRPF consisted of three breathing movements—deep breath using both the lungs, deep breath of unilateral lower lung, and	At 6 months improvement in: - improvements in lung function values (FVC, FEV1, and DLCO) - HRQoL	Not measured.

				deep breath of the upper lung. The breathing exercises were done three times a day and lasted 4–6 minutes each, with a one-minute rest in between.	At 12 months improvement in: - Exercise capacity - lung function values (FVC, FEV1, and DLCO. - HRQoL - Lower Acute exacerbation incidence and one-year mortality in intervention group.	
7	Lanza et al 2019 and 2020 (Lanza et al., 2019)	Abstract only 24 IPF	RCT	The intervention group attended a three-month PRP, with a 90-minute exercise training session twice a week (total of 24 sessions); those in the control group maintained their usual physical activity.	Improvement in: - Physical activity - HRQoL - Exercise capacity	Not measured

4.4.5 Patient-reported outcome surveys

Health-related quality of life (HRQoL) was evaluated using the K-BILD and fatigue was assessed through the FSS. This study was unable to demonstrate any difference in HRQoL and FSS between the pre-PRP and post-PRP stages. A pre-median score of 74 and post-median score of 68 for K-BILD was found for the intervention group and pre and post median scores of 57 and 57.5, respectively, was observed in the control group.

Further, with regard to the FSS, no change was observed in this study in both the intervention and control groups. The intervention group had pre and post median scores of 4.78 and 4.89, respectively. The control group had pre and post median scores of 5.22 and 4.89, respectively. The MCID of 5 for the overall K-BILD score and 0.45–0.88 for the FSS were not achieve in this study.

Several published randomized controlled trials in patients with ILD (see Table 19)) have shown that a PRP is effective in improving HRQoL (Baradzina, 2013, Behnke et al., 2003, Dale et al., 2014, Dowman et al., 2017b, Vivek et al., 2017, Wallaert et al., 2020, Xiao et al., 2019). Similar findings were also seen in randomized control trial in patients with IPF (see Table 20)(Gaunaurd et al., 2014, Jarosch et al., 2020, Lanza et al., 2019, Nishiyama et al., 2008, Shen et al., 2016, Shen et al., 2021). Further, Holland et al. have shown improvements in fatigue, as measured by the Chronic Respiratory Disease Questionnaire ($p < 0.01$) following exercise training in patients with ILD. Moreover, similar to the present study, Swigris et al. used the FSS scale to assess fatigue in patients with IPF who attended a PRP and showed improvements (Holland et al., 2008, Swigris et al., 2011). This study was unable to detect a change in either HRQoL as measured by K-BILD or in fatigue as measured by FSS after a PRP. Additional studies with a larger sample size may be needed to detect a change in HRQoL and fatigue in patients with ILD.

Since patients with ILDs suffer from disabling symptoms of dyspnoea, persistent cough, and deteriorating exercise tolerance, depression and anxiety are common in these patients. It has been reported that 31% of patients with ILD have anxiety and 23% have depression with dyspnoea, with comorbidities being significant contributors (Holland et al., 2014a). Naz et al. compared patients with ILD who underwent 8 weeks

of PR versus those who underwent 12 weeks of PR. In their study, depression and anxiety improved after 8 weeks of pulmonary rehabilitation, but there were no further improvements after 12 weeks of pulmonary rehabilitation programme. They reported a median (interquartile range) of 6 (5,10) and 4 (1, 10) for anxiety and depression, respectively (Naz et al., 2018). In our study, higher levels of anxiety and depression were seen with a median (interquartile range) of 9 (3.5, 10) and 6 (3, 7.5) for anxiety and depression, respectively. The results of the present study are heterogenous with regard to changes in anxiety and depression. In both the intervention and control groups, depression was maintained with trends towards slight worsening. Anxiety seemed to show trends towards improvement in the intervention group, but seemed to worsen in the control group. This finding was concordant with a study conducted by Dowman et al., who reported a trend of improvement in anxiety after nine weeks of exercise training ($p = 0.06$) (Dowman et al., 2017b). No significant change in depression was found in their study (Dowman et al., 2017b). Jarosch et al. reported improvement in both anxiety and depression in patients with IPF who attended a PRP (Jarosch et al., 2020). Thus, the findings of the present study indicate the need for a larger sample size to conduct further confirmative studies and conclusions.

4.4.6 Pulmonary function test

This study did not find any significant change in lung capacity measured as FVC post the PRP, with or without IMT. This is in accordance with the literature where pulmonary rehabilitation in patients with ILD has no significant effects on lung function (Nishiyama et al., 2008).

Others have reported improvement in lung function, including FVC, FEV1, maximum expiratory flow, expiratory flow when vital capacity was 25% and when it was 75% after the PRP in patients with coal workers' pneumoconiosis (Xiao et al., 2019). Shen et al. also assessed the effect of a breathing exercise programme that they developed (LHP's respiratory rehabilitation for pulmonary fibrosis) in patients with IPF. They also reported significant improvements in FVC, FEV1, and TLCO (Shen et al., 2021).

Further, Miller and Cooper recently demonstrated that a decrease in TLCO predicts survival and that TLCO might be superior in this matter compared to FEV1 or FVC. They proposed a four-tier classification for grading of TLCO z-scores: ≥-1.645 = normal, ≥-3.0 = mild, ≥-5.0 = moderate, and <-5.0 = severe (Miller and Cooper, 2021). Due to the low number of participants in this study, it is difficult to make definite conclusions, but most of the participants in this study were patients with ILD and had a moderate grade TLCO z-score. In this study, the TLCO z-score showed no change or a slight decrease after the PRP, thereby indicating that a PRP might not have a strong effect on lung diffusion capacity. A larger sample would be required to confirm these findings.

4.4.7 Major body muscles strength

Patients with ILD often exhibit peripheral muscle dysfunction, which is believed to play a significant role in exercise tolerance. In patients with IPF, weakness in quadriceps has shown to be significantly associated with decreased exercise tolerance as well as impairment in lung function. Quadriceps muscle strength was also an independent predictor of peak exercise capacity in patients with IPF (Nishiyama et al., 2005). Further, in patients with COPD, skeletal muscle weakness—particularly in the quadriceps—is well acknowledged (Bernard et al., 1998). To the best of my knowledge, for patients with ILD, there are only two studies that have evaluated quadriceps muscle strength using a handheld dynamometer (Iwanami et al., 2022,

Dowman et al., 2016). Since skeletal muscle strength possibly influences exercise tolerance and the potential possible benefits of exercise training, assessing skeletal muscle strength in patients with ILD could be beneficial.

This study evaluated the muscle strength of three major peripheral extremity muscles—quadriceps, deltoids, and biceps muscles—for patients with ILD before and after a PRP. The right and left quadriceps muscle strength of patients with ILD showed heterogenous results, with a trend toward maintenance for the right quadriceps muscle and a trend toward decreasing strength in the left quadriceps muscle.

The right and left deltoid muscle strength also showed wide variability in this study, with a trend toward improvement. The participants in this study in both intervention and control groups attended a six-eight week PRP in which they received exercise training, treadmill, and weightlifting. These exercises targeted major body muscles and, therefore, an improvement in muscles strength was the goal and was expected.

The strength of the right and left biceps was also evaluated and indicated heterogenous results, with a trend towards a decrease in the strength of these muscles. In an attempt to assess the reliability of the handheld dynamometer in evaluating muscle strength, Dowman et al. evaluated the strength of knee extensors and elbow flexors in 30 patients with ILD. They reported a knee extensor strength mean (SD) of 19 kg (5.6) and an elbow flexor strength mean (SD) of 16.7 kg (5.0) (Dowman et al., 2016). In the present study, we found higher means for the strength of knee extensors and elbow flexors at 57.6 kg and 69.1 kg, respectively. Our study included participants with ILD with similar lung function results as those in Dowman et al.; thus, the explanation that we had patients with milder disease is not applicable here. In this study, the results of major body muscle strength were heterogenous, which could be attributed to the heterogenous nature of the disease. However, also, the tester (me) also faced difficulties in measuring muscle strength in this study, as it appears likely that my strength level might have affected the reliability of this data as well. The handheld dynamometer microFET2 used to assess muscle strength is designed to fit into the tester's palm, allowing the tester to apply resistance directly to the movement of a participant's extremity to determine the muscle's force output. The amount of resistance the tester is applying against the participant's muscle movement is variable and depends on the tester's strength. Similar concerns have been reported

by others such as Dowman et al., who assessed participants in two sessions where two independent testers assessed the muscle strength of 30 ILD patients. Dowman et al. concluded that the handheld dynamometer was a reliable instrument in measuring muscle strength in patients with ILD. However, they noted that there was a trend for one of the testers to obtain slightly higher muscle strength values in strong study participants. The researchers explained that this was possibly related to the strength of the testers (Dowman et al., 2016). It has been shown that the reliability of measurements made by the handheld dynamometer is affected by the tester's strength, with the strongest tester producing greater measurements of strength than other testers (Wikholm and Bohannon, 1991).

Further, Dowman et al. reported minimal detectable difference (MDD) in the handheld dynamometer measurements to determine the least amount of change required to show a true improvement or decline. In patients with ILD, the strength of the knee extensor would need to improve by 2.5 kg and the elbow flex strength would need to improve by 1.9 kg to have 95% confidence that a real change had occurred when tests are conducted by the same assessor (Dowman et al., 2016).

Iwanami et al. recently published a study that evaluated the effects of a PRP in patients with IPF who are receiving antifibrotic medication. This was a non-randomized controlled study in which participants were classified into four groups— pulmonary rehabilitation group, pulmonary rehabilitation + antifibrotic medication group, control group, and antifibrotic medication group. Superior results were found in the pulmonary rehabilitation and antifibrotic medication groups. One of the outcomes in their study was quadriceps muscle strength measured using a handheld dynamometer. There was no significant change in quadriceps muscle strength in all groups (Iwanami et al., 2022).

4.4.8 Blood biomarker matrix metalloproteinase 7 (MMP-7)

MMP-7 is a blood biomarker that has often been described as being increased in patients with IPF. In this study, the MMP-7 levels pre and post the PRP showed a trend for a decrease in the MMP-7 levels or for the MMP-7 levels to remain the same rather than increasing. Out of the nine participants, there was a decrease in MMP-7 levels for six of them, an increase for two of them, and no change for one (see Table 18).

In a recent systematic review and data meta-analysis of MMP-7 in patients with IPF, 12 studies reported MMP-7, and in 9 of them individual participants' data were obtained from 1664 participants and 11 different cohorts were analysed. The meta-analysis revealed that MMP-7 was associated with a 23% increased risk of mortality with moderate certainty in patients with IPF. MMP-7 was also associated with disease progression and change in FVC with high certainty. Interestingly, short term change in MMP-7 over a three-month period was not associated with mortality or disease progression in IPF (Khan et al., 2022).

Maher et al. conducted a two-stage discovery analysis using the PROFILE study cohort and showed that MMP-7 in patients with IPF was increased compared to that in healthy matched controls and could predict disease outcome (Maher et al., 2017). In another multicentre prospective 52-week study, MMP-7 was identified along with other biomarkers as being increased in patients with IPF when compared to healthy matched controls (Raghu et al., 2018b)

Bauer et al. evaluated serum samples from the BUILD-3 randomized clinical trial that evaluated the use of Bosentan in IPF (King et al., 2011). The researchers evaluated serum samples from 342 patients with IPF and attempted to evaluate the prognostic ability of four IPF biomarkers. MMP-7 was the only biomarker that was significantly increased in patients with IPF at all stages, baselines, after four months, and at end of the study when compared to healthy control samples. The following are the serum MMP-7 mean concentrations and p-values of patients with IPF compared to health control samples (1.25 ng/mL): IPF baseline (2.25 ng/ml, $p < 0.0001$), IPF at four months (1.97 ng/ml, $p < 0.01$), and IPF at the end of the study (2.64 ng/ml, $p < 0.0001$) (Bauer et al., 2017). Hamai et al. identified 5.56 ng/ml MMP-7 serum level as a cut-off

value with a discriminating capability to differentiate patients with IPF from healthy controls (Hamai et al., 2016).

4.5 Limitations

This study had a few limitations. The low number of participants in this study might affect the generalizability of the results, although they are in accordance with the results obtained by other studies in extant literature. The long-term maintenance of the outcomes of a PRP with or without inspiratory muscle training in patients with ILD were not evaluated. The effect of PR and IMT on the survival of patients with ILD was not evaluated in this study but could be considered for future research. In addition, well-designed randomised controlled trials are essential for identifying the optimal exercise programme and determining how to maximise long-term benefits.

4.6 Conclusion

This study was a feasibility randomised controlled trial that added important information regarding the use of IMT in conjunction with pulmonary rehabilitation in patients with ILD. With limited data on patients with ILD and no data on patients with CPFE, this study demonstrated the feasibility of incorporating IMT into a pulmonary rehabilitation programme for these patient categories. This study had good attendance and completion rates and no adverse events were reported during exercise training. A PRP with or without IMT in patients with ILD could probably improve maximal inspiratory pressure and functional exercise capacity immediately after the PRP. No change in health related quality of life, fatigue, anxiety and depression, PFT, and strength of major body muscles was seen. This could be attributed to the low number of participants.

Even in a group that included individuals with CPFE, the PRP was safe for ILD patients to implement. Concerns have been raised by the clinical staff at the RVI regarding the capacity of patients with CPFE to participate in and complete pulmonary rehabilitation. This study demonstrated the possibility of pulmonary rehabilitation for patients with CPFE with no adverse events reported during this study.

As a result of these findings, the pulmonary consultants and physical therapy department at the RVI are committed to offering a pulmonary rehabilitation programme tailored to patients with ILD. Previously, patients with ILD participated in pulmonary

rehabilitation programmes alongside patients with other lung conditions, such as COPD.

Future research should evaluate the long-term benefits and effects on survival of IMT combined with pulmonary rehabilitation in ILD patients. Since the optimal exercise programme for ILD patients is still unknown, future research is required to evaluate this. In order to recruit large number of participants from this group of patients with a rare disease, multi-centre randomised controlled trial studies are required.

Chapter 5: Physical Activity and Sarcopenia in Patients with ILD Undergoing Pulmonary Rehabilitation

5.1 Introduction

5.1.1 Physical activity

Patients with ILDs present with worsening dyspnoea and physical activity (PA). In routine clinical examinations, these patients are assessed through clinical measures such as pulmonary function tests, the six-minute walk test, high resolution computed tomography, and, sometimes, serum ILD biomarkers. The relationship between these clinical parameters and PA levels in patients with ILD is still not clearly understood.

Evaluating PA levels in patients with ILD has the potential to improve the evaluation of the disease's progression in an individualised, patient-centred way. Therapeutic interventions and assessment of prognosis may also be informed by assessments of PA, which can be measured by accelerometery devices worn on the patient's wrist, waist, or thigh (Chen and Bassett, 2005).

In patients with COPD, PA level is a recognised, significant predictor of all-cause mortality (Waschki et al., 2011), but only a few studies have evaluated PA in patients with ILD (Nakayama et al., 2015, Wallaert et al., 2013, Langer et al., 2012). These studies show that PA declines in patients with ILD compared to healthy individuals (Wallaert et al., 2013).

5.1.2 Sarcopenia

Sarcopenia is an age-related, generalised, involuntary, progressive condition of the skeletal muscles that leads to a loss of muscle strength and mass, increasing the risk of adverse events, such as falls, physical impairment, fractures, and mortality (Cruz-Jentoft et al., 2019). Sarcopenia starts as early as the fourth decade of life, and research shows that both skeletal muscle mass and strength decrease in a linear manner; by the eighth decade of life, up to 50% of muscle mass is lost (Metter et al., 1997).

Since muscle mass contributes up to 60% of total body mass, pathological changes to the skeletal muscles can have serious consequences in the older population.

Sarcopenia can be caused by reduced activity, insufficient nutrition, increased inflammation, and a decrease in hormone levels and the number of neuromuscular junctions (Walston, 2012).

The effects of sarcopenia can be severe in older adults, causing adverse health outcomes as a result of decreases in strength and function. These include disability, loss of function, and frailty (Dufour et al., 2013, Marsh et al., 2011, Xue et al., 2011). Sarcopenia is also linked to increased insulin resistance, falls, fatigue, acute and chronic diseases, and mortality (Landi et al., 2012, Newman et al., 2006, Peng et al., 2012). Rheumatologic conditions, such as rheumatoid arthritis in women, are also associated with sarcopenia (Giles et al., 2008).

One study found that sarcopenia as diagnosed by dual-energy X-ray absorptiometry is highly prevalent in patients with COPD (Costa et al., 2015). In these patients, the reduction in lean muscle mass is problematic, as it reduces exercise capacity, which can exacerbate the loss of muscle mass, resulting in a vicious circle (Costa et al., 2015). Sheean et al., (2014), found that sarcopenia is also very prevalent in patients with respiratory failure. In IPF, the fibrotic changes of the lungs result in a restrictive pattern and hypoxia, which leads to an increased respiratory muscle load and shortness of breath, which further worsens a sedentary lifestyle and eventually results in muscle deconditioning and sarcopenia (Sheean et al., 2014).

This research adopted the European Working Group on Sarcopenia in Older People's (EWGSOP) definition of how to assess sarcopenia in a cohort of patients with ILD. In 2010, the EWGSOP published a document that defined sarcopenia and aimed to promote advances in its diagnosis and treatment (Cruz-Jentoft et al., 2010). In 2018, the working group revised the original definition to reflect the growing body of scientific and clinical data over the previous 10 years (Cruz-Jentoft et al., 2019). The EWGSOP2 paper emphasises that clinical care practitioners have growing opportunities to prevent, postpone, treat, and occasionally even reverse sarcopenia with effective and early interventions.

The identified prevalence of sarcopenia in patients with COPD ranges from 15.5% (Sepúlveda-Loyola et al., 2020) to 21.6% (Benz et al., 2019). Few studies have evaluated sarcopenia in patients with ILD or IPF, representing a gap in the literature.

Both PA and sarcopenia are drawing interest internationally as emerging topics in advanced cardiopulmonary rehabilitation (Advanced Cardiopulmonary Rehabilitation Workshop session, European Respiratory Society, International Congress, 4–6 Sept. 2022, Barcelona, Spain), representing an opportunity to contribute to the knowledge of sarcopenia in patients with ILD. This chapter addresses the lack of data in the literature by describing the assessment of PA levels and sarcopenia in patients with ILD. The study also evaluated the effect of pulmonary rehabilitation programme with or without IMT on outcomes in patients with ILD.

5.2 Methods

5.2.1 Participants of study

In this chapter, physical activity and sarcopenia outcomes of the same 14 participants recruited in Chapter 4 were evaluated. Physical activity and sarcopenia data were measured at baseline (pre-measurement) and after eight weeks of the pulmonary rehabilitation programme (post-measurement).

5.2.2 Physical activity

All the participants wore an accelerometer (GENEActiv Actiwatch; GENEActiv, UK) (see Figure 40) on their left wrist 24 hours daily for seven consecutive days. We asked the participants to wear it while sleeping, as the accelerometer records sleep activity, and, because it is waterproof, they could wear it while showering or swimming. The activity data were analysed using the GENEActiv R Markdown package, which provides an activity report including daily steps, time spent in sleep, sedentary time, light activity duration, moderate activity duration, and vigorous activity duration.

Figure 40 The GENEActiv Actiwatch

5.2.3 Sarcopenia

The EWGSOP2 have published a practical algorithm for identifying, diagnosing, and determining the severity of sarcopenia cases (Cruz-Jentoft et al., 2019). It recommends using the Find-Assess-Confirm-Severity (F-A-C-S) pathway in clinical practice and research settings. The EWGSOP2 focuses on muscle weakness rather than muscle mass as a determinant of sarcopenia in three stages:

1. Probable sarcopenia. Characterised by low muscle strength only; handgrip strength: <27 kg in males; <16 kg in females
2. Confirmed sarcopenia. Both low muscle strength and low muscle quantity; appendicular skeletal muscle mass (ASM) divided by square of height ASM/height^2: <7.0 kg/m^2 in males; <5.5 kg/m^2 in females
3. Severe sarcopenia. The prior criteria plus poor physical performance; gait speed: ≤0.8 m/sec

The EWGSOP2 developed these three stages for application as a testing series in which subsequent measurements are sequentially performed only when the result of the first measurement is positive.

5.2.3.1 Muscle strength: handgrip

Handgrip strength was measured by a handheld dynamometer (Jamar Hydraulic Hand Dynamometer, UK) (see Figure 41) following the instruction of the *NIH Toolbox Training Manual* (Gershon et al., 2013). The dynamometer was set on the second notch. The patients were instructed to sit in a chair with their feet on the floor and their knees at a 90° angle. The arm tested was positioned at a 90° angle next to the patient's body without contact by the researcher. During the test, the researcher helped to support the dynamometer. The participants were told to squeeze its handle as strongly as possible when instructed, four times on each hand alternatively (one practice and three test trials on each hand). The average of three trials was recorded for analysis. The researcher instructed the patient by saying, 'Ready? Three, two, one, squeeze'. After three to four seconds, the researcher said, 'Stop', and the dynamometer was reset to zero after each test trial. The EWGSOP2 identify a cutoff point for grip strength of <27 kg in males and <16kg in females.

Figure 41 The Jamar Hydraulic Hand Dynamometer

5.2.3.2 Muscle quantity: Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) to assess muscle quantity was conducted using the Tanita MC780 body composition analyser (Tanita Corp., Japan) (see Figure 42). BIA assesses the volume of lean body mass and fat. The participants were asked to remove their shoes, socks, and any items they were carrying (keys, money, wallets, etc.) and to take off outer garments so as to wear a single layer of clothing. A preset tare value of 1 kg was entered if the subject was lightly dressed and 2 kg if heavily dressed. The participants were told to step on the scale barefoot when 'Step on' appeared on the screen. They were instructed to keep their knees straight and to look forward with their head up, inner thighs not touching, and arms hanging but not touching their sides. The participant's ID, sex, age, and height in cm were recorded by the researcher. When the device flashed, the participants were told to hold the grips on both hands and maintain their position. When the device displayed 'Grip off', the participants were instructed to return the grips. The data were automatically saved to a memory card. The EWGSOP2 identify an ASM/height^2 cutoff point of <7.0 kg/m^2 for males and <5.5 kg/m^2 for females.

Figure 42 The Tanita MC780 body composition analyser

5.2.3.3 Physical performance: four-metre gait speed

Four-metre gait speed provides an informative assessment in frailty studies. The present research followed the *NIH Toolbox Training Manual* (Gershon et al., 2013) in measuring four-metre gait speed. A five-metre path was measured and marked by a cone at the start point and another cone five metres from the start point. If the participants felt the need to use a cane or walking assistance device during the test, they were allowed to do so, and the researcher made a note of it. The participants were told to walk normally at their usual speed 'as if they were walking on the street to get to a shop'. They were instructed to start walking from the first cone and continue past the other cone before stopping. The researcher began timing the participants when their first foot crossed the starting line and then walked behind and to the side of the participant. Timing was stopped when one of the participant's feet had completely crossed the finish line (at four metres, not at the five-metre cone). The participants performed one practice and two test trials, and the average of the test

trials was used for analysis. The EWGSOP2 have defined a cutoff speed of ≤0.8 m/sec to indicate severe sarcopenia.

5.2.4 Statistical analysis

The analysis for descriptive exploratory statistics was done with the GraphPad Prism 9 (GraphPad Software, Inc.). Means, medians, standard deviations, and interquartile ranges were used to describe the continuous variables. Absolute values and frequencies (%) were used to describe the categorical variables. As this was a feasibility pilot study of a randomised controlled trial, no statistical analysis of hypothesis was conducted. A quote from Leon et al. supports this "A pilot study is not a hypothesis testing study. Therefore, no inferential statistical tests should be proposed in a pilot study protocol. With no inferential statistical tests, a pilot study will not provide p-value" (Leon et al., 2011).

5.3 Results

5.3.1 Characteristics of participants

Physical activity and Sarcopenia outcomes of the same 14 participants recruited in chapter 4 were evaluated in this chapter. For characteristics of participants (see Table 11) and (see Table 12). Pre-measurements were taken at the baseline, and post-measurements were taken after attending eight weeks of pulmonary rehabilitation programme.

5.3.2 Physical activity

5.3.2.1 Steps count

This study collected the average daily steps count for one week using the GENEActiv watch (see Figure 43). The intervention group had two participants, and the average daily steps count increased in one participant and decreased in the other after a pulmonary rehabilitation programme + IMT. Data were available for five participants in the control group, with one showing an increase in average daily steps count and four showing a decrease after the pulmonary rehabilitation programme. The control group had a median daily steps count of 4,870 steps before the pulmonary rehabilitation programme, which fell slightly or did not change among the participants, yielding a median of 4,665 steps after the pulmonary rehabilitation programme.

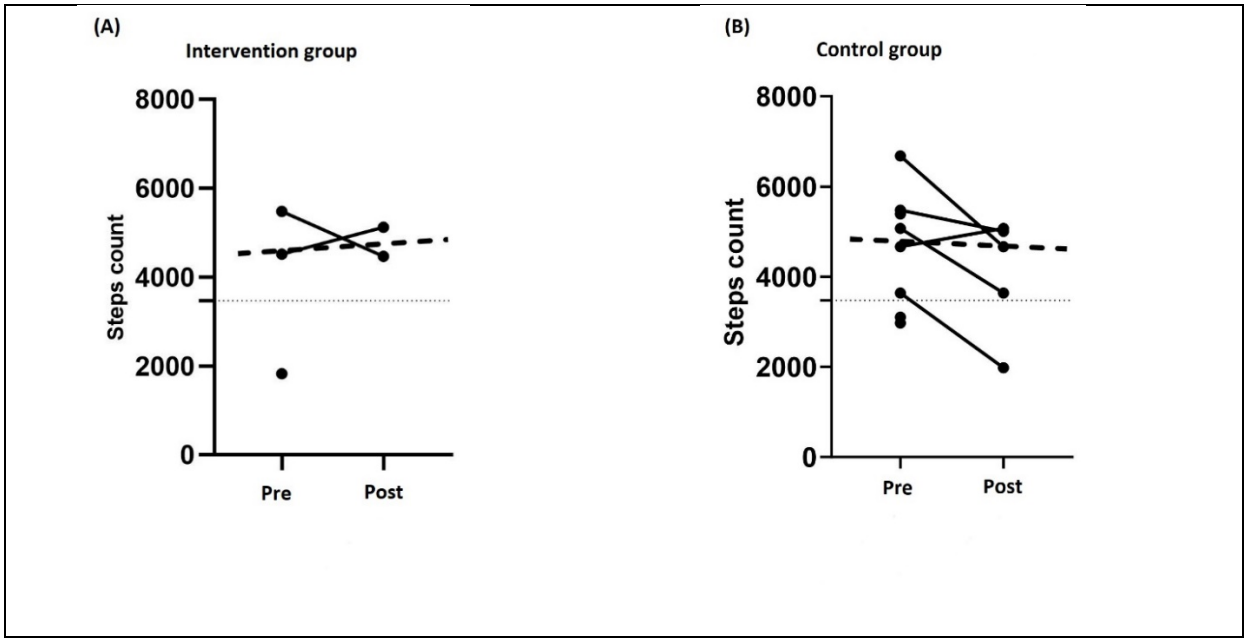


Figure 43 Change in daily steps count.

The data are individual values. The black dotted lines represent pre and post median values. Graph A: intervention group pre and post data. Graph B: control group pre and post data. Steps count are the average daily steps of each individual. The horizontal dashed line represents the cutoff point of 3,473 steps/day reported for patients with ILD.

5.3.2.2 Sedentary time

The time spent in sedentary activity per week was collected from the GENEActiv watch (see Figure 44). The intervention group had two participants, one showing an increase in sedentary time and the other a decrease after the pulmonary rehabilitation programme + IMT. Data from five participants were available for the control group. Two participants decreased their sedentary time, while the other three increased it after the pulmonary rehabilitation programme. The control group had a median sedentary time/week of 4,956 minutes before the pulmonary rehabilitation programme, which increased to a median of 5,352 minutes after the pulmonary rehabilitation programme.

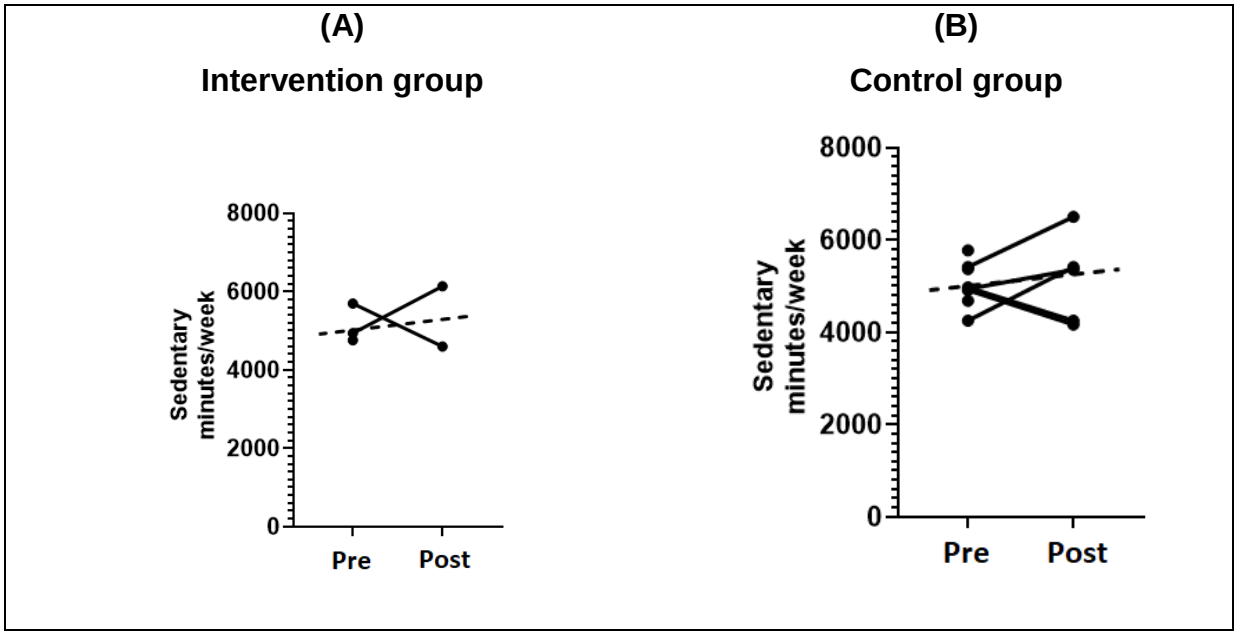


Figure 44 Change in sedentary time per week in minutes.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.2.3 Light activity time

The GENEActiv watch provided the time spent in light activity per week (see Figure 45). The data of two participants were available from the intervention group, both of whom showed a decrease in light activity time after the pulmonary rehabilitation programme + IMT. The control group provided the data of five participants, one of whom showed an increase, while the other four showed a decrease in light activity time/week after the pulmonary rehabilitation programme. The control group had a median of 1,868 minutes before the pulmonary rehabilitation programme, which decreased to 1,174 minutes of light activity/week after the programme.

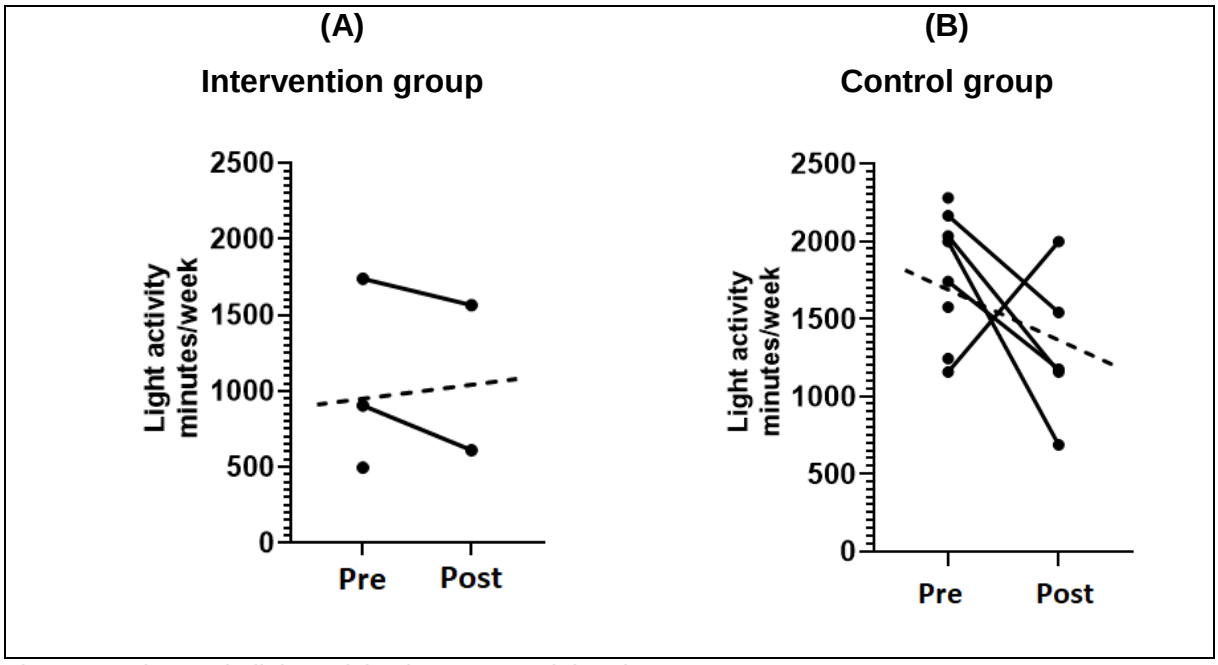


Figure 45 Change in light activity time per week in minutes.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.2.4 Moderate and vigorous activity time

The time spent in moderate and vigorous activity (MVA) per week was collected through the GENEActiv device (see Figure 46). The data of two participants were available from the intervention group, and both showed a decrease in MVA after the pulmonary rehabilitation + IMT. The data of five participants were available from the control group; two participants showed an increase, two participants showed no change or a slight decrease, and one participant decreased in MVA after the pulmonary rehabilitation programme. The control group had a median of 255.6 minutes of MVA before the pulmonary rehabilitation programme, which fell slightly to a median of 226.2 minutes after the programme.

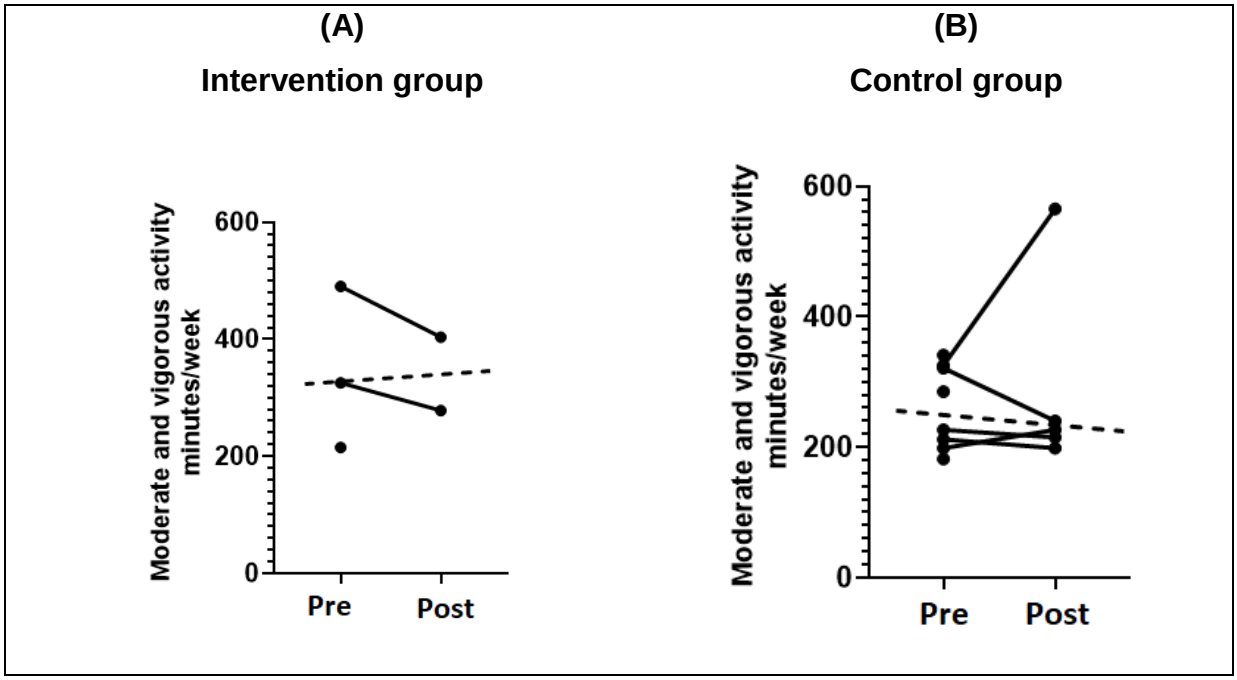


Figure 46 Change in moderate and vigorous activity time per week in minutes.

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.3 Sarcopenia parameters

5.3.3.1 Muscle strength: Handgrip

5.3.3.1.1 Right hand grip strength

Muscle strength was assessed by handgrip strength measurement using the Jamar device (see Figure 47). None of the participants (0 of 3) in the intervention group had low right handgrip strength as defined by EWGSOP2 before the pulmonary rehabilitation programme + IMT, and one of three participants in the group had low right handgrip strength after the programme + IMT. In the control group, one of six participants had a decreased right handgrip strength prior to the pulmonary rehabilitation programme, and one of six participants had low right handgrip strength after the programme.

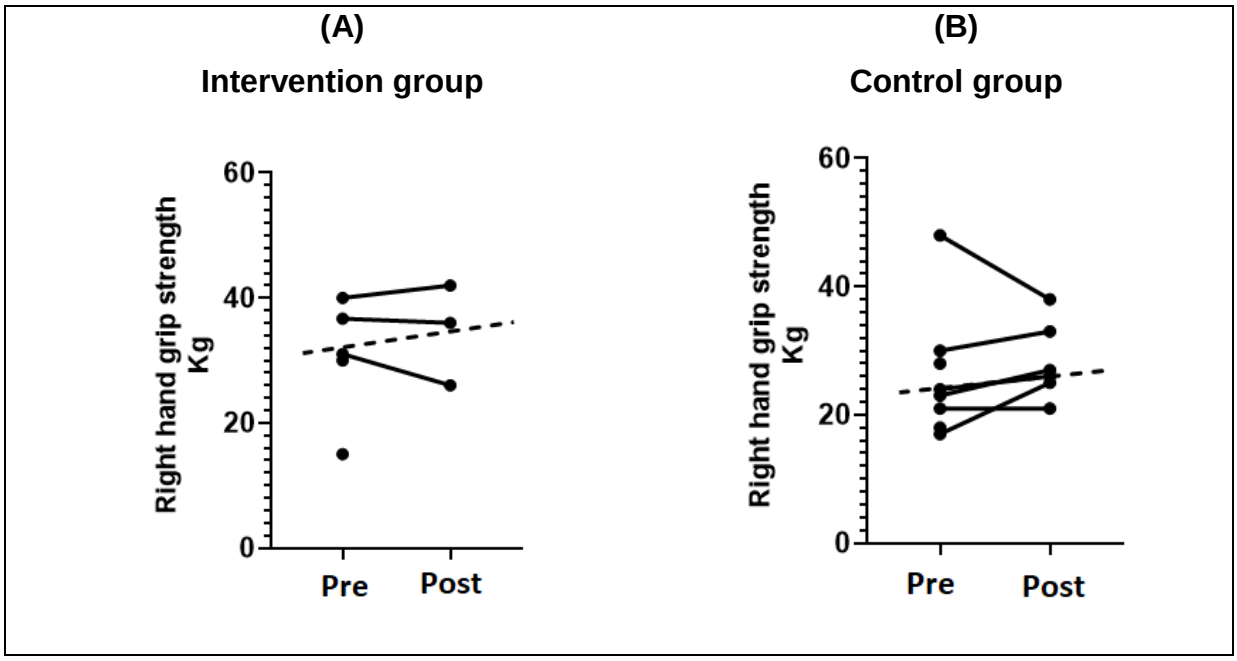


Figure 47 Change in right hand grip strength (Kg).

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.3.1.2 Left hand grip strength

In the intervention group, none of the participants (0 of 3) had a low left handgrip strength before the pulmonary rehabilitation programme + IMT, and none of the participants (0 of 3) had low left handgrip strength after the programme + IMT. In the control group, one of six participants had low left handgrip strength before the pulmonary rehabilitation programme, while one of six participants had low left handgrip strength after the programme (see Figure 48).

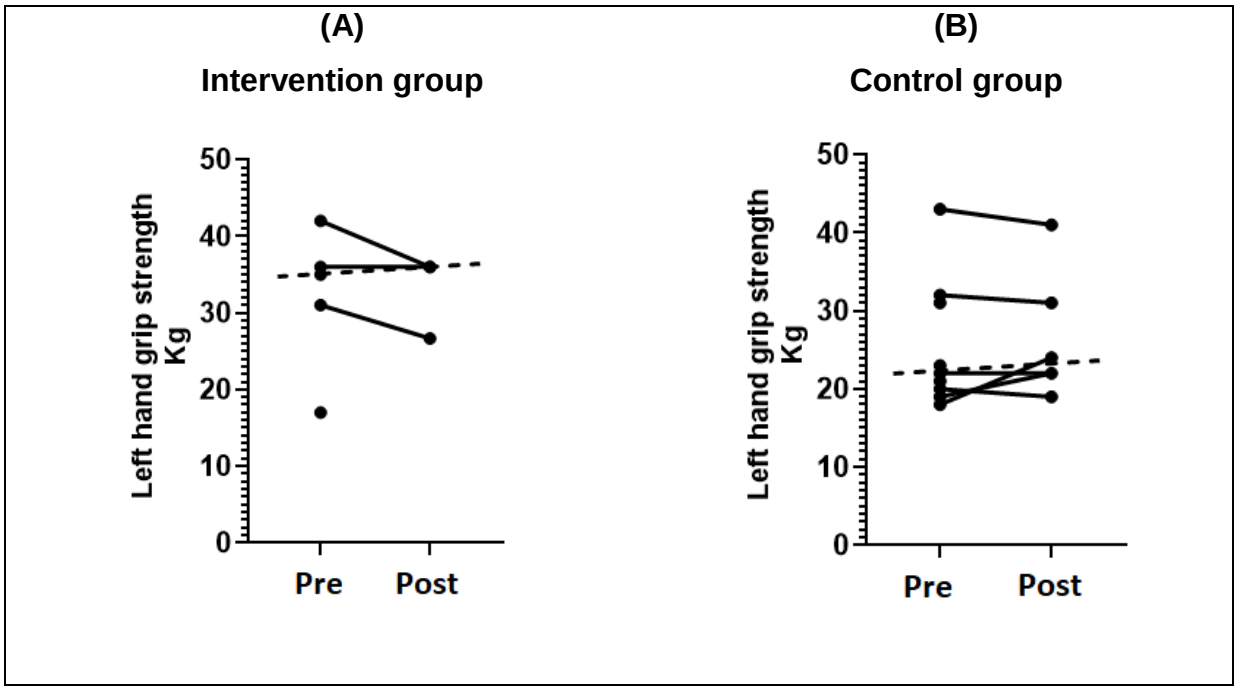


Figure 48 Change in left hand grip strength (Kg).

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.3.2 Muscle quantity: Bioimpedance analysis

Muscle quantity was evaluated with a bioimpedance analysis device, the Tanita MC780 (see Figure 49). Based on the EWGSOP2's definition, none of the participants (0 of 3) in the intervention group had low muscle quantity before the pulmonary rehabilitation programme + IMT; none of the participants (0 of 3) had low muscle quantity after the programme + IMT. In the control group, one of six participants had low muscle quantity before the pulmonary rehabilitation programme, and one of six participants showed low muscle quantity after the programme.

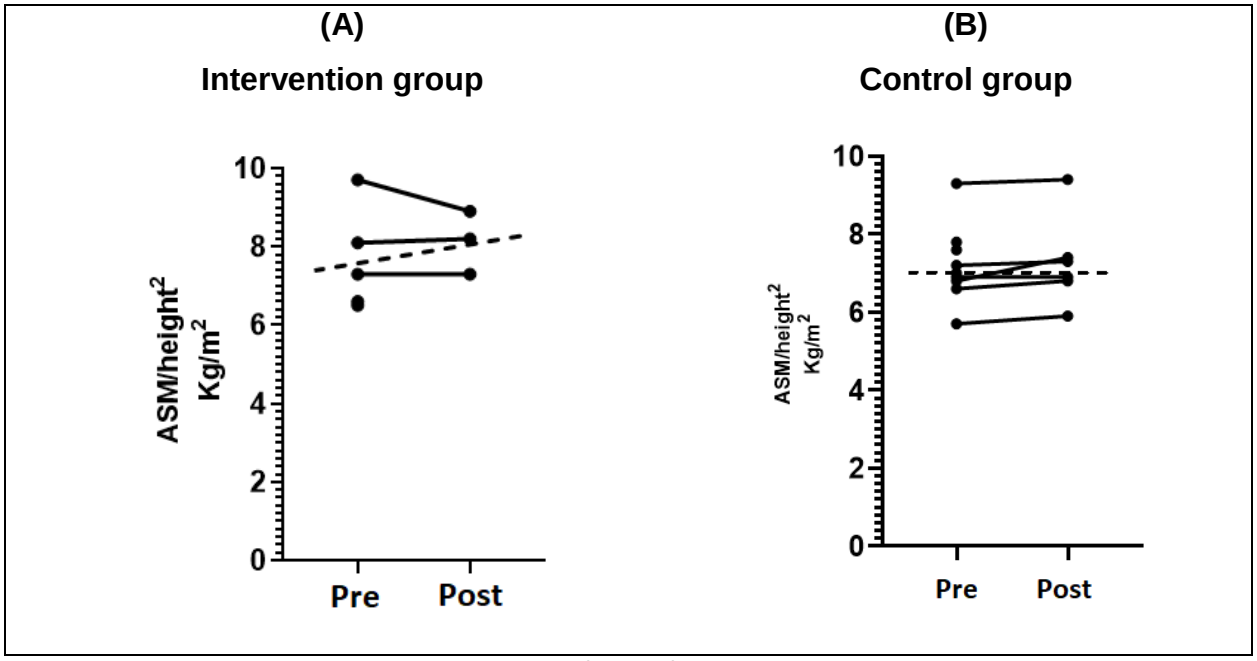


Figure 49 Change in muscle quantity ASM/height^2 (kg/m^2).

Data are given as individual values. The black dotted lines represent pre and post median values. Graph (A) Pre and post data for the intervention group. Graph (B): Pre and post data for the control group.

5.3.3.3 Physical Performance: four-metre gait speed

Physical performance was assessed in this study by four-metre gait speed (see Figure 50). Based on the EWGSOP2's definition, the intervention group had no participants (0 of 3) with low gait speed before the pulmonary rehabilitation programme + IMT and likewise none (0 of 3) after the programme + IMT. The control group had one of six participants with decreased gait speed before the pulmonary rehabilitation programme and none (0 of 6) with decreased gait speed after the programme.

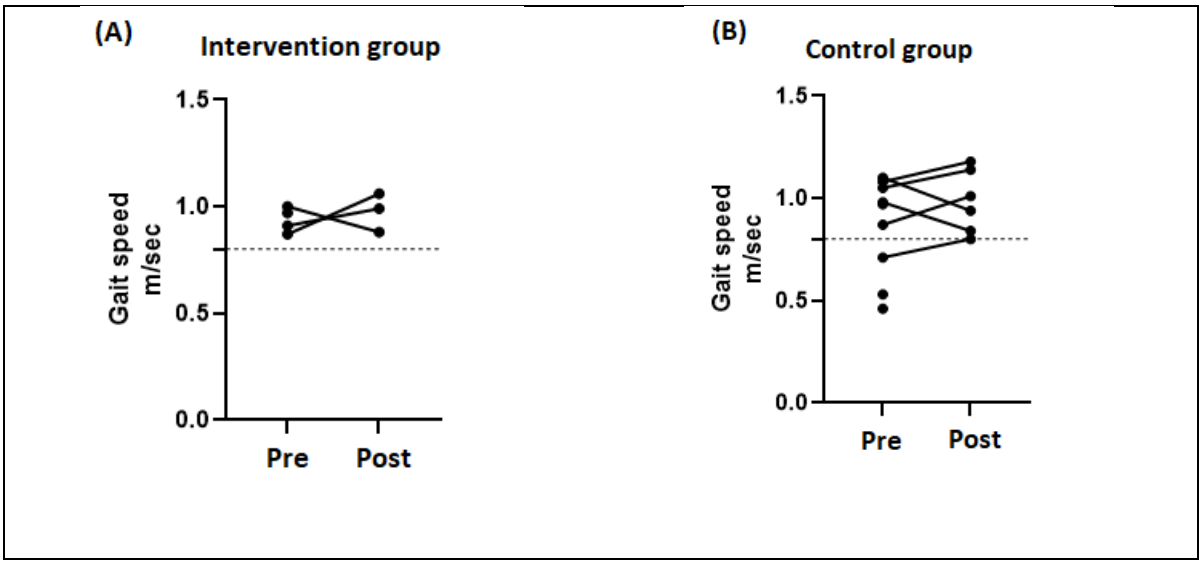


Figure 50 Change in gait speed (m/sec).

The data represent individual values. Graph A: intervention group pre and post data. Graph B: control group pre and post data. The horizontal dashed line represents low physical performance based on the EWGSOP2's 2019 definition of Sarcopenia.

Table 21 Descriptive statistics of PA outcome variables pre and post pulmonary rehabilitation programme.

Outcomes	**Intervention group n=3**			**Control group n=8**		
Median (interquartile range)	Pre	Post	Change	Pre	Post	Change
Steps count	4,516 (1,828–5,477)	4,794 (4,466–5,123)	**278**	4,870 (3,236–5,456)	4,665 (2,811–5,041)	–205
Sleep time/week (minutes)	3,063 (2,785–3,909)	2,856 (2,088–3,624)	–207	2,673 (2,339–2,987)	2,976 (2,469–3,891)	303
Sedentary time/week (minutes)	4,938 (4,758–5,694)	5,364 (4,596–6,132)	426	4,956 (4,739–5,402)	5,352 (4,206–5,955)	396
Light activity/week (minutes)	904.2 (495–1,739)	1,087 (609-1,565)	**183**	1,868 (1,325-2,130)	1,174 (920.1–1,768.0)	–694
MVA/week (minutes)	325.2 (214.8–490.2)	340.5 (277.8-403.2)	**15.3**	255.6 (201.5–324.2)	226.2 (206.4–402.6)	–28.8

The data are presented as medians (interquartile range). Bolded and underlined indicates positive improvement. Abbreviations: MVA, moderate and vigorous activity time.

Table 22 Descriptive statistics of sarcopenia outcome variables pre and post pulmonary rehabilitation programme.

Outcomes	**Intervention group n=5**			**Control group n=9**		
Median (interquartile range)	**Pre**	**Post**	**Change**	**Pre**	**Post**	**Change**
Grip strength (right hand) (kg)	31 (22.5–38.4)	36 (26–42)	**5**	23 (19.5–29.0)	26.5 (24.0–34.3)	**3.5**
Grip strength (left hand) (kg)	35 (24–39)	36 (26.7–36.0)	**1**	22 (19.5–31.5)	23 (21.3–33.5)	**1**
ASM/height^2 (kg/m^2)	7.3 (6.6–8.9)	8.2 (7.3–8.9)	**0.9**	7 (6.7–7.7)	7.1 (6.6–7.9)	**0.1**
Four-metre gait speed (m/sec)	0.97 (0.89–1.00)	0.99 (0.88–1.06)	**0.02**	0.97 (0.62–1.07)	0.98 (0.83–1.15)	**0.01**
Sarcopenia	1 of 5 (20%) participants with probable sarcopenia	1 of 3 (33.3%) participants with probable sarcopenia	-	2 of 9 (22.2%) participants with either sarcopenia or probable sarcopenia	1 of 6 (16.7%) participants with sarcopenia	-

The data are presented as medians (interquartile range). Bolded and underlined indicates positive improvement. Abbreviations: ASM/height^2, appendicular skeletal muscle mass divided by the square height

Table 23 Change post pulmonary rehabilitation programme of PA data in all participants of the study.

	Diagnosis	**Steps count**	**MVA/week** MCID of 26 minutes	**Sedentary time minutes/week**	**Light activity minutes/week**
101	CPFE	+407	–13.8	–726	–877.8
102	CPFE	+607	–87	–1,098	–118.8
103	CPFE	–2,016.14	–81	–750	–623.0
104	CPFE	Dropout	Dropout	Dropout	Dropout
105	CPFE	Dropout	Dropout	Dropout	Dropout
106	CPFE	Dropout	Dropout	Dropout	Dropout
107	CPFE	Dropout	Dropout	Dropout	Dropout
108	CPFE	Dropout	Dropout	Dropout	Dropout
109	CPFE	–1,011	–47.4	+1,194	–174.0
110	HP	–1433.57	28.2	+1,164	+841.8
111	HP	–1,656	–11.4	+1,086	–1,311.6
112	IPF	Missing data	Missing data	Missing data	Missing data
113	CTD-ILD	Missing data	Missing data	Missing data	Missing data
114	IPF	–467.72	240	414	–564.6

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; HP, hypersensitivity pneumonia; IPF, idiopathic pulmonary fibrosis; CTD-ILD, connective tissue disease type interstitial lung diseases; MVA, moderate and vigorous activity time; MCID, minimal clinical important difference.

Table 24 Change post pulmonary rehabilitation programme in Sarcopenia data in all participants of the study.

	Diagnosis	**Grip strength (Rt hand)**	**Grip strength (Lt hand)**	**ASM/height^2**	**Gait speed**	**Pre sarcopenia**	**Post sarcopenia**
101	CPFE	2.0	–1.0	0.0	0.1	Sarcopenia	Sarcopenia
102	CPFE	–5	–4.33	0.1	0.19	No sarcopenia	Probable sarcopenia
103	CPFE	8.0	6.0	0.2	–0.16	No sarcopenia	No sarcopenia
104	CPFE	Dropout	Dropout	Dropout	Dropout	No sarcopenia	Dropout
105	CPFE	Dropout	Dropout	Dropout	Dropout	No sarcopenia	Dropout
106	CPFE	Dropout	Dropout	Dropout	Dropout	Probable sarcopenia	Dropout
107	CPFE	Dropout	Dropout	Dropout	Dropout	Probable sarcopenia	Dropout
108	CPFE	Dropout	Dropout	Dropout	Dropout	No sarcopenia	Dropout
109	CPFE	2.0	0.0	0.0	0.08	No sarcopenia	No sarcopenia
110	HP	0.0	3.0	0.6	0.14	No sarcopenia	No sarcopenia
111	HP	4.0	0.0	0.2	0.09	No sarcopenia	No sarcopenia
112	IPF	–10.0	–2.0	0.1	–0.14	No sarcopenia	No sarcopenia
113	CTD-ILD	–0.7	–6.0	–0.8	–0.12	No sarcopenia	No sarcopenia
114	IPF	3.0	–1.0	0.1	0.09	No sarcopenia	No sarcopenia

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; HP, hypersensitivity pneumonia; IPF, idiopathic pulmonary fibrosis; CTD-ILD, connective tissue disease type interstitial lung diseases; ASM/height2, appendicular skeletal muscle mass divided by the square height.

5.4 Discussion

5.4.1 Physical activity

This chapter described the assessment of PA in patients with ILDs using an accelerometer device, providing rare data in this patient group. The patients well tolerated the assessment of PA, indicating that this is a practical way of gathering individual multifactorial data in future studies.

A baseline median average daily steps count of 4,516 was observed in the intervention group and 4,870 in the control group. A recent study (Shingai et al., 2021) reports that patients with ILD who walked 3,473 steps/day (the cutoff point) had a lower mortality than patients walking more than 3,473 steps/day. All the participants in the present study had a baseline daily steps count exceeding the 3,473 cutoff except for three participants; one dropped out of the study, and the other two had advanced disease based on lung function results. (see Table 21) shows published PA data of patients with ILD or IPF. The participants in our study generally maintained their step counts, with a trend towards a slight decrease in daily step counts after the pulmonary rehabilitation programme with or without IMT.

The GENEActiv watch also captured information on time spent in sedentary activity. A previous study by Atkins et al. report that a wrist-worn GENEActiv watch provides a feasible measure of sedentary time in patients with IPF; they recorded a mean of 551.7 minutes/day spent in sedentary time (Atkins et al., 2018). Our study observed a median sedentary time of 4,938 minutes/week (or 705 minutes/day) (see Table 21), which is higher than that reported by Atkins et al. This may be attributable to our participants' having more advanced disease, with a predicted FVC and DLCO percentage of 73.14 and 43.5%, respectively, compared to 82.7 and 51.6%, respectively, in Atkins et al. (2018). Those authors included patients with IPF in their study, while our study included patients with ILD. Atkins et al. also identified 6MWD as a predictor of activity in patients with IPF (Atkins et al., 2018).

A recent study by Hur et al. identified a minimal important difference (MID) of 26 minutes of moderate to vigorous physical activity (MVPA) per week using a waist-worn activity monitor in patients with ILD (Hur et al., 2019). This MID of 26 minutes was achieved in two participants in the control group that underwent a pulmonary rehabilitation programme and in none of the participants in the intervention group that

underwent a pulmonary rehabilitation programme + IMT. Thus, a meaningful improvement in MVA was achieved by those two participants in the control group. Three participants—two from the intervention group and one from the control group—had a meaningful decrease in MVA (see Table 23)).

Patients with IPF have decreased levels of daily PA. Prasad et al. recently conducted a study evaluating PA in such patients and its change over a 12-month period. They report a mean daily steps count of 3,887, which is lower than our study's median of 4,667 steps/day. Those authors also report an MVA of 17.4 minutes/day, which is likewise lower than in our study (median=285 min/week or 40.7 minutes/day). The sedentary time in their study, 1,243 minutes/day, was lower than ours (median=4,938 minutes/week or 705 minutes/day). The participants in our study exhibited a better PA level than those in Prassad et al., which may be attributed to several causes. Those authors included only patients with IPF in their study, while ours had patients with ILD. Their participants had a slightly more advanced lung disease, with a predicted FVC of 69.9% compared to our study's predicted FVC of 73.14%. They found that, over a 12-month period, the decrease in PA was greater than the decrease in lung function, which suggests that PA should be considered as an additional measure in assessing disease prognosis and severity in IPF (Prasad et al., 2021). Bahmer et al. evaluated the clinical correlates of decreased PA in patients with IPF, the participants used an armband accelerometer for seven days. The PA parameters were steps per day (SPD), minutes of at least moderate activity and physical activity level which was calculated as total daily energy expenditure divided by sleep time energy expenditure. Their results show that fatigue as measured by the Multidimensional Fatigue Inventory (MFI-20) was a predictor of SPD. A one-point increase in MFI-20 was related to a 120 step reduction in patients with IPF, indicating that fatigue may limit routine PA in IPF. The authors also discovered that health-related quality of life and generic quality of life were predictors of daily PA. Lung function and exercise capacity as measured by 6MWT are also reported by Bahmer et al. as predictors of daily PA in patients with IPF. They describe a significant association between exercise capacity and PA. Their findings indicate that both patient-reported outcome questionnaires and clinical functional measures were able to identify patients with IPF who had impaired daily PA (Bahmer et al., 2016). The authors also evaluated the longitudinal change and prognosis of PA in patients with IPF and report the novel finding that PA is a predictor

of mortality. Furthermore, they found that PA as measured by daily steps count decreased by almost half in patients with IPF at three-year follow-up (Bahmer et al., 2017).

Wallaert et al. were the first to assess daily PA and its relationship to clinical characteristics in patients with fibrotic idiopathic interstitial pneumonia (Wallaert et al., 2013). Both they and Nakayama et al. found an association between PA and exercise capacity (Nakayama et al., 2015, Wallaert et al., 2013). Others have shown that, in patients with IPF, PA as measured by daily steps has a greater effect on 6MWD than quadriceps force and physiological lung function (Morino et al., 2017).

In our study, PA data from participants with ILD undergoing a pulmonary rehabilitation programme with or without IMT were assessed using an accelerometer. The PA outcomes of our participants were heterogenous, with a trend towards a decrease or maintenance of PA levels after the pulmonary rehabilitation programme (see Table 21). ILDs are a group of progressive lung diseases, which may explain the slight decrease in PA levels; maintaining PA levels is a reasonable goal of a pulmonary rehabilitation programme

Table 25 Published studies evaluating PA level in patients with ILDs or IPF.

Articles	Participants (n)	FVC %	TLCO %	Accelerometer	Daily steps count	MVA	Sedentary time (minutes)
Our study	11 ILD	73.1 (26.7)	43.5 (13.5)	GENEActive Actiwatch	4,667 (3,102–5,477)	285 (211.8–325.2) min/week	4,938 (4,758–5,412) min/week
(Atkins et al., 2018)	39 IPF	82.7 (17.8)	51.6 (14.4)	GENEActiv Actiwatch	-	-	551.7 (403.1–765.3) min/day
(Prasad et al., 2021)	54 IPF	69.9 (16.7)	46 (16.6)	SenseWear Armband	3,887 (395)	17.4 (3.1)	1,243 (17.9)
(Bahmer et al., 2017)	46 IPF Survivors	85.1 (21.4)	48.7 (13.5)	SenseWear Armband	6,606 (3,064)	-	-
	Non-survivors	64.3 (17.2)	35.9 (12.9)		3,433 (2,655)		
(Bahmer et al., 2016)	48 IPF	75.4 (22.9)	43.1 (14.6)	SenseWear Armband	5,017 (3,360)	90.4 (36.3–146.0) min/day	-
(Nakayama et al., 2015)	31 IPF	88.7 (20.5)	78.8 (21.8)	Lifecorder GS uniaxial physical activity monitor (waist)	6,520 (3,340)	?	-

(Wallaert et al., 2013)	50 FIIP	71 (21)	37 (13)	SenseWear Armband	4,157 (3,014)	149 (149) min/day	-
(Morino et al., 2017)	38 IPF	88.2 (19.6)	47.8 (17.0)	Kenz Lifecorder uniaxial accelerometer (waist)	5,148.4 (3,295.7)	-	-

Abbreviations: ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; FIIP, fibrotic idiopathic interstitial pneumonia; FVC%, forced vital capacity percentage predicted; TLCO%, transfer factor of carbon monoxide percentage predicted; MVA, moderate and vigorous activity time.

5.4.2 Sarcopenia

The prevalence of sarcopenia in our cohort of patients with ILD was 21.42% before and 22.22% after the pulmonary rehabilitation programme. The global prevalence of sarcopenia has been reported as 10% using the EWGSOP2 definition (Petermann-Rocha et al., 2022). Hanada et al. report a 30% prevalence of sarcopenia in patients with ILD in a Japanese cohort (Hanada et al., 2022). Fujito et al. also assessed the prevalence of sarcopenia in a Japanese cohort of patients with IPF and report a 39.3% prevalence (Fujita et al., 2022). Both these studies found a slightly higher prevalence of sarcopenia than ours, but they were conducted in Japanese cohorts and used the Asian Working Group for Sarcopenia (AWGS) 2019 definition (Chen et al., 2020). Moreover, Faverio et al. report a prevalence of sarcopenia (22.9%) similar to that in our study in patients with IPF from nine hospitals in northern Italy using the EWGSOP2 definition (as in this study); they also show that sarcopenia was significantly associated with a sedentary lifestyle and advanced severity of disease (Faverio et al., 2022). Fujita et al. also found an association between sarcopenia and patients' reported outcomes and physical performance as assessed by a six-minute walk test (Fujita et al., 2022).

In our study, all sarcopenia determinant outcomes—muscle strength, muscle mass, and physical performance—either slightly improved or were maintained after a pulmonary rehabilitation programme with or without IMT(see Table 22). Our data show that attending an ILD pulmonary rehabilitation programme was associated with a slightly improved and/or maintained skeletal muscle function in patients with ILD. This supports the value and importance of pulmonary rehabilitation for patients with ILD.

Table 26 Published studies evaluating sarcopenia in patients with ILDs or IPF

Article	Participants	FVC%	TLCO%	Sarcopenia criteria	Prevalence of sarcopenia
Our study	14 ILD UK	73.14 (26.71)	43.5 (13.45)	EWGSOP2	21.42% (n=3)
(Hanada et al., 2022)	78 ILD Japan	85 (68–97)	64 (45–80)	AWGS 2019	32.1% (n=25)
(Fujita et al., 2022)	56 IPF Japan	80.1 (16.2)	66.4 (18.5)	AWGS 2019	39.3% (n=22)
(Faverio et al., 2022)	83 IPF Italy	85.7 (21.3)	54.2 (18.6)	EWGSOP2	22.9% (n=19)

Abbreviations: ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; FVC%, forced vital capacity percentage predicted; TLCO%, transfer factor of carbon monoxide percentage predicted; EWGSOP2, the European Working Group on Sarcopenia in Older People's; AWGS, the Asian Working Group for Sarcopenia.

5.5 Conclusion

In this pilot randomised controlled trial study, accelerometer data were collected from patients with ILD participating in a pulmonary rehabilitation programme with or without IMT. The PA outcomes of the participants were variable, with a trend towards a maintenance or a decrease of PA levels following the pulmonary rehabilitation program. ILD's are a group of progressive lung diseases, which may explain the slight decline in PA levels; an improvement or maintenance of PA levels is a reasonable goal for this group of patients as a result of their participation in a pulmonary rehabilitation programme. This study demonstrated the feasibility of using an accelerometer to capture PA data from patients with ILD participating in a pulmonary rehabilitation programme. Patients tolerated the PA assessment well, indicating that this is a feasible method for collecting individual multifactorial data in future research. Increasing evidence supports the use of PA level data as an additional measure for determining the prognosis and severity of IPF. This may have implications for clinical practise as step counts (a measure of PA level) are readily accessible to patients via a variety of devices, including fitness monitoring watches and smartphones. Typically, the memory capacity of these devices ranges from seven days to several months.

Consequently, clinicians can evaluate the status of patients when they attend clinical appointments. Prior to this study, the effect of pulmonary rehabilitation program on sarcopenia outcomes in patients with ILD was unknown. Very few studies have been published evaluating sarcopenia in patients with ILD or IPF (see Table 26), and none evaluating the effect of PRP on sarcopenia in this group of patients, which makes these preliminary data valuable. Our cohort of patients showed a trend towards maintenance or slight improvement of their sarcopenia parameters (muscle strength, muscle quantity, and physical performance) after the pulmonary rehabilitation programme (see Table 22). Sarcopenia may be prevented or treated in patients with ILD through PRP which supports the value and importance of PRP in this group of patients. Further studies with larger sample sizes are required to test this important question. This study demonstrates that it is practicable to collect sarcopenia measurements in a range of patients with ILD, including some patients with CPFE attending PRP. Future randomised controlled trials evaluating PRP in patients with ILD should consider assessing sarcopenia outcomes that may be improved due to the exercise training and nutritional guidance provided during PRP.

Chapter 6: Feedback from Patients with ILD Attending Pulmonary Rehabilitation Programme

6.1 Introduction

One of the aims in my PhD was to evaluate the feasibility of inspiratory muscle training as part of a pulmonary rehabilitation programme in patients with ILD, including some patients with CPFE. Although we have collected quantitative data evaluating this aim as shown in chapters four and five, we have also complimented this with collected qualitative feedback from patients using a feedback form with three open ended questions. The questions inquired about the positives, difficulties, and suggestions for improving the programme as perceived by this group of patients with ILDs including some with CPFE.

The insights gained from patients with ILD and their views of the provided pulmonary rehabilitation programme provides key information for the health care providers who must interact with these patients. It will assist health care providers to better understand the patients' expectations and needs and concerns in order to provide better treatment. Therefore, adjusting pulmonary rehabilitation programmes for patients with ILD according to patients needs and constrains may result in improving adherence to pulmonary rehabilitation programmes (Arnold et al., 2006).

In this chapter we aimed to gather feedback on the pulmonary rehabilitation programme using a simple written survey with open-ended questions in patients with ILD, including some with CPFE.

6.2 Methods

A feedback form regarding the ILD rehabilitation programme was given to all participants at the end of the programme. The feedback form had the following three open ended questions:

Question 1: As a participant in the programme, what is/are the thing(s) you liked the most?

Question 2: As a participant in the programme, what is/are the thing(s) you hated the most?

Question 3: As a participant in the programme, what is/are the thing(s) that would like us to change or improve?

In order to describe patients' responses to the open-ended questions on the feedback form, a word cloud was generated for each question using Word Cloud Plus webpage (Wordcloudplus, 2023).

6.3 Results

Out of the 14 participants who were enrolled into the study, 9 participants completed the programme and were given a feedback form to be completed at the end of the pulmonary rehabilitation programme for both control and intervention group.

6.3.1 Question 1: As a participant in the programme, what is/are the thing(s) you liked the most?

Figure 51 Word cloud question 1 feedback form.

Question 1: As a participant in the programme, what is/are the thing(s) you liked the most?

The first question asked participants what are the things they liked the most(see Figure 51).

The thematic analysis of the responses to the first question regarding the things participants liked the most identified three themes: “exercises”, “meeting others with same disease”, and “education”.

6.3.1.1 Exercises

Patients with ILD and CPFE who participated in this study liked the exercises provided at the pulmonary rehabilitation programme. One participant mentioned “exercise program was excellent” *Participant 114.* Participants also mentioned that they liked the staff providing instructions on exercises. One participant stated, *“I like how each*

participant in group was paced differently depending on his condition and how Fran adjusted everyone exercises based on their condition" *Participant 109*.

6.3.1.2 Meeting others with same disease

A lot of the participants have mentioned that they liked meeting other people with the same condition/problem as them. The ILDs are a rare grouo of diseases, so study participants valued the opportunity to meet others with the same condition. One participant stated "Meeting people who have the same problems as me" *Participant 111*.

6.3.1.3 Education

Participants also liked learning information provided during the educational component of the programme. Participants have also liked the friendly atmosphere. "Learning about lung pathology plus how to deal with them" *Participant 113*.

6.3.2 Question 2: As a participant in the programme, what is/are the thing(s) you hated the most?

Figure 52 Word cloud of question 2 feedback form.

Question2: As a participant in the programme, what is/are the thing(s) you hated the most?

The second question of the feedback form asked participants about what they hated in the programme(see Figure 52). The thematic analysis of the responses to the second question regarding the things participants hated the most revealed two themes: “None” and “facility”.

6.3.2.1 None:

Most of the responses from the participants on this question was nothing/none. There were no recurring complaints from participants. One participant stated “Nothing really, it was actually better than I expected” *Participant 102*.

6.3.2.2 Facility:

One participant mentioned that she did not like the muscle strength measurement done using a handheld dynamometer microFET on pre and post measurement days. Difficulty of parking was mentioned by a participant. “I did not like the things pressed against muscles to measure your strength. Difficulty parking. Nothing else really” *Participant 110*. One participant said that he did not like that was not able to push himself more in the programme.

6.3.3 Question 3: As a participant in the programme, what is/are the thing(s) that would like us to change or improve?

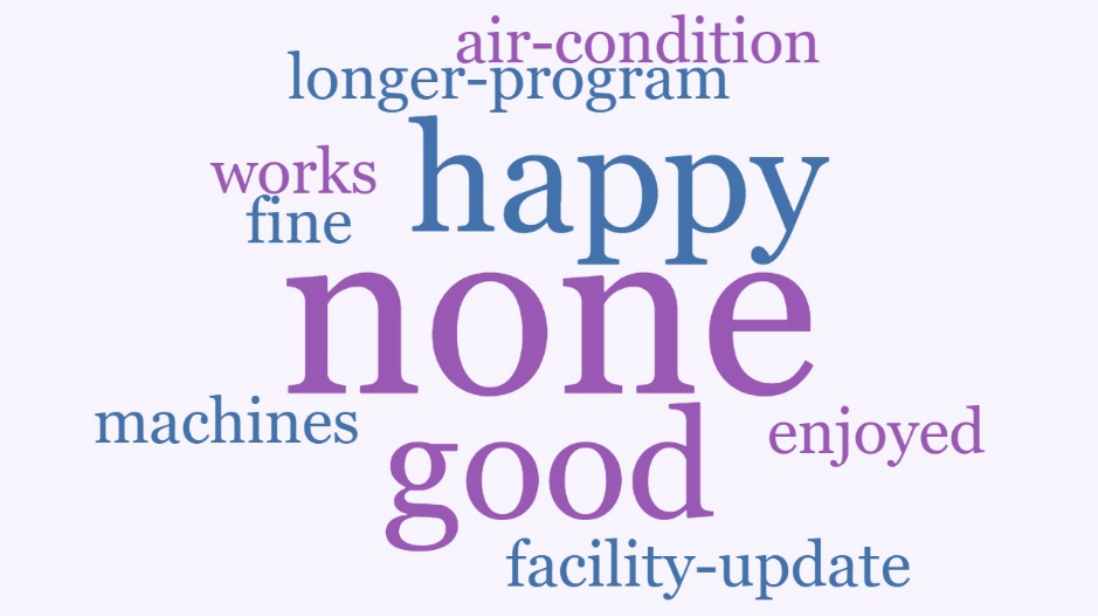


Figure 53 Word cloud of question 3 feedback form.

Question3: As a participant in the programme, what is/are the thing(s) that would like us to change or improve?

The third question of the feedback form was asking the participants what are the things to change or improve in the programme (see Figure 53). Thematic analysis of the responses to the third question regarding what are the things to change or improve in the programme identified two themes: “nothing to change” and “facility and program duration”.

6.3.3.1 Nothing to change:

Most of the participants replied that there is none/nothing they would change as one participant stated “None, quite happy with everything” *Participant 101*.The majority of the participant had no suggestions for a needed change to improve the programme.

6.3.3.2 Facility and program duration:

.One participant mentioned that a facility update is needed for air conditioning. During the summertime the Gym room at the RVI where the pulmonary rehabilitation programme was being conducted, had no air conditioning and became uncomfortable. Another participant stated, “*The only thing I would change is to make the programme*

longer, I enjoyed it that much” Also, one participant mentioned that the Easi-Breathe inhaler had helped through the programme.

6.4 Discussion

This chapter showed that patients with ILD including some with CPFE attending pulmonary rehabilitation programme valued the exercises provided during the sessions, staff supervisions, individualised programme, meeting other people with same condition, and the educational sessions. Participants were generally satisfied with no suggestions for change except for a longer duration programme, and facility update including air conditioning. The feedback therefore endorsed our strategy of combining education and functional conditioning approaches, in an holistic attempt to help patients with ILD including some with CPFE.

Hoffman et al. have recently published a study evaluating referral to pulmonary rehabilitation programme for patients with ILD and patient experience. They have conducted semi-structured interviews using open-ended questions to interview patients with ILD who were referred to pulmonary rehabilitation. Qualitative interviews revealed that the most valued aspects of pulmonary rehabilitation were the constant supervision and individualization of the programme, improved self confidence in performing exercises, and the educational sessions (Hoffman et al., 2021b). In our study patients with ILD that participated in a pulmonary rehabilitation programme liked the exercises provided during the programme. One participant stated *"I like how each participant in group was paced differently depending on his condition and how Fran adjusted everyone exercises based on their condition*". Hoffman et al. have reported similar findings as participants in their study valued the individualized programmes with supervision provided from a health care professional (Hoffman et al., 2021b).

In our study a lot of the participants mentioned that they liked meeting other people with the same lung condition as they had. Interstitial lung diseases including CPFE are considered rare disease, so the opportunity to meet others with the same condition was valued by the participants in this study. Hoffman et al. have also reported similar findings as almost all the participants in their study mentioned that the interaction with other participants at the pulmonary rehabilitation programme motivated them to complete the programme. Exercising alongside peers who also had similar lung disease was noted as an additional motivator to perform the activities during the session and enabled them to share experience of disease management and symptoms (Hoffman et al., 2021b). Similar finding were also reported by others in patients with COPD (de Sousa Pinto et al., 2013).

Participants in our study also liked learning information provided during the pulmonary rehabilitation programme educational sessions. Similarly, Hoffman et al. also reported that participants in their study valued the educational sessions. Participants in our study also liked the friendly atmosphere and they liked the staff providing pulmonary rehabilitation programme. Hoffman et al. study participants also valued the supervision provided by health care professionals. They felt safe to perform the exercise programme due to the presence of the physiotherapist and the regular monitoring of their oxygen saturation and heart rate (Hoffman et al., 2021b).

The second question on the feedback form inquired about the aspects of the programme that participants did not like. Most of the participants responded with nothing or none. Difficulty in parking was mentioned by one of the participants in this study. This was also reported in patients with COPD undergoing pulmonary rehabilitation, as reported by a systematic review of qualitative research (de Sousa Pinto et al., 2013).

The third question on the feedback form asked about what are the thing that need to be changed or improved in the programme. Participants in this study replied mostly with nothing. There is a limitation in using written feedback forms with open-ended questions as sometimes participants reply with nothing to change or all good, it is possible that well conducted interviews would provide more insights. One participant's statement was "*The only thing I would change is to make the programme longer, I enjoyed it that much*". There were suggestions to update the machines and have air conditioning from one of our participants.

Although in our study we used a written survey with open-ended questions our findings are in accordance with that reported by Hoffman et al. using semi structured interviews of 21 patients with ILD (Hoffman et al., 2021b).

6.5 Conclusion

Patients with ILD including some with CPFE attending our pulmonary rehabilitation programme valued the exercise, meeting others with same lung disease, and the educational sessions. As demonstrated in Chapter 3 of this thesis, ILD and specifically CPFE is a rare, uncommon lung disease; therefore, the pulmonary rehabilitation programme offered participants the chance to meet others with the same lung disease. This was greatly appreciated by the participants because it created a sense of community. The pulmonary rehabilitation programme provided the participants a place to exercise with staff supervision, learn about their disease, and form connections with others.

Although quantitative research attempts to explain the presence and strength of associations, qualitative research tends to develop an ever-expanding explanation. Qualitative studies in patients with ILD attending pulmonary rehabilitation programmes might supplement quantitative findings. For future research, a semi-structured interview for qualitative research evaluating patients with ILD and CPFE experience of pulmonary rehabilitation programme could be considered.

Chapter 7: General Discussion and Suggested Future Work

7.1 General Discussion

CPFE is a rare lung disease with limited published data describing its prevalence and characteristics. At the start of this PhD, we were unaware of the prevalence of patients with CPFE at the RVI clinic. Additionally, we were unaware of their characteristics, strength, and capacity to perform exercises as part of a pulmonary rehabilitation programme. The retrospective study showed that over a five-year period, the ILD MDT meeting in the Northeast and Northwest regions of the UK diagnosed 203 patients with CPFE out of 3,060 patients with ILD. Approximately 6.6% of ILD clinic patients are patients with CPFE, per the data. To our knowledge this is the first data describing a UK cohort of patients with CPFE with limited published data internationally as well. Patients with CPFE were relatively old, male, and had a history of smoking. IPF was the prevalent form of fibrosis in 62% of patients with CPFE. Their PFT results showed normal or mildly impaired lung volumes and decreases lungs diffusion. The results of the retrospective study in chapter 3 are of value for the ILD clinic at the RVI in order to better understand the characteristics of patients with CPFE and for conducting patient-specific resource planning for optimal CPFE management.

Our findings confirm the hypothesis that CPFE has a worse prognosis than other ILDs. This adds to a very limited published literature, which included some contradicting research, where researchers had found that CPFE did not have a poor prognosis. The retrospective study data showed that patients with CPFE have poor prognosis with a median survival time of 2.8 years for IPF subtype CPFE and 4.6 years for non-IPF subtype CPFE. The Gap index and staging system as well as the mGAP index demonstrated prognostic capability in patients with IPF subtype CPFE. This is a useful finding as the GAP index has not been widely studied in CPFE to my knowledge.

The retrospective study revealed that at least half the patients with CPFE were not referred to a pulmonary rehabilitation programme. Despite the recommendation, patients with chronic lung disease should participate in pulmonary rehabilitation. At the start of this PhD, the clinical staff at the RVI raised concerns about the ability of patients with CPFE to participate and complete a pulmonary rehabilitation programme. They had the impression that patients with CPFE are too weak to perform exercises and have poor prognosis. This demonstrated a clear need to develop and evaluate a pulmonary rehabilitation programme tailored to patients with ILD including those with

CPFE. A feasibility randomised controlled trial was conducted during this PhD that added valuable information regarding the use of IMT in conjunction with pulmonary rehabilitation in patients with ILD. With limited data on ILD patients and no data on CPFE patients, this study demonstrated the feasibility of incorporating IMT into a pulmonary rehabilitation programme for these patient populations. The data of this study showed that IMT in combination with pulmonary rehabilitation programme was feasible in patients with ILD and those with CPFE with good attendance and completion rates. No adverse events were observed during exercise training. This has reassured the pulmonary consultants and physical therapists at the RVI, that patients with CPFE are capable of participating in a pulmonary rehabilitation programme. According to data from the retrospective study in chapter 3, at least fifty percent of patients with CPFE were not being referred to pulmonary rehabilitation. The results of the feasibility study will hopefully stimulate an increase in referrals so that more patients with CPFE will be able to benefit from the pulmonary rehabilitation programme. The feasibility randomised controlled trial have also shown that PRP with or without IMT in patients with ILD could improve MIP and functional exercise capacity and further larger studies are warranted.

As part of the randomised controlled trial, PA levels were collected using an accelerometer to demonstrate the feasibility of collecting PA data from patients with ILD undergoing pulmonary rehabilitation. A growing body of evidence supports the use of PA levels data as an additional tool for determining the severity and prognosis of IPF. If PA levels indicators such as (steps counter) are established as predictors of disease prognosis in ILD, this may have important implications for clinical practice since step counts are easily accessible to patients via variety of devices, such as fitness monitoring watches and smartphones. These devices typically have a memory capacity of seven days to months, enabling clinician to assess the condition of patients during clinical appointments.

To our knowledge, this is the first study to evaluate the effect of pulmonary rehabilitation programme on sarcopenia outcomes in patients with ILD. There was a trend towards maintenance or slight improvement in sarcopenia in our cohort of patients with ILD post pulmonary rehabilitation programme. These preliminary data are of value and the first to demonstrate that pulmonary rehabilitation programmes

might be able to prevent or treat sarcopenia in patients with ILD. However, further research with larger sample size are needed.

We have received generally positive feedback from patients with ILD including some with CPFE that participated in the PRP. Our patients valued the pulmonary rehabilitation programme, it provided participants with a place to exercise under the supervision of staff, gain knowledge about their disease, and form connections with others with same disease condition.

7.2 Future work

In a scarce literature it was appropriate to perform investigations that were pilot in nature with limited samples in this thesis. The results suggest that the future studies are appropriate:

- Further work can be done on the important five-year retrospective study data set of patients with CPFE. We aim to evaluate the prognostic value of the extent of fibrosis in patients with CPFE as measured by an automated quantification of CT scan images.
- Larger multi-centre studies evaluating the effect of IMT and PRP in patients with CPFE are needed to reach conclusive results.
- It would be worth investigating the long-term maintenance of benefits and effect on survival post IMT and PRP in patients with ILD and those with CPFE.
- Future studies could aim to investigate the best exercise regime in patients with ILD and those with CPFE and this is yet unknown.

Publications, Abstracts and presentations derived from this PhD project.

Review article “Early diagnosis and treatment of idiopathic pulmonary fibrosis: a narrative review”. Alsomali H, Palmer E, Aujayeb A, Funston W. Early Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis: A Narrative Review. Pulm Ther. 2023 Jun;9(2):177-193.

A retrospective study exploring GAP index as a predictor of mortality in patients with combined pulmonary fibrosis and emphysema. Poster abstract presented at the European Respiratory Society (ERS) congress in Spain 5th of September 2022.

H Alsomali. European Respiratory Journal Sep 2022, 60 (suppl 66) 2117; DOI: 10.1183/13993003.congress-2022.2117

Successful provision of a specialised interstitial lung diseases (ILD) pulmonary rehabilitation programme during COVID-19 using recorded ILD educational videos developed by allied health professionals. Presented as a poster at the European Respiratory Society (ERS) congress in Spain 5th of September 2022.

H Alsomali, F Chambers, E Palmer, et al. European Respiratory Journal Sep 2022, 60 (suppl 66) 2152; DOI: 10.1183/13993003.congress-2022.2152

Improvement of inspiratory muscle and one minute sit to stand function associated with interstitial lung diseases pulmonary rehabilitation. Accepted as a spoken presentation at the British Thoracic Society (BTS) winter meeting 2022 23/11/2022. *Alsomali H, Chambers F, McNeillie L, et alS11 Improvement of Inspiratory Muscle and One Minute Sit to Stand function associated with Interstitial Lung Diseases pulmonary rehabilitationThorax 2022;77:A10-A11*

A retrospective study exploring GAP index as a predictor of mortality in patients with combined pulmonary fibrosis and emphysema presented as a poster at the British Thoracic Society (BTS) winter meeting 2022 23/11/2022.

Alsomali H, Funston W, Wiscombe S, et alP24 A retrospective study exploring GAP index as a predictor of mortality in patients with combined pulmonary fibrosis and emphysema Thorax 2022;77:A93.

I have participated in The Three Minute Thesis competition and was selected as one of the finalists from the medical school, Newcastle University 15th June 2022.

I have given a presentation “Pulmonary rehabilitation in interstitial lung diseases” for the medical students and doctors of the NHS on their Monday teaching session 8th August 2022.

A retrospective study exploring GAP index as a predictor of mortality in patients with combined pulmonary fibrosis and emphysema. Poster abstract presented at the Institute of Cellular Medicine (ICM) Directors Day 14th September 2018.

References

2002. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med,* 166**,** 111-7.

ADEGUNSOYE, A., OLDHAM, J. M., BELLAM, S. K., MONTNER, S., CHURPEK, M. M., NOTH, I., VIJ, R., STREK, M. E. & CHUNG, J. H. 2019. Computed Tomography Honeycombing Identifies a Progressive Fibrotic Phenotype with Increased Mortality across Diverse Interstitial Lung Diseases. *Ann Am Thorac Soc,* 16**,** 580-588.

AGUSTI, A. G., ROCA, J., GEA, J., WAGNER, P. D., XAUBET, A. & RODRIGUEZ-ROISIN, R. 1991. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis,* 143**,** 219-25.

AIELLO, M., BERTORELLI, G., BOCCHINO, M., CHETTA, A., FIORE-DONATI, A., FOIS, A., MARINARI, S., OGGIONNI, T., POLLA, B., ROSI, E., STANZIOLA, A., VARONE, F. & SANDUZZI, A. 2017. The earlier, the better: Impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther,* 44**,** 7-15.

AJRCCM. 1999. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med,* 159**,** S1-40.

AKIRA, M., INOUE, Y., ARAI, T., OKUMA, T. & KAWATA, Y. 2011. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. *Thorax,* 66**,** 61-5.

AKIRA, M., YAMAMOTO, S., INOUE, Y. & SAKATANI, M. 2003. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. *AJR Am J Roentgenol,* 181**,** 163-9.

ALBERA, C., COSTABEL, U., FAGAN, E. A., GLASSBERG, M. K., GORINA, E., LANCASTER, L., LEDERER, D. J., NATHAN, S. D., SPIRIG, D. & SWIGRIS, J. J. 2016. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. *Eur Respir J,* 48**,** 843-51.

ARIZONO, S., TANIGUCHI, H., SAKAMOTO, K., KONDOH, Y., KIMURA, T., KATAOKA, K., OGAWA, T., WATANABE, F., TABIRA, K. & KOZU, R. 2017. Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis: comparison with chronic obstructive pulmonary disease. *Sarcoidosis Vasc Diffuse Lung Dis,* 34**,** 283-289.

ARMSTRONG, M. & VOGIATZIS, I. 2019. Personalized exercise training in chronic lung diseases. *Respirology,* 24**,** 854-862.

ARNOLD, E., BRUTON, A. & ELLIS-HILL, C. 2006. Adherence to pulmonary rehabilitation: A qualitative study. *Respir Med,* 100**,** 1716-23.

ATKINS, C., BAXTER, M., JONES, A. & WILSON, A. 2018. Measuring sedentary behaviors in patients with idiopathic pulmonary fibrosis using wrist-worn accelerometers. *Clin Respir J,* 12**,** 746-753.

BAHMER, T., KIRSTEN, A. M., WASCHKI, B., RABE, K. F., MAGNUSSEN, H., KIRSTEN, D., GRAMM, M., HUMMLER, S., BRUNNEMER, E., KREUTER, M. & WATZ, H. 2016. Clinical Correlates of Reduced Physical Activity in Idiopathic Pulmonary Fibrosis. *Respiration,* 91**,** 497-502.

BAHMER, T., KIRSTEN, A. M., WASCHKI, B., RABE, K. F., MAGNUSSEN, H., KIRSTEN, D., GRAMM, M., HUMMLER, S., BRUNNEMER, E., KREUTER, M. & WATZ, H. 2017. Prognosis and longitudinal changes of physical activity in idiopathic pulmonary fibrosis. *BMC Pulm Med,* 17**,** 104.

BARADZINA, H. 2013. Shot and long-term effects of pulmonary rehabilitation program in sarcoidosis. *European Respiratory Journal,* 42**,** P3788.

BARRATT, S. L., CREAMER, A., HAYTON, C. & CHAUDHURI, N. 2018. Idiopathic Pulmonary Fibrosis (IPF): An Overview. *J Clin Med,* 7.

BAUER, Y., WHITE, E. S., DE BERNARD, S., CORNELISSE, P., LECONTE, I., MORGANTI, A., ROUX, S. & NAYLER, O. 2017. MMP-7 is a predictive biomarker of disease progression in patients with idiopathic pulmonary fibrosis. *ERJ Open Res,* 3.

BAUSEWEIN, C., FARQUHAR, M., BOOTH, S., GYSELS, M. & HIGGINSON, I. J. 2007. Measurement of breathlessness in advanced disease: a systematic review. *Respir Med,* 101**,** 399-410.

BEHNKE, M., SCHWERTFEGER, I., ZIMMERMAN, I., KIRSTEN, D., JOERRES, R. & MAGNUSSEN, H. 2003. Home based exercise training in patients with interstitial lung disease. *European Respiratory Journal,* 22**,** 1081.

BEHR, J., KREUTER, M., HOEPER, M. M., WIRTZ, H., KLOTSCHE, J., KOSCHEL, D., ANDREAS, S., CLAUSSEN, M., GROHÉ, C., WILKENS, H., RANDERATH, W., SKOWASCH, D., MEYER, F. J., KIRSCHNER, J., GLÄSER, S., HERTH, F. J., WELTE, T., HUBER, R. M., NEUROHR, C., SCHWAIBLMAIR, M., KOHLHÄUFL, M., HÖFFKEN, G., HELD, M., KOCH, A., BAHMER, T. & PITTROW, D. 2015. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J,* 46**,** 186-96.

BELLOLI, E. A., BECKFORD, R., HADLEY, R. & FLAHERTY, K. R. 2016. Idiopathic non-specific interstitial pneumonia. *Respirology,* 21**,** 259-68.

BENZ, E., TRAJANOSKA, K., LAHOUSSE, L., SCHOUFOUR, J. D., TERZIKHAN, N., DE ROOS, E., DE JONGE, G. B., WILLIAMS, R., FRANCO, O. H., BRUSSELLE, G. & RIVADENEIRA, F. 2019. Sarcopenia in COPD: a systematic review and meta-analysis. *Eur Respir Rev,* 28.

BERNARD, S., LEBLANC, P., WHITTOM, F., CARRIER, G., JOBIN, J., BELLEAU, R. & MALTAIS, F. 1998. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 158**,** 629-34.

BOHANNON, R. W., SMITH, J., HULL, D., PALMERI, D. & BARNHARD, R. 1995. Deficits in lower extremity muscle and gait performance among renal transplant candidates. *Arch Phys Med Rehabil,* 76**,** 547-51.

BORG, G. A. 1982. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc,* 14**,** 377-81.

BRUNETTI, G., MALOVINI, A., MANISCALCO, M., BALESTRINO, A., CARONE, M., VISCA, D., CAPELLI, A., VITACCA, M., BELLAZZI, R., PIAGGI, G., FUSCHILLO, S., ALIANI, M., SPANEVELLO, A., PRINCE, I., PANERONI, M. & AMBROSINO, N. 2021. Pulmonary rehabilitation in patients with interstitial lung diseases: Correlates of success. *Respir Med,* 185**,** 106473.

CHAE, K. J., JIN, G. Y., HAN, Y. M., KIM, Y. S., CHON, S. B., LEE, Y. S., KWON, K. S., CHOI, H. M. & LYNCH, D. 2015. Prevalence and progression of combined pulmonary fibrosis and emphysema in asymptomatic smokers: A case-control study. *Eur Radiol,* 25**,** 2326-34.

CHAHAL, A., SHARIF, R., WATTS, J., DE ANDRADE, J., LUCKHARDT, T., KIM, Y. I., RAMCHANDRAN, R. & SONAVANE, S. 2019. Predicting Outcome in Idiopathic Pulmonary Fibrosis: Addition of Fibrotic Score at Thin-Section CT of the Chest to Gender, Age, and Physiology Score Improves the Prediction Model. *Radiol Cardiothorac Imaging,* 1**,** e180029.

CHEN, K. Y. & BASSETT, D. R., JR. 2005. The technology of accelerometry-based activity monitors: current and future. *Med Sci Sports Exerc,* 37**,** S490-500.

CHEN, L. K., WOO, J., ASSANTACHAI, P., AUYEUNG, T. W., CHOU, M. Y., IIJIMA, K., JANG, H. C., KANG, L., KIM, M., KIM, S., KOJIMA, T., KUZUYA, M., LEE, J. S. W., LEE, S. Y., LEE, W. J., LEE, Y., LIANG, C. K., LIM, J. Y., LIM, W. S., PENG, L. N., SUGIMOTO, K., TANAKA, T., WON, C. W., YAMADA, M., ZHANG, T., AKISHITA, M. & ARAI, H. 2020. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc,* 21**,** 300-307.e2.

CICCARESE, F., ATTINA, D. & ZOMPATORI, M. 2016. Combined pulmonary fibrosis and emphysema (CPFE): what radiologist should know. *Radiologia Medica,* 121**,** 564-72.

COPLEY, S. J., LEE, Y. C., HANSELL, D. M., SIVAKUMARAN, P., RUBENS, M. B., NEWMAN TAYLOR, A. J., RUDD, R. M., MUSK, A. W. & WELLS, A. U. 2007. Asbestos-induced and smoking-related disease: apportioning pulmonary function deficit by using thin-section CT. *Radiology,* 242**,** 258-66.

COSTA, T. M., COSTA, F. M., MOREIRA, C. A., RABELO, L. M., BOGUSZEWSKI, C. L. & BORBA, V. Z. 2015. Sarcopenia in COPD: relationship with COPD severity and prognosis. *J Bras Pneumol,* 41**,** 415-21.

COSTABEL, U., INOUE, Y., RICHELDI, L., COLLARD, H. R., TSCHOEPE, I., STOWASSER, S. & AZUMA, A. 2016. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS. *Am J Respir Crit Care Med,* 193**,** 178-85.

COTTIN, V. 2013. The impact of emphysema in pulmonary fibrosis. *Eur Respir Rev,* 22**,** 153-7.

COTTIN, V. & CORDIER, J. F. 2009. The syndrome of combined pulmonary fibrosis and emphysema. *Chest,* 136**,** 1-2.

COTTIN, V., LE PAVEC, J., PREVOT, G., MAL, H., HUMBERT, M., SIMONNEAU, G. & CORDIER, J. F. 2010. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J,* 35**,** 105-11.

COTTIN, V., NUNES, H., BRILLET, P. Y., DELAVAL, P., DEVOUASSOUX, G., TILLIE-LEBLOND, I., ISRAEL-BIET, D., COURT-FORTUNE, I., VALEYRE, D. & CORDIER, J. F. 2005. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J,* 26**,** 586-93.

COTTIN, V., SELMAN, M., INOUE, Y., WONG, A. W., CORTE, T. J., FLAHERTY, K. R., HAN, M. K., JACOB, J., JOHANNSON, K. A., KITAICHI, M., LEE, J. S., AGUSTI, A., ANTONIOU, K. M., BIANCHI, P., CARO, F., FLORENZANO, M., GALVIN, L., IWASAWA, T., MARTINEZ, F. J., MORGAN, R. L., MYERS, J. L., NICHOLSON, A. G., OCCHIPINTI, M., POLETTI, V., SALISBURY, M. L., SIN, D. D., SVERZELLATI, N., TONIA, T., VALENZUELA, C., RYERSON, C. J. & WELLS, A. U. 2022a. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. *Am J Respir Crit Care Med,* 206**,** e7-e41.

COTTIN, V., TOMASSETTI, S., VALENZUELA, C., WALSH, S. L. F., ANTONIOU, K. M., BONELLA, F., BROWN, K. K., COLLARD, H. R., CORTE, T. J., FLAHERTY, K. R., JOHANNSON, K. A., KOLB, M., KREUTER, M., INOUE, Y., JENKINS, R. G., LEE, J. S., LYNCH, D. A., MAHER, T. M., MARTINEZ, F. J., MOLINA-MOLINA, M., MYERS, J. L., NATHAN, S. D., POLETTI, V., QUADRELLI, S., RAGHU, G., RAJAN, S. K., RAVAGLIA, C., REMY-JARDIN, M., RENZONI, E., RICHELDI, L. K., SPAGNOLO, P., TROY, L., WIJSENBEEK, M., WILSON, K. C., WUYTS, W., WELLS, A. U. & RYERSON, C. J. 2022b. Integrating Clinical Probability into the Diagnostic Approach to Idiopathic Pulmonary Fibrosis: An International Working Group Perspective. *Am J Respir Crit Care Med,* 206**,** 247-259.

CRESTANI, B., HUGGINS, J. T., KAYE, M., COSTABEL, U., GLASPOLE, I., OGURA, T., SONG, J. W., STANSEN, W., QUARESMA, M., STOWASSER, S. & KREUTER, M. 2019. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. *Lancet Respir Med,* 7**,** 60-68.

CRUZ-JENTOFT, A. J., BAEYENS, J. P., BAUER, J. M., BOIRIE, Y., CEDERHOLM, T., LANDI, F., MARTIN, F. C., MICHEL, J. P., ROLLAND, Y., SCHNEIDER, S. M., TOPINKOVÁ, E., VANDEWOUDE, M. & ZAMBONI, M. 2010. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing,* 39**,** 412-23.

CRUZ-JENTOFT, A. J., BAHAT, G., BAUER, J., BOIRIE, Y., BRUYÈRE, O., CEDERHOLM, T., COOPER, C., LANDI, F., ROLLAND, Y., SAYER, A. A., SCHNEIDER, S. M., SIEBER, C. C., TOPINKOVA, E., VANDEWOUDE, M., VISSER, M. & ZAMBONI, M. 2019. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing,* 48**,** 16-31.

DALE, M. T., MCKEOUGH, Z. J., MUNOZ, P. A., CORTE, P., BYE, P. T. & ALISON, J. A. 2014. Exercise training for asbestos-related and other dust-related respiratory diseases: a randomised controlled trial. *BMC Pulm Med,* 14**,** 180.

DE GIACOMI, F., WHITE, D., COX, C. W. & MOUA, T. 2018. Evolution of diagnostic UIP computed tomography patterns in idiopathic pulmonary fibrosis: Disease spectrum and implications for survival. *Respir Med,* 142**,** 53-59.

DE SADELEER, L. J., HERMANS, F., DE DYCKER, E., YSERBYT, J., VERSCHAKELEN, J. A., VERBEKEN, E. K., VERLEDEN, G. M., VERLEDEN, S. E. & WUYTS, W. A. 2020. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. *Eur Respir J,* 55.

DE SADELEER, L. J., HERMANS, F., DE DYCKER, E., YSERBYT, J., VERSCHAKELEN, J. A., VERBEKEN, E. K., VERLEDEN, G. M. & WUYTS, W. A. 2018. Effects of Corticosteroid Treatment and Antigen

Avoidance in a Large Hypersensitivity Pneumonitis Cohort: A Single-Centre Cohort Study. *J Clin Med,* 8.

DE SIMONE, G., AQUINO, G., DI GIOIA, C., MAZZARELLA, G., BIANCO, A. & CALCAGNO, G. 2015. Efficacy of aerobic physical retraining in a case of combined pulmonary fibrosis and emphysema syndrome: a case report. *J Med Case Rep,* 9**,** 85.

DE SOUSA PINTO, J. M., MARTÍN-NOGUERAS, A. M., MORANO, M. T., MACÊDO, T. E., ARENILLAS, J. I. & TROOSTERS, T. 2013. Chronic obstructive pulmonary disease patients' experience with pulmonary rehabilitation: a systematic review of qualitative research. *Chron Respir Dis,* 10**,** 141-57.

DEMPSEY, T. M., SANGARALINGHAM, L. R., YAO, X., SANGHAVI, D., SHAH, N. D. & LIMPER, A. H. 2019. Clinical Effectiveness of Antifibrotic Medications for Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med,* 200**,** 168-174.

DIAS, O. M., BALDI, B. G., COSTA, A. N. & CARVALHO, C. R. 2014. Combined pulmonary fibrosis and emphysema: an increasingly recognized condition. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia,* 40**,** 304-12.

DONG, F., ZHANG, Y., CHI, F., SONG, Q., ZHANG, L., WANG, Y. & CHE, C. 2015. Clinical efficacy and safety of ICS/LABA in patients with combined idiopathic pulmonary fibrosis and emphysema. *Int J Clin Exp Med,* 8**,** 8617-25.

DOWMAN, L., HILL, C. J., MAY, A. & HOLLAND, A. E. 2021. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev,* 2**,** Cd006322.

DOWMAN, L., MCDONALD, C. F., HILL, C. J., LEE, A., BARKER, K., BOOTE, C., GLASPOLE, I., GOH, N., SOUTHCOTT, A., BURGE, A., NDONGO, R., MARTIN, A. & HOLLAND, A. E. 2016. Reliability of the hand held dynamometer in measuring muscle strength in people with interstitial lung disease. *Physiotherapy,* 102**,** 249-55.

DOWMAN, L. M., MCDONALD, C. F., BOZINOVSKI, S., VLAHOS, R., GILLIES, R., POUNIOTIS, D., HILL, C. J., GOH, N. S. L. & HOLLAND, A. E. 2017a. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. *Respirology,* 22**,** 957-964.

DOWMAN, L. M., MCDONALD, C. F., HILL, C. J., LEE, A. L., BARKER, K., BOOTE, C., GLASPOLE, I., GOH, N. S. L., SOUTHCOTT, A. M., BURGE, A. T., GILLIES, R., MARTIN, A. & HOLLAND, A. E. 2017b. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax,* 72**,** 610-619.

DRAKE, T. M., DOCHERTY, A. B., HARRISON, E. M., QUINT, J. K., ADAMALI, H., AGNEW, S., BABU, S., BARBER, C. M., BARRATT, S., BENDSTRUP, E., BIANCHI, S., VILLEGAS, D. C., CHAUDHURI, N., CHUA, F., COKER, R., CHANG, W., CRAWSHAW, A., CROWLEY, L. E., DOSANJH, D., FIDDLER, C. A., FORREST, I. A., GEORGE, P. M., GIBBONS, M. A., GROOM, K., HANEY, S., HART, S. P., HEIDEN, E., HENRY, M., HO, L. P., HOYLES, R. K., HUTCHINSON, J., HURLEY, K., JONES, M., JONES, S., KOKOSI, M., KREUTER, M., MACKAY, L. S., MAHENDRAN, S., MARGARITOPOULOS, G., MOLINA-MOLINA, M., MOLYNEAUX, P. L., O'BRIEN, A., O'REILLY, K., PACKHAM, A., PARFREY, H., POLETTI, V., PORTER, J. C., RENZONI, E., RIVERA-ORTEGA, P., RUSSELL, A. M., SAINI, G., SPENCER, L. G., STELLA, G. M., STONE, H., STURNEY, S., THICKETT, D., THILLAI, M., WALLIS, T., WARD, K., WELLS, A. U., WEST, A., WICKREMASINGHE, M., WOODHEAD, F., HEARSON, G., HOWARD, L., BAILLIE, J. K., OPENSHAW, P. J. M., SEMPLE, M. G., STEWART, I. & JENKINS, R. G. 2020. Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study. *Am J Respir Crit Care Med,* 202**,** 1656-1665.

DU BOIS, R. M., ALBERA, C., BRADFORD, W. Z., COSTABEL, U., LEFF, J. A., NOBLE, P. W., SAHN, S. A., VALEYRE, D., WEYCKER, D. & KING, T. E., JR. 2014. 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J,* 43**,** 1421-9.

DU BOIS, R. M., WEYCKER, D., ALBERA, C., BRADFORD, W. Z., COSTABEL, U., KARTASHOV, A., LANCASTER, L., NOBLE, P. W., RAGHU, G., SAHN, S. A., SZWARCBERG, J., THOMEER, M.,

VALEYRE, D. & KING, T. E., JR. 2011. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med,* 184**,** 459-66.

DUCHEMANN, B., ANNESI-MAESANO, I., JACOBE DE NAUROIS, C., SANYAL, S., BRILLET, P. Y., BRAUNER, M., KAMBOUCHNER, M., HUYNH, S., NACCACHE, J. M., BORIE, R., PIQUET, J., MEKINIAN, A., VIRALLY, J., UZUNHAN, Y., CADRANEL, J., CRESTANI, B., FAIN, O., LHOTE, F., DHOTE, R., SAIDENBERG-KERMANAC'H, N., ROSENTAL, P. A., VALEYRE, D. & NUNES, H. 2017. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *Eur Respir J,* 50.

DUFOUR, A. B., HANNAN, M. T., MURABITO, J. M., KIEL, D. P. & MCLEAN, R. R. 2013. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: the Framingham Study. *J Gerontol A Biol Sci Med Sci,* 68**,** 168-74.

DURHEIM, M. T., KIM, S., GULACK, B. C., BURFEIND, W. R., GAISSERT, H. A., KOSINSKI, A. S. & HARTWIG, M. G. 2017. Mortality and Respiratory Failure After Thoracoscopic Lung Biopsy for Interstitial Lung Disease. *Ann Thorac Surg,* 104**,** 465-470.

EDEY, A. J., DEVARAJ, A. A., BARKER, R. P., NICHOLSON, A. G., WELLS, A. U. & HANSELL, D. M. 2011. Fibrotic idiopathic interstitial pneumonias: HRCT findings that predict mortality. *Eur Radiol,* 21**,** 1586-93.

EISNER, M. D., ANTHONISEN, N., COULTAS, D., KUENZLI, N., PEREZ-PADILLA, R., POSTMA, D., ROMIEU, I., SILVERMAN, E. K. & BALMES, J. R. 2010. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 182**,** 693-718.

FARRAND, E., VITTINGHOFF, E., LEY, B., BUTTE, A. J. & COLLARD, H. R. 2020. Corticosteroid use is not associated with improved outcomes in acute exacerbation of IPF. *Respirology,* 25**,** 629-635.

FAVERIO, P., FUMAGALLI, A., CONTI, S., MADOTTO, F., BINI, F., HARARI, S., MONDONI, M., OGGIONNI, T., BARISIONE, E., CERUTI, P., PAPETTI, M. C., BODINI, B. D., CAMINATI, A., VALENTINO, A., CENTANNI, S., LANZI, P., DELLA ZOPPA, M., CROTTI, S., GROSSO, M., SUKKAR, S. G., MODINA, D., ANDREOLI, M., NICALI, R., SUIGO, G., BUSNELLI, S., PACIOCCO, G., LETTIERI, S., MANTOVANI, L. G., CESANA, G., PESCI, A. & LUPPI, F. 2022. Sarcopenia in idiopathic pulmonary fibrosis: a prospective study exploring prevalence, associated factors and diagnostic approach. *Respir Res,* 23**,** 228.

FERNÁNDEZ PÉREZ, E. R., KONG, A. M., RAIMUNDO, K., KOELSCH, T. L., KULKARNI, R. & COLE, A. L. 2018. Epidemiology of Hypersensitivity Pneumonitis among an Insured Population in the United States: A Claims-based Cohort Analysis. *Ann Am Thorac Soc,* 15**,** 460-469.

FERNÁNDEZ PÉREZ, E. R., SWIGRIS, J. J., FORSSÉN, A. V., TOURIN, O., SOLOMON, J. J., HUIE, T. J., OLSON, A. L. & BROWN, K. K. 2013. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest,* 144**,** 1644-1651.

FERREIRA, A., GARVEY, C., CONNORS, G. L., HILLING, L., RIGLER, J., FARRELL, S., CAYOU, C., SHARIAT, C. & COLLARD, H. R. 2009. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. *Chest,* 135**,** 442-447.

FIDDLER, C. A., SIMLER, N., THILLAI, M. & PARFREY, H. 2019. Use of mycophenolate mofetil and azathioprine for the treatment of chronic hypersensitivity pneumonitis-A single-centre experience. *Clin Respir J,* 13**,** 791-794.

FIGUEIREDO, R. I. N., AZAMBUJA, A. M., CUREAU, F. V. & SBRUZZI, G. 2020. Inspiratory Muscle Training in COPD. *Respir Care,* 65**,** 1189-1201.

FISCHER, A., ANTONIOU, K. M., BROWN, K. K., CADRANEL, J., CORTE, T. J., DU BOIS, R. M., LEE, J. S., LESLIE, K. O., LYNCH, D. A., MATTESON, E. L., MOSCA, M., NOTH, I., RICHELDI, L., STREK, M. E., SWIGRIS, J. J., WELLS, A. U., WEST, S. G., COLLARD, H. R. & COTTIN, V. 2015. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J,* 46**,** 976-87.

FISHER, J. H., AL-HEJAILI, F., KANDEL, S., HIRJI, A., SHAPERA, S. & MURA, M. 2017. Multi-dimensional scores to predict mortality in patients with idiopathic pulmonary fibrosis undergoing lung transplantation assessment. *Respir Med,* 125**,** 65-71.

FISHMAN, A., FESSLER, H., MARTINEZ, F., MCKENNA, R. J., JR., NAUNHEIM, K., PIANTADOSI, S., WEINMANN, G. & WISE, R. 2001. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med,* 345**,** 1075-83.

FLAHERTY, K. R., THWAITE, E. L., KAZEROONI, E. A., GROSS, B. H., TOEWS, G. B., COLBY, T. V., TRAVIS, W. D., MUMFORD, J. A., MURRAY, S., FLINT, A., LYNCH, J. P., 3RD & MARTINEZ, F. J. 2003. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax,* 58**,** 143-8.

FLAHERTY, K. R., WELLS, A. U., COTTIN, V., DEVARAJ, A., WALSH, S. L. F., INOUE, Y., RICHELDI, L., KOLB, M., TETZLAFF, K., STOWASSER, S., COECK, C., CLERISME-BEATY, E., ROSENSTOCK, B., QUARESMA, M., HAEUFEL, T., GOELDNER, R.-G., SCHLENKER-HERCEG, R. & BROWN, K. K. 2019. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine,* 381**,** 1718-1727.

FLORIAN, J., WATTE, G., TEIXEIRA, P. J. Z., ALTMAYER, S., SCHIO, S. M., SANCHEZ, L. B., NASCIMENTO, D. Z., CAMARGO, S. M., PERIN, F. A., CAMARGO, J. J., FELICETTI, J. C. & MOREIRA, J. D. S. 2019. Pulmonary rehabilitation improves survival in patients with idiopathic pulmonary fibrosis undergoing lung transplantation. *Sci Rep,* 9**,** 9347.

FOUNDATION., E. L. & SOCIETY., E. R. 2019. IPF - Idiopathic Pulmonary Fibrosis. *Breathe (Sheff).* 2019/06/14 ed.

FUJITA, K., OHKUBO, H., NAKANO, A., MORI, Y., FUKUMITSU, K., FUKUDA, S., KANEMITSU, Y., UEMURA, T., TAJIRI, T., MAENO, K., ITO, Y., OGURI, T., OZAWA, Y., MURASE, T. & NIIMI, A. 2022. Frequency and impact on clinical outcomes of sarcopenia in patients with idiopathic pulmonary fibrosis. *Chron Respir Dis,* 19**,** 14799731221117298.

FURINI, F., CARNEVALE, A., CASONI, G. L., GUERRINI, G., CAVAGNA, L., GOVONI, M. & SCIRÉ, C. A. 2019. The Role of the Multidisciplinary Evaluation of Interstitial Lung Diseases: Systematic Literature Review of the Current Evidence and Future Perspectives. *Front Med (Lausanne),* 6**,** 246.

GARBER, C. E., BLISSMER, B., DESCHENES, M. R., FRANKLIN, B. A., LAMONTE, M. J., LEE, I. M., NIEMAN, D. C. & SWAIN, D. P. 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc,* 43**,** 1334-59.

GAUNAURD, I. A., GÓMEZ-MARÍN, O. W., RAMOS, C. F., SOL, C. M., COHEN, M. I., CAHALIN, L. P., CARDENAS, D. D. & JACKSON, R. M. 2014. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. *Respir Care,* 59**,** 1872-9.

GEDDES, E. L., O'BRIEN, K., REID, W. D., BROOKS, D. & CROWE, J. 2008. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med,* 102**,** 1715-29.

GERSHON, R. C., WAGSTER, M. V., HENDRIE, H. C., FOX, N. A., COOK, K. F. & NOWINSKI, C. J. 2013. NIH toolbox for assessment of neurological and behavioral function. *Neurology,* 80**,** S2-6.

GILES, J. T., LING, S. M., FERRUCCI, L., BARTLETT, S. J., ANDERSEN, R. E., TOWNS, M., MULLER, D., FONTAINE, K. R. & BATHON, J. M. 2008. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. *Arthritis Rheum,* 59**,** 807-15.

GIRARD, N., MARCHAND-ADAM, S., NACCACHE, J. M., BORIE, R., URBAN, T., JOUNEAU, S., MARCHAND, E., RAVEL, A. C., KIAKOUAMA, L., ETIENNE-MASTROIANNI, B., CADRANEL, J., COTTIN, V. & CORDIER, J. F. 2014. Lung cancer in combined pulmonary fibrosis and emphysema: a series of 47 Western patients. *J Thorac Oncol,* 9**,** 1162-70.

GRAHAM, B. L., BRUSASCO, V., BURGOS, F., COOPER, B. G., JENSEN, R., KENDRICK, A., MACINTYRE, N. R., THOMPSON, B. R. & WANGER, J. 2017. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *European Respiratory Journal,* 49**,** 1600016.

GRAHAM, B. L., STEENBRUGGEN, I., MILLER, M. R., BARJAKTAREVIC, I. Z., COOPER, B. G., HALL, G. L., HALLSTRAND, T. S., KAMINSKY, D. A., MCCARTHY, K., MCCORMACK, M. C., OROPEZ, C. E., ROSENFELD, M., STANOJEVIC, S., SWANNEY, M. P. & THOMPSON, B. R. 2019. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med,* 200**,** e70-e88.

GRANEY, B. A. & LEE, J. S. 2018. Impact of novel antifibrotic therapy on patient outcomes in idiopathic pulmonary fibrosis: patient selection and perspectives. *Patient related outcome measures,* 9**,** 321-328.

GRANSEE, H. M., MANTILLA, C. B. & SIECK, G. C. 2012. Respiratory muscle plasticity. *Compr Physiol,* 2**,** 1441-62.

GROUP, N. O. T. T. 1980. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med,* 93**,** 391-8.

GUENTHER, A., KRAUSS, E., TELLO, S., WAGNER, J., PAUL, B., KUHN, S., MAURER, O., HEINEMANN, S., COSTABEL, U., BARBERO, M. A. N., MÜLLER, V., BONNIAUD, P., VANCHERI, C., WELLS, A., VASAKOVA, M., PESCI, A., SOFIA, M., KLEPETKO, W., SEEGER, W., DRAKOPANAGIOTAKIS, F. & CRESTANI, B. 2018. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respir Res,* 19**,** 141.

GULER, S. A., HUR, S. A., STICKLAND, M. K., BRUN, P., BOVET, L., HOLLAND, A. E., BONDARENKO, J., HAMBLY, N., WALD, J., MAKHDAMI, N., KREUTER, M., GLOECKL, R., JAROSCH, I., TAN, B., JOHANNSON, K. A., MCBRIDE, S. A., DE BOER, K., SANDOZ, J. S., SUN, K., ASSAYAG, D., BHATT, S. P., MORISSET, J., FERRARO, V., GARVEY, C., CAMP, P. G. & RYERSON, C. J. 2021. Survival after inpatient or outpatient pulmonary rehabilitation in patients with fibrotic interstitial lung disease: a multicentre retrospective cohort study. *Thorax*.

HAMAI, K., IWAMOTO, H., ISHIKAWA, N., HORIMASU, Y., MASUDA, T., MIYAMOTO, S., NAKASHIMA, T., OHSHIMO, S., FUJITAKA, K., HAMADA, H., HATTORI, N. & KOHNO, N. 2016. Comparative Study of Circulating MMP-7, CCL18, KL-6, SP-A, and SP-D as Disease Markers of Idiopathic Pulmonary Fibrosis. *Dis Markers,* 2016**,** 4759040.

HAMBLIN, M., PROSCH, H. & VAŠÁKOVÁ, M. 2022. Diagnosis, course and management of hypersensitivity pneumonitis. *Eur Respir Rev,* 31.

HANADA, M., SAKAMOTO, N., ISHIMOTO, H., KIDO, T., MIYAMURA, T., OIKAWA, M., NAGURA, H., TAKEUCHI, R., KAWAZOE, Y., SATO, S., HASSAN, S. A., ISHIMATSU, Y., TAKAHATA, H., MUKAE, H. & KOZU, R. 2022. A comparative study of the sarcopenia screening in older patients with interstitial lung disease. *BMC Pulm Med,* 22**,** 45.

HANSELL, D. M., BANKIER, A. A., MACMAHON, H., MCLOUD, T. C., MÜLLER, N. L. & REMY, J. 2008. Fleischner Society: glossary of terms for thoracic imaging. *Radiology,* 246**,** 697-722.

HANSEN, J. E. & WASSERMAN, K. 1996. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest,* 109**,** 1566-76.

HARRIS-EZE, A. O., SRIDHAR, G., CLEMENS, R. E., ZINTEL, T. A., GALLAGHER, C. G. & MARCINIUK, D. D. 1996. Role of hypoxemia and pulmonary mechanics in exercise limitation in interstitial lung disease. *Am J Respir Crit Care Med,* 154**,** 994-1001.

HATABU, H., HUNNINGHAKE, G. M., RICHELDI, L., BROWN, K. K., WELLS, A. U., REMY-JARDIN, M., VERSCHAKELEN, J., NICHOLSON, A. G., BEASLEY, M. B., CHRISTIANI, D. C., SAN JOSÉ ESTÉPAR, R., SEO, J. B., JOHKOH, T., SVERZELLATI, N., RYERSON, C. J., GRAHAM BARR, R., GOO, J. M., AUSTIN, J. H. M., POWELL, C. A., LEE, K. S., INOUE, Y. & LYNCH, D. A. 2020. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med,* 8**,** 726-737.

HEWITT, R. J., BARTLETT, E. C., GANATRA, R., BUTT, H., KOURANOS, V., CHUA, F., KOKOSI, M., MOLYNEAUX, P. L., DESAI, S. R., WELLS, A. U., JENKINS, R. G., RENZONI, E. A., KEMP, S. V., DEVARAJ, A. & GEORGE, P. M. 2022. Lung cancer screening provides an opportunity for early diagnosis and treatment of interstitial lung disease. *Thorax*.

HEWSON, T., MCKEEVER, T. M., GIBSON, J. E., NAVARATNAM, V., HUBBARD, R. B. & HUTCHINSON, J. P. 2017. Timing of onset of symptoms in people with idiopathic pulmonary fibrosis. *Thorax*.

HILBERG, F., ROTH, G. J., KRSSAK, M., KAUTSCHITSCH, S., SOMMERGRUBER, W., TONTSCH-GRUNT, U., GARIN-CHESA, P., BADER, G., ZOEPHEL, A., QUANT, J., HECKEL, A. & RETTIG, W. J. 2008. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res,* 68**,** 4774-82.

HOFFMAN, M. 2021. Inspiratory muscle training in interstitial lung disease: a systematic scoping review. *J Bras Pneumol,* 47**,** e20210089.

HOFFMAN, M., ASSIS, M. G., AUGUSTO, V. M., SILVEIRA, B. M. F. & PARREIRA, V. F. 2018. The effects of inspiratory muscle training based on the perceptions of patients with advanced lung disease: a qualitative study. *Braz J Phys Ther,* 22**,** 215-221.

HOFFMAN, M., AUGUSTO, V. M., EDUARDO, D. S., SILVEIRA, B. M. F., LEMOS, M. D. & PARREIRA, V. F. 2021a. Inspiratory muscle training reduces dyspnea during activities of daily living and improves inspiratory muscle function and quality of life in patients with advanced lung disease. *Physiother Theory Pract,* 37**,** 895-905.

HOFFMAN, M., MELLERICK, C., SYMONS, K., GLASPOLE, I. & HOLLAND, A. E. 2021b. Pulmonary rehabilitation for interstitial lung disease: Referral and patient experiences. *Chron Respir Dis,* 18**,** 14799731211046022.

HOLLAND, A. E., DOWMAN, L. M. & HILL, C. J. 2015. Principles of rehabilitation and reactivation: interstitial lung disease, sarcoidosis and rheumatoid disease with respiratory involvement. *Respiration,* 89**,** 89-99.

HOLLAND, A. E., FIORE, J. F., JR., BELL, E. C., GOH, N., WESTALL, G., SYMONS, K., DOWMAN, L. & GLASPOLE, I. 2014a. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology,* 19**,** 1215-21.

HOLLAND, A. E., HILL, C. J., CONRON, M., MUNRO, P. & MCDONALD, C. F. 2008. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax,* 63**,** 549-54.

HOLLAND, A. E., HILL, C. J., GLASPOLE, I., GOH, N. & MCDONALD, C. F. 2012. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respir Med,* 106**,** 429-35.

HOLLAND, A. E., SPRUIT, M. A., TROOSTERS, T., PUHAN, M. A., PEPIN, V., SAEY, D., MCCORMACK, M. C., CARLIN, B. W., SCIURBA, F. C., PITTA, F., WANGER, J., MACINTYRE, N., KAMINSKY, D. A., CULVER, B. H., REVILL, S. M., HERNANDES, N. A., ANDRIANOPOULOS, V., CAMILLO, C. A., MITCHELL, K. E., LEE, A. L., HILL, C. J. & SINGH, S. J. 2014b. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *European Respiratory Journal,* 44**,** 1428-1446.

HOYER, N., PRIOR, T. S., BENDSTRUP, E., WILCKE, T. & SHAKER, S. B. 2019. Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. *Respir Res,* 20**,** 103.

HUMPHRIES, S. M., MACKINTOSH, J. A., JO, H. E., WALSH, S. L. F., SILVA, M., CALANDRIELLO, L., CHAPMAN, S., ELLIS, S., GLASPOLE, I., GOH, N., GRAINGE, C., HOPKINS, P. M. A., KEIR, G. J., MOODLEY, Y., REYNOLDS, P. N., WALTERS, E. H., BARAGHOSHI, D., WELLS, A. U., LYNCH, D. A. & CORTE, T. J. 2022. Quantitative computed tomography predicts outcomes in idiopathic pulmonary fibrosis. *Respirology*.

HUR, S. A., GULER, S. A., KHALIL, N., CAMP, P. G., GUENETTE, J. A., SWIGRIS, J. J. & RYERSON, C. J. 2019. Minimal Important Difference for Physical Activity and Validity of the International Physical Activity Questionnaire in Interstitial Lung Disease. *Ann Am Thorac Soc,* 16**,** 107-115.

HUTCHINSON, J. P., MCKEEVER, T. M., FOGARTY, A. W., NAVARATNAM, V. & HUBBARD, R. B. 2016. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997-2008. *Eur Respir J,* 48**,** 1453-1461.

HUUSKONEN, O., KIVISAARI, L., ZITTING, A., KALEVA, S. & VEHMAS, T. 2004. Emphysema findings associated with heavy asbestos-exposure in high resolution computed tomography of finnish construction workers. *J Occup Health,* 46**,** 266-71.

IWAKURA, M., OKURA, K., KUBOTA, M., SUGAWARA, K., KAWAGOSHI, A., TAKAHASHI, H. & SHIOYA, T. 2021. Estimation of minimal clinically important difference for quadriceps and inspiratory muscle strength in older outpatients with chronic obstructive pulmonary disease: a prospective cohort study. *Physical therapy research,* 24**,** 35-42.

IWANAMI, Y., EBIHARA, K., NAKAO, K., SATO, N., MIYAGI, M., NAKAMURA, Y., SAKAMOTO, S., KISHI, K., HOMMA, S. & EBIHARA, S. 2022. Benefits of Pulmonary Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis Receiving Antifibrotic Drug Treatment. *J Clin Med,* 11.

IYER, S. N., GURUJEYALAKSHMI, G. & GIRI, S. N. 1999. Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. *J Pharmacol Exp Ther,* 291**,** 367-73.

JACKSON, R. M., GÓMEZ-MARÍN, O. W., RAMOS, C. F., SOL, C. M., COHEN, M. I., GAUNAURD, I. A., CAHALIN, L. P. & CARDENAS, D. D. 2014. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. *Lung,* 192**,** 367-76.

JACOB, J., BARTHOLMAI, B. J., RAJAGOPALAN, S., KOKOSI, M., NAIR, A., KARWOSKI, R., RAGHUNATH, S. M., WALSH, S. L. F., WELLS, A. U. & HANSELL, D. M. 2016. Automated Quantitative Computed Tomography Versus Visual Computed Tomography Scoring in Idiopathic Pulmonary Fibrosis: Validation Against Pulmonary Function. *Journal of Thoracic Imaging,* 31**,** 304-311.

JACOB, J., BARTHOLMAI, B. J., RAJAGOPALAN, S., VAN MOORSEL, C. H. M., VAN ES, H. W., VAN BEEK, F. T., STRUIK, M. H. L., KOKOSI, M., EGASHIRA, R., BRUN, A. L., NAIR, A., WALSH, S. L. F., CROSS, G., BARNETT, J., DE LAURETIS, A., JUDGE, E. P., DESAI, S., KARWOSKI, R., OURSELIN, S., RENZONI, E., MAHER, T. M., ALTMANN, A. & WELLS, A. U. 2018a. Predicting Outcomes in Idiopathic Pulmonary Fibrosis Using Automated Computed Tomographic Analysis. *Am J Respir Crit Care Med,* 198**,** 767-776.

JACOB, J., ODINK, A., BRUN, A. L., MACALUSO, C., DE LAURETIS, A., KOKOSI, M., DEVARAJ, A., DESAI, S., RENZONI, E. & WELLS, A. U. 2018b. Functional associations of pleuroparenchymal fibroelastosis and emphysema with hypersensitivity pneumonitis. *Respir Med,* 138**,** 95-101.

JANKOWICH, M. D. & ROUNDS, S. 2010. Combined pulmonary fibrosis and emphysema alters physiology but has similar mortality to pulmonary fibrosis without emphysema. *Lung,* 188**,** 365-73.

JANKOWICH, M. D. & ROUNDS, S. I. S. 2012. Combined pulmonary fibrosis and emphysema syndrome: a review. *Chest,* 141**,** 222-231.

JAROSCH, I., SCHNEEBERGER, T., GLOECKL, R., KREUTER, M., FRANKENBERGER, M., NEUROHR, C., PRASSE, A., FREISE, J., BEHR, J., HITZL, W., KOCZULLA, A. R. & KENN, K. 2020. Short-Term Effects of Comprehensive Pulmonary Rehabilitation and its Maintenance in Patients with Idiopathic Pulmonary Fibrosis: A Randomized Controlled Trial. *J Clin Med,* 9.

JEE, A. S., SHEEHY, R., HOPKINS, P., CORTE, T. J., GRAINGE, C., TROY, L. K., SYMONS, K., SPENCER, L. M., REYNOLDS, P. N., CHAPMAN, S., DE BOER, S., REDDY, T., HOLLAND, A. E., CHAMBERS, D. C., GLASPOLE, I. N., JO, H. E., BLEASEL, J. F., WROBEL, J. P., DOWMAN, L., PARKER, M. J. S., WILSHER, M. L., GOH, N. S. L., MOODLEY, Y. & KEIR, G. J. 2021. Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand. *Respirology,* 26**,** 23-51.

JIN, G. Y., LYNCH, D., CHAWLA, A., GARG, K., TAMMEMAGI, M. C., SAHIN, H., MISUMI, S. & KWON, K. S. 2013. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology,* 268**,** 563-71.

JO, H. E., GLASPOLE, I., GRAINGE, C., GOH, N., HOPKINS, P. M., MOODLEY, Y., REYNOLDS, P. N., CHAPMAN, S., WALTERS, E. H., ZAPPALA, C., ALLAN, H., KEIR, G. J., HAYEN, A., COOPER, W. A., MAHAR, A. M., ELLIS, S., MACANSH, S. & CORTE, T. J. 2017. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J,* 49.

JO, H. E., GLASPOLE, I., MOODLEY, Y., CHAPMAN, S., ELLIS, S., GOH, N., HOPKINS, P., KEIR, G., MAHAR, A., COOPER, W., REYNOLDS, P., HAYDN WALTERS, E., ZAPPALA, C., GRAINGE, C., ALLAN, H., MACANSH, S. & CORTE, T. J. 2018. Disease progression in idiopathic pulmonary fibrosis with mild physiological impairment: analysis from the Australian IPF registry. *BMC Pulmonary Medicine,* 18**,** 19.

JUGE, P. A., LEE, J. S., LAU, J., KAWANO-DOURADO, L., ROJAS SERRANO, J., SEBASTIANI, M., KODURI, G., MATTESON, E., BONFIGLIOLI, K., SAWAMURA, M., KAIRALLA, R., CAVAGNA, L., BOZZALLA CASSIONE, E., MANFREDI, A., MEJIA, M., RODRÍGUEZ-HENRIQUEZ, P., GONZÁLEZ-PÉREZ, M. I., FALFÁN-VALENCIA, R., BUENDIA-ROLDÁN, I., PÉREZ-RUBIO, G., EBSTEIN, E., GAZAL, S., BORIE, R., OTTAVIANI, S., KANNENGIESSER, C., WALLAERT, B., UZUNHAN, Y., NUNES, H., VALEYRE, D., SAIDENBERG-KERMANAC'H, N., BOISSIER, M. C., WEMEAU-STERVINOU, L., FLIPO, R. M., MARCHAND-ADAM, S., RICHETTE, P., ALLANORE, Y., DROMER, C., TRUCHETET, M. E., RICHEZ, C., SCHAEVERBEKE, T., LIOTÉ, H., THABUT, G., DEANE, K. D., SOLOMON, J. J., DOYLE, T., RYU, J. H., ROSAS, I., HOLERS, V. M., BOILEAU, C., DEBRAY, M. P., PORCHER, R., SCHWARTZ, D. A., VASSALLO, R., CRESTANI, B. & DIEUDÉ, P. 2021. Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J,* 57.

KAKUGAWA, T., SAKAMOTO, N., SATO, S., YURA, H., HARADA, T., NAKASHIMA, S., HARA, A., ODA, K., ISHIMOTO, H., YATERA, K., ISHIMATSU, Y., OBASE, Y., KOHNO, S. & MUKAE, H. 2016. Risk factors for an acute exacerbation of idiopathic pulmonary fibrosis. *Respir Res,* 17**,** 79.

KAUSHAL, M., ALI, M. S., SHARMA, R. K. & TALWAR, D. 2019. Effect of respiratory muscle training and pulmonary rehabilitation on exercise capacity in patients with interstitial lung disease: A prospective quasi-experimental study. *Eurasian journal of pulmonology,* 21**,** 87.

KHAN, F. A., STEWART, I., SAINI, G., ROBINSON, K. A. & JENKINS, R. G. 2022. A systematic review of blood biomarkers with individual participant data meta-analysis of matrix metalloproteinase-7 in idiopathic pulmonary fibrosis. *Eur Respir J,* 59.

KHOR, Y. H., GUTMAN, L., ABU HUSSEIN, N., JOHANNSON, K. A., GLASPOLE, I. N., GULER, S. A., FUNKE-CHAMBOUR, M., GEISER, T., GOH, N. S. L. & RYERSON, C. J. 2021. Incidence and Prognostic Significance of Hypoxemia in Fibrotic Interstitial Lung Disease: An International Cohort Study. *Chest,* 160**,** 994-1005.

KIM, D. S., COLLARD, H. R. & KING, T. E., JR. 2006. Classification and natural history of the idiopathic interstitial pneumonias. *Proc Am Thorac Soc,* 3**,** 285-92.

KIM, Y. J., SHIN, S. H., PARK, J. W., KYUNG, S. Y., KANG, S. M., LEE, S. P., SUNG, Y. M., KIM, Y. K. & JEONG, S. H. 2014. Annual Change in Pulmonary Function and Clinical Characteristics of Combined Pulmonary Fibrosis and Emphysema and Idiopathic Pulmonary Fibrosis: Over a 3-Year Follow-up. *Tuberc Respir Dis (Seoul),* 77**,** 18-23.

KING, T. E., BRADFORD, W. Z., CASTRO-BERNARDINI, S., FAGAN, E. A., GLASPOLE, I., GLASSBERG, M. K., GORINA, E., HOPKINS, P. M., KARDATZKE, D., LANCASTER, L., LEDERER, D. J., NATHAN, S. D., PEREIRA, C. A., SAHN, S. A., SUSSMAN, R., SWIGRIS, J. J. & NOBLE, P. W. 2014. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. *The New England journal of medicine,* 370**,** 2083-2092.

KING, T. E., JR., BROWN, K. K., RAGHU, G., DU BOIS, R. M., LYNCH, D. A., MARTINEZ, F., VALEYRE, D., LECONTE, I., MORGANTI, A., ROUX, S. & BEHR, J. 2011. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med,* 184**,** 92-9.

KING, T. E., JR., TOOZE, J. A., SCHWARZ, M. I., BROWN, K. R. & CHERNIACK, R. M. 2001. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med,* 164**,** 1171-81.

KIRTLAND, S. H. & WINTERBAUER, R. H. 1997. Pulmonary Function Tests and Idiopathic Pulmonary Fibrosis: Simple May Be Better. *Chest,* 111**,** 7-8.

KISHABA, T., SHIMAOKA, Y., FUKUYAMA, H., NAGANO, H., NEI, Y., YAMASHIRO, S. & TAMAKI, H. 2015. Clinical characteristics of idiopathic pulmonary fibrosis patients with gender, age, and physiology staging at Okinawa Chubu Hospital. *J Thorac Dis,* 7**,** 843-9.

KISHABA, T., SHIMAOKA, Y., FUKUYAMA, H., YOSHIDA, K., TANAKA, M., YAMASHIRO, S. & TAMAKI, H. 2012. A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema. *BMJ Open,* 2.

KITAGUCHI, Y., FUJIMOTO, K., HANAOKA, M., HONDA, T., HOTTA, J. & HIRAYAMA, J. 2014. Pulmonary function impairment in patients with combined pulmonary fibrosis and emphysema with and without airflow obstruction. *Int J Chron Obstruct Pulmon Dis,* 9**,** 805-11.

KITAGUCHI, Y., FUJIMOTO, K., HAYASHI, R., HANAOKA, M., HONDA, T. & KUBO, K. 2013. Annual changes in pulmonary function in combined pulmonary fibrosis and emphysema: over a 5-year follow-up. *Respir Med,* 107**,** 1986-92.

KOBAYASHI, H., NAITO, T., OMAE, K., OMORI, S., NAKASHIMA, K., WAKUDA, K., ONO, A., KENMOTSU, H., MURAKAMI, H., ENDO, M. & TAKAHASHI, T. 2018. ILD-NSCLC-GAP index scoring and staging system for patients with non-small cell lung cancer and interstitial lung disease. *Lung Cancer,* 121**,** 48-53.

KOBAYASHI, H., OMORI, S., NAKASHIMA, K., WAKUDA, K., ONO, A., KENMOTSU, H., NAITO, T., MURAKAMI, H., ENDO, M. & TAKAHASHI, T. 2017. Modified GAP index for prediction of acute exacerbation of idiopathic pulmonary fibrosis in non-small cell lung cancer. *Respirology,* 22**,** 1379-1385.

KOLB, M. & COLLARD, H. R. 2014. Staging of idiopathic pulmonary fibrosis: past, present and future. *Eur Respir Rev,* 23**,** 220-4.

KOLB, M., RICHELDI, L., BEHR, J., MAHER, T. M., TANG, W., STOWASSER, S., HALLMANN, C. & DU BOIS, R. M. 2017. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax,* 72**,** 340-346.

KONDOH, Y., TANIGUCHI, H., KATSUTA, T., KATAOKA, K., KIMURA, T., NISHIYAMA, O., SAKAMOTO, K., JOHKOH, T., NISHIMURA, M., ONO, K. & KITAICHI, M. 2010. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis,* 27**,** 103-10.

KOULOPOULOU, M., CHUA, F., KOUTOUMANOU, E., NARAYAN, S. & NIKOLETOU, D. 2016. Inspiratory muscle training (IMT) in interstitial lung disease (ILD) - A pilot study. *European Respiratory Journal,* 48**,** 1.

KREUTER, M., WUYTS, W. A., WIJSENBEEK, M., BAJWAH, S., MAHER, T. M., STOWASSER, S., MALE, N., STANSEN, W., SCHOOF, N., ORSATTI, L. & SWIGRIS, J. 2020. Health-related quality of life and symptoms in patients with IPF treated with nintedanib: Analyses of patient-reported outcomes from the INPULSIS® trials. *Respiratory research,* 21**,** 36-36.

KRUPP, L. B., LAROCCA, N. G., MUIR-NASH, J. & STEINBERG, A. D. 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol,* 46**,** 1121-3.

LANDELLS, L. J., NAIDOO, B., ROBERTSON, J. & CLARK, P. 2013. NICE guidance on pirfenidone for treating idiopathic pulmonary fibrosis. *The Lancet Respiratory Medicine,* 1**,** 191-192.

LANDI, F., LIPEROTI, R., RUSSO, A., GIOVANNINI, S., TOSATO, M., CAPOLUONGO, E., BERNABEI, R. & ONDER, G. 2012. Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. *Clin Nutr,* 31**,** 652-8.

LANGER, D., CEBRIÀ I IRANZO, M. A., BURTIN, C., VERLEDEN, S. E., VANAUDENAERDE, B. M., TROOSTERS, T., DECRAMER, M., VERLEDEN, G. M. & GOSSELINK, R. 2012. Determinants of physical activity in daily life in candidates for lung transplantation. *Respir Med,* 106**,** 747-54.

LANZA, M., MEOLI, I., CAUTERUCCIO, R., STEFANELLI, F., DI GIORGIO, A., ANNUNZIATA, A. & FIORENTINO, G. 2019. Short and long-term effects of pulmonary rehabilitation in Idiopatic Pulmonary Fibrosis: The evidence of benefits of exercise training. Eur Respiratory Soc.

LAURENSON, S., SIDHU, R., GOODALL, M. & ADLER, A. I. 2016. NICE guidance on nintedanib for treating idiopathic pulmonary fibrosis. *Lancet Respir Med,* 4**,** 176-7.

LEDERER, D. J. & MARTINEZ, F. J. 2018. Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine,* 378**,** 1811-1823.

LEE, J. W., SHEHU, E., GJONBRATAJ, J., BAHN, Y. E., RHO, B. H., LEE, M. Y. & CHOI, W. I. 2015. Clinical findings and outcomes in patients with possible usual interstitial pneumonia. *Respir Med,* 109**,** 510-6.

LEE, S. H., KIM, S. Y., KIM, D. S., KIM, Y. W., CHUNG, M. P., UH, S. T., PARK, C. S., JEONG, S. H., PARK, Y. B., LEE, H. L., SHIN, J. W., LEE, E. J., LEE, J. H., JEGAL, Y., LEE, H. K., KIM, Y. H., SONG, J. W., PARK, S. W. & PARK, M. S. 2016. Predicting survival of patients with idiopathic pulmonary fibrosis using GAP score: a nationwide cohort study. *Respir Res,* 17**,** 131.

LEE, S. H., PARK, J. S., KIM, S. Y., KIM, D. S., KIM, Y. W., CHUNG, M. P., UH, S. T., PARK, C. S., PARK, S. W., JEONG, S. H., PARK, Y. B., LEE, H. L., SHIN, J. W., LEE, E. J., LEE, J. H., JEGAL, Y., LEE, H. K., KIM, Y. H., SONG, J. W. & PARK, M. S. 2018. Comparison of CPI and GAP models in patients with idiopathic pulmonary fibrosis: a nationwide cohort study. *Sci Rep,* 8**,** 4784.

LEITH, D. E. & BRADLEY, M. 1976. Ventilatory muscle strength and endurance training. *J Appl Physiol,* 41**,** 508-16.

LEON, A. C., DAVIS, L. L. & KRAEMER, H. C. 2011. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res,* 45**,** 626-9.

LEUNG, R. W., ALISON, J. A., MCKEOUGH, Z. J. & PETERS, M. J. 2010. Ground walk training improves functional exercise capacity more than cycle training in people with chronic obstructive pulmonary disease (COPD): a randomised trial. *J Physiother,* 56**,** 105-12.

LEVIN, O. S., POLUNINA, A. G., DEMYANOVA, M. A. & ISAEV, F. V. 2014. Steroid myopathy in patients with chronic respiratory diseases. *J Neurol Sci,* 338**,** 96-101.

LEY, B., COLLARD, H. R. & KING, T. E., JR. 2011. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med,* 183**,** 431-40.

LEY, B., ELICKER, B. M., HARTMAN, T. E., RYERSON, C. J., VITTINGHOFF, E., RYU, J. H., LEE, J. S., JONES, K. D., RICHELDI, L., KING, T. E., JR. & COLLARD, H. R. 2014. Idiopathic pulmonary fibrosis: CT and risk of death. *Radiology,* 273**,** 570-9.

LEY, B., RYERSON, C. J., VITTINGHOFF, E., RYU, J. H., TOMASSETTI, S., LEE, J. S., POLETTI, V., BUCCIOLI, M., ELICKER, B. M., JONES, K. D., KING, T. E., JR. & COLLARD, H. R. 2012. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med,* 156**,** 684-91.

LI, Q., WALLACE, L., PATNAIK, P., ALVES, M., GAHLEMANN, M., KOHLBRENNER, V., RAABE, C., WANG, J. R. & GARRY, E. M. 2021. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. *Rheumatology (Oxford),* 60**,** 1915-1925.

LYNCH, D. A., AUSTIN, J. H., HOGG, J. C., GRENIER, P. A., KAUCZOR, H. U., BANKIER, A. A., BARR, R. G., COLBY, T. V., GALVIN, J. R., GEVENOIS, P. A., COXSON, H. O., HOFFMAN, E. A., NEWELL, J. D., JR., PISTOLESI, M., SILVERMAN, E. K. & CRAPO, J. D. 2015. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. *Radiology,* 277**,** 192-205.

MACKINTOSH, J. A., MARSHALL, H. M., SLAUGHTER, R., REDDY, T., YANG, I. A., BOWMAN, R. V. & FONG, K. M. 2019. Interstitial lung abnormalities in the Queensland Lung Cancer Screening Study: prevalence and progression over 2 years of surveillance. *Intern Med J,* 49**,** 843-849.

MAHER, T. M., BENDSTRUP, E., DRON, L., LANGLEY, J., SMITH, G., KHALID, J. M., PATEL, H. & KREUTER, M. 2021. Global incidence and prevalence of idiopathic pulmonary fibrosis. *Respir Res,* 22**,** 197.

MAHER, T. M., OBALLA, E., SIMPSON, J. K., PORTE, J., HABGOOD, A., FAHY, W. A., FLYNN, A., MOLYNEAUX, P. L., BRAYBROOKE, R., DIVYATEJA, H., PARFREY, H., RASSL, D., RUSSELL, A. M., SAINI, G., RENZONI, E. A., DUGGAN, A. M., HUBBARD, R., WELLS, A. U., LUKEY, P. T., MARSHALL, R. P. & JENKINS, R. G. 2017. An epithelial biomarker signature for idiopathic

pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. *Lancet Respir Med,* 5**,** 946-955.

MAHER, T. M. & STREK, M. E. 2019. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. *Respir Res,* 20**,** 205.

MALDONADO, F., DANOFF, S. K., WELLS, A. U., COLBY, T. V., RYU, J. H., LIBERMAN, M., WAHIDI, M. M., FRAZER, L., HETZEL, J., RICKMAN, O. B., HERTH, F. J. F., POLETTI, V. & YARMUS, L. B. 2020. Transbronchial Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: CHEST Guideline and Expert Panel Report. *Chest,* 157**,** 1030-1042.

MALDONADO, F., MOUA, T., RAJAGOPALAN, S., KARWOSKI, R. A., RAGHUNATH, S., DECKER, P. A., HARTMAN, T. E., BARTHOLMAI, B. J., ROBB, R. A. & RYU, J. H. 2014. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. *Eur Respir J,* 43**,** 204-12.

MALLI, F., PAPAKOSTA, D., ANTONIOU, K., DIMADI, M., POLYCHRONOPOULOS, V., MALAGARI, K., OIKONOMOU, A., BOUROS, D. E. & DANIIL, Z. 2019. Combined pulmonary fibrosis and emphysema characteristics in a Greek cohort. *ERJ Open Res,* 5.

MALTAIS, F., LEBLANC, P., SIMARD, C., JOBIN, J., BÉRUBÉ, C., BRUNEAU, J., CARRIER, L. & BELLEAU, R. 1996. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 154**,** 442-7.

MAN, W. D., SOLIMAN, M. G., GEARING, J., RADFORD, S. G., RAFFERTY, G. F., GRAY, B. J., POLKEY, M. I. & MOXHAM, J. 2003. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 168**,** 562-7.

MARSH, A. P., REJESKI, W. J., ESPELAND, M. A., MILLER, M. E., CHURCH, T. S., FIELDING, R. A., GILL, T. M., GURALNIK, J. M., NEWMAN, A. B. & PAHOR, M. 2011. Muscle strength and BMI as predictors of major mobility disability in the Lifestyle Interventions and Independence for Elders pilot (LIFE-P). *J Gerontol A Biol Sci Med Sci,* 66**,** 1376-83.

MARTINEZ, F. J., CHISHOLM, A., COLLARD, H. R., FLAHERTY, K. R., MYERS, J., RAGHU, G., WALSH, S. L., WHITE, E. S. & RICHELDI, L. 2017. The diagnosis of idiopathic pulmonary fibrosis: current and future approaches. *Lancet Respir Med,* 5**,** 61-71.

MATSUO, S., OKAMOTO, M., IKEUCHI, T., ZAIZEN, Y., INOMOTO, A., HARAGUCHI, R., MORI, S., SASAKI, R., NOUNO, T., TANAKA, T., HOSHINO, T. & TSUDA, T. 2021. Early Intervention of Pulmonary Rehabilitation for Fibrotic Interstitial Lung Disease Is a Favorable Factor for Short-Term Improvement in Health-Related Quality of Life. *J Clin Med,* 10.

MATSUOKA, S., YAMASHIRO, T., MATSUSHITA, S., KOTOKU, A., FUJIKAWA, A., YAGIHASHI, K. & NAKAJIMA, Y. 2015. Quantitative CT evaluation in patients with combined pulmonary fibrosis and emphysema: correlation with pulmonary function. *Acad Radiol,* 22**,** 626-31.

MCCARTHY, B., CASEY, D., DEVANE, D., MURPHY, K., MURPHY, E. & LACASSE, Y. 2015. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*.

MCDERMOTT, G. C., DOYLE, T. J. & SPARKS, J. A. 2021. Interstitial lung disease throughout the rheumatoid arthritis disease course. *Curr Opin Rheumatol,* 33**,** 284-291.

MEJÍA, M., CARRILLO, G., ROJAS-SERRANO, J., ESTRADA, A., SUÁREZ, T., ALONSO, D., BARRIENTOS, E., GAXIOLA, M., NAVARRO, C. & SELMAN, M. 2009. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest,* 136**,** 10-15.

MENON, B., VIJAYAN, V., BANSAL, V. & PRAJAPAT, B. 2011. Effect of pulmonary rehabilitation on gas exchange, muscle cross section area and functional parameters in interstitial lung disease. Eur Respiratory Soc.

MERCURIO, V., CARLOMAGNO, G. & FAZIO, S. 2012. Response to pulmonary vasodilator treatment in a former smoker with combined interstitial lung disease complicated by pulmonary hypertension: case report and review of the literature. *Heart Lung,* 41**,** 512-7.

METTER, E. J., CONWIT, R., TOBIN, J. & FOZARD, J. L. 1997. Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci,* 52**,** B267-76.

MEYER, K. C., RAGHU, G., BAUGHMAN, R. P., BROWN, K. K., COSTABEL, U., DU BOIS, R. M., DRENT, M., HASLAM, P. L., KIM, D. S., NAGAI, S., ROTTOLI, P., SALTINI, C., SELMAN, M., STRANGE, C. & WOOD, B. 2012. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med,* 185**,** 1004-14.

MILLER, M. R. & COOPER, B. G. 2021. Reduction in T (LCO) and survival in a clinical population. *Eur Respir J,* 58.

MÖNKÄRE, S. & HAAHTELA, T. 1987. Farmer's lung--a 5-year follow-up of eighty-six patients. *Clin Allergy,* 17**,** 143-51.

MORI, Y. & KONDOH, Y. 2021. What parameters can be used to identify early idiopathic pulmonary fibrosis? *Respir Investig,* 59**,** 53-65.

MORINO, A., TAKAHASHI, H., CHIBA, H. & ISHIAI, S. 2017. Daily physical activity affects exercise capacity in patients with idiopathic pulmonary fibrosis. *J Phys Ther Sci,* 29**,** 1323-1328.

MORISSET, J., JOHANNSON, K. A., VITTINGHOFF, E., ARAVENA, C., ELICKER, B. M., JONES, K. D., FELL, C. D., MANGANAS, H., DUBÉ, B. P., WOLTERS, P. J., COLLARD, H. R., RYERSON, C. J. & LEY, B. 2017a. Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis. *Chest,* 151**,** 619-625.

MORISSET, J., VITTINGHOFF, E., LEE, B. Y., TONELLI, R., HU, X., ELICKER, B. M., RYU, J. H., JONES, K. D., CERRI, S., MANFREDI, A., SEBASTIANI, M., GROSS, A. J., LEY, B., WOLTERS, P. J., KING, T. E., JR., KIM, D. S., COLLARD, H. R. & LEE, J. S. 2017b. The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease. *Respir Med,* 127**,** 51-56.

MURA, M., ZOMPATORI, M., PACILLI, A. M., FASANO, L., SCHIAVINA, M. & FABBRI, M. 2006. The presence of emphysema further impairs physiologic function in patients with idiopathic pulmonary fibrosis. *Respir Care,* 51**,** 257-65.

NAKAYAMA, M., BANDO, M., ARAKI, K., SEKINE, T., KUROSAKI, F., SAWATA, T., NAKAZAWA, S., MATO, N., YAMASAWA, H. & SUGIYAMA, Y. 2015. Physical activity in patients with idiopathic pulmonary fibrosis. *Respirology,* 20**,** 640-6.

NAKAZAWA, A., COX, N. S. & HOLLAND, A. E. 2017. Current best practice in rehabilitation in interstitial lung disease. *Ther Adv Respir Dis,* 11**,** 115-128.

NATHAN, S. D., COSTABEL, U., ALBERA, C., BEHR, J., WUYTS, W. A., KIRCHGAESSLER, K. U., STAUFFER, J. L., MORGENTHIEN, E., CHOU, W., LIMB, S. L. & NOBLE, P. W. 2019. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. *Respir Med,* 153**,** 44-51.

NATSUIZAKA, M., CHIBA, H., KURONUMA, K., OTSUKA, M., KUDO, K., MORI, M., BANDO, M., SUGIYAMA, Y. & TAKAHASHI, H. 2014. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med,* 190**,** 773-9.

NAZ, I., SAHIN, H., DEMIRCI UÇSULAR, F. & YALNıZ, E. 2018. A comparison trial of eight weeks versus twelve weeks of exercise program in interstitial lung diseases. *Sarcoidosis Vasc Diffuse Lung Dis,* 35**,** 299-307.

NEWMAN, A. B., KUPELIAN, V., VISSER, M., SIMONSICK, E. M., GOODPASTER, B. H., KRITCHEVSKY, S. B., TYLAVSKY, F. A., RUBIN, S. M. & HARRIS, T. B. 2006. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci,* 61**,** 72-7.

NICI, L., DONNER, C., WOUTERS, E., ZUWALLACK, R., AMBROSINO, N., BOURBEAU, J., CARONE, M., CELLI, B., ENGELEN, M., FAHY, B., GARVEY, C., GOLDSTEIN, R., GOSSELINK, R., LAREAU, S., MACINTYRE, N., MALTAIS, F., MORGAN, M., O'DONNELL, D., PREFAULT, C., REARDON, J., ROCHESTER, C., SCHOLS, A., SINGH, S. & TROOSTERS, T. 2006. American Thoracic

Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med,* 173**,** 1390-413.

NISHIYAMA, O., KONDOH, Y., KIMURA, T., KATO, K., KATAOKA, K., OGAWA, T., WATANABE, F., ARIZONO, S., NISHIMURA, K. & TANIGUCHI, H. 2008. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology,* 13**,** 394-9.

NISHIYAMA, O., TANIGUCHI, H., KONDOH, Y., KIMURA, T., OGAWA, T., WATANABE, F. & ARIZONO, S. 2005. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest,* 127**,** 2028-33.

NOBLE, P. W., ALBERA, C., BRADFORD, W. Z., COSTABEL, U., GLASSBERG, M. K., KARDATZKE, D., KING, T. E., JR., LANCASTER, L., SAHN, S. A., SZWARCBERG, J., VALEYRE, D. & DU BOIS, R. M. 2011. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet,* 377**,** 1760-9.

NOLAN, C. M., POLGAR, O., SCHOFIELD, S. J., PATEL, S., BARKER, R. E., WALSH, J. A., INGRAM, K. A., GEORGE, P. M., MOLYNEAUX, P. L., MAHER, T. M. & MAN, W. D. 2022. Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis and COPD: A Propensity-Matched Real-World Study. *Chest,* 161**,** 728-737.

O'SHEA, S. D., TAYLOR, N. F. & PARATZ, J. D. 2009. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest,* 136**,** 1269-1283.

OH, J. Y., LEE, Y. S., MIN, K. H., HUR, G. Y., LEE, S. Y., KANG, K. H. & SHIM, J. J. 2018. Presence of lung cancer and high gender, age, and physiology score as predictors of acute exacerbation in combined pulmonary fibrosis and emphysema: A retrospective study. *Medicine (Baltimore),* 97**,** e11683.

OLSON, A. L., PATNAIK, P., HARTMANN, N., BOHN, R. L., GARRY, E. M. & WALLACE, L. 2021. Prevalence and Incidence of Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype in the United States Estimated in a Large Claims Database Analysis. *Adv Ther,* 38**,** 4100-4114.

OLTMANNS, U., KAHN, N., PALMOWSKI, K., TRAGER, A., WENZ, H., HEUSSEL, C. P., SCHNABEL, P. A., PUDERBACH, M., WIEBEL, M., EHLERS-TENENBAUM, S., WARTH, A., HERTH, F. J. & KREUTER, M. 2014. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. *Respiration,* 88**,** 199-207.

OZALEVLI, S., OZDEN, A., ITIL, O. & AKKOCLU, A. 2007. Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. *Respir Med,* 101**,** 286-93.

PAPIRIS, S. A., TRIANTAFILLIDOU, C., MANALI, E. D., KOLILEKAS, L., BAOU, K., KAGOURIDIS, K. & BOUROS, D. 2013. Combined pulmonary fibrosis and emphysema. *Expert Rev Respir Med,* 7**,** 19-31; quiz 32.

PARTY, M. R. C. W. 1981. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet.* 1981/03/28 ed.

PATEL, A. S., SIEGERT, R. J., BRIGNALL, K., GORDON, P., STEER, S., DESAI, S. R., MAHER, T. M., RENZONI, E. A., WELLS, A. U., HIGGINSON, I. J. & BIRRING, S. S. 2012. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax,* 67**,** 804-10.

PENG, P., HYDER, O., FIROOZMAND, A., KNEUERTZ, P., SCHULICK, R. D., HUANG, D., MAKARY, M., HIROSE, K., EDIL, B., CHOTI, M. A., HERMAN, J., CAMERON, J. L., WOLFGANG, C. L. & PAWLIK, T. M. 2012. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *J Gastrointest Surg,* 16**,** 1478-86.

PETERMANN-ROCHA, F., BALNTZI, V., GRAY, S. R., LARA, J., HO, F. K., PELL, J. P. & CELIS-MORALES, C. 2022. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle,* 13**,** 86-99.

PETNAK, T., LERTJITBANJONG, P., THONGPRAYOON, C. & MOUA, T. 2021. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. *Chest,* 160**,** 1751-1763.

POWERS, S. K. & CRISWELL, D. 1996. Adaptive strategies of respiratory muscles in response to endurance exercise. *Med Sci Sports Exerc,* 28**,** 1115-22.

PRASAD, J. D., PAUL, E., HOLLAND, A. E., GLASPOLE, I. N. & WESTALL, G. P. 2021. Physical activity decline is disproportionate to decline in pulmonary physiology in IPF. *Respirology,* 26**,** 1152-1159.

RAGHU, G., ANSTROM, K. J., KING, T. E., JR., LASKY, J. A. & MARTINEZ, F. J. 2012. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med,* 366**,** 1968-77.

RAGHU, G., CHEN, S. Y., YEH, W. S., MARONI, B., LI, Q., LEE, Y. C. & COLLARD, H. R. 2014. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med,* 2**,** 566-72.

RAGHU, G., COLLARD, H. R., EGAN, J. J., MARTINEZ, F. J., BEHR, J., BROWN, K. K., COLBY, T. V., CORDIER, J. F., FLAHERTY, K. R., LASKY, J. A., LYNCH, D. A., RYU, J. H., SWIGRIS, J. J., WELLS, A. U., ANCOCHEA, J., BOUROS, D., CARVALHO, C., COSTABEL, U., EBINA, M., HANSELL, D. M., JOHKOH, T., KIM, D. S., KING, T. E., JR., KONDOH, Y., MYERS, J., MULLER, N. L., NICHOLSON, A. G., RICHELDI, L., SELMAN, M., DUDDEN, R. F., GRISS, B. S., PROTZKO, S. L. & SCHUNEMANN, H. J. 2011. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med,* 183**,** 788-824.

RAGHU, G., NATHAN, S. D., BEHR, J., BROWN, K. K., EGAN, J. J., KAWUT, S. M., FLAHERTY, K. R., MARTINEZ, F. J., WELLS, A. U., SHAO, L., ZHOU, H., HENIG, N., SZWARCBERG, J., GILLIES, H., MONTGOMERY, A. B. & O'RIORDAN, T. G. 2015a. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *Eur Respir J,* 46**,** 1370-7.

RAGHU, G., REMY-JARDIN, M., MYERS, J. L., RICHELDI, L., RYERSON, C. J., LEDERER, D. J., BEHR, J., COTTIN, V., DANOFF, S. K., MORELL, F., FLAHERTY, K. R., WELLS, A., MARTINEZ, F. J., AZUMA, A., BICE, T. J., BOUROS, D., BROWN, K. K., COLLARD, H. R., DUGGAL, A., GALVIN, L., INOUE, Y., JENKINS, R. G., JOHKOH, T., KAZEROONI, E. A., KITAICHI, M., KNIGHT, S. L., MANSOUR, G., NICHOLSON, A. G., PIPAVATH, S. N. J., BUENDÍA-ROLDÁN, I., SELMAN, M., TRAVIS, W. D., WALSH, S. & WILSON, K. C. 2018a. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med,* 198**,** e44-e68.

RAGHU, G., REMY-JARDIN, M., RICHELDI, L., THOMSON, C. C., INOUE, Y., JOHKOH, T., KREUTER, M., LYNCH, D. A., MAHER, T. M., MARTINEZ, F. J., MOLINA-MOLINA, M., MYERS, J. L., NICHOLSON, A. G., RYERSON, C. J., STREK, M. E., TROY, L. K., WIJSENBEEK, M., MAMMEN, M. J., HOSSAIN, T., BISSELL, B. D., HERMAN, D. D., HON, S. M., KHEIR, F., KHOR, Y. H., MACREA, M., ANTONIOU, K. M., BOUROS, D., BUENDIA-ROLDAN, I., CARO, F., CRESTANI, B., HO, L., MORISSET, J., OLSON, A. L., PODOLANCZUK, A., POLETTI, V., SELMAN, M., EWING, T., JONES, S., KNIGHT, S. L., GHAZIPURA, M. & WILSON, K. C. 2022. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med,* 205**,** e18-e47.

RAGHU, G., REMY-JARDIN, M., RYERSON, C. J., MYERS, J. L., KREUTER, M., VASAKOVA, M., BARGAGLI, E., CHUNG, J. H., COLLINS, B. F., BENDSTRUP, E., CHAMI, H. A., CHUA, A. T., CORTE, T. J., DALPHIN, J. C., DANOFF, S. K., DIAZ-MENDOZA, J., DUGGAL, A., EGASHIRA, R., EWING, T., GULATI, M., INOUE, Y., JENKINS, A. R., JOHANNSON, K. A., JOHKOH, T., TAMAE-KAKAZU, M., KITAICHI, M., KNIGHT, S. L., KOSCHEL, D., LEDERER, D. J., MAGETO, Y., MAIER, L. A., MATIZ, C., MORELL, F., NICHOLSON, A. G., PATOLIA, S., PEREIRA, C. A., RENZONI, E. A., SALISBURY, M. L., SELMAN, M., WALSH, S. L. F., WUYTS, W. A. & WILSON, K. C. 2020. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med,* 202**,** e36-e69.

RAGHU, G., RICHELDI, L., JAGERSCHMIDT, A., MARTIN, V., SUBRAMANIAM, A., OZOUX, M. L., ESPERET, C. A. & SOUBRANE, C. 2018b. Idiopathic Pulmonary Fibrosis: Prospective, Case-Controlled Study of Natural History and Circulating Biomarkers. *Chest,* 154**,** 1359-1370.

RAGHU, G., ROCHWERG, B., ZHANG, Y., GARCIA, C. A., AZUMA, A., BEHR, J., BROZEK, J. L., COLLARD, H. R., CUNNINGHAM, W., HOMMA, S., JOHKOH, T., MARTINEZ, F. J., MYERS, J., PROTZKO, S. L., RICHELDI, L., RIND, D., SELMAN, M., THEODORE, A., WELLS, A. U., HOOGSTEDEN, H. & SCHÜNEMANN, H. J. 2015b. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med,* 192**,** e3-19.

RAGHU, G., WELLS, A. U., NICHOLSON, A. G., RICHELDI, L., FLAHERTY, K. R., LE MAULF, F., STOWASSER, S., SCHLENKER-HERCEG, R. & HANSELL, D. M. 2017. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. *Am J Respir Crit Care Med,* 195**,** 78-85.

RAGHU, G., WEYCKER, D., EDELSBERG, J., BRADFORD, W. Z. & OSTER, G. 2006. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med,* 174**,** 810-6.

RAIMUNDO, K., SOLOMON, J. J., OLSON, A. L., KONG, A. M., COLE, A. L., FISCHER, A. & SWIGRIS, J. J. 2019. Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality. *J Rheumatol,* 46**,** 360-369.

RAY, K., COENEGRACHTS, T., VAN STEENBERGEN, S., HALILOVIC, A., MAES, J., DE SADELEER, L., JANSSENS, W. & TOPALOVIC, M. 2022. Artificial Intelligence Powered Spirometry Enables Early Detection of Interstitial Lung Disease. *C103. IT'S NOT JUST ABOUT IPF.* American Thoracic Society.

RICHELDI, L., DU BOIS, R. M., RAGHU, G., AZUMA, A., BROWN, K. K., COSTABEL, U., COTTIN, V., FLAHERTY, K. R., HANSELL, D. M., INOUE, Y., KIM, D. S., KOLB, M., NICHOLSON, A. G., NOBLE, P. W., SELMAN, M., TANIGUCHI, H., BRUN, M., LE MAULF, F., GIRARD, M., STOWASSER, S., SCHLENKER-HERCEG, R., DISSE, B. & COLLARD, H. R. 2014. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. *The New England journal of medicine,* 370**,** 2071-2082.

ROMEI, C., TAVANTI, L., SBRAGIA, P., DE LIPERI, A., CARROZZI, L., AQUILINI, F., PALLA, A. & FALASCHI, F. 2015. Idiopathic interstitial pneumonias: do HRCT criteria established by ATS/ERS/JRS/ALAT in 2011 predict disease progression and prognosis? *Radiol Med,* 120**,** 930-40.

ROMEI, C., TAVANTI, L. M., TALIANI, A., DE LIPERI, A., KARWOSKI, R., CELI, A., PALLA, A., BARTHOLMAI, B. J. & FALASCHI, F. 2020. Automated Computed Tomography analysis in the assessment of Idiopathic Pulmonary Fibrosis severity and progression. *Eur J Radiol,* 124**,** 108852.

ROONEY, S., MCFADYEN, D. A., WOOD, D. L., MOFFAT, D. F. & PAUL, P. L. 2019. Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis. *Mult Scler Relat Disord,* 35**,** 158-163.

ROUBILLE, C. & HARAOUI, B. 2014. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum,* 43**,** 613-26.

ROZANSKI, C. & MURA, M. 2014. Multi-dimensional indices to stage idiopathic pulmonary fibrosis: a systematic review. *Sarcoidosis Vasc Diffuse Lung Dis,* 31**,** 8-18.

RYERSON, C. J., CAYOU, C., TOPP, F., HILLING, L., CAMP, P. G., WILCOX, P. G., KHALIL, N., COLLARD, H. R. & GARVEY, C. 2014a. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med,* 108**,** 203-10.

RYERSON, C. J., HARTMAN, T., ELICKER, B. M., LEY, B., LEE, J. S., ABBRITTI, M., JONES, K. D., KING, T. E., JR., RYU, J. & COLLARD, H. R. 2013. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest,* 144**,** 234-240.

RYERSON, C. J., VITTINGHOFF, E., LEY, B., LEE, J. S., MOONEY, J. J., JONES, K. D., ELICKER, B. M., WOLTERS, P. J., KOTH, L. L., KING, T. E., JR. & COLLARD, H. R. 2014b. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest,* 145**,** 723-728.

SALISBURY, M. L., TOLLE, L. B., XIA, M., MURRAY, S., TAYOB, N., NAMBIAR, A. M., SCHMIDT, S. L., LAGSTEIN, A., MYERS, J. L., GROSS, B. H., KAZEROONI, E. A., SUNDARAM, B., CHUGHTAI, A. R.,

MARTINEZ, F. J. & FLAHERTY, K. R. 2017. Possible UIP pattern on high-resolution computed tomography is associated with better survival than definite UIP in IPF patients. *Respir Med,* 131**,** 229-235.

SALVI, S. S. & BARNES, P. J. 2009. Chronic obstructive pulmonary disease in non-smokers. *Lancet,* 374**,** 733-43.

SATO, T., TSUJINO, I., TANINO, M., OHIRA, H. & NISHIMURA, M. 2013. Broad and heterogeneous vasculopathy in pulmonary fibrosis and emphysema with pulmonary hypertension. *Respirol Case Rep,* 1**,** 10-3.

SCHNEEBERGER, T., GLOECKL, R., JAROSCH, I., DRECHSEL, F., KOCZULLA, A. R. & KENN, K. 2018. The minimal important difference for the 1-minute sit-to-stand test following pulmonary rehabilitation in patients with COPD – a prospective observational trial. *European Respiratory Journal,* 52**,** PA1431.

SCHOENHEIT, G., BECATTELLI, I. & COHEN, A. H. 2011. Living with idiopathic pulmonary fibrosis: an in-depth qualitative survey of European patients. *Chron Respir Dis,* 8**,** 225-31.

SEALEDENVELOPE. 2023. *Randomisation and Online Databases for Clinical Trials,* [Online]. sealed envelope. Available: https://www.sealedenvelope.com/ [Accessed 2022].

SEPÚLVEDA-LOYOLA, W., OSADNIK, C., PHU, S., MORITA, A. A., DUQUE, G. & PROBST, V. S. 2020. Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle,* 11**,** 1164-1176.

SHARP, C., ADAMALI, H. & MILLAR, A. B. 2016. Ambulatory and short-burst oxygen for interstitial lung disease. *Cochrane Database Syst Rev,* 7**,** Cd011716.

SHEEAN, P. M., PETERSON, S. J., GOMEZ PEREZ, S., TROY, K. L., PATEL, A., SCLAMBERG, J. S., AJANAKU, F. C. & BRAUNSCHWEIG, C. A. 2014. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. *JPEN J Parenter Enteral Nutr,* 38**,** 873-9.

SHEN, L., LI, Q. & WENG, D. The Preliminary Evaluation Of The Effectiveness And Safety Of'pulmonary Fibrosis Rehabilitation Exercise'. American Journal of Respiratory and Critical Care Medicine, 2016. AMER THORACIC SOC 25 BROADWAY, 18 FL, NEW YORK, NY 10004 USA.

SHEN, L., ZHANG, Y., SU, Y., WENG, D., ZHANG, F., WU, Q., CHEN, T., LI, Q., ZHOU, Y., HU, Y., JIANG, X., JIN, X., ZHANG, A. & LI, H. 2021. New pulmonary rehabilitation exercise for pulmonary fibrosis to improve the pulmonary function and quality of life of patients with idiopathic pulmonary fibrosis: a randomized control trial. *Ann Palliat Med,* 10**,** 7289-7297.

SHINGAI, K., MATSUDA, T., KONDOH, Y., KIMURA, T., KATAOKA, K., YOKOYAMA, T., YAMANO, Y., OGAWA, T., WATANABE, F., HIRASAWA, J. & KOZU, R. 2021. Cutoff Points for Step Count to Predict 1-year All-Cause Mortality in Patients with Idiopathic Pulmonary Fibrosis. *Respiration,* 100**,** 1151-1157.

SILVA, M., FERNANDES, A., PEREIRA, A. R., MADANELO, S., CLEMÊNCIO, T. & FERREIRA, P. G. 2022. Awareness towards the main ILD among primary care physicians. *Multidiscip Respir Med,* 17**,** 848.

SINGH, S., BAIRWA, M., COLLINS, B. F., SHARMA, B. B., JOSHI, J. M., TALWAR, D., SINGH, N., PILANIA, K., BHATTACHARYA, P., GUPTA, N., CHETAMBATH, R., GHOSHAL, A. G., KANT, S., KOUL, P. A., DHAR, R., SWARNAKAR, R., SINGH, V. & RAGHU, G. 2021. Survival predictors of interstitial lung disease in India: Follow-up of Interstitial Lung Disease India registry. *Lung India,* 38**,** 5-11.

SINGH, S., COLLINS, B. F., SHARMA, B. B., JOSHI, J. M., TALWAR, D., KATIYAR, S., SINGH, N., HO, L., SAMARIA, J. K., BHATTACHARYA, P., GUPTA, R., CHAUDHARI, S., SINGH, T., MOOND, V., PIPAVATH, S., AHUJA, J., CHETAMBATH, R., GHOSHAL, A. G., JAIN, N. K., DEVI, H. J., KANT, S., KOUL, P., DHAR, R., SWARNAKAR, R., SHARMA, S. K., ROY, D. J., SARMAH, K. R., JANKHARIA, B., SCHMIDT, R., KATIYAR, S. K., JINDAL, A., MANGAL, D. K., SINGH, V. & RAGHU, G. 2017. Interstitial Lung Disease in India. Results of a Prospective Registry. *Am J Respir Crit Care Med,* 195**,** 801-813.

SINHA, A., PATEL, A. S., SIEGERT, R. J., BAJWAH, S., MAHER, T. M., RENZONI, E. A., WELLS, A. U., HIGGINSON, I. J. & BIRRING, S. S. 2019. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ open respiratory research,* 6**,** e000363-e000363.

SONG, J. W., HONG, S.-B., LIM, C.-M., KOH, Y. & KIM, D. S. 2011. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *European Respiratory Journal,* 37**,** 356-363.

SPAGNOLO, P., RYERSON, C. J., PUTMAN, R., OLDHAM, J., SALISBURY, M., SVERZELLATI, N., VALENZUELA, C., GULER, S., JONES, S., WIJSENBEEK, M. & COTTIN, V. 2021. Early diagnosis of fibrotic interstitial lung disease: challenges and opportunities. *Lancet Respir Med,* 9**,** 1065-1076.

SPRUIT, M. A., SINGH, S. J., GARVEY, C., ZUWALLACK, R., NICI, L., ROCHESTER, C., HILL, K., HOLLAND, A. E., LAREAU, S. C., MAN, W. D., PITTA, F., SEWELL, L., RASKIN, J., BOURBEAU, J., CROUCH, R., FRANSSEN, F. M., CASABURI, R., VERCOULEN, J. H., VOGIATZIS, I., GOSSELINK, R., CLINI, E. M., EFFING, T. W., MALTAIS, F., VAN DER PALEN, J., TROOSTERS, T., JANSSEN, D. J., COLLINS, E., GARCIA-AYMERICH, J., BROOKS, D., FAHY, B. F., PUHAN, M. A., HOOGENDOORN, M., GARROD, R., SCHOLS, A. M., CARLIN, B., BENZO, R., MEEK, P., MORGAN, M., RUTTEN-VAN MOLKEN, M. P., RIES, A. L., MAKE, B., GOLDSTEIN, R. S., DOWSON, C. A., BROZEK, J. L., DONNER, C. F. & WOUTERS, E. F. 2013. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med,* 188**,** e13-64.

SUGINO, K., ISHIDA, F., KIKUCHI, N., HIROTA, N., SANO, G., SATO, K., ISOBE, K., SAKAMOTO, S., TAKAI, Y. & HOMMA, S. 2014. Comparison of clinical characteristics and prognostic factors of combined pulmonary fibrosis and emphysema versus idiopathic pulmonary fibrosis alone. *Respirology,* 19**,** 239-245.

SUMIKAWA, H., JOHKOH, T., COLBY, T. V., ICHIKADO, K., SUGA, M., TANIGUCHI, H., KONDOH, Y., OGURA, T., ARAKAWA, H., FUJIMOTO, K., INOUE, A., MIHARA, N., HONDA, O., TOMIYAMA, N., NAKAMURA, H. & MÜLLER, N. L. 2008. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. *Am J Respir Crit Care Med,* 177**,** 433-9.

SUZUKI, A., KONDOH, Y. & FISCHER, A. 2017. Recent advances in connective tissue disease related interstitial lung disease. *Expert Rev Respir Med,* 11**,** 591-603.

SUZUKI, Y., MORI, K., AONO, Y., KONO, M., HASEGAWA, H., YOKOMURA, K., NAOI, H., HOZUMI, H., KARAYAMA, M., FURUHASHI, K., ENOMOTO, N., FUJISAWA, T., NAKAMURA, Y., INUI, N., NAKAMURA, H. & SUDA, T. 2021. Combined assessment of the GAP index and body mass index at antifibrotic therapy initiation for prognosis of idiopathic pulmonary fibrosis. *Sci Rep,* 11**,** 18579.

SVERZELLATI, N., GUERCI, L., RANDI, G., CALABRÒ, E., LA VECCHIA, C., MARCHIANÒ, A., PESCI, A., ZOMPATORI, M. & PASTORINO, U. 2011. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J,* 38**,** 392-400.

SWIGRIS, J. J., FAIRCLOUGH, D. L., MORRISON, M., MAKE, B., KOZORA, E., BROWN, K. K. & WAMBOLDT, F. S. 2011. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care,* 56**,** 783-9.

TASHKIN, D. P., ALTOSE, M. D., BLEECKER, E. R., CONNETT, J. E., KANNER, R. E., LEE, W. W. & WISE, R. 1992. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. *Am Rev Respir Dis,* 145**,** 301-10.

TERRAS ALEXANDRE, A., MARTINS, N., RAIMUNDO, S., MELO, N., CATETANO MOTA, P., NOVAIS, E. B. H., PEREIRA, J. M., CUNHA, R., GUIMARÃES, S., SOUTO MOURA, C. & MORAIS, A. 2020. Impact of Azathioprine use in chronic hypersensitivity pneumonitis patients. *Pulm Pharmacol Ther,* 60**,** 101878.

TODD, N. W., JEUDY, J., LAVANIA, S., FRANKS, T. J., GALVIN, J. R., DEEPAK, J., BRITT, E. J. & ATAMAS, S. P. 2011. Centrilobular emphysema combined with pulmonary fibrosis results in improved survival. *Fibrogenesis Tissue Repair,* 4**,** 6.

TOMASSETTI, S., RAVAGLIA, C., WELLS, A. U., CAVAZZA, A., COLBY, T. V., ROSSI, G., LEY, B., RYU, J. H., PUGLISI, S., ARCADU, A., MARCHI, M., SULTANI, F., MARTINELLO, S., DONATI, L., GURIOLI, C., GURIOLI, C., TANTALOCCO, P., HETZEL, J., DUBINI, A., PICIUCCHI, S., KLERSY, C., LAVORINI, F. & POLETTI, V. 2020. Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study. *Lancet Respir Med,* 8**,** 786-794.

TOMASSETTI, S., RYU, J. H. & POLETTI, V. 2015. Staging systems and disease severity assessment in interstitial lung diseases. *Curr Opin Pulm Med,* 21**,** 463-9.

TOMIOKA, H., MAMESAYA, N., YAMASHITA, S., KIDA, Y., KANEKO, M. & SAKAI, H. 2016. Combined pulmonary fibrosis and emphysema: effect of pulmonary rehabilitation in comparison with chronic obstructive pulmonary disease. *BMJ Open Respir Res,* 3**,** e000099.

TOPALOVIC, M., DAS, N., BURGEL, P.-R., DAENEN, M., DEROM, E., HAENEBALCKE, C., JANSSEN, R., KERSTJENS, H. A. M., LIISTRO, G., LOUIS, R., NINANE, V., PISON, C., SCHLESSER, M., VERCAUTER, P., VOGELMEIER, C. F., WOUTERS, E., WYNANTS, J. & JANSSENS, W. 2019. Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. *European Respiratory Journal,* 53**,** 1801660.

TORRISI, S. E., LEY, B., KREUTER, M., WIJSENBEEK, M., VITTINGHOFF, E., COLLARD, H. R. & VANCHERI, C. 2019. The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicentre observational study. *Eur Respir J,* 53.

TRAVIS, W. D., COSTABEL, U., HANSELL, D. M., KING, T. E., JR., LYNCH, D. A., NICHOLSON, A. G., RYERSON, C. J., RYU, J. H., SELMAN, M., WELLS, A. U., BEHR, J., BOUROS, D., BROWN, K. K., COLBY, T. V., COLLARD, H. R., CORDEIRO, C. R., COTTIN, V., CRESTANI, B., DRENT, M., DUDDEN, R. F., EGAN, J., FLAHERTY, K., HOGABOAM, C., INOUE, Y., JOHKOH, T., KIM, D. S., KITAICHI, M., LOYD, J., MARTINEZ, F. J., MYERS, J., PROTZKO, S., RAGHU, G., RICHELDI, L., SVERZELLATI, N., SWIGRIS, J. & VALEYRE, D. 2013. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med,* 188**,** 733-48.

TROOSTERS, T., CASABURI, R., GOSSELINK, R. & DECRAMER, M. 2005. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 172**,** 19-38.

TROY, L. K., GRAINGE, C., CORTE, T. J., WILLIAMSON, J. P., VALLELY, M. P., COOPER, W. A., MAHAR, A., MYERS, J. L., LAI, S., MULYADI, E., TORZILLO, P. J., PHILLIPS, M. J., JO, H. E., WEBSTER, S. E., LIN, Q. T., RHODES, J. E., SALAMONSEN, M., WROBEL, J. P., HARRIS, B., DON, G., WU, P. J. C., NG, B. J., OLDMEADOW, C., RAGHU, G. & LAU, E. M. T. 2020. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med,* 8**,** 171-181.

UENO, F., KITAGUCHI, Y., SHIINA, T., ASAKA, S., YASUO, M., WADA, Y., KINJO, T., YOSHIZAWA, A. & HANAOKA, M. 2020. The Interstitial Lung Disease-Gender-Age-Physiology Index Can Predict the Prognosis in Surgically Resected Patients with Interstitial Lung Disease and Concomitant Lung Cancer. *Respiration,* 99**,** 9-18.

VIVEK, K., JANMEJA, A. K., AGGARWAL, D. & SOOD, P. 2017. Pulmonary rehabilitation in patients with interstitial lung diseases in an outpatient setting: a randomised controlled trial. *The Indian journal of chest diseases & allied sciences,* 59**,** 75-80.

VOGIATZIS, I., NANAS, S., KASTANAKIS, E., GEORGIADOU, O., PAPAZAHOU, O. & ROUSSOS, C. 2004. Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *Eur Respir J,* 24**,** 385-90.

VOGIATZIS, I., NANAS, S. & ROUSSOS, C. 2002. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J,* 20**,** 12-9.

WALLAERT, B., KYHENG, M., LABREUCHE, J., STELIANIDES, S., WEMEAU, L. & GROSBOIS, J. M. 2020. Long-term effects of pulmonary rehabilitation on daily life physical activity of patients with stage IV sarcoidosis: A randomized controlled trial. *Respir Med Res,* 77**,** 1-7.

WALLAERT, B., MONGE, E., LE ROUZIC, O., WÉMEAU-STERVINOU, L., SALLERON, J. & GROSBOIS, J. M. 2013. Physical activity in daily life of patients with fibrotic idiopathic interstitial pneumonia. *Chest,* 144**,** 1652-1658.

WALSTON, J. D. 2012. Sarcopenia in older adults. *Curr Opin Rheumatol,* 24**,** 623-7.

WASCHKI, B., KIRSTEN, A., HOLZ, O., MÜLLER, K. C., MEYER, T., WATZ, H. & MAGNUSSEN, H. 2011. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest,* 140**,** 331-342.

WELLS, A. U., DESAI, S. R., RUBENS, M. B., GOH, N. S., CRAMER, D., NICHOLSON, A. G., COLBY, T. V., DU BOIS, R. M. & HANSELL, D. M. 2003. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med,* 167**,** 962-9.

WELLS, A. U., FLAHERTY, K. R., BROWN, K. K., INOUE, Y., DEVARAJ, A., RICHELDI, L., MOUA, T., CRESTANI, B., WUYTS, W. A., STOWASSER, S., QUARESMA, M., GOELDNER, R. G., SCHLENKER-HERCEG, R. & KOLB, M. 2020. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med,* 8**,** 453-460.

WIGGINS, J., STRICKLAND, B. & TURNER-WARWICK, M. 1990. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. *Respir Med,* 84**,** 365-9.

WIJSENBEEK, M. & COTTIN, V. 2020. Spectrum of Fibrotic Lung Diseases. *N Engl J Med,* 383**,** 958-968.

WIJSENBEEK, M., KREUTER, M., OLSON, A., FISCHER, A., BENDSTRUP, E., WELLS, C. D., DENTON, C. P., MOUNIR, B., ZOUAD-LEJOUR, L., QUARESMA, M. & COTTIN, V. 2019. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. *Curr Med Res Opin,* 35**,** 2015-2024.

WIJSENBEEK, M., SUZUKI, A. & MAHER, T. M. 2022. Interstitial lung diseases. *Lancet,* 400**,** 769-786.

WIKHOLM, J. B. & BOHANNON, R. W. 1991. Hand-held Dynamometer Measurements: Tester Strength Makes a Difference. *J Orthop Sports Phys Ther,* 13**,** 191-8.

WORDCLOUDPLUS. 2023. *Word cloud generator* [Online]. WordCloud+. Available: https://wordcloudplus.com/ [Accessed 2023].

WU, X., KIM, G. H., SALISBURY, M. L., BARBER, D., BARTHOLMAI, B. J., BROWN, K. K., CONOSCENTI, C. S., DE BACKER, J., FLAHERTY, K. R., GRUDEN, J. F., HOFFMAN, E. A., HUMPHRIES, S. M., JACOB, J., MAHER, T. M., RAGHU, G., RICHELDI, L., ROSS, B. D., SCHLENKER-HERCEG, R., SVERZELLATI, N., WELLS, A. U., MARTINEZ, F. J., LYNCH, D. A., GOLDIN, J. & WALSH, S. L. F. 2019. Computed Tomographic Biomarkers in Idiopathic Pulmonary Fibrosis. The Future of Quantitative Analysis. *Am J Respir Crit Care Med,* 199**,** 12-21.

XIAO, K., LIU, J. H., DING, X. P., CUI, F. T., WANG, H. B., WANG, M. M. & SHEN, F. H. 2019. [Comprehensive rehabilitation of individualized exercise program for coal workers pneumoconiosis in Huaibei Coal Mine Group]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi,* 37**,** 357-361.

XUE, Q. L., WALSTON, J. D., FRIED, L. P. & BEAMER, B. A. 2011. Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: the women's health and aging study. *Arch Intern Med,* 171**,** 1119-21.

YAMAUCHI, H., BANDO, M., BABA, T., KATAOKA, K., YAMADA, Y., YAMAMOTO, H., MIYAMOTO, A., IKUSHIMA, S., JOHKOH, T., SAKAI, F., TERASAKI, Y., HEBISAWA, A., KAWABATA, Y., SUGIYAMA, Y. & OGURA, T. 2016. Clinical Course and Changes in High-Resolution Computed Tomography Findings in Patients with Idiopathic Pulmonary Fibrosis without Honeycombing. *PLoS One,* 11**,** e0166168.

YAMAZAKI, R., NISHIYAMA, O., YOSHIKAWA, K., TOHDA, Y. & MATSUMOTO, H. 2022. Outcome of patients who were incidentally diagnosed with idiopathic pulmonary fibrosis: How early in the disease should we identify patients? *Respir Med,* 201**,** 106933.

ZAKI, S., MOIZ, J. A., MUJADDADI, A., ALI, M. S. & TALWAR, D. 2022. Does inspiratory muscle training provide additional benefits during pulmonary rehabilitation in people with interstitial lung disease? A randomized control trial. *Physiother Theory Pract***,** 1-11.

ZHANG, L., ZHANG, C., DONG, F., SONG, Q., CHI, F., LIU, L., WANG, Y. & CHE, C. 2016a. Combined pulmonary fibrosis and emphysema: a retrospective analysis of clinical characteristics, treatment and prognosis. *BMC Pulm Med,* 16**,** 137.

ZHANG, M., YOSHIZAWA, A., KAWAKAMI, S., ASAKA, S., YAMAMOTO, H., YASUO, M., AGATSUMA, H., TOISHI, M., SHIINA, T., YOSHIDA, K., HONDA, T. & ITO, K. I. 2016b. The histological characteristics and clinical outcomes of lung cancer in patients with combined pulmonary fibrosis and emphysema. *Cancer Med,* 5**,** 2721-2730.

ZIGMOND, A. S. & SNAITH, R. P. 1983. The hospital anxiety and depression scale. *Acta Psychiatr Scand,* 67**,** 361-70.

ZINELLU, A., COLLU, C., ZINELLU, E., AHMAD, K., NASSER, M., TRACLET, J., SOTGIU, E., MELLINO, S., MANGONI, A. A., CARRU, C., PIRINA, P., COTTIN, V. & FOIS, A. G. 2021. IC4: a new combined predictive index of mortality in idiopathic pulmonary fibrosis. *Panminerva Med*.

Appendices

Appendix 1 Letter of Approval

NHS
Health Research Authority

North East - Newcastle & North Tyneside 2 Research Ethics Committee

NHS BT Blood Donor Centre
Holland Drive
Newcastle upon Tyne
Tyne and Wear
NE2 4NQ

Tel: 02071048026

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

29 January 2019

Mr Maher AlQuaimi
Cookson 1.072, Floor1 , Cookson Building Medical School
Newcastle University
Newcastle
NE2 4HH

Dear Mr AlQuaimi

Study title:	**The feasibility of respiratory muscle training as part of an interstitial lung disease pulmonary rehabilitation programme**
REC reference:	**18/NE/0037**
Protocol number:	**n/a**
Amendment number:	**Substantial amendment 1, 04-01-19**
Amendment date:	**20 December 2018**
IRAS project ID:	**211628**

The above amendment was reviewed on 22 January 2019 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

A Research Ethics Committee established by the Health Research Authority

Appendix 2 Recorded Educational Sessions Abstract

09.02 - Physiotherapists

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Successful provision of a specialised Interstitial Lung Diseases (ILD) pulmonary rehabilitation program during COVID-19 using recorded ILD educational videos developed by allied health professionals

Chronic diseases, Education, Covid-19

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Introduction: Newcastle Hospitals NHS Trust established a regional specialist ILD pulmonary rehabilitation program (PRP) in 2017. COVID-19 required an adaptation of the education element for the service to remain viable, due to social distancing requirements and staffing. **Aim:** To produce and qualitatively evaluate multi-disciplinary educational videos for ILD patients attending PRP. **Methods:** The existing education programme was modified with input from a focus group of ILD patients. Six ILD educational videos were recorded using video conferencing platforms. These covered ILD disease and management, management of breathlessness, nutrition in ILD, inspiratory muscle training, palliative care, and the benefits and maintenance of exercise. Palliative care and ILD consultants, ILD specialist nurses, respiratory specialist physiotherapist, and a dietitian provided content. Videos were used by patients in hospital PRP and at home. Qualitative patient feedback was collected. **Results:** 18 patients were able to access the videos. Feedback was positive: "useful", "informative", "I regret looking at the internet" and "I would rather receive knowledge from clinicians I know". Patient feedback led to modification of the initial video. **Conclusion:** Recorded educational videos were successfully incorporated into an existing PRP, allowing continuity of quality during pandemic. This allowed patients and carers access to quality information at their own pace. Positive patient feedback was received, and clinician workload was reduced. Videos will continue to be incorporated in a regional blended PRP model.

Appendix 3 K-BILD Questionnaire

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.

1. Every time 2. Most times 3. Several Times 4. Some times 5. Occasionally 6. Rarely 7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung complaint?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

4. In the last 2 weeks have you avoided doing things that make you breathless?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. None of the time 2. Hardly any of the time 3. A little of the time 4. Some of the time 5. A good bit of the time 6. Most of the time 7. All of the time

6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

12. In the last 2 weeks have you expected your lung complaint to get worse?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount 2. A large amount 3. A considerable amount 4.A reasonable amount 5. A small amount 6. Hardly at all 7. Not at all

Appendix 4 Fatigue Severity Scale

FATIGUE SEVERITY SCALE (FSS)

Date _____ Name _____

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

VISUAL ANALOGUE FATIGUE SCALE (VAFS)

Please mark an "X" on the number line which describes your global fatigue with 0 being worst and 10 being normal.

0	1	2	3	4	5	6	7	8	9	10

Appendix 5 Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)