Proof of Concept of a Tailored Rehabilitation Programme for Interstitial Lung Disease, including Idiopathic Pulmonary Fibrosis

Maher Al Quaimi MsRC, RRT-NPS

Student Number: 150617710

Email: m.m.s.al-quaimi2@newcastle.ac.uk

PhD Candidate

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Translational and Clinical Research Institute
Medical School
Newcastle University

Supervisors: Prof. Chris Ward and Dr. Ian Forrest

Abstract

Although the National Institute for Health and Care Excellence (NICE) recommended pulmonary rehabilitation program (PRP) for subjects with interstitial lung disease (ILD), tailored services and research in this key treatment area are limited.

In this project UK Biobank data was retrieved and analysed for 122 subjects with ILD. A regional service of PR for ILD was established and 18 subjects with ILD were recruited. This was followed by a proof of concept RCT for 20 subjects with ILD. Similar methodology for the clinical regional service and the RCT was used and in the RCT subjects were allocated/ and or randomised to intervention inspiratory muscle training (IMT) with PRP or PRP alone. The subjects attended an 8 week program in a hospice care setting with one supervised and two unsupervised sessions. The supervised session was conducted in a novel hospice care partnership setting and included education, exercise, and relaxation sessions. After PRP, feedback was collected from all subjects.

The UK Biobank data provided limited data for ILD, however, sedentary time showed correlation with weight (r=0.39, n=51, p=0.004), and with moderate and vigorous activities (r=-0.32, n=51, p=0.021). The regional PRP service and RCT were shown to be feasible and appreciated by patients and carers, and attendance for RCT was 81%. In the RCT in general, when IMT was used, improvement was seen in maximum inspiratory pressure (MIP and six-minute walk test (6MWT). Circulating (Matrix Metallopeptidase 7 (MMP7) levels and 6MWT data showed improvement regardless the use of IMT. Variability was seen in other outcomes, where they either maintained, dropped, or improved. The feedback showed an appreciation for 'exercise', 'information' and 'group', stressing the importance of the education talks in the group therapy. There were also suggestions/requests for longer PRP, showing subjects appreciation for the program. In conclusion, UK Biobank contained limited data specifically for ILD research. A novel tailored PRP was established and was feasible in collaboration with a hospice healthcare partner. This was valued by subjects, carers and healthcare colleagues. Response to outcomes varied considerably in the RCT and regional service but the data suggested potential end points for further research trials. These could be investigated in future studies with larger sample sizes.

Declaration

This thesis is based on research performed in the Institute for Cell and Molecular Biosciences, Newcastle University, Marie Curie Hospice Care, Newcastle, and the Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle. I performed the laboratory and hospital work, breathing muscle training and assessment, and analysis of the results. I also coordinated the tailored pulmonary rehabilitation programme. Exceptions to the above are outlined below:

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Laura and Jessica did the 6-minute walk test;

Laura and Fran did the exercise sessions;

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6MWT	**Six-minute walk test**
ACE	Angiotensin-converting enzyme
ANA	Antinuclear antibodies
BDI	Baseline Dyspnoea Index
BMI	Body mass index
CBT	Cognitive behaviour therapy
COP	Cryptogenic organising pneumonia
CPET	Cardiopulmonary exercise testing
CPFE	Combined pulmonary fibrosis and emphysema
CRQ	Chronic respiratory disease questionnaire
CXR	Chest x-ray
DIP	Desquamative interstitial pneumonia
DLCO	Diffusing capacity of the lungs for carbon monoxide
FAS	Fatigue Assessment Scale
FEV_1	Forced expiratory volume in the first second
FSS	Fatigue Severity Scale
FVC	Forced vital capacity
HADS	Hospital Anxiety and Depression Scale
HHD	Handheld dynameter
HP	Hypersensitivity pneumonitis

HRCT	High-resolution computed tomography
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IMT	Inspiratory muscle training
IPF	Idiopathic pulmonary fibrosis
IV	Intravenous
K-Bild	King's brief interstitial lung disease
LIP	Lymphoid interstitial pneumonia
mBorg	Modified Borg
MCID	Minimal clinically important difference
MDT	Multidisciplinary team
MIP	Maximum inspiratory pressure
MMP7	Matrix metalloproteinase-7
MRC	Medical Research Council
MVV	Maximal voluntary ventilation
NICE	National Institute for Health and Care Excellence
NMD	Neuromuscular disease
NSIP	Non-specific interstitial pneumonia
PFT	Pulmonary function test
PPI	Proton pump inhibitor
PR	Pulmonary rehabilitation

PRP	Pulmonary rehabilitation programme
PT	Physiotherapist
QOL	Quality of life
RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
RCT	Randomised control trial
RVI	Royal Victoria Infirmary
SF-36	36-item short form survey
SGRQ	St George's Respiratory Questionnaire
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SS	Systemic sclerosis
UIP	Usual interstitial pneumonia

Publications, Presentations and Awards directly related to my PhD project

M. Al Quaimi, L. McNeillie, C. Donaldson, J. Harper, J. Hartley, S. Cassidy (2017). 'P159 preliminary experience of a tailored ILD pulmonary rehabilitation programme and inspiratory muscle training delivered in a hospice and home setting. Thorax 72, A170.

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Prizes

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Shortlisted by NICE for the 20 best shared learning case studies in the UK, 2019.

Two-time winner of the Saudi Embassy Award for high achieving PhD students.

Publications during my PhD project not directly related to my PhD project

1: Althuwaybi A, **Al Quaimi M,** Krishnan A, Jones R, Pearson J, Ward C. Hospitalization Outcomes for COVID-19 in Patients with Interstitial Lung Disease: A Potential Role for Aerodigestive Pathophysiology? Am J Respir Crit Care Med. 2021 Feb 15;203(4):521-522. doi: 10.1164/rccm.202010-4031LE. PMID: 33217241; PMCID: PMC7885845.

2: Alqahtani JS, Mendes RG, Aldhahir A, Rowley D, AlAhmari MD, Ntoumenopoulos G, Alghamdi SM, Sreedharan JK, Aldabayan YS, Oyelade T, Alrajeh A, Olivieri C, **AlQuaimi M**, Sullivan J, Almeshari MA, Esquinas A. Global Current Practices of Ventilatory Support Management in COVID-19 Patients: An International Survey. J Multidiscip Healthc. 2020 Nov 18;13:1635-1648. doi: 10.2147/JMDH.S279031. PMID: 33239884; PMCID: PMC7680685.

3: **Maher Mubarak AlQuaimi**, James B Fink and Arzu Ari Efficiency of Different Aerosol Devices and Masks during Noninvasive Positive Pressure Ventilation in a Simulated Adult Lung Model, Journal of Respiratory Medicine and Lung Disease, 2017

4:Arzu Ari, Robert Harwood, Meryl Sheard, **Maher Mubarak Alquaimi**, Bshayer Alhamad and James B Fink Quantifying Aerosol Delivery in Simulated Spontaneously Breathing Patients With Tracheostomy Using Different Humidification Systems With or Without Exhaled Humidity Respiratory Care May 2016, 61 (5) 600-606; DOI: https://doi.org/10.4187/respcare.04127

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Chapter 1. Introduction

Interstitial lung disease (ILD) covers more than 200 chronic lung diseases with different aetiologies. The most common and serious of these is idiopathic pulmonary fibrosis (IPF), which is a chronic, progressive ILD with a median survival time of 3–5 years. Although pulmonary rehabilitation is advocated by the National Institute of Clinical Excellence (NICE), treatment options are limited and often not curative. Moreover, publications and available data on pulmonary rehabilitation in ILD are limited.

The American Thoracic Society and the European Thoracic Society's policy statement (2015) defines pulmonary rehabilitation as 'comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours'. In most UK cases and generally worldwide, although ILD patients receive pulmonary rehabilitation with other chronic lung diseases such as COPD, this creates barriers against optimal rehabilitation and education for ILD patients and it is against NICE recommendations. We therefore decided to establish a pulmonary rehabilitation service tailored to ILD in Newcastle upon Tyne in collaboration with Marie Curie Hospice Care, Newcastle University, and the Newcastle upon Tyne Hospitals, NHS Foundation Trust.

1.1 Methods

The ILD clinic at the RVI Newcastle, in collaboration with Newcastle University, developed a tailored pulmonary rehabilitation programme (PRP) in response to NICE recommendations. The healthcare team included respiratory physiotherapists and nurses, a consultant respiratory physician, and a consultant in palliative care. The eight-week PRP involved three days of exercises performed weekly, one conducted in a Marie Curie hospice and two at home. This involved aerobic, strength, and stretching exercises, with integrated education and relaxation sessions. Inspiratory muscle training (IMT) was undertaken by most patients. The PRP was initially conducted as a clinical service without randomisation, and then a randomised control trial (RCT) was conducted with the same protocol. In addition to the PRP, UK Biobank data were retrieved and analysed for 122 subjects with ILD.

1.2 Results

The clinical service data were collected from 18 patients who had all completed the PRP, with an improvement in maximum inspiratory pressures (MIP) for the intervention group. In the RCT, the study was conducted with 20 subjects with ILD; this was feasible, with the average attendance rate being 81%. An improvement was seen in MIP in the intervention group with a median change of 28 cm H_2O compared to 9 cm H_2O in the control group. The UK Biobank showed correlations in sedentary time with weight, and in sedentary time with moderate to vigorous activity time.

1.3 Conclusion

Our initial experience indicated that a tailored PRP was feasible in people with ILD. All patients were strongly supportive of the initiative and took part in the design of a pilot proof of concept RCT in patients with IPF. These findings suggest that a larger sample study is recommended.

1.4 Thesis Overview

In Chapter Two, I present a literature review on ILD and pulmonary rehabilitation, while Chapter Three covers the methodology. Chapter Four focuses on the Regional Pulmonary Rehabilitation Service we provided for our ILD patients, and in Chapter Five I present the proof-of-concept trial of inspiratory muscle training, in addition to pulmonary rehabilitation in patients with ILD. In Chapter Six, the characteristics of ILD subjects are reviewed from the large dataset, UK BioBank, to create the base of knowledge for our programme. In Chapter Seven, I present the feedback we received from our patients about the programme. Chapter Eight concludes by covering my personal experience with COVID-19.

Chapter 2. Review of the Literature

2.1 Interstitial Lung Disease

2.1.1 Introduction

Interstitial lung disease (ILD) is in fact a group of chronic lung diseases with around 200 different aetiologies, with high disability and mortality rates. The disease affects the interstitium of the lung and limits oxygen transportation across the alveolar capillary membrane. Patients with ILD suffer from limited daily activity, breathlessness, and cough, and this may be associated with depression and anxiety. Idiopathic pulmonary fibrosis is the most common ILD in the UK, with an estimated incidence of 7.44 per 100,000 population and an estimated prevalence of 23.4 cases per 100,000 in Europe and 63 per 100,000 in the United States (Wallis & Spinks, 2015).

IPF is more common in people aged over 45 years with a median age of diagnosis of 70 years. The median survival of IPF patients is three years from diagnosis, and only 20% of IPF patients survive more than five years (NICE, 2015). ILDs have different survival rates depending on the primary diagnosis and its timing, the timing of the treatment, and the presence of other co-morbidities. ILD negatively impacts health, personal wellbeing, and social life, as well as government budgets.

2.1.2 Classification of Interstitial Lung Diseases

ILD is a diverse and complex group of restrictive lung diseases with different primary causes, both known and unknown. Although there is no agreement on a standard classification of ILD, a simplified clinical classification, according to the main cause, can be used to guide its management (Wallis & Spinks, 2015). There are several forms of ILD, including interstitial pneumonias and granulomatous ILD as well as, respectively, ILDs related to connective tissue, inhalation exposure, or drugs. Unclassified ILD cases account for about 10% of all cases. These diseases will now be explored in turn.

Regarding interstitial pneumonias, idiopathic interstitial pneumonias (IIP) are a group of diffuse lung diseases primarily affecting the pulmonary interstitium and septal and bronchovascular tissues. They can also affect alveolar spaces, pulmonary vasculature, and airways. The pathological processes, inflammation, and fibrosis differ between diseases (Chapman et al., 2014). IPF is the most common type of IIP, and is marked by fibrosis of the lung (Wallis & Spinks, 2015). Diagnosis of IIP is based on high-resolution computed tomography (HRCT),

histological changes, history, and clinical findings. Recently, the routine use of surgical and transbronchial biopsy has been discouraged due to an increased risk of mortality, but in some difficult to diagnose cases, biopsy is recommended to make a definitive diagnosis. Before undertaking a biopsy, the risks and benefits must be weighed in addition to considering treatment choices. A biopsy may not be required, depending on the pre-test probability when HRCT and clinical evaluation have secured a diagnosis. Therefore, more emphasis has been placed on the utilisation of HRCT and a multidisciplinary team (MDT) approach.

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial pneumonia characterised by a restrictive pattern of pulmonary function with temporal and septal heterogeneity, and areas of fibrosis and structural change scattered across areas of normal lung. The prevalence of IPF varies from 6 to 17:100,000 and can reach levels of 175:100,000 in patients over 75 years (Wallis & Spinks, 2015). In the UK, a higher incidence can be seen in the North West and Northern Ireland and a lower in the South East (Strongman et al., 2018). The disease's pathology is postulated to result from repeated alveolar injury, thus leading to the activation of mesenchymal cells and the creation of fibroblasts and myofibroblastic foci. The activated mesenchymal cells release excessive extracellular matrix, mainly collagens. Possible genetic involvement of IPF is suggested through polymorphisms of MUC5B and ELMOD2. The findings from the ongoing 100,000 Genomes Project also support that MUC5B is an important gene in IPF and a significant risk factor (Mathai et al., 2016). Clinically, patients with IPF present with the gradual onset of a dry cough and breathlessness, with fine basal inspiratory crackles. About half of patients present with digital clubbing. Cyanosis and cor pulmonale are present in severe cases. Diagnosis is preferably made by specialists within an MDT setting and an HRCT is the gold standard tool for diagnosis. HRCT findings in IPF are bilateral, peripheral and subpleural reticulation, traction bronchiectasis, honeycombing appearance, and architectural distortion (Figure 3). These findings are predominantly basal but can be in middle or upper lung zones if the disease has progressed severely. A ground glass appearance is not common in IPF and can suggest other IIP or ILD diseases. IPF management is challenging, especially with a lack of full understanding of the disease's pathological processes, alongside the heterogeneity of numerous comorbidities, including, but not limited to, cor pulmonale, pulmonary hypertension, and pneumonia. Historically, IPF was managed pharmacologically with steroids as monotherapy or as combinations of prednisolone, azathioprine, and acetylcysteine, or anticoagulants. None of these therapies continue to be recommended as the evidence shows they increase mortality (Idiopathic Pulmonary Fibrosis Clinical Research et al., 2012; Noth et al., 2012).

Currently, a new era of antifibrotic therapies has emerged with promising outcomes. Nintedanib and pirfenidone are the two recommended pharmacological agents for IPF patients with forced vital capacity (FVC) between 50–80% (NICE, 2013) and these two medications have been shown to slow progression of FVC reduction (Fraser & Hoyles, 2016). Pirfenidone was the first of the two drugs approved for IPF. Its use improves six-minute walk test (6MWT) distance and a prolonged progression-free survival time. Evidence shows that disease progression was reduced when pirfenidone began to be used in IPF, as verified by a reduction in the mean decline in FVC by 195 ml. The data analysis from the CAPACITY and ASCEND trials showed a reduction in both all-cause and IPF-related mortality (Noble et al., 2011; King et al., 2014). Pirfenidone is given as nine tablets a day and can lead to photosensitivity in about 12% of patients, and thus screen protection, factor 50 SPF, is advised (Wallis & Spinks, 2015). A study of nintedanib in IPF has been shown to slow the rate of IPF deterioration based on FVC (-114.7 ml with nintedanib versus -239.9 ml with placebo) (Richeldi et al., 2014). Diarrhoea is a common side effect, and the regular dose is two tablets a day.

With non-specific interstitial pneumonia (NSIP), patients are usually affected at a younger age than IPF as the age of onset is 40–50 (Chapman et al., 2014). NSIP can be idiopathic or associated with other systematic diseases like connective tissue disease (Belloli et al., 2016). It has better prognosis compared with IPF and it generally responds to steroids. NSIP has clinical features of weight loss (Belloli et al., 2016), breathlessness and cough. Onset can be gradual or subacute, involving crackles at the bases of the lungs during auscultation, and digital clubbing in a small percentage of patients. Following HRCT, NSIP usually shows as ground glass appearance in the bases with or without reticulation and traction bronchiectasis (Figure 3). The appearance is homogenous in most cases (unlike IPF, where a heterogeneous appearance is more common). Typical pharmacological treatment is corticosteroid (prednisolone 0.5mg/kg) (Chapman et al., 2014).

Cryptogenic organising pneumonia (COP) is another idiopathic disease featuring granulation tissues and the presence of buds (Cordier, 2004). These buds present in the alveolar spaces that are involved in the disease process and can extend into the bronchioles (Chapman et al., 2014). The disease is more common in non-smokers, with a mean age of onset of 55. Typically, patients with COP have a short history of breathlessness with dry cough, usually associated with malaise, fever, weight loss, and myalgia. HRCT usually shows areas of consolidation and air bronchograms, and there may also be a ground glass appearance or small nodules. These are often basal, subpleural and peribronchial. If reticulation is present, this can suggest a poor

treatment response. Steroids, mainly, are the pharmacological treatment for COP, with an initial dose of 1–1.5 mg/kg daily for three months of oral prednisolone. However, in severe cases, IV methylprednisolone 750 mg- 1g/kg/day for three days can be used. COP, generally, has a good prognosis and most patients have a good response to steroids; nonetheless, relapse is not uncommon and prolonged treatment of 6–12 months is usually required (Chapman et al., 2014).

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) occurs in a small percentage of smokers or ex-smokers with bronchiolitis. It is believed to result from the accumulation of pigmented macrophages in the bronchioles and alveolar space (Wells et al., 2003). Mild breathlessness and cough are usually present with crackles on examination, while severe dyspnoea and respiratory failure are less common. HRCT shows centrilobular nodules, ground glass changes (Figure 3), and thick-walled airways. These are usually co-present with centrilobular emphysema. Smoking cessation is an essential step in the disease's management. Corticosteroids are also used but with no clear benefits (Chapman et al., 2014).

Desquamative interstitial pneumonia (DIP) is a rare type of ILD that presents in smokers with similar pathophysiology as RB-ILD but with more extensive diffusion of pigmented macrophages. Indeed, it has been argued that RB-ILD and DIP are the same disease with different levels of severity (Wells et al., 2003). Cough and breathlessness are common over weeks to months, with digital clubbing. HRCT shows a ground glass appearance in all cases, typically lower zone or peripheral. Honeycombing and reticulation may be present but is usually mild (Figure 3). Smoking cessation and corticosteroids are the initial management of DIP, and a high response rate has been reported in retrospective studies (Chapman et al., 2014).

Lymphoid interstitial pneumonia (LIP) is a very rare type of ILD more common in women than men. While it may be idiopathic, it is sometimes related to systematic immune disorders (Cha et al., 2006). It is characterised by diffuse lymphoid infiltrates and often lymphoid hyperplasia. It presents with a steady onset of breathlessness and cough over several years. Fever and weight loss can be present with crackles on examination. HRCT shows a general ground glass appearance (Figure 3), with reticulation and cysts and occasional honeycombing and nodules. Steroids usually improve the symptoms (Chapman et al., 2014).

Connective tissue-related (ILD) disease can be caused or related to a primary connective tissue disease and patients should be seen by a chest specialist. In some conditions, ILD develops from using an immunosuppressant like methotrexate. Typical symptoms can be cough,

dyspnoea, fever or chest pain (Chapman et al., 2014). Different types of connective tissue-related ILD are reviewed below.

Rheumatoid arthritis (RA) is a disease which causes inflammation of the joints, and is usually persistent and peripheral. However, pleural and pulmonary disease involvement is common in men and smokers and this sometimes occurs prior to joint disorders. Rheumatoid arthritis-associated ILD (RA-ILD) has a mean survival of less than three years (Iqbal & Kelly, 2015). Moreover, about 20% of RA patients die due to pneumonia (Chapman et al., 2014). Pulmonary fibrosis is not always symptomatic but can be found in 60% of lung biopsies and tends to occur in patients with systematic diseases like vasculitis, or in patients with seropositive disease or high anti-nuclear antibodies titres. Pulmonary fibrosis in RA presents with progressive dyspnoea, basal crackles, and a restrictive pattern in pulmonary function tests (PFT). HRCT may show a usual interstitial pneumonia (UIP) picture with subpleural basal reticular pattern. Treatment regimens that can be used are steroids, immunosuppressants (Chapman et al., 2014), or disease-modifying antirheumatic drugs (Iqbal & Kelly, 2015).

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting all organs and it is more common in women with dsDNA antibodies present in high concentration. SLE can also be induced by drugs (isoniazid, procainamide, hydralazine, minocycline, penicillamine, anticonvulsants). The American College of Rheumatology has created a list of 12 criteria to diagnose SLE. If four or more of these criteria are present, SLE can be diagnosed. These criteria are: malar or discoid rashes, photosensitivity, oral ulcers, arthritis, serositis, pleuritis or pericarditis, renal, neurological, haematological, immunological disorders, and ANA (antinuclear antibodies) in a raised titre (Chapman et al., 2014). In a cohort of more than 3,000 patients with SLE, only 2% had ILD (Narvaez et al., 2018).

Systemic sclerosis (SS) is more common in women than men at a ratio of 4:1. There are five subtypes with pulmonary complications being the most common cause of death. Pulmonary fibrosis is seen in up to 80% of patients after autopsy and ANA is usually high in SS cases, which varies between different autoimmune diseases (Figure 1). Patients usually present with dyspnoea and fine basal crackles. PFTs show a restrictive pattern with reduced diffusion capacity. HRCT typically shows an NSIP pattern but can also be UIP. Pharmacological treatment can include steroids and cyclophosphamide (Cappelli et al., 2015). Prognosis is better in SS-associated ILD when compared with pure UIP, as this might be related to slower progression rather than response to treatments (Chapman et al., 2014).

Antinuclear antibody (ANA)	**+ve in**
SLE	99%
Rheumatoid arthritis	32%
Juvenile rheumatoid arthritis	76%
Chronic active hepatitis	75%
Sjögren's syndrome	68%
Systemic sclerosis	64%
Polymyositis	
Polyarteritis nodosa	
Myasthenia gravis	
Autoimmune thyroid disease	
Extensive burns	
Normal controls	0–2%
Extractable nuclear antigen (ENA)	**(done by lab if ANA positive)**
Anti-double-stranded DNA—SLE	
Anti Sm—SLE	
Antitopoisomerase 1—diffuse scleroderma	
Anticentromere—limited scleroderma	
Anti Scl-70—pulmonary fibrosis in scleroderma	
Anti Jo-1—myositis	
Anti Ro—Sjögren's, SLE, fetal heart block	
Anti RNP—SLE, scleroderma, myositis, mixed connective tissue disease, and rheumatoid arthritis	
Rheumatoid factor	**+ve in**
Rheumatoid arthritis	70–80%
Sjögren's syndrome	<100%
Felty's syndrome	<100%
Systemic sclerosis	30%
Still's disease	Rarely positive
Infective endocarditis	<50%
SLE	<40%
Normal controls	5–10%
Also: Neoplasms after radio- or chemotherapy Hyperglobulinaemic states Dermatomyositis	

Figure 1. Autoantibodies and disease associations (Wallis & Spinks, 2015)

Another type of ILD caused by inhalation exposure. A history of inhalation exposure to both organic and inorganic materials is a very important aspect of pulmonary and respiratory

diseases. Specifically, in ILD many diseases are caused by prolonged exposure of certain substances, both known and unknown. Two major subtypes of inhalation exposure-related ILD are hypersensitivity pneumonitis and pneumoconiosis, discussed in turn below.

Hypersensitivity pneumonitis (HP) is a group of ILD diseases mostly related to inhalation exposure to organic material, although some inorganic exposure is also called HP. Subjects with HP usually have abnormal or extra allergic responses to specific antigens (Table 1. Significant predictors of hypersensitivity pneumonitis, reproduced from Lacasse et al. (2012, p. 211)), leading to HP in the pulmonary system. The prevalence of HP is generally unknown, but 8% of budgerigar and pigeon guardians can develop HP, and it also occurs in about 5% of farmers. Antigens can vary regarding their source and variably lead to the development of disease (Table 2), with unclear pathology. Diagnosis can be based on a history of exposure and clinical presentation of breathlessness and dry cough. Crackles and squeaks might be heard during auscultation (Chapman et al., 2014). Although antigen and antibody laboratory tests are neither highly specific nor sensitive, they can be very helpful in diagnosis in addition to other available criteria (Lacasse et al., 2012). HRCT in HP shows patchy infiltrates with a ground glass appearance in general (Figure 3), but mosaic attenuation and centrilobular nodules are possible. Honeycombing and traction attenuation is also possible in HP, but mainly in the upper lobes (Chapman et al., 2014). Management of HP can start with avoidance of the antigen, or an instruction to wear respiratory protection if avoidance is difficult or impossible. Prednisone is a typical pharmacological treatment of chronic HP, with prednisone 05mg/kg given until a noticeable improvement, via HRCT or clinical signs, is found. Doses can then be weaned slowly to 10 mg daily. Prognosis of HP is very variable, with death in rare cases.

Variables	OR	95% CI
Exposure to a known offending antigen	38.8	11.6-129.6
Positive precipitating antibodies	5.3	2.7-10.4
Recurrent episodes of symptoms	3.3	1.5-7.5
Inspiratory crackles	4.5	1.8-11.7
Symptoms 4-8 h after exposure	7.2	1.8-28.6
Weight loss	2.0	1.8-28.6

Table 1. Significant predictors of hypersensitivity pneumonitis, reproduced from Lacasse et al. (2012, p. 211)

Antigen	Sources	Diseases
Organisms		
Thermophilic actinomycetes *(Micropolyspora faeni, Thermoactinomyces vulgaris)*, *Aspergillus* spp	Mouldy hay; sugarcane; compost; mushrooms; contaminated water in humidifiers and air conditioners	Farmer's lung; bagassosis; compost lung; mushroom worker's lung; humidifier lung
Aspergillus clavatus	Mouldy barley	Malt worker's lung
Trichosporon cutaneum	House dust	Summer-house HP (Japan)
Cladosporium spp	Ceiling mould	Hot tub lung
Animal protein		
Bird proteins	Bloom on bird feathers and droppings	Bird fancier's lung
Rat proteins	Rat droppings	Rat lung
Chemical		
Toluene diisocyanate	Paints	Isocyanate HP

Table 2. Antigens, sources and diseases in HP reproduced from Chapman et al. (2014, p. 255)

Another major subtype of inhalation exposure related ILD is pneumoconiosis, which is a subgroup of ILD disease characterised mainly by a reaction to inorganic materials or dust inhalational exposure (Chong et al., 2006; Chapman et al., 2014). It can be classified as fibrotic or non-fibrotic depending on clinical and pathological findings (Chong et al., 2006). The specific disease name is usually associated with the particular exposure (Table 3). Symptoms can vary from productive cough to breathlessness on exertion. On examination, no crackles or digital clubbing can typically be found. Chest x-ray (CXR) and HRCT may show some nodules and management should start with avoidance of culprit source. Additionally, steroids can be considered and lung transplant occurs in a few severe cases (Chapman et al., 2014).

Mineral dust	Disease	Examples of exposure
Coal dust	Simple pneumoconiosis Progressive massive fibrosis Caplan's syndrome	Coal mining, especially hard coal
Silica	Silicosis Caplan's syndrome	Foundry work, sandblasting, stone cutting, hard rock mining
Asbestos	Asbestosis Benign asbestos-related pleural disease Mesothelioma Lung cancer	Mining, milling, and fabrication Installation and removal of insulation
Beryllium	Acute berylliosis Beryllium granulomatosis	Mining, fabrication of electrical and electronic equipment, workers in nuclear and aerospace industry
Iron oxide	Siderosis	Welding
Barium sulphate	Baritosis	Mining
Tin oxide	Stannosis	Mining
Aluminium	Like silicosis (bauxite worker's lung, Shaver's disease)	Mining, firework, painting, and armament manufacture

Table 3. Examples of different exposures and diseases

Within this sub-group of ILD diseases, drug-associated respiratory toxicity can develop as a reaction to a medication, which can vary between patients but is usually associated with prolonged use of medication. Nitrofurantoin and methotrexate can cause acute HP, while amiodarone, angiotensin-converting-enzyme (ACE) inhibitors and sulfasalazine can cause interstitial pneumonitis. Amiodarone and bleomycin can also cause chronic organising pneumonia and pulmonary fibrosis; the latter can also be caused by nitrofurantoin or beta blockers. A large number of medications can provoke different reactions in the respiratory system and the website, http://www.pneumotox.com/, provides a comprehensive list of medication and the type of possible reaction (Chapman et al., 2014). Fortunately, most patients experience a complete resolution from disease upon stopping the medication that provoked the reaction (Wallis & Spinks, 2015).

Granulomatous ILD is another main type of the disease, and within this sarcoidosis is a multi-system disease with common lung involvement due to an unknown cause that results from environmental and genetic interactions. It is common between the ages of 20–40 and prevalent in African American, western Indian, and Irish populations. The incidence in the UK is 5–10:100,000. Pulmonary sarcoidosis results from an abnormal immunological reaction to benign unknown triggers or antigens. After the reaction and multiple inflammation processes, immune granuloma formation occurs. The granulomata then cause an increase in local fibroblast

stimulation. Clinically, patients with sarcoidosis may present with fever, arthralgia, and or hilar lymphadenopathy, with or without infiltrates in the lung. PFTs usually are restrictive with decreased diffusion capacity. HRCT can show micronodules and a subpleural and bronchovascular distribution with hilar and mediastinal lymphadenopathy. Additionally, air trapping can be seen due to small airway granulomas. Baughman et al. (2011) have developed an algorithm for sarcoidosis diagnosis (Figure 2) which can aid clinical diagnosis. Angiotensin-converting enzyme levels are usually elevated in 80% of patients with sarcoidosis and pharmacological treatment is only started in symptomatic cases. Sarcoidosis can resolve spontaneously in many cases, but if not the first treatment is usually oral steroids; bisphosphonates should be used to minimise osteoporosis caused by steroids (Chapman et al., 2014). In severe cases and/or with cardiac and neurological involvement, immunosuppressive therapy should be considered. A lung transplant can be considered for end stage and O_2-dependent cases.

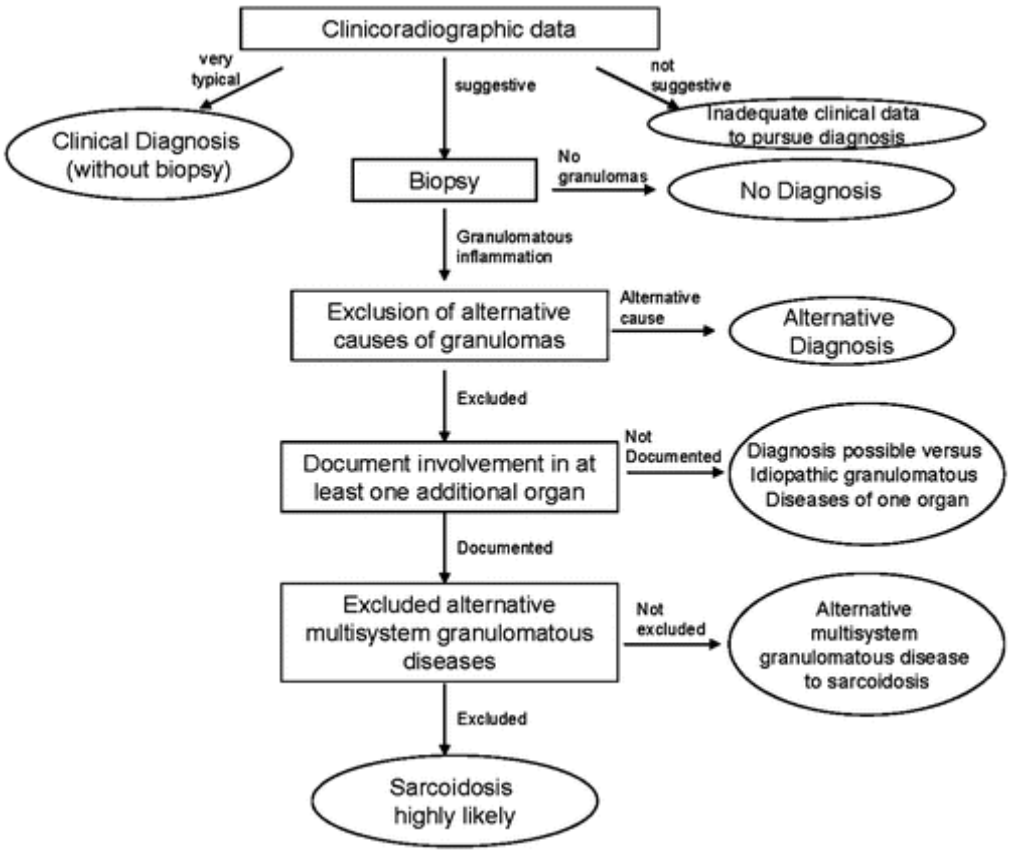


Figure 2. Algorithm to diagnose sarcoidosis

Alongside the extensive classifications of ILD given above, about 10% of ILD cases fit no classification and this group of patients has better outcomes compared to IPF (Wallis & Spinks, 2015).

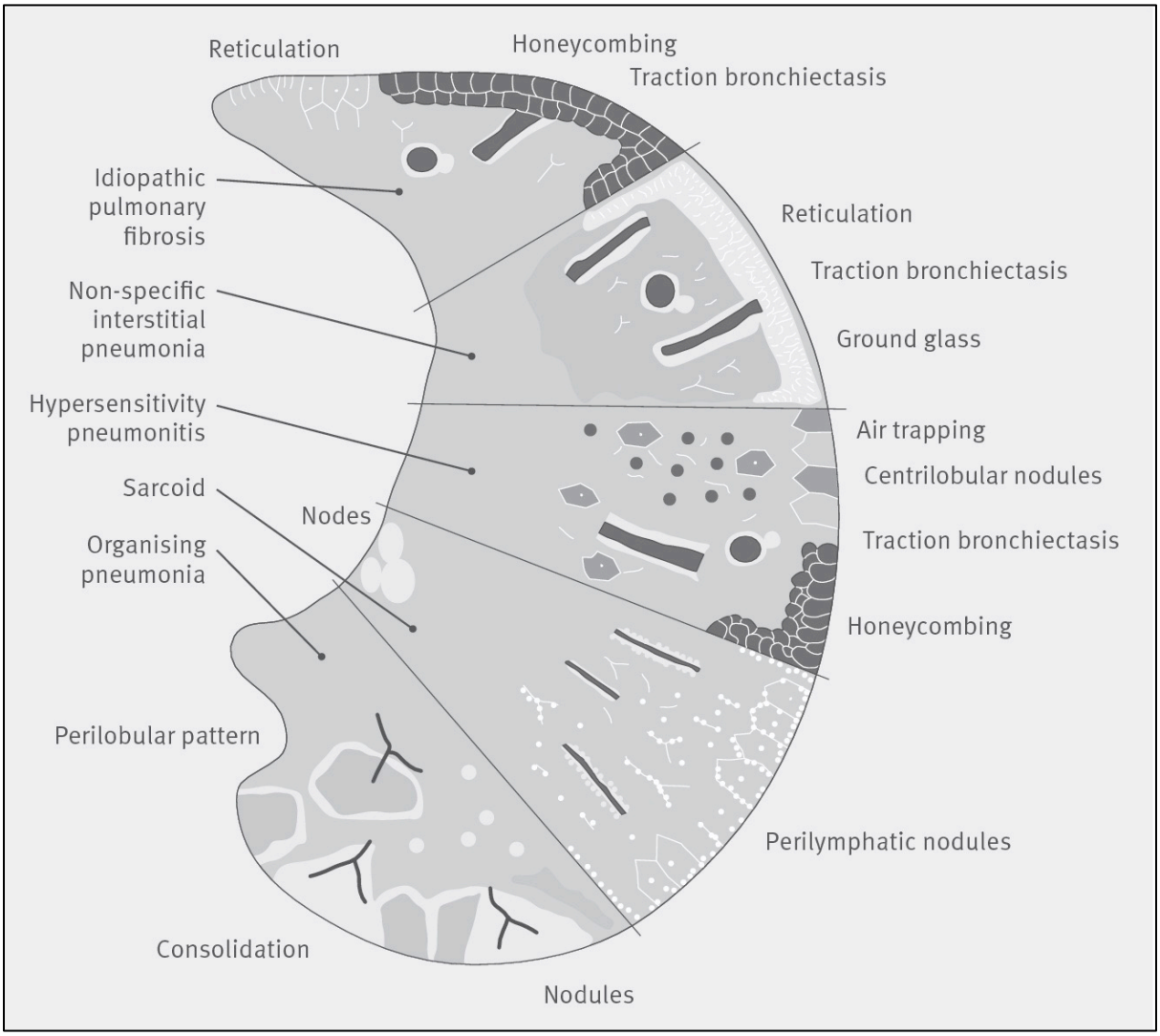


Figure 3. Summary of common findings in HRCT in ILD patients (Wallis & Spinks, 2015)

2.2 Pulmonary Rehabilitation in Interstitial Lung Disease

Pulmonary rehabilitation (PR) is an essential, non-pharmacological, management strategy in chronic lung diseases. The ATS/ERS consensus states that 'Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors' (Rochester et al., 2015). Numerous studies and guidelines have been conducted and developed on PR and COPD, but there is a scarcity of studies on ILD or IPF (Spruit et al., 2013). This results in a lack of understanding about the role of PR in ILD or IPF and could lead to providing untailored PR to them. Arguably, this is sub-optimal and may even be inappropriate because oxygen requirements are very different in people with COPD compared with people with IPF. I conducted a literature search, aiming both to establish a baseline of knowledge on PRP in ILD and to help in choosing outcomes and intervention for my work. Multiple databases (CINHAL, Embase, Medline, PubMed, SCOPUS, and Web of Science) were utilised, the key terms for which were: idiopathic pulmonary fibrosis, interstitial lung disease, pulmonary rehab*, rehab*, exercis*, train*, inspiratory muscle exercise, and breathing exercises. Additional search terms were: human, journal article, clinical trial, and peer review articles. Review and conference talks were excluded when appropriate. The numbers of published articles from each database are presented in

Table 4, while Figure 4 shows the exclusion steps, which produced 28 studies. These studies are summarised in Table 5 and a detailed version can be found in the Appendix. Detailed studies summary.

CINHAL	**20**
Embase	87

Medline	76
PubMed	43
SCOPUS	207
Web of Science	166
Total	599

Table 4. Number of articles from different databases

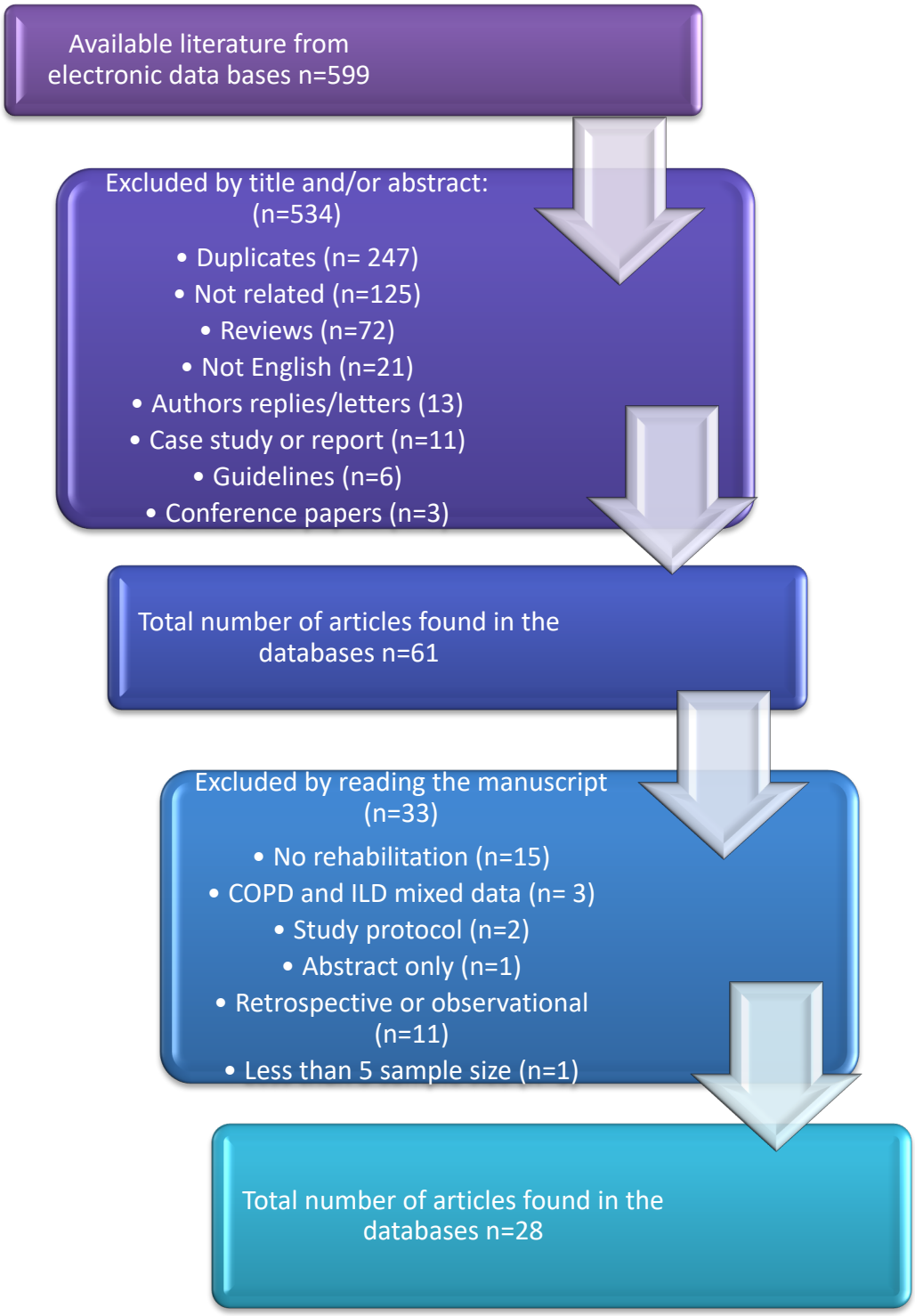


Figure 4. The exclusion steps in the articles found in the databases about ILD rehabilitation

After the exclusion processes, the remaining 28 articles identified by the literature search were extensively reviewed. These are summarised later in this chapter that presents the intervention characteristics, subjective outcomes, objective outcomes, sampling type, control group, time, and length of the rehabilitation programme.

Sample size	Type of training		Subjective outcomes				Objective outcome			Primary outcome	Publication year and authors
	Endurance	Resistance	MRC	SGRQ	SF-36	BDI	PFT	CPET	6MWT		
404	Not clearly stated	Not clearly stated								6MWT	Dreher (2015)
24										Not clearly stated	Strookappe (2015)
18										Not clearly stated	Marcellis (2015)
34										6MWD and VO_2 peak	Vainshelboim (2015)
13										O_2 delivery and O_2 extraction	Keyser (2015)
35										6MWD	Dale (2014)
21										Not clearly stated	Gaunaurd (2014)
21										6MWD	Jackson (2014)
46										Daily physical activities	Rifaat (2014)
54										6MWD	Ryerson (2014)
53										Not clearly stated	Shinichi (2014)
32										6MWD and VO_2 peak	Vainshelboim (2014)
10										Not clearly stated	Kaymaz[1](2013)
44										6MWD	Holland (2012)
440										Not clearly stated	Huppmann (2012)
90										Not clearly stated	Kozu (2011)
65										6MWD SF-36	Kozu (2011)
17										Not clearly stated	Rammaert (2011)
21										Not clearly stated	Swigris (2011)
29										6MWD	Salhi (2010)
17										Not clearly stated	Ozalevli (2010)
57										6MWD	Holland (2008)
30										Not clearly stated	Nishiyama (2008)
30										Not clearly stated	Jastrzębski (2007)
46										Not clearly stated	Naji (2006)
38										Not clearly stated	Jastrzebski (2006)

Table 5. Summary of pulmonary rehabilitation studies. Green indicates presence of an outcome. MRC (Medical Research Council), SGRQ (St George's Respiratory Questionnaire), SF-36 (36-Item Short Form Survey), BDI (Baseline Dyspnoea Index), PFT (pulmonary function tests) CPET (cardiopulmonary exercise testing), 6MWT (six-minute walk test)

2.2.1 Randomised studies

Only six out of 28 (21%) of the published studies included in this review were randomised (Figure 5), and these are: Holland et al. (2008); Dale et al. (2014); Gaunaurd et al. (2014); Jackson et al. (2014); Vainshelboim et al. (2014); Vainshelboim et al. (2015). The non-randomised studies either used the one group model, where the same group served as the control, or used a COPD control group (Kozu et al., 2011b; Swigris et al., 2011) or ILD as a comparison (Jastrzebski et al., 2008; Nishiyama et al., 2008). During sampling, most of the studies were focusing on ILD or IPF, with variable inclusion and exclusion criteria; however, the ability to ambulate was a common inclusion criterion.

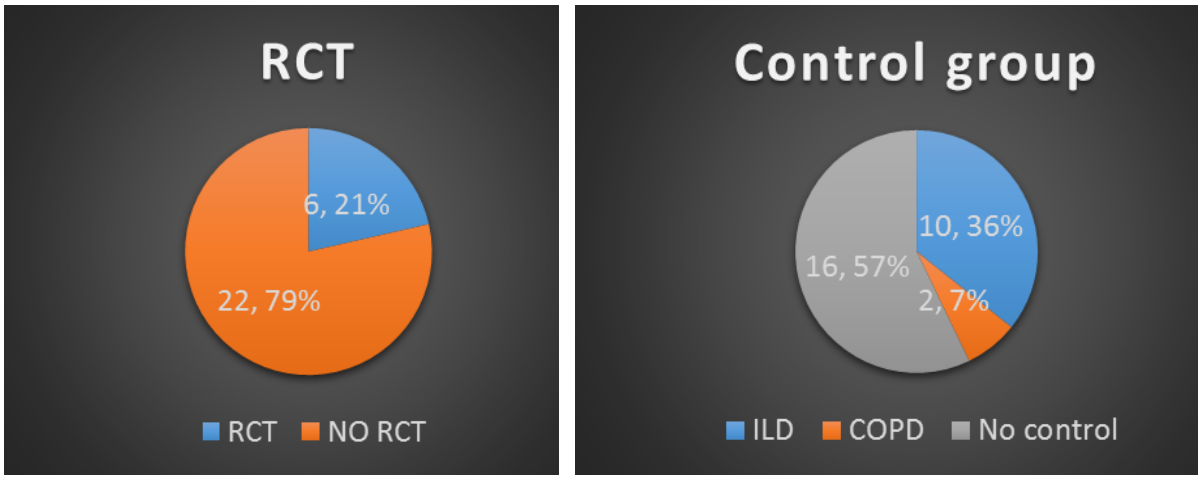


Figure 5. Left: pulmonary rehabilitation studies showing comparison of randomised control trials and non-randomised control trials. Right: showing the type of control group

2.2.2 Programme length

The length of a rehabilitation programme is the time in weeks or months that a participant follows an entire programme package, including exercise, education, and other elements. Programme length in the literature ranged from 4–24 weeks with an average of ten weeks, although the reported length could be misleading due to the variation of session time, weekly frequency, and intensity of the exercise. In general, programme length was not associated with major complications.

2.2.3 Outcome measurements

Outcomes were obtained to detect differences before and after the rehabilitation intervention or between two groups. These outcomes can be classified into subjective outcomes, where data were collected in the form of a questionnaire, and objective outcomes, where data were obtained from the participants using various measurement techniques. These objective outcomes can be functional, or physiological.

Regarding subjective outcomes, the following were used to obtain subjective information about participants' symptoms in the literature reviewed: the MRC (Medical Research Council), SGRQ (St George's Respiratory Questionnaire), CRQ (Chronic Respiratory Disease Questionnaire), QOL (quality of life), FAS (Fatigue Assessment Scale), mBorg (Modified Borg), SF-36 (36-Item Short Form Survey), BDI (Baseline Dyspnoea Index), HADS (Hospital Anxiety and Depression) (Figure 6). The main focus was on dyspnoea and breathlessness, but fatigue and QOL were also considered. In more recent studies, depression, anxiety, and emotions have also been addressed. K-Bild (King's Brief Interstitial Lung Disease) is a specific questionnaire for ILD which has recently been used in pulmonary rehabilitation studies and found to have a minimal clinical difference of 3.9 (Nolan et al., 2019).

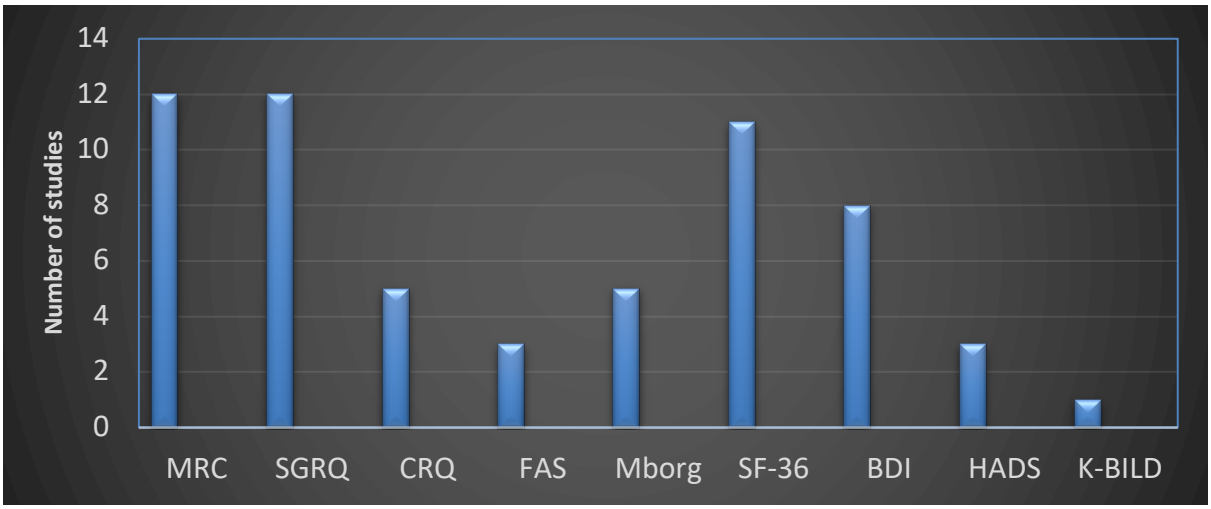


Figure 6. Different subjective outcomes used in selected published studies

MRC: Medical Research Council, SGRQ: St George's Respiratory Questionnaire, CRQ: Chronic Respiratory Disease Questionnaire, QOL: Quality of Life, FAS: Fatigue Assessment Scale. Morag: Modified Borg, SF-36:36-Item Short Form Survey, BDI: Baseline Dyspnoea Index, HADS Hospital Anxiety and Depression Scale

Regarding objective outcomes, these are important in PR to provide assessment for changes post PR. In my review, different outcomes were used in different studies (Figure 7). PFT tests

measure lung volume and capacity, are a gold standard in ILDs for diagnosing and monitoring prognosis, and as such have been used as primary end points in clinical trials. They were used in 19 rehabilitation studies.

The six-minute walk test (6MWT) is used extensively in research and clinics to diagnose and measure prognosis. Subjects are asked to walk continuously for six minutes back and forth between two cones 30 feet apart on a flat surface. Distance is measured at the end of the sixth minute. Twenty of the 28 studies reviewed used the 6MWT and, while positive improvement was found in all of them, this improvement was not always statistically significant. Cardiopulmonary exercise testing (CPET) was utilised in 13 studies with a tendency to conduct this using a submaximal effort protocol. Peripheral muscle strength was measured directly in five studies and indirectly by the 30-second chair-stand test (Vainshelboim et al., 2014), which was found to have an association with overall improvement after a rehabilitation programme. Maximum inspiratory pressure (MIP) was measured in five studies (Jastrzebski et al., 2008; Salhi et al., 2010; Shinichi et al., 2014; Strookappe et al., 2015), two of which had an intervention directed at exercising breathing muscles. Echocardiogram and fat free mass were utilised in only one study. Biomarkers were measured in two studies, which used: C-reactive protein (CRP), soluble interleukin-2 receptor (sIL-2R) and serum angiotensin-converting enzyme (ACE) (Marcellis et al., 2015), measured only at baseline. Natriuretic pro brain natriuretic peptide (NT-proBNP), 15-F2t-isoprostanes, and amino acids (AA) were measured by Jackson et al. (2014), who found that NT-pro BNP and All AA increased significantly after the rehabilitation programme but 15-F2t-isoprostanes did not change significantly.

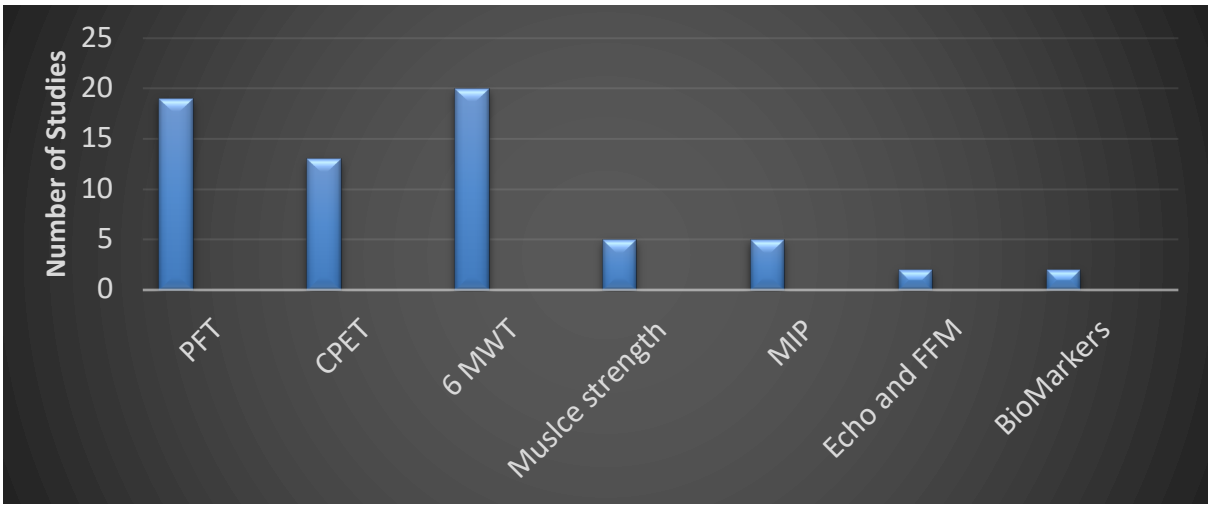


Figure 7. Number of different objective outcomes used in selected published studies
PFT: Pulmonary Function Test. CPET Cardiopulmonary Exercise Test. 6 MWT: 6 Minutes Exercise Test. MIP: Maximum Inspiratory Pressure. FFM: Fat Free Mass

2.2.4 Education

Patient knowledge about disease process and symptom management is an important aspect of disease management. Thirteen of the 28 studies reported providing some form of education but information about the type and length of education was rarely reported. Additionally, no single study considered evaluating patient understanding or knowledge of the disease. A summary of the education components employed during the PRP is listed below.

Reference	Method of Delivery	Topics
Vainshelboim et al. (2014)	Not mentioned	• Symptom management • Physical activity
Ryerson (2014)	Not mentioned	• Symptom control • Use of oxygen • Disease self-management strategies
Rifaat (2014)	Not mentioned	Not mentioned
Jackson (2014)	Lectures	• Medication use • Breathing techniques • Exercise strategies • Proper nutrition • Pulmonary physiology • Psychological coping mechanisms
Gaunaurd (2014)	Lectures and handouts	• Medication use • Breathing techniques • Exercise training • Nutrition • Pulmonary physiology • Psychological coping mechanisms among others
Kaymaz (2013)	Not mentioned	• Disease education • Education of families • Bronchial hygiene • Breathing control techniques • Energy conservation • Relaxation
Huppmann (2012)	Not mentioned	• Promoting self-management • Self-medication • Management of infections and exacerbations • Dyspnoea • Use of oxygen • Return to activities of daily living • Maintaining and improving physical function

Swigris (2011)	Not mentioned	• Oxygen use • Medications • Relaxation • Psychosocial support • Energy • Nutrition • End-of-life issues.
Rammaert (2011)	Picture folder and fact sheets.	• Recognition of dyspnoea • Keeping active • Exercise maintenance
Kozu, Jenkins, Senjyu (2011)	Not mentioned	• Benefits and importance of exercise • Energy conservation techniques • Self-management of exacerbations
Kozu (2011)	Classes	• Benefits and importance of daily exercise • Pacing and energy-conservation Techniques to manage ADL • Self-management strategies for coping with an exacerbation
Salhi (2010)	Not mentioned	Not mentioned
Nishiyama (2008)	Lectures	Not mentioned

Table 6. Summary of articles used as the education component in the PRP for patients with ILD

2.2.5 Psychological support

Many ILD patients complain of different psychological disorders that can impair their general health and motivation to exercise. Only four studies of the 28 reported some utilisation of psychological support for their ILD patients during a rehabilitation programme.

2.2.6 Relaxation

None of the study reported the use of relaxation techniques.

2.2.7 Oxygen use

Eleven of the 28 studies reported the use of oxygen during exercise, which is believed to improve exercise capacity.

2.2.8 Types of exercise

Exercising was the major aspect of rehabilitation programmes in all pulmonary rehabilitation for ILD studies, but there was some variation in terms of what exercises were done or how the intensity of the exercise was targeted. Endurance and resistance exercise were the most commonly used, while breathing, flexibility, and IMT were less used (Figure 8). Endurance exercises were targeted based on heart rate, VO_2, mBorg (modified borg), CPEX, 6MWT speed, or as tolerated.

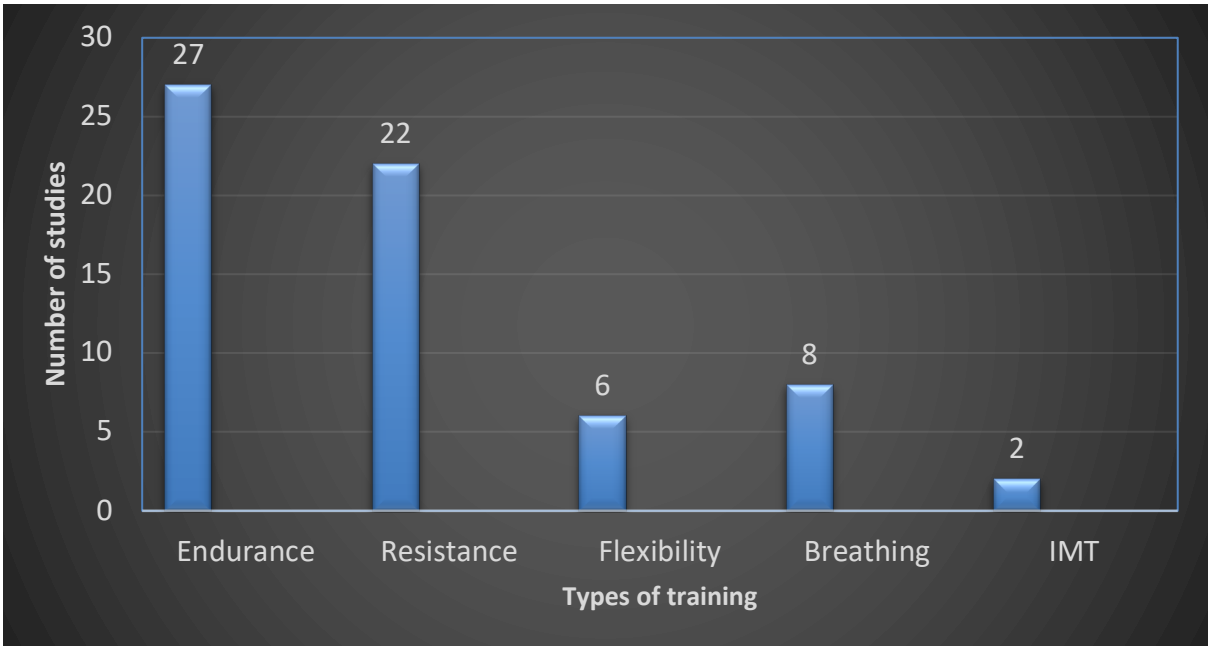


Figure 8. Types of training in selected published studies. Y axis*:* number of studies used*;* X axis*:* types of training. IMT: Inspiratory Muscle Training

Exercise is a corner stone when it comes to pulmonary rehabliation and can improve exercise capacity, symptoms, and QOL (Figure 9) (Vainshelboim, 2016).

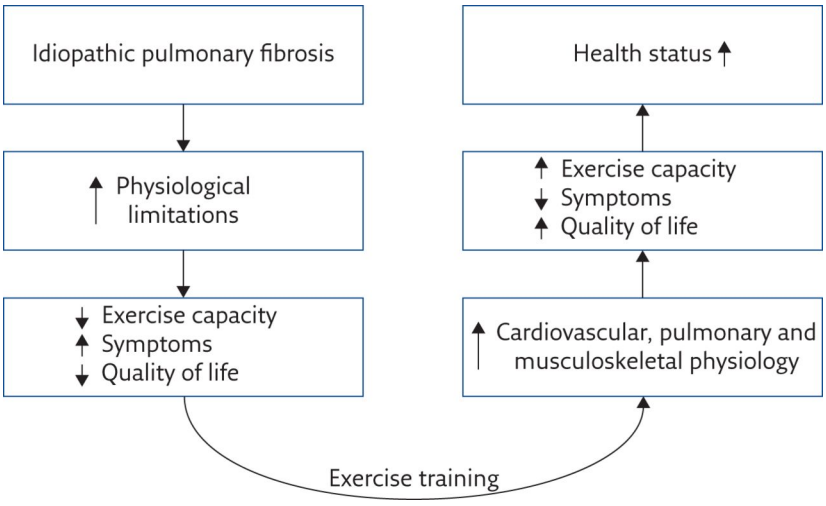


Figure 9. Expected benefits from exercise training in ILD

2.3 Inspiratory Muscle Training

2.3.1 Introduction

One of the most common causes of exercise intolerance in chronic respiratory diseases, and specifically in ILD, is dyspnoea. The imbalance between the respiratory demand and the compromised ability of the respiratory system caused by disease processes in ILD leads to what subjects describe as difficulty in breathing. In lung fibrosis, the inspiratory muscles may have normal strength but this strength may provide insufficient ventilation. In ILD, there is a general reduction in lung compliance, leading to less inspired volume, which may not satisfy total body demands, thus leading to more effort. Inspiratory muscle training in ILD might therefore be an important addition to routine pulmonary rehabilitation programmes (McConnell, 2013).

2.3.2 Types of inspiratory muscle training

Training the muscles, in general, aims to overload the muscle by either applying a force more than usual, strength training, or applying a specific load for longer than usual, combined with endurance training. Both types of training are mutually beneficial, which means if a subject's target was to improve the strength of the muscle, some improvement can also occur in endurance ability. Similarly, inspiratory muscle training can be divided into two categories: resistive training and endurance training. Resistive training is targeted at improving MIP and may therefore improve other PFTs, functional tests, or dyspnoea. This training is, usually, prescribed to healthy or unhealthy subjects as a percentage of MIP and is performed twice a day for 30 breaths. The percentage of MIP can be increased every week for a minimum of four

weeks. Endurance training is targeted at maximum voluntary ventilation (MVV) and the exercise can be prescribed to target 60–70% of MVV for 30 minutes 3–5 times a week. The resulting hypocapnia can cause dizziness and headache due to a reduction of CO_2, and a dead space system may be required to normalise CO_2 (McConnell, 2013).

2.3.3 Uses of inspiratory muscle training in respiratory diseases

IMT has been used in respiratory diseases (McConnell, 2013) and has led to either an improvement or no change. Importantly, IMT has not been shown to cause major side effects or deterioration in conditions. COPD, asthma, or patients on prolonged mechanical ventilator support seem to derive potentially promising benefits from IMT (McConnell, 2013). Where patients are post-weaning from mechanical ventilation, IMT improved quality of life and inspiratory muscle strength; however, mortality rate was higher when IMT was used, at the borderline of significance (p.=0.051) (Bissett et al., 2016). An RCT was conducted on 34 subjects with COPD with preserved inspiratory muscle strength (MIP > 60 cm H_2O) and a significant improvement was found in the multi-dimensional dyspnea profile only in subjects with FEV1 less than 50% predicated, while other outcomes such as 6MWT did not improve (Beaumont et al., 2015). In ILD, several studies claim to have used breathing exercises or training in their studies, and these are summarised in Table 7 below. In general, the studies lack control groups, randomisation, or an IMT device. The use of inspiratory muscle training in ILD is uncommon and remains largely unevaluated. IMT in ILD. could be a very attractive method of exercise due to the limitation in, and reduction of, volume and capacity resulting from lack of lung expansion caused by the restricted pattern. This pattern results from a considerable reduction of lung compliance. Theoretically, IMT may improve lung expansion and, to some extent, overcome the lack of lung compliance in ILD.

Sample size	Control group	Randomi-sation	IMT prescrip-tion	IMT device	Significantly Improved outcome(s)	Reference
402			Not specific		• 6MWT • SF-36	Huppmann (2012)
14	COPD		Not specific		• 6MWT • FSS	Swigris (2011)
65			Not specific		• 6MWT • SF-36	Kozu (2011)
			Not specific		• 6MWT • SF-36	Ozalevli[1] (2009)
38			30 breaths	Thresh-old	• SGRQ • SF-36	Jastrzêbski (2006)
30			30 breaths and 30% MIP	Thresh-old	(hard to find, study was in Polish)	Jastrzêbski (2008)
16			30 breaths twice a day at 40% MIP	Power-Breathe	Significant was not tested	Current study

Table 7. Summary of PR studies in ILD that involved breathing muscle training(s). The six-minute walk test (6MWT), 36-Item Short Form Survey (SF-36), Fatigue Severity Scale (FSS), St George's Respiratory Questionnaire (SGRQ)

2.4 Palliative Care in ILD

Palliative care 'is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' (WHO, 2020). It is not uncommon for a patient with ILD to need palliative care. In fact, NICE recommendations (CG163-1.5.5–1.5.10 (2013)) on the management of IPF and best supportive care include information for patients, symptom management, and end of life care. However, it has been reported that patients with chronic lung disease receive less palliative care compared to cancer patients (Brown et al., 2016). This could be related to lack of knowledge, concerns about use of opioids, or uncertainty about prognosis (Brown et al., 2016). A review article by Kreuter et al. (2017) explores the needs of ILD patients (Figure 10), and the authors suggest that palliative care should be provided for patients with ILD, specifically IPF since diagnosis. Palliative care includes pharmacological and nonpharmacological therapies, and both are used to minimise and inhibit

unpleasant symptoms like dyspnoea, cough, fatigue, pain, depression and anxiety. Sgalla et al. (2015) conducted a one-year prospective study on mindfulness-based stress reduction with 19 patients with ILD. The programme was well attended (a mean of 8 per 9 sessions) with about a 10% dropout. The authors concluded that the programme has potential benefits, especially on patients' mood.

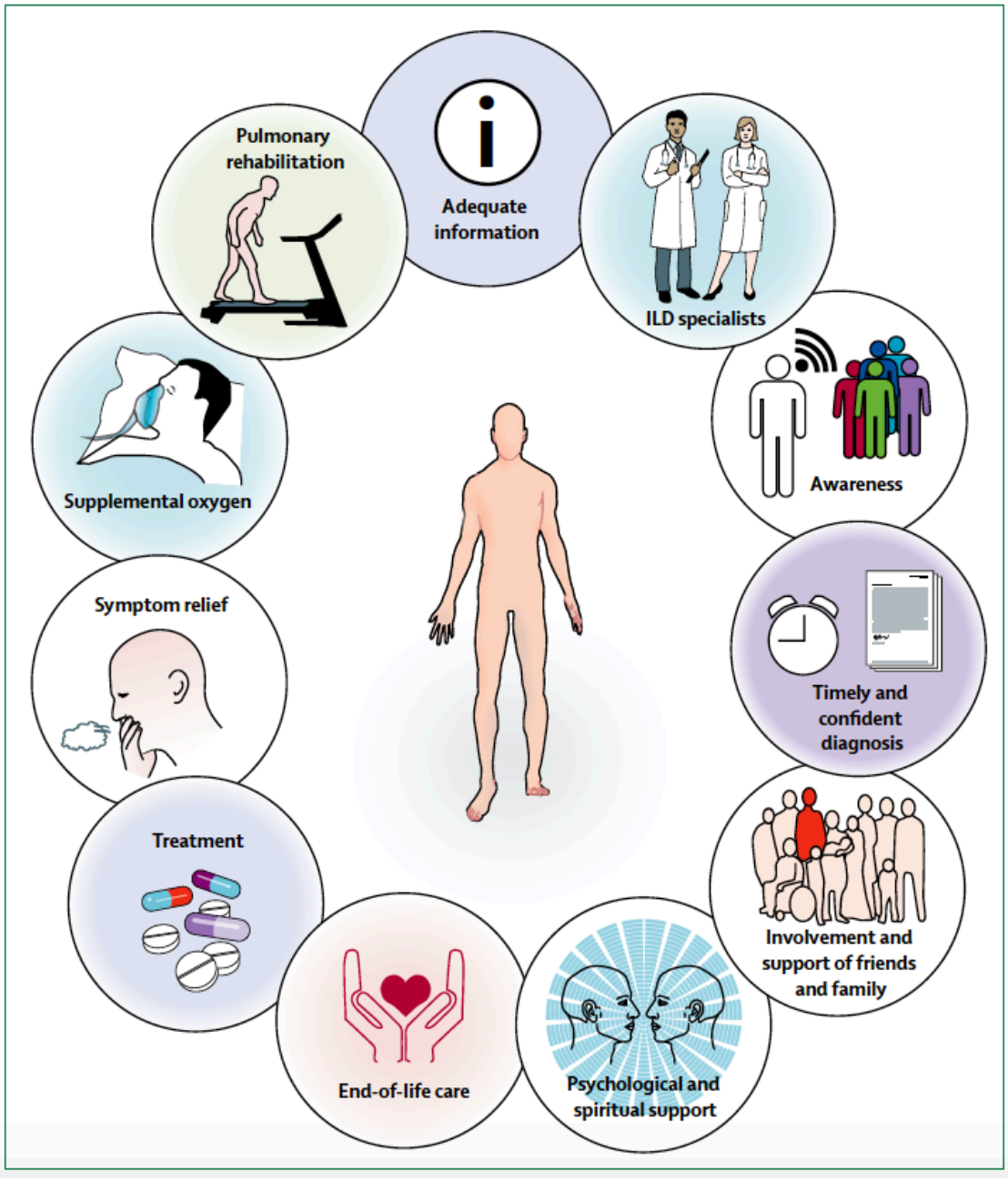


Figure 10. Factors needed for palliative care in ILD and IPF

Chapter 3. Methodology

3.1 Introduction

During my PhD, I catalysed and became involved in the development of a new, bespoke clinical rehabilitation service for ILD, as developments were made in the patient care pathway in response to both NICE guidelines and formal patient requests from the IPF Support Group Northern Region. Previously there was no such clinical provision. The service has been informed by my literature review and my professional training as a respiratory therapist. The Newcastle ILD pulmonary rehabilitation programme is led by Dr Ian Forrest, who established the regional ILD clinical service. The tailored rehabilitation programme involves an integrated approach comprised of education, exercise-based intervention, and evaluation using validated questionnaire instruments. Healthcare practitioners were involved in designing, developing, and conducting this programme.

The existing clinical care pathway providing pulmonary rehabilitation was used to perform an academic evaluation of IMT, and I evaluated a respiratory muscle training intervention in patients with ILD or IPF, using a proof-of-concept design (https://doi.org/10.1186/ISRCTN92567676). Patient recruitment for the study took place in the Royal Victoria Infirmary hospital, Newcastle, and the Marie Curie Hospice Care Centre, with 36 patients with a working diagnosis of IPF or ILD made by a multi-disciplinary team. Patients were included in the study if their MRC dyspnoea score was between 2–5.

3.1.1 Inclusion criteria

- 40 years old or more
- Working diagnosis of IPF or ILD made by a multi-disciplinary team
- MRC dyspnoea score is between 2–5
- Ability to perform general exercises and follow instructions

3.1.2 Exclusion criteria

- Uncontrolled hypertension
- Uncontrolled cardiac disease
- Inability to perform exercises, for example: neuromuscular or orthopaedic diseases

- Inability to follow instructions, for example: learning difficulties
- Inability to commit to transportation to the exercise facility during the study
- Participation in pulmonary rehabilitation in the last six months
- History of syncope on exertion
- Other lung diseases associated with occupation or drug exposure
- Respiratory consultant decision to exclude the subject due to disease instability.

After patient selection, patients were randomised into two groups, each with 18 patients in a parallel group design. Randomisation was conducted by a computerised programme (sealedenvelope.com), a website that provides a platform for randomisation. The intervention group received the pulmonary rehabilitation programme and inspiratory muscle training (PRP + IMT) and the control group received PRP only.

3.2 Outpatient Sessions (once a week, 120 minutes per session)

- Educational sessions were provided in a lecture style once a week. Each session was 20 minutes long with ten minutes for open questions and informal discussion (Table 8);
- Patients were instructed to warm up for five minutes;
- Aerobic exercise was conducted for 20 minutes using a cycle ergometer, and the target was mBORG scale to 5. SpO_2 and HR were monitored during aerobic exercise. If SpO_2 fell below 80%, Oxygen was provided at 2–5 LPM, aiming to improve SpO_2 to 90%;
- Strengthening exercises for the following muscles or areas were carried out: biceps, triceps, pectorals, deltoid, back, abdomen, quadriceps, hamstring, and calf. Each strengthening exercise was repeated 6 times, with two repeats to 50% of the highest tolerable load. The load was increased 10% each week as tolerated;
- Stretching exercises were taught to the patients for all major muscle groups;
- There was a cool down period for five minutes;
- Patients attended a relaxation session provided by a facilitator, which included comfortable chairs, low lighting, and relaxing music;
- Patients receiving the intervention were given a PowerBreathe KH2 device and instructed how to use it at home twice daily for 30 breaths each session over the whole rehabilitation

programme. The training level was 40% of IMP, measured every week (only for intervention group).

3.3 Home Exercises (twice a week, 40 minutes per session)

- Patient were instructed to warm up for five minutes;
- The cycle ergometer was used for 20 minutes (pedal exerciser with digital display);
- Stretching of all muscle groups;
- Patients used Therabands to practise nine sets of exercises twice a week. Each set was repeated twice for six counts. These exercises were given to the subjects through Physioltools in a printed form with detailed instructions, and were also accessible through a smartphone app (http://www.ptmomentum.com/.) The app also provided motivation and monitoring functions;
- Walking four days a week;
- Baseline daily walk steps were measured and averaged over a week using a pedometer. Patients were asked to increase their walking steps by 10% each week. Patients were asked to walk on days that they did not exercise.

<table>
<tr><th>Weeks</th><th>0</th><th>1</th><th>2 through 9 (8 weeks)</th><th>10</th></tr>
<tr><td>PRP and IMT</td><td rowspan="2">Patient requirements and consenting</td><td rowspan="2">Measurement of baseline observation</td><td>PRP+ IMT</td><td rowspan="2">Measurement of outcomes at the end of the PRP</td></tr>
<tr><td>PRP</td><td>PRP only</td></tr>
</table>

Figure 11. Study timeline for PRP and IMT, and PRP

3.4 Outcomes

Analysis was performed in keeping with recommendations regarding a proof-of-concept study design. All outcomes were measured or collected before and after the 8-week programme. The feasibility of collecting the following parameters was examined in a real-world study setting:

3.4.1 Primary outcome

The number of people who completed the study was measured using study records at baseline and eight weeks.

3.4.2 Secondary outcomes

- 6MWT
- PFT
- Peripheral muscle strength
- MIP
- K-BILD
- IPOS, the palliative care outcome scale
- Fatigue Severity Scale
- Hospital Anxiety and Depression Scale
- Feasibility of integrating MUC5B polymorphism assessments in a rehabilitation study
- Feasibility of integrating Matrix metalloproteinase-7 (MMP7) measurements in a rehabilitation study

The 6 MWT was performed in accordance with the ERS/ATS technical standards (Holland et al., 2014b) on a flat, straight, hard surface. Cones were placed at the start and end of a 30 m course. SpO_2 was measured throughout. Subjects were asked to repeat the test once they were comfortable to do so. The operator terminated the test if subject was no longer able to complete the test, or if SpO_2 fell to or below 80%. The mBORG scale was used before and after the walk to assess breathlessness.

Regarding spirometry with TLCO, forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) were measured in accordance with BTS/ARTP guidelines (British Thoracic Society and the Association of Respiratory Technicians and Physiologists, 1994) with ECCS equation to calculate predicted values. After patient preparation and equipment calibration, patients were instructed to breathe as deeply as possible and then seal their lips around the mouthpiece. Each patient was then encouraged to blow as hard and fast as possible until no more air came out of their lungs. The test was repeated at least three times and the highest two FEV1 and FVC measurements reported. Transfer factor of the lung using carbon

monoxide (TLCO) was measured in accordance with the same 1994 BTS/ARTP guidelines. Patients were tested to obtain at least two acceptable procedures and the average of the two was reported. Patients rested for four minutes between attempts. Concerning the K-BILD questionnaire, a 15-item ILD specific questionnaire with a seven-point scale for each question was provided to subjects before and after the rehabilitation programme (Patel et al., 2012). This questionnaire has recently been used in a pulmonary rehabilitation context (Nolan et al.).

To measure inspiratory muscle pressure (IMP), subjects were asked to sit on a chair without supporting their back. Holding the PowerBreathe KH2 in their hand and with a good seal on the mouthpiece, subjects were asked to exhale through their mouth to the maximum and then take a full, forceful and fast breath through their mouth. IMP was measured three times and should have been within 20%. The maximum reading was recorded.

Three other scales were also used. First, IPOS, the palliative care outcome scale, was used to measure subjects' symptoms, psychological status, emotional conditions, spiritual, informational and support needs (Strongman et al., 2018). Second, the Fatigue Severity Scale was used, which is a nine-item instrument with seven levels in each item, and a separate section for visual analogue fatigue scale (VAFS) (Marcellis et al., 2015). The third scale used was the Hospital Anxiety and Depression Scale, a 14-item questionnaire with four levels in each item. Scoring interpretation is 0–7 normal, 8–10 borderline abnormal, and 11–21 abnormal (Naji et al., 2006).

Peripheral muscle strength measurements were also taken. Quadriceps strength has been assessed in several studies (Salhi et al., 2010; Kozu et al., 2011a; Kozu et al., 2011b; Shinichi et al., 2014; Marcellis et al., 2015). Guidelines on quadriceps strength measurement are explained in Dowman et al. (2016). Briefly, subjects were asked to lie in a supine position with a pillow under their knees and asked to relax for five minutes. The handheld dynameter (HHD) (microFET) was placed just above the ankle to try to extend the knee, and subjects were asked to push forcefully on the HHD. The same procedure was repeated three times for both legs and the maximum reading recorded in kilograms (kgs). Regarding elbow flexion strength, this has also been explained in Dowman et al. (2016). Also from a supine position, subjects were instructed to place their elbow on the bed to form 90 degrees, and then the HHD was placed below the wrist. The subject was then instructed to flex as hard as possible against the HHD. This procedure was performed three times and the maximum reading recorded in kgs. (Marcellis et al., 2015). For shoulder abduction, subjects were asked to sit on the side of the bed. With the HHD placed laterally to the deltoid muscle, subjects were asked to elevate the

shoulder against the HHD. Again, the procedure was conducted three times and the maximum reading recorded in kgs.

The feasibility of including biomarkers and genetic analysis in PRP studies in ILD was also assessed. The biomarker measured in this study was matrix metalloproteinase-7 (MMP7). To do so, 10 ml of venous blood sample was obtained from subjects before and after the rehabilitation programme. Blood contents were prepared, separated, and frozen at -80C as a biobank for the assessment of biomarkers to be determined later.

With regard to genetic testing, MUC5B is a single-nucleotide polymorphism (SNP) rs35705950 gene that encodes for mucin 5B, and this was tested in all subjects involved in the study. This gene is seen as a target for ILD and IPF research (Seibold et al., 2011). It is the strongest risk factor for developing IPF, but is known to improve the outcome of IPF (Keith et al., 2019).

Week	Title of Session	Objective
1 **10/2/17**	ILD rehab programme	Introduction to the rehab programme Home exercise
2 **17/2/17**	Know the disease	Normal pulmonary system What is ILD/IPF? Possible treatment and management
3 **24/2/17**	Inspiratory muscle training	Anatomy of breathing muscles Introduction to the IMT device Training on the use of the IMT device
4 **3/3/17**	Positive thinking and self-control	Cognitive behavioural therapy: application and instruction
5 **10/3/17**	Nutrition in ILD	Overview of a healthy diet in chronic lung diseases
6 **17/3/17**	Nonpharmacological symptoms management	Relaxed breathing, pacing breathing Blow as you go breathing, pursed lip breathing, Ice for cough, mini fan for dyspnoea
7 **24/3/17**	Introduction to palliative care	Overview of palliative care as a way to treat symptoms, and services available for subjects with ILD
8 **31/3/17**	Maintenance Exercise	How to maintain exercise after PRP Resources for PRP Contact information about local IPF support group

Table 8. Example of education session schedule

3.5 Aim of the Study

3.5.1 Purpose and theory

Overall, this study developed and evaluated a rehabilitation programme tailored to each patient with idiopathic pulmonary disease. The package had to fulfil this patient-specific situation and was created through my PhD activities to date.

3.5.2 Aims

- Develop a tailored rehabilitation programme for IPF;
- Evaluate the feasibility of conducting a hybrid rehabilitation programme for IPF with out-patient and home components;
- Evaluate the feasibility of introducing a breathing exercise device into rehabilitation programme in IPF.

Chapter 4. Pilot for the Randomised Feasibility Clinical Trial: Establishment and Initial Experience of a Regional ILD PRP in Collaboration with Newcastle University, Newcastle upon Tyne NHS Trust, and Marie Curie Hospice

4.1 Chapter Overview

Pulmonary rehabilitation for patients with ILD is recommended in NICE guidelines (2013), and so a pulmonary rehabilitation programme (PRP) was developed for the regional ILD clinic in the North-East of England. Eighteen subjects were allocated but not randomised to receive either PRP alone 'control' (n=3) or PRP and inspiratory muscle training (IMT) 'intervention' (n=15) with the service, delivered in a novel setting in the Marie Curie Hospice, Elswick, Newcastle upon Tyne. Physiological outcomes and questionnaires were collected before and after an 8-week programme. The main outcome for the clinical service was the feasibility of the programme, and it was found to be acceptable to both patients and healthcare providers, being positively received by both. Patients in the control group showed interest in trying IMT, which was provided to them after the PRP. Subjects' responses to PRP varied between and within groups, and some suggestions were made for improving the PRP and IMT group. In summary, PRP, augmented by IMT, was delivered in a Marie Curie Hospice setting as a clinical service and found to be feasible and acceptable by both patients and the healthcare provider team.

4.2 Introduction

As a PhD student, I met with experts from the neuromuscular disease group, physiotherapists with experience in inspiratory muscle training, and a representative from PowerBreathe, a breathing training device provider. Additionally, multiple meetings with clinical and academic colleagues were conducted to plan for a new pulmonary rehabilitation programme (PRP) to be conducted in collaboration with Newcastle University, The Newcastle upon Tyne Hospitals NHS Foundation Trust, and Marie Curie Hospice Care. I served as coordinator and planner for most of these meetings. The team involved a consultant pulmonologist, a consultant in palliative care, a senior ILD specialised nurse, a senior physiotherapist, a senior physiologist, and administrators. We discussed the importance of PRP for ILD, reviewed the literature, and chose feasible and important outcomes and logistics. We decided to start the PRP as a clinical service in the Marie Curie Hospice with a view to following this initial experience with an RCT.

4.3 Methods

PRP was initially conducted on 18 subjects as a clinical service via the aforementioned collaboration. These patients were allocated, but not randomised, for PRP and inspiratory muscle training (IMT) as the intervention group, or PRP only in the control group. Subjects were allocated to groups, with 3–4 subjects per group. I participated in several training sessions from the PowerBreathe company about the use of electronic and manual IMT devices, initially for healthy subjects and then those with ILD. I also received a certificate from the company stating that I have the required knowledge and skills to use the devices. We initially recruited groups sequentially to PRP and IMT, then PRP only; however, we noticed potential signals of better performance in the first group studied and wanted to have more data with the IMT device, so we decided to recruit all subsequent subjects to the PRP and IMT intervention group. The same protocol as outlined in Chapter Three was used, except blood analysis and accelerometry were not performed. Feedback was collected after each group of PRP in the form of three questions asking subjects what they liked and disliked about the programme, and whether they had any suggestions for it. All subjects completed the follow up session, apart from one patient from a PRP and IMT group who was unable to complete due to a panic attack. Data were entered using Microsoft Excel and then transferred and analysed using SPSS v23. Since there were only three subjects in the PRP group, individual data were reported. For both groups, median, maximum, and minimum values are reported.

4.4 Results

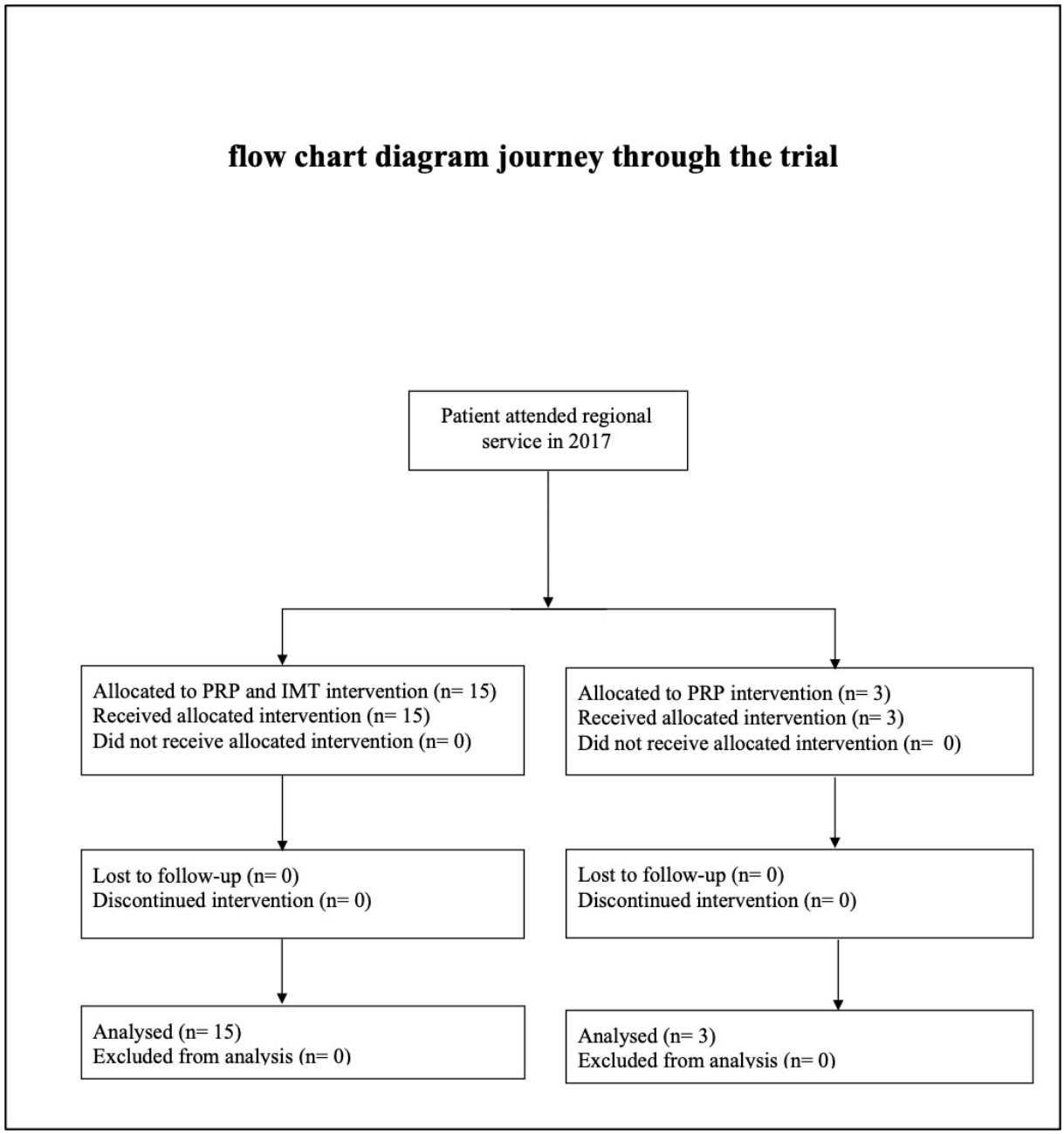


Figure 12. Journey of the first eighteen patients to attend the regional clinical PRP service

Outcome	PRP group, n=3 [Control]									PRP and IMT, n = 15 [Intervention]		
	Baseline			Follow up after PRP			Change from baseline to follow up			Baseline	Follow up after PRP	Change from baseline to follow up
	Individual patient data									n Median (Min, Max)		
	S4*	S5	S6	S4	S5	S6	S4	S5	S6			
Age in years	72	86	83							74 (54,87)		
Sex	M	M	F							2 F, 13 M		
										15	15	15
MIP in cmH2O	97	79	22	73	72	11	-24	-7	-11	50 (22,108)	76 (48,130)	32 (6,69)
										15	14	14
FVC in litres	3.07	2.72	1.57	3.07	2.42	1.50	0	-0.3	-0.07	2.40(1.76,3.49)	2.37(1.66,3.11)	-0.1 (-1, 0.25)

									14	14	13
6 MWT in metres	564	353	150	583	333	136	19	-20	-14	293 (44,493)	373 (50 ,480)	45 (-13, 189)
									15	14	14
K-BILD	84	60	61	71	80	57	-13	20	-4	65 (57,96)	72 (53, 104)	7 (-28,18)
									15	14	14
HADS-D	3	3	13	1	2	13	-2	-1	0	5 (1,11)	3.5 (0,9)	-1(-7,3)
									15	14	14
HADS-A	2	6	7	3	2	8	1	-4	1	5 (2,11)	3.5 (0,8)	-1 (-8,2)
									15	14	14
FSS	37	39	59	32	41	61	-5	2	2	52 (24,63)	41.5 (9,62)	-4.5 (-49,17)
									14	13	12
FSS-V	4	3	3	8	5	1	4	2	-2	5 (0,8)	6 (2,9)	1.5 (-5,5)
									15	14	14

R-Quads in newtons	518	216	230	353	256	197	-165	-39	33	288 (111,342)	250 (161,398)	19 (-121, 121)
										15	14	14
L-Quads in newtons	450	237	201	430	238	146	-20	1	-55	257 (113,373)	253 (119,369)	13 (-134, 102)
										15	14	14
R-Biceps	219	166	81	226	174	76	7	9	-5	186 (96, 267)	166 (113,222)	-1.4 (-59,61)
										15	14	14
L-Biceps	206	143	85	226	161	86	20	18	1	169 (80,264)	166 (113,222)	0.3(-51,77)
										15	14	14
R-Deltoid	217	152	59	196	167	81	-21	14	22	143 (77,221)	150 (88,190)	3.5(-61,62)
										15	14	14
L-Deltoid	209	137	75	182	129	105	-27	-7	30	127 (38,187)	143 (55,207)	13 (-28,64)

Table 9. Median, minimum, and maximum of variables at baseline and after PRP. PRP (pulmonary rehabilitation programme) IMT (inspiratory muscle training) MIP (maximum inspiratory pressure) FVC (forced vital capacity) 6MWT (Six-minute walk test), K-Bild (King's Brief Interstitial Lung Disease)

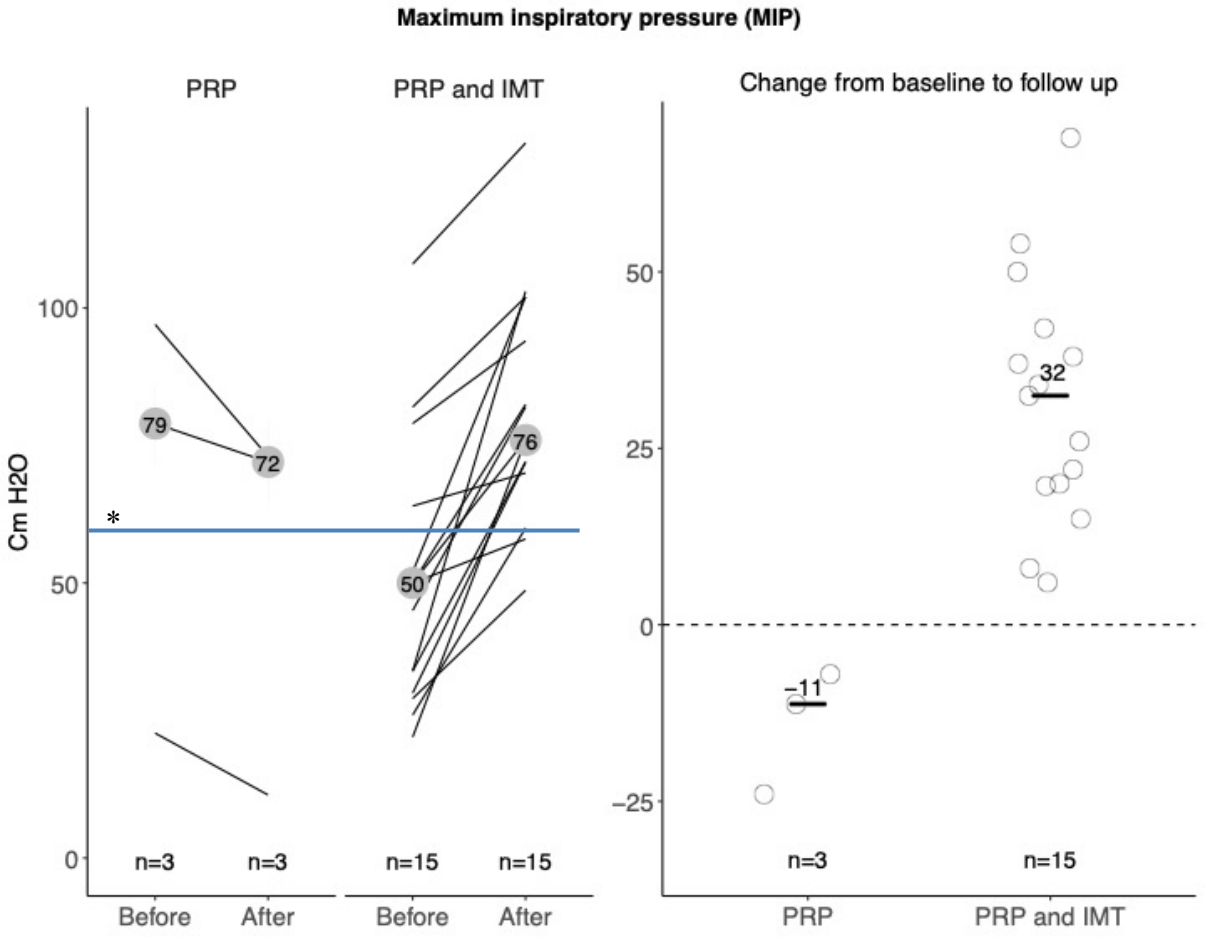


Figure 13. Maximum inspiratory pressure (MIP) before/after 8-week PRP or PRP and IMT. The black lines in the left plot represent individual subjects, while the right plot shows MIP changes in subjects. The horizontal black lines in the right plot and the grey circles in the left plot represent median values. The grey dotted line on the right represents the zero value, below which there is a deterioration in the variable and above which improvement in the variable. The asterisk (*) on the horizontal blue line in the left plot represents 60 cm H_2O, above which there was an association of 100% survival in neuromuscular disease (NMD)

MIP can be obtained by instructing the subject to take a deep, fast breath after normal or maximum expiration. Normal MIP in 50- to 83-year old healthy subjects is between 58–118. In our sample, only six subjects had a baseline MIP of above 58. After PRP, all subjects in the PRP and IMT group showed improved MIP while all subjects in the PRP group showed deteriorated MIP, indicating that IMT may have a positive influence on MIP. Schoser et al. (2017) looked at the association of survival and MIP levels in neuromuscular disease (NMD) and found that all those with an MIP above 60 cm H_2O survived to 18 months. In two studies on pulmonary sarcoidosis by Kabitz et al. (2006) and Karadalli et al. (2016), the mean MIP was

114 and 139 cm H_2O, respectively. Our study involved patients with more severe disease and different ILD diagnosis, which may be why the MIP in our patients was much lower.

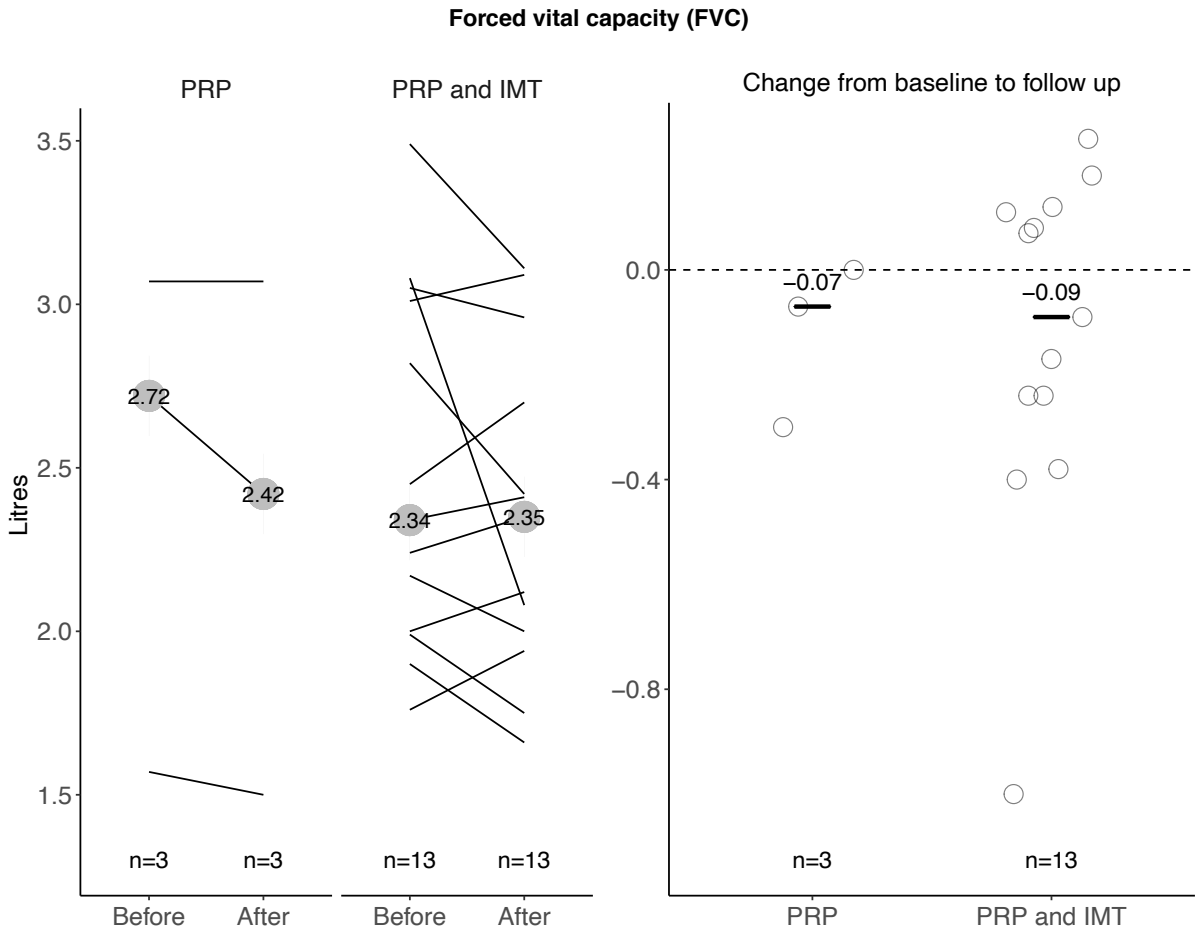


Figure 14. Forced vital capacity (FVC) before/after eight weeks of PRP, or PRP and IMT. In the left plot, individual subjects are represented by black lines

In this cohort, FVC either remained the same (1 out of 16), dropped (9 out of 16), or minimally improved (6 out of 16) over the 8-week period of PRP, and this change is expected in patients with ILD. FVC is an essential tool in the diagnosis and management of subjects with ILD, as it provides a physiological marker for antifibrotic treatment and can predict mortality. The risk of death increases 8.2 times in ILD subjects with an FVC of less than 50% predicted (Lassenius et al., 2019).

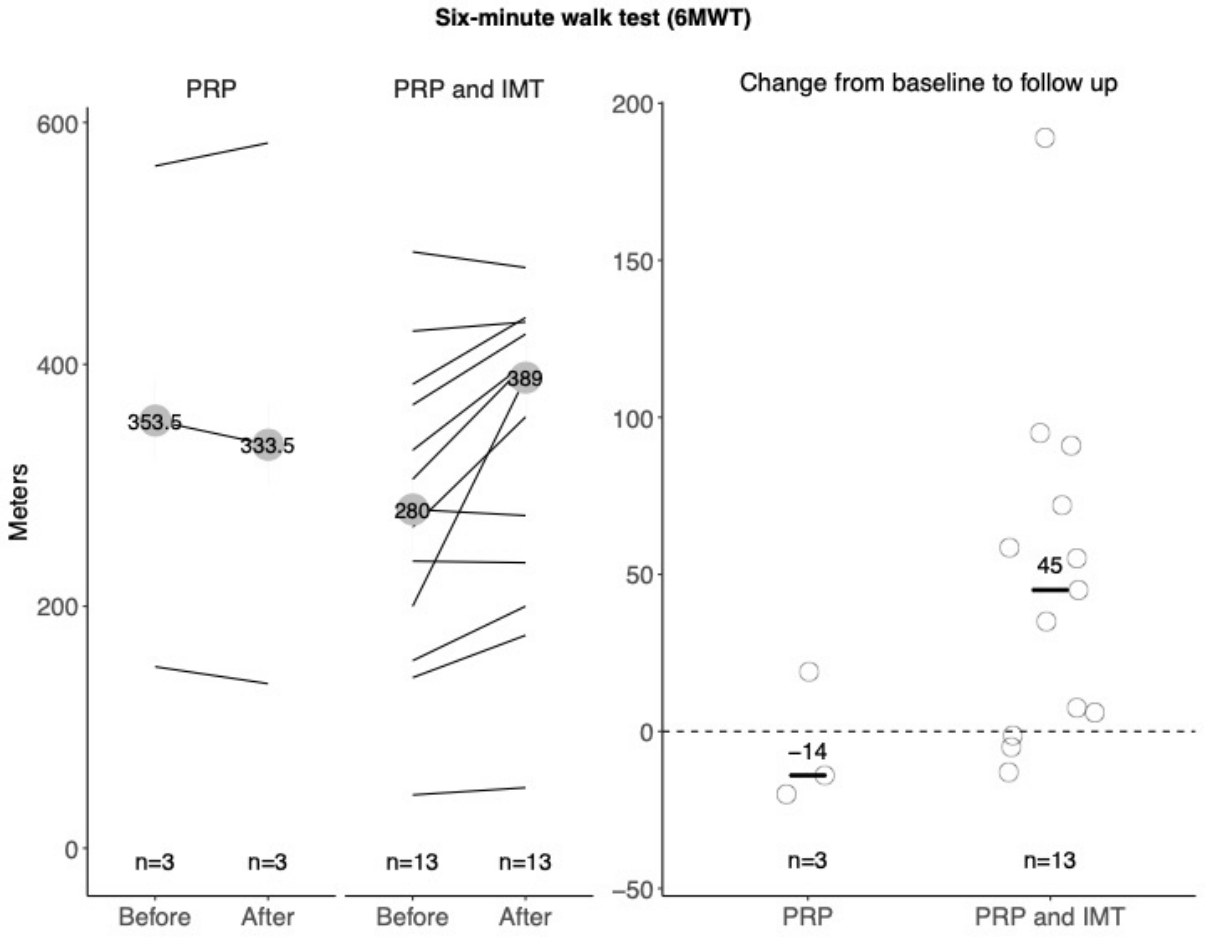


Figure 15. Six-minute walk test (6MWT) before/after 8-week PRP or PRP and IMT. Left: individual subjects are represented by black lines. Right: changes in 6MWT (after minus before). The grey circles on the left plot and the horizontal black lines on the right plot represent median values. The grey dotted line on the right plot represents zero, below which there is a deterioration in the variable and above which improvement

The 6MWT is a common assessment tool in PRP and could, along with other outcomes, measure exercise capacity. In the PRP group, two out of three patients dropped their 6MWT scores, while in the PRP and IMT group, ten out of 13 improved. With no randomisation and the limited sample size, it is difficult to generate a conclusion about this finding, but there were signs of improvement in the 6MWT in the PRP and IMT group. Du Bois et al. (2011) looked at 6MWT in 822 patients in different times and found that change over a period of 24 weeks was a strong predicator of mortality; a loss of more than 50 m was associated with four times the risk of death in a single year. No patients in the current study lost 50 m, but our measurements were only eight weeks apart.

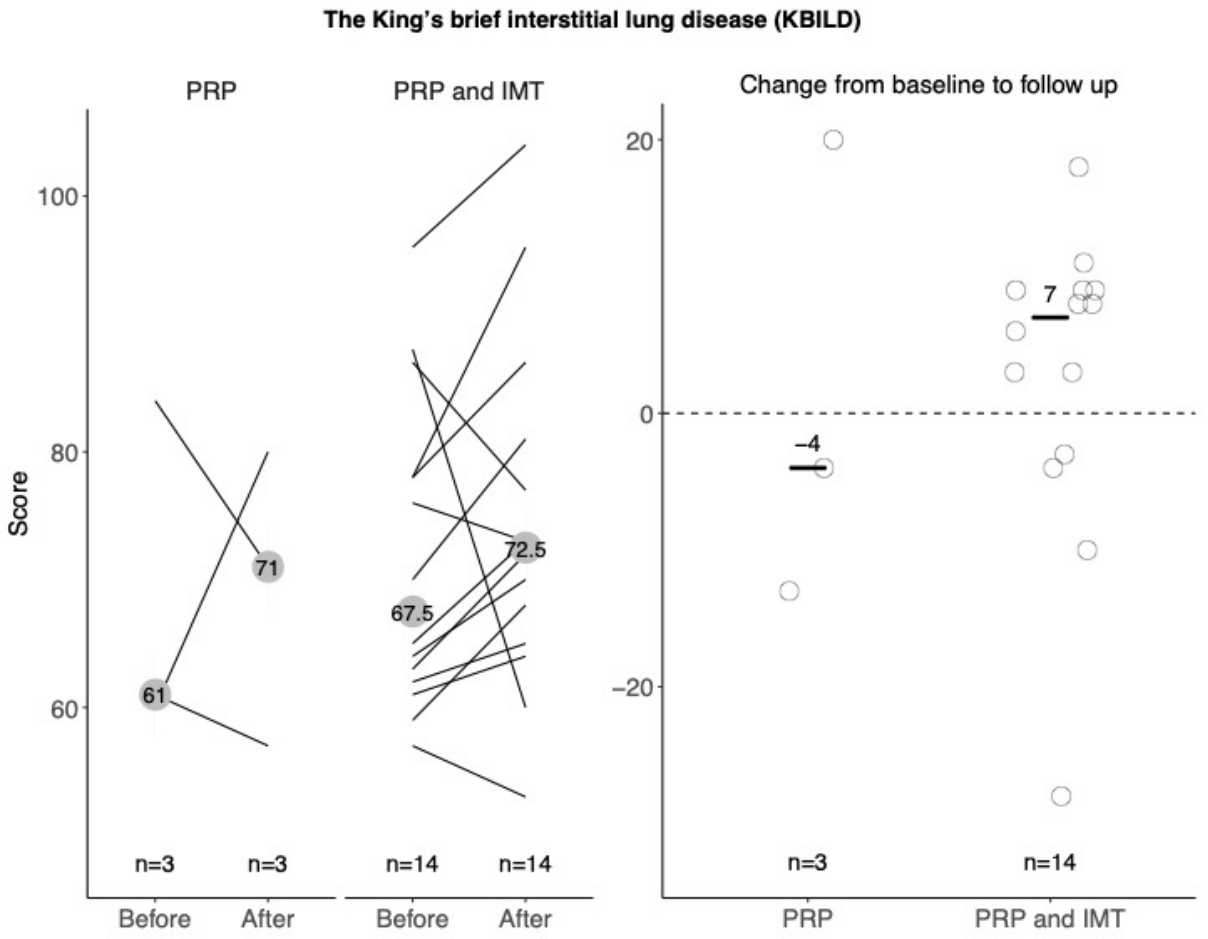


Figure 16. K-Bild scores before/after 8-weeks of PRP or PRP and IMT. The black lines on the left plot represent individual subjects, while the right plot shows changes in K-Bild score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration and above which improvement in the variable

King's brief interstitial lung disease (K-Bild) is a self-administered questionnaire specifically for subjects with ILD. It contains 15 items covering the psychological, breathlessness, and chest symptom aspects of a condition. Scores range from 0–100, where higher numbers indicate better health status (Patel et al., 2012). In our cohort, two out of three in the PRP group had reduced K-Bild scores while four out of 14 improved in the PRP and IMT group. Nolan et al. (2019) considered the minimal clinically important difference (MCID) of K-Bild in ILD and found it to be 3.9. Taking this into consideration, eight subjects in the PRP and IMT, and one in the PRP group, improved by more than 3.9.

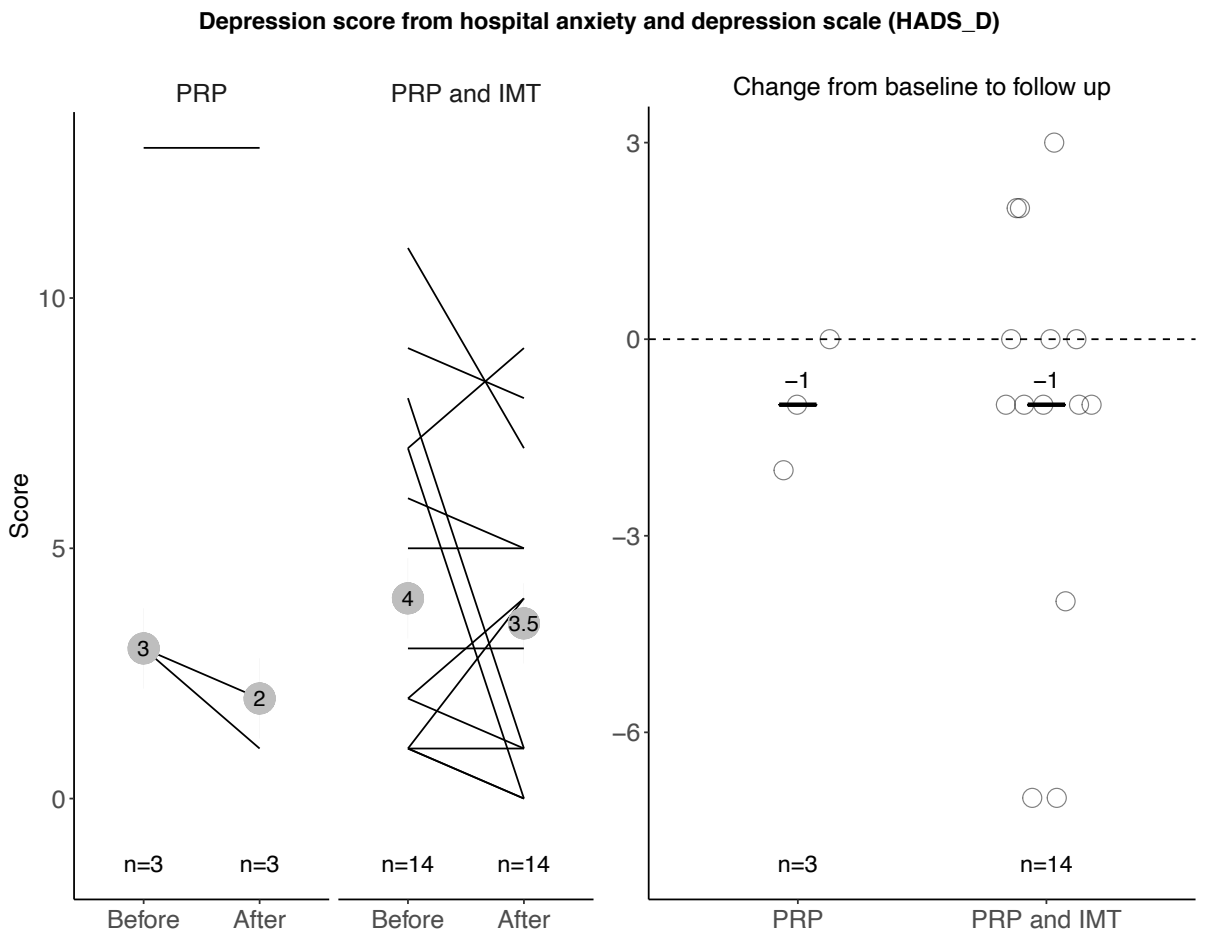


Figure 17. HADS depression scores before/ after the 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in depression score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents the zero value, below which there is an improvement in the variable and above which there is deterioration

The Hospital Anxiety and Depression Scale (HADS) is a self-administered scale which allows each main part to be reported separately. Higher numbers indicate worsening in severity of depression or anxiety, and scores below 7 are not considered to indicate depression (Stern, 2014). In our cohort, four out of 14 had depression scores of more than seven, with general improvement in both groups. This is in line with a study by Holland et al. (2014a), who found the prevalence of depression in ILD to be 23%. This underlines the importance of providing psychological support for subjects with ILD. In our PRP programme, we thus included a nurse with training in cognitive behaviour therapy (CBT) as well as a palliative care nurse.

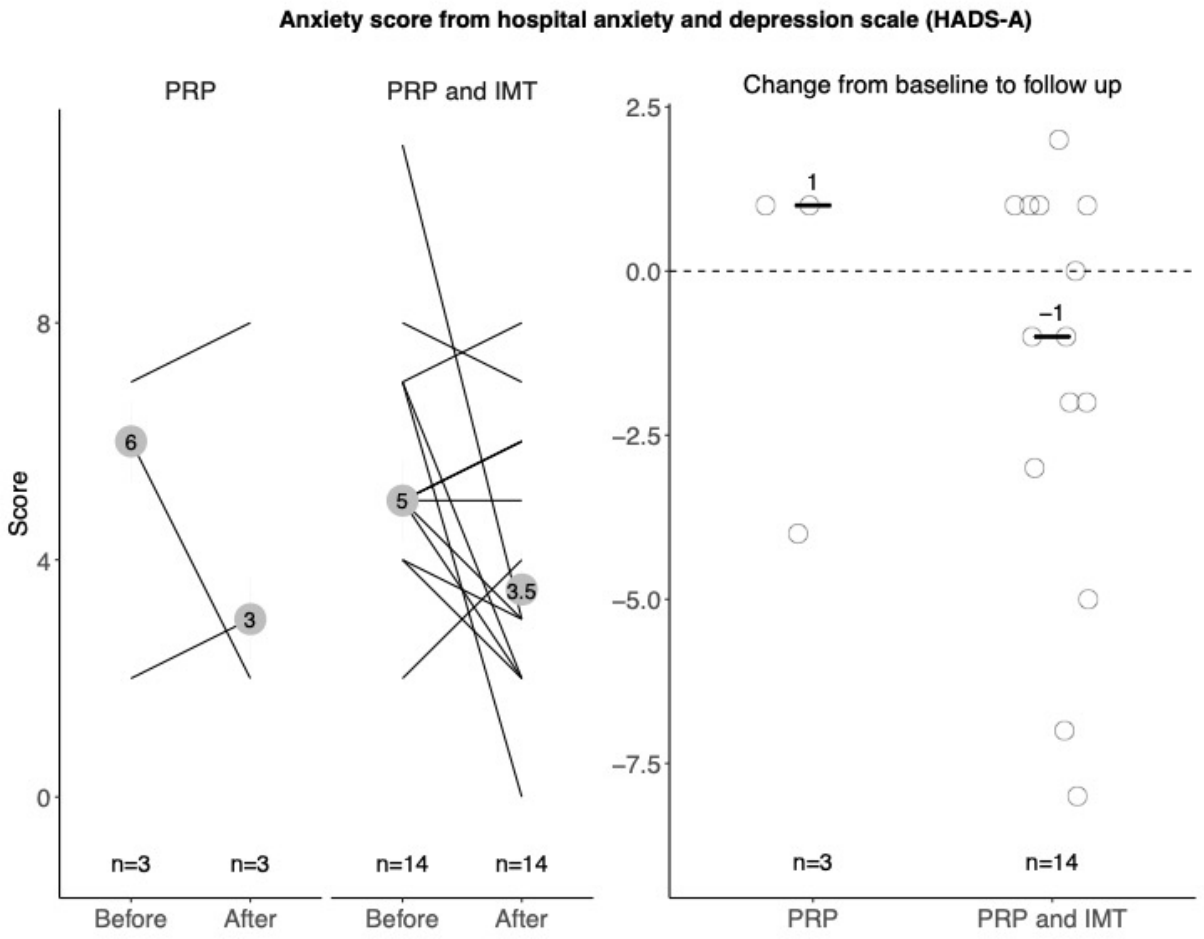


Figure 18. HADS anxiety scores before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in anxiety score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values, while the grey dotted line represents zero, below which there is a deterioration in the variable and above improvement

As described above for depression, the HADS can be filled in by patients and higher numbers indicate worse severity in anxiety; scores below seven are not considered to indicate anxiety (Stern, 2014). Only one subject in our cohort had an anxiety score over eight, while three patients scored eight and the remaining subjects under eight. This indicates that a low number of cases in this cohort could be considered to have anxiety. Holland et al. (2014a) observed the prevalence of anxiety in subjects with ILD (n=124) and found that 31% and 12% had significant anxiety. This is a higher level than that found in our sample, but again with such a small sample size it is difficult to draw a conclusion.

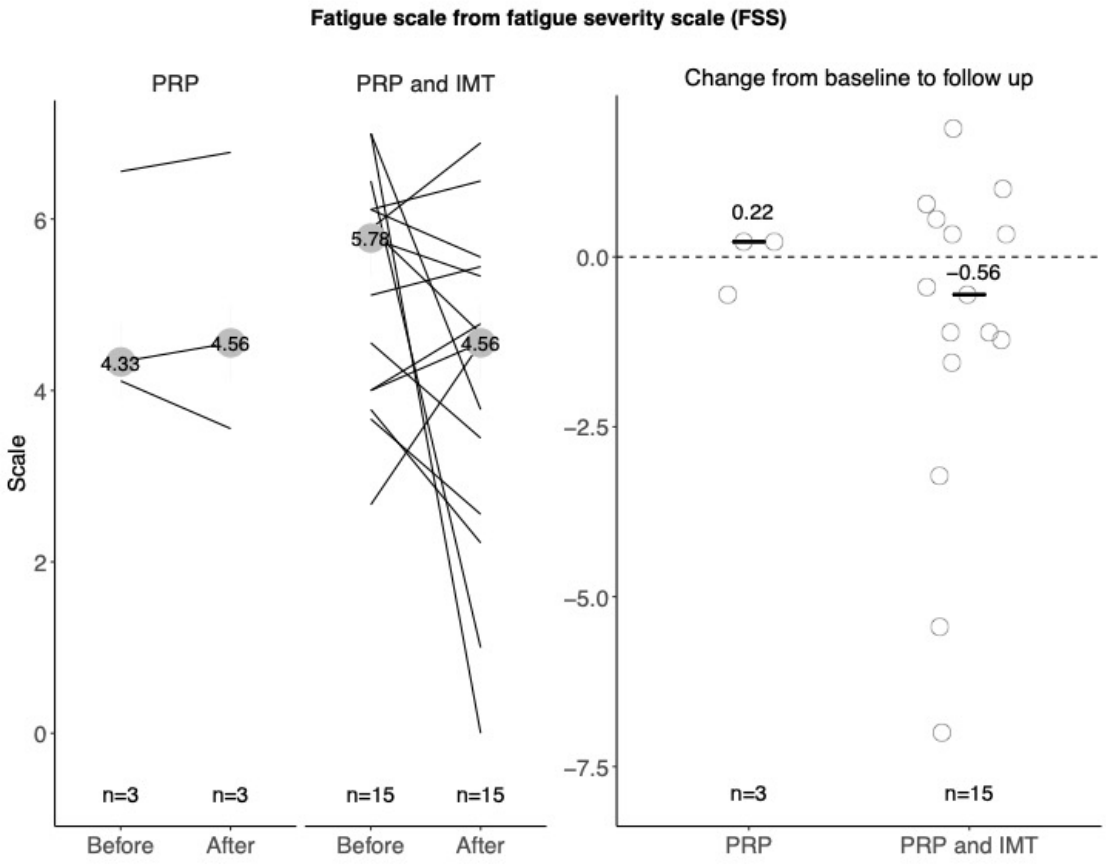


Figure 19. Fatigue severity scale before/after 8-weeks PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in fatigue severity scale. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

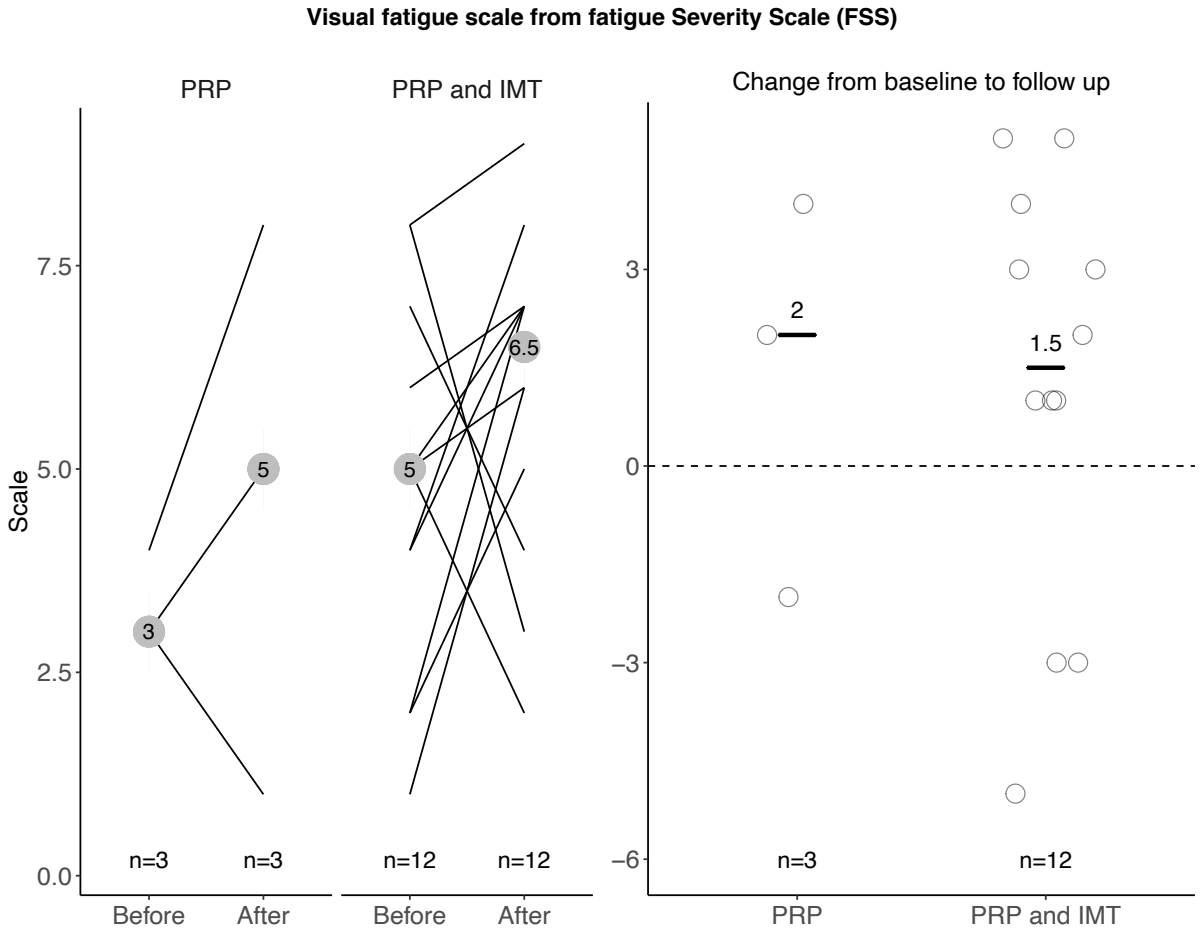


Figure 20. Visual fatigue score from the fatigue severity scale, before/after 8-weeks PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in visual fatigue score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

In Figure 19 and

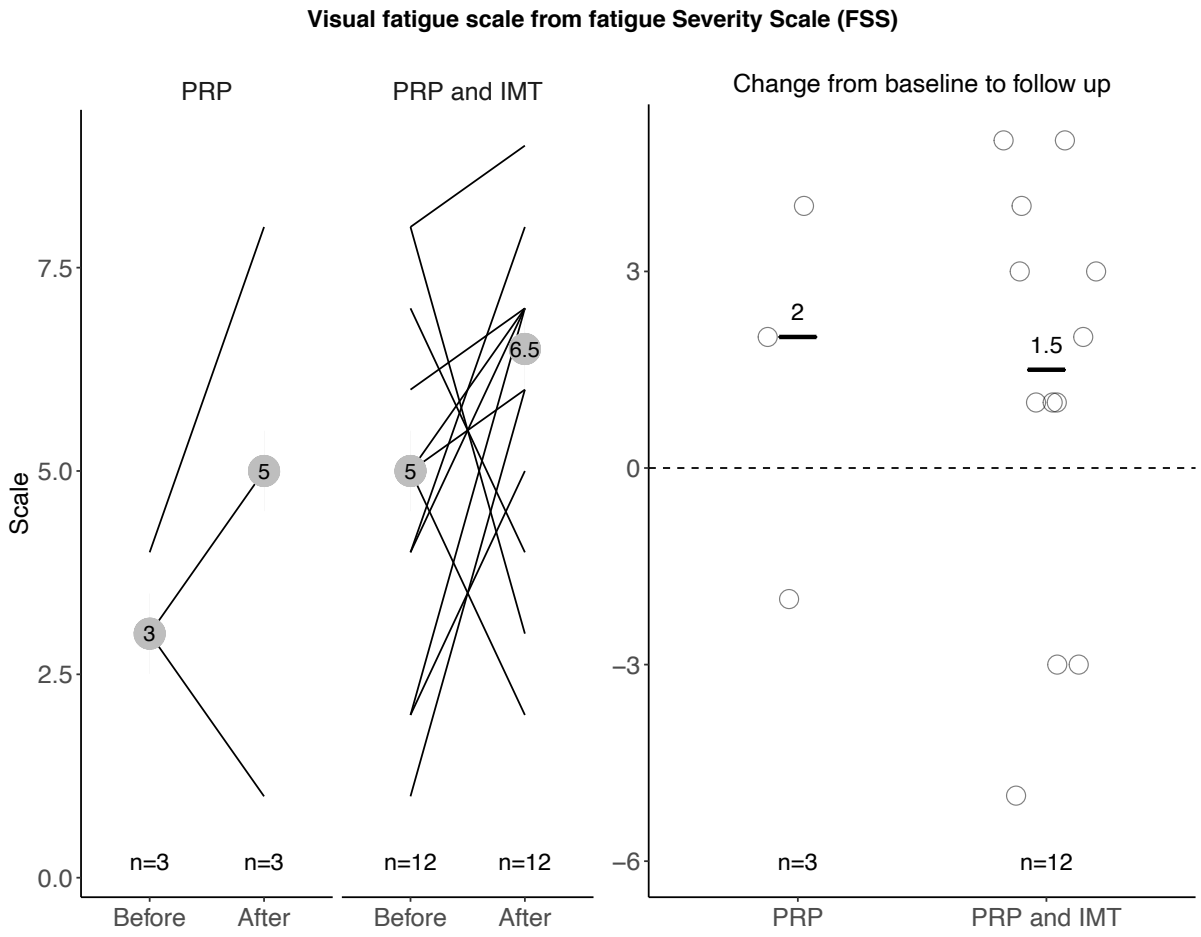


Figure 20, fatigue severity and visual fatigue scores are presented. The Fatigue Severity Scale (FSS) is a self-administrated questionnaire for quantifying fatigue. It has two main parts. The first has nine questions and the second is a visual analogue scale for fatigue. In the first part, each question is answered using a 7-point Likert scale, with 1 indicating strongly disagree and 7 strongly agree. Higher scores mean subjects have more fatigue. After answering all the questions, the total can be divided by nine to obtain the average scale. Guenther et al. (2018) looked at the reported symptoms in 525 subjects with IPF and found dyspnoea was reported 90% of the time, and fatigue 70% of the time. In our cohort, there was a general reduction (14 out of 18) in FSS scores in both groups, but in the visual fatigue scale, there was an increase in fatigue. This is surprising since both scales showed a correlation with Keyser et al. (2015), who reported a mean FSS of 4.1 + - 1.2 before and 3.5 + - 0.9 PRP. Their PRP involved thrice weekly training conducted with 13 subjects with ILD. In general, the FSS in our cohort was higher than in Keyser's study, possibly because our subjects experienced less disease severity.

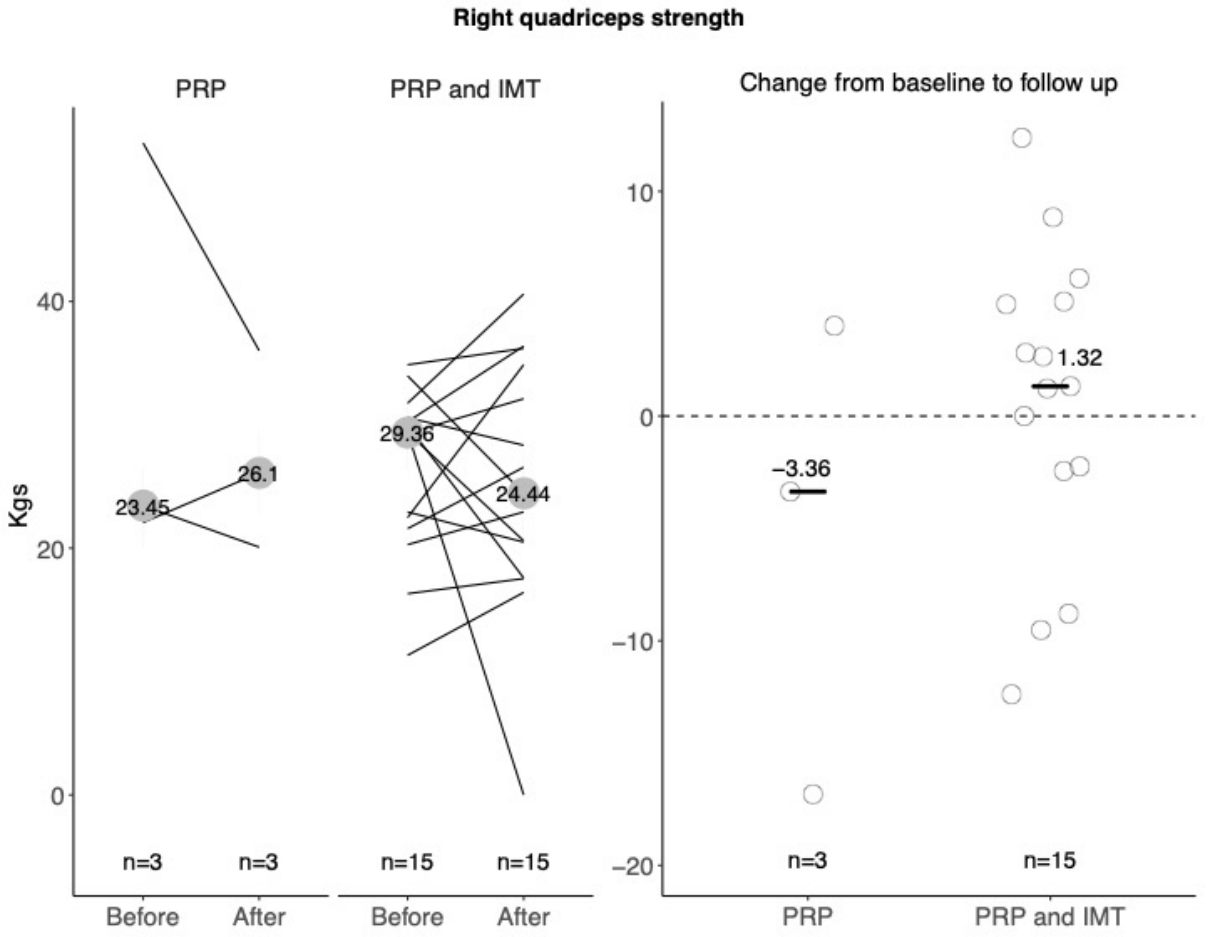


Figure 21. Right quadriceps strength before/after 8-week PRP or PRP and IMT groups. Left: black lines represent individual subjects. Right: changes in right quadriceps strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Right quadriceps muscle strength was measured using an HHD by the same assessor pre and post PRP. The measurement was done in accordance with Dowman et al. (2016) who used HHD to measure peripheral muscle strength. In our cohort, 10 out of 18 subjects improved their strength and the other deteriorate. This is not unusual with such diverse diagnosis and progression of in this group. In Dowman et al. (2016) study, the quadriceps strength was measure at two interval and were found to be 18.3 (4.8) and 19.0 (5.6) kgs. Their strength is less that what we reported in this group, with such small sample size and lack of randomisation, it is hard to compare. However, there are few patients in our cohort who had much lower strength.

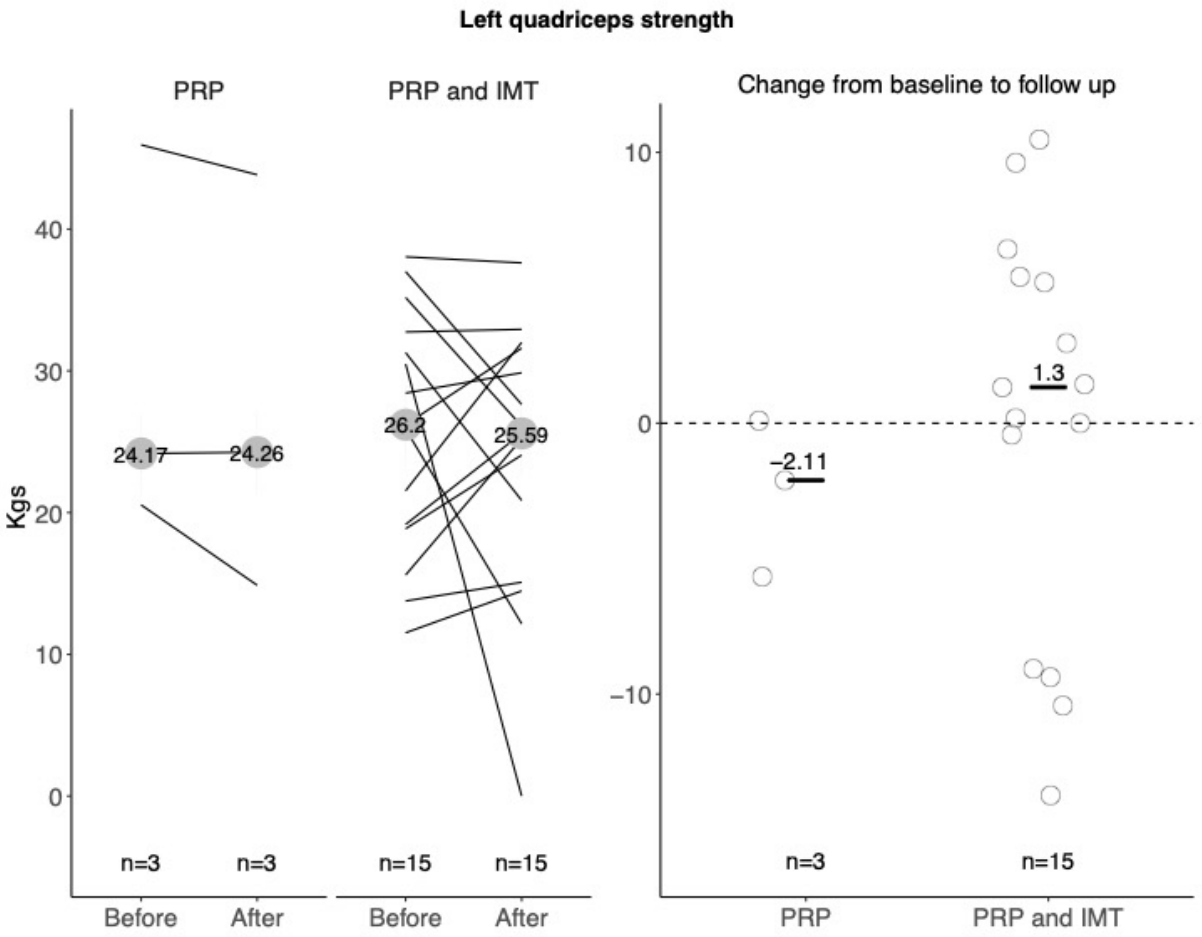


Figure22 **.** Left quadriceps strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left quadriceps strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Left quadriceps strength was measured as explained by Dowman et al. (2016). Twelve out of 18 subjects either maintained or improved strength while the remaining six lost strength. This is not uncommon with ILD where diagnosis and disease progression differ from patient to patient. Quadriceps strength was tested twice in Dowman et al. (2016) and found to be 18.3 (4.8) and 19.0 (5.6) kgs, which is lower than our medians of 24–26; this finding was the same with right quadriceps. However, due to the lack of randomisation and our sample size calculation, it is difficult to draw any conclusion.

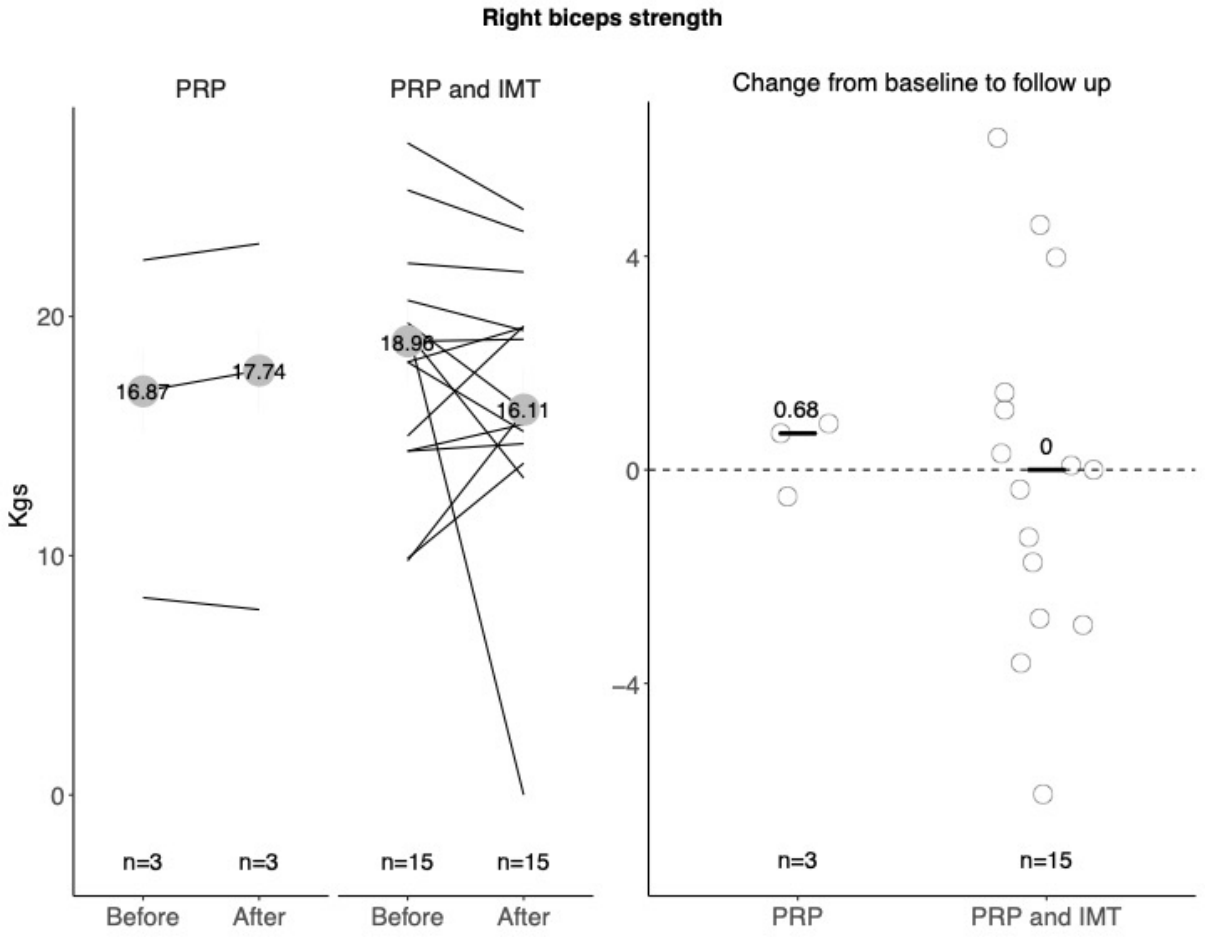


Figure 23. Right bicep strength before/after 8-week PRP or PRP and IMT. The black lines on the left plot represent individual subjects. The right plot shows subjects' changes in right bicep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Bicep strength was measured using an HHD. Patients were instructed to lie supine as tolerated with their elbow placed and stabilised on the bed, and then they were instructed to flex their arm against the HHD to their maximum ability for at least three seconds. The highest reading from three acceptable trials was reported. This procedure is explained in Dowman et al. (2016). In both groups in our cohort, about half of the subjects improved strength and the other half lost, which is expected with different in progression of the disease.

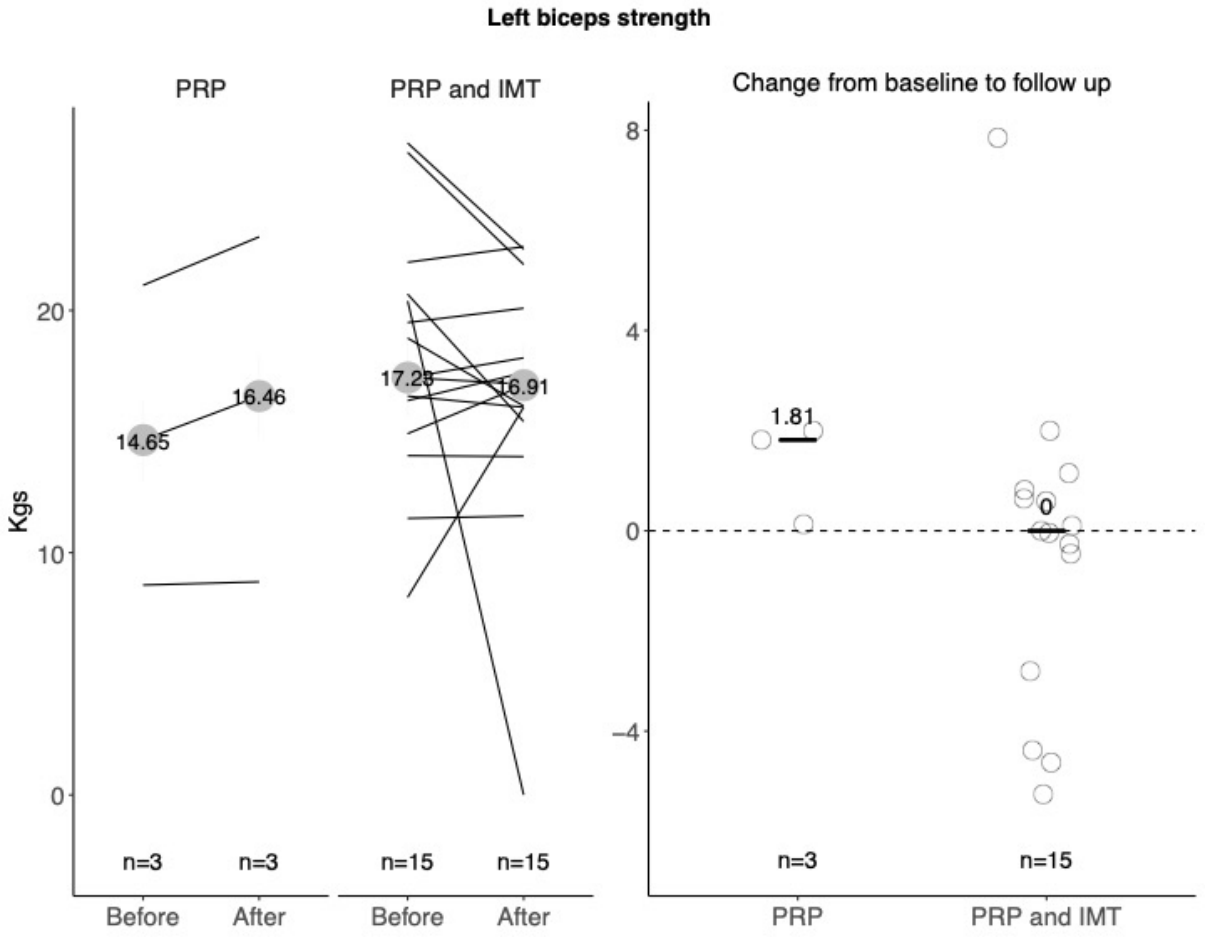


Figure.24 Left bicep strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left bicep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Bicep strength measured using an HHD, as explained by Dowman et al. (2016), was reported to be 16.8 (+-6.5) kg; this is very close to our medians of 14–17 kg. However, about half of our subjects lost some strength, which could be related to worsening of their condition.

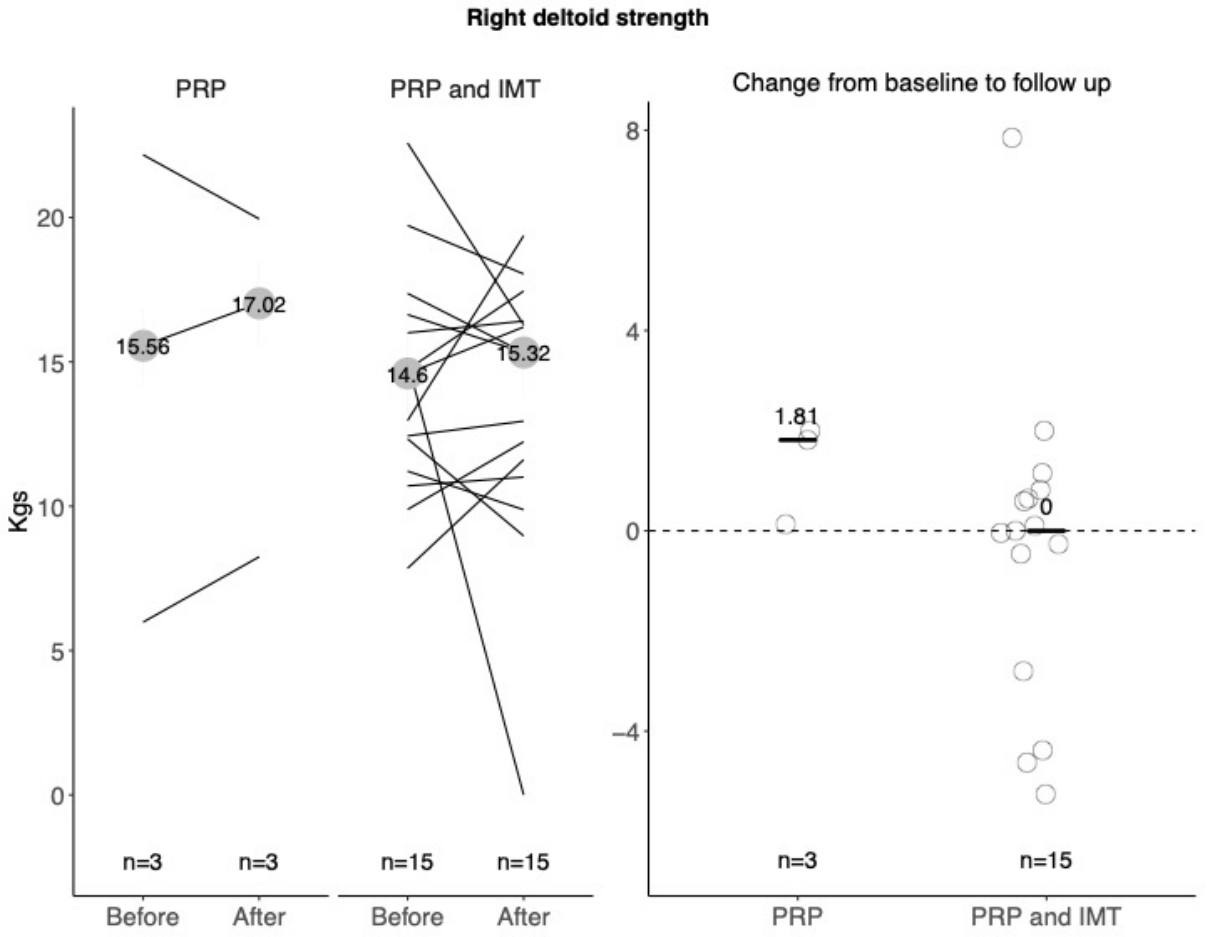


Figure 25. Right deltoid strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in right deltoid strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

In the right deltoid muscle, as with the biceps, about half of the patients from both groups lost strength, and again this could be related to disease progression. For comparison, to my knowledge, no previous study has looked at deltoid muscle strength in ILD.

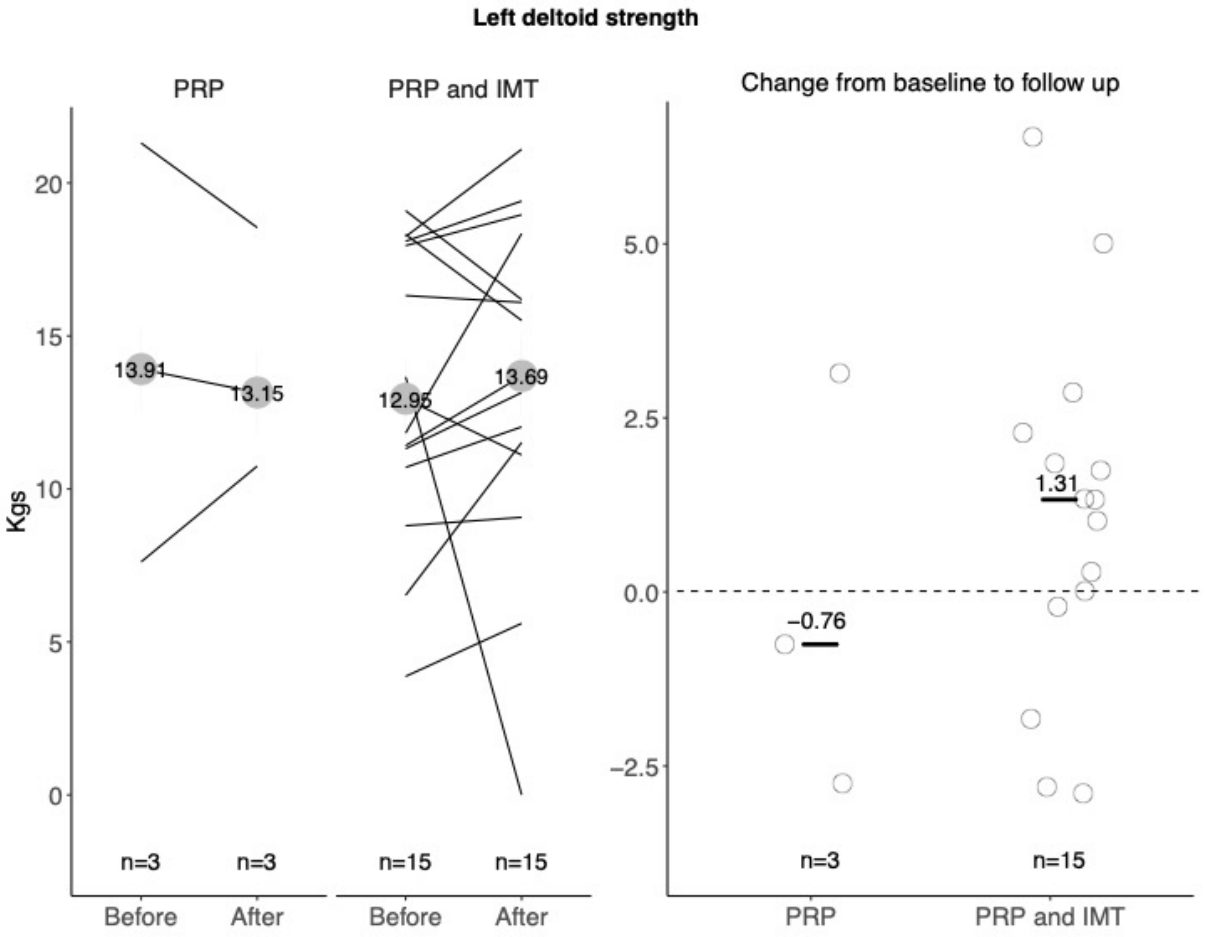


Figure.26 Left deltoid strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left deltoid strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

For the left deltoid muscle, most of the improvement seen was in the PRP and IMT group (10 out of 15), which is unusual since the right deltoid muscle improved less in the same patients. This may be because their initial strength was lower (13 vs. 14.6 for the right deltoid), indicating there was more room for improvement, but it is difficult to draw conclusions with such a small sample size and lack of randomisation. To my knowledge, no previous published study has examined deltoid muscle strength in subjects with ILD.

4.5 Overall Discussion

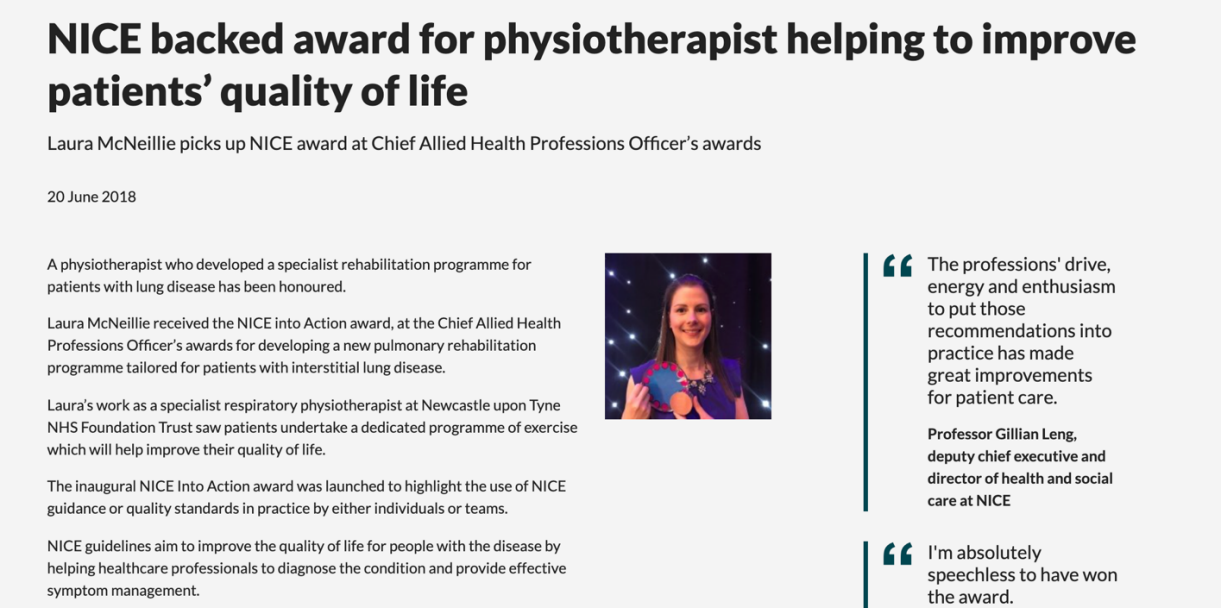
The main outcome for the clinical service was the feasibility of delivering PRP with or without IMT in a hospice care setting augmented by home exercise. These results show that the programme was feasible and received positive feedback from carers, patients, and healthcare providers. The completion rate was 100% for this cohort because the subjects were recruited from the local IPF support group, and the programme was friendly and enjoyable for both patients and carers. There was a suggestion from the first group about bringing carers or family members to attend but not perform the PRP session, and this was acted on in the subsequent groups and the RCT. There were no complications during the programme, except for one patient who had a panic attack on the assessment day following the rehabilitation programme. This patient decided not to perform the assessment. From the healthcare provider's perspective, there were difficulties with transportation, resolved by support funds from The Newcastle upon Tyne Hospitals NHS Foundation Trust. Another issue related to the 6MWT, which was conducted once before and after the programme. After discussions, we decided to perform this twice before the programme and twice after to achieve greater accuracy with the test and diminish the training effect. We reported the highest walking distance. Initially, patients were instructed to perform two home exercise sessions, but these were not followed or documented. After the first group, a log of a single page of home exercises was developed for patients to document and follow the exercises (see Appendix. Home exercise log). This log was followed by our PT and adjusted according to subjects' ability. To improve safety and training during PRP sessions, a physiotherapist technician was added to the team and they attended every session to help the primary PT with training. All supervised sessions were attended by a PhD student, a senior nurse, and two physiotherapists.

Because MIP was assessed every week in IMT group, there may have been a learning effect which caused MIP to improve in most of the patients. Given the lack of randomisation, blinding, and low number of subjects in the PRP (control group), these data should be interpreted with caution.

The secondary outcomes of this descriptive clinical service analysis indicate a potential improvement in some outcomes which was profound in the scores for MIP, 6MWT, K-Bild, FSS. However, HADS-D, HADS-A, the visual fatigue scale, and all peripheral muscle strength measurement outcomes indicated that patients had different responses by either improving, deteriorating or maintaining levels. FVC showed progressive deterioration in most of our patients, which is not uncommon in subjects with ILD. As stated, it is difficult to draw

conclusions due to the small sample size, no randomisation, and unequal control group. Having an equal control group decreases the risk of placebo and or time effect for the outcomes.

After developing and conducting the PRP for ILD, our team won the NICE into Action award and our achievement was displayed on the NICE website https://www.nice.org.uk/news, and https://www.nice.org.uk/sharedlearning, as well the that of the Chartered Society of Physiotherapy https://www.csp.org.uk/news.



NICE backed award for physiotherapist helping to improve patients' quality of life

Laura McNeillie picks up NICE award at Chief Allied Health Professions Officer's awards

20 June 2018

A physiotherapist who developed a specialist rehabilitation programme for patients with lung disease has been honoured.

Laura McNeillie received the NICE into Action award, at the Chief Allied Health Professions Officer's awards for developing a new pulmonary rehabilitation programme tailored for patients with interstitial lung disease.

Laura's work as a specialist respiratory physiotherapist at Newcastle upon Tyne NHS Foundation Trust saw patients undertake a dedicated programme of exercise which will help improve their quality of life.

The inaugural NICE Into Action award was launched to highlight the use of NICE guidance or quality standards in practice by either individuals or teams.

NICE guidelines aim to improve the quality of life for people with the disease by helping healthcare professionals to diagnose the condition and provide effective symptom management.

Figure 27. Laura McNeillie, our senior physiotherapist, represented the team during the awards ceremony

The award was given to our programme because it applies a NICE recommendation on subjects with ILD clinical guidelines (https://www.nice.org.uk/guidance) (CG163), which recommends rehabilitation as the first point in the management section.

Because of the COVID-19 crisis, no access to patient characteristic data was possible and so these were not reported.

Conclusion

This novel PRP clinical service in a hospice care and home setting was feasible and appreciated by patients, carers, and healthcare providers. Conducting the clinical service before the RCT was helpful in refining the programme and logistics. The variable response regarding different outcomes is not unusual in subjects with ILD, which have different aetiologies and can have

different progression of disease with the same aetiology. Winning the NICE award was very supportive of the importance of PRP in ILD.

Chapter 5. Results of the Randomised Feasibility Clinical Trial

5.1 Chapter Overview

After positive feedback from the clinical PRP service, we conducted a clinical feasibility trial comparing PRP to PRP supplemented with IMT, aiming to compare subjects' outcomes between PRP alone and PRP with IMT. It was felt that this could serve as a foundation for a larger clinical trial. Blinding was considered but thought impossible as both the patients and healthcare team could see the use of the IMT intervention. Future powered studies could consider the use of a 'sham IMT', e.g., lacking resistance and any efficacy as a muscle training strategy. The programme was conducted in a novel collaboration with Newcastle University, The Newcastle upon Tyne Hospitals NHS Foundation Trust, and Marie Curie Hospice care. Twenty-two subjects with ILD were recruited and 20 were randomised to receive PRP and IMT or PRP only. Subjects were enrolled into an 8-week PRP with or without IMT. The PRP involved education sessions and tailored physical exercises. SPSS, Excel, R, and RStudio were used for descriptive analyses and graphical presentation of the data, in keeping with recommendations regarding the analysis of feasibility studies. The attendance rate for the 20 randomised subjects was 81%. Twelve patients were randomised to PRP alone and eight to PRP with IMT. Sixteen subjects attended baseline and follow up sessions. There was positive feedback regarding the programme from patients, carers, and the healthcare team. The novel initiative of integrating biomarker measurements into the study indicated that measurement was possible in this setting, including the assessment of serum MMP-7, a biomarker associated with morbidity and mortality in IPF.

In summary, PRP in ILD with or without IMT in a hybrid of outpatient and home settings was feasible for most patients and led to positive feedback. There were variable responses for patient-related outcomes for most patients, broadly showing either stability of the outcome measures or suggestions of potential improvement over the course of the programme. This study indicates that future research integrating the use of biomarkers, physiological end points, and PRP intervention is possible in a collaborative environment and preliminary data suggest this is worthwhile.

5.2 Introduction

Pulmonary rehabilitation (PR) is defined as a 'comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and

psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours' (Rochester et al., 2015). PR is an essential component in the management of ILD/IPF. With limited treatment for some interstitial lung diseases, especially IPF, PR that includes exercises is an important treatment for potential improvement in symptoms and QOL. Tikellis et al. (2021) looked at the top ten research priorities for pulmonary fibrosis ranked by healthcare provider, patients, care givers, and researchers, and the 'best exercise programme' ranked tenth. NICE (2017) also placed PR as a top priority when recommending future research, in particular focusing on designing a tailored rehabilitation programme for IPF which might differ from what is established for COPD. It also emphasised the importance of QOL and patient-related outcomes. Based on these recommendations and feedback from our patients, and with experienced input from our regional MDT team, I developed and conducted a tailored IPF/ILD pulmonary rehabilitation feasibility RCT, which also incorporated the collection of blood for biomarkers and genetic markers of disease. The RCT compared IMT combined with PRP in one group and PRP only in the other. Ethical approval was obtained prior to starting the study (see Appendix. Letters of Approval). For ethical reasons, there was no non-intervention arm to the RCT and the comparison was intervention arm versus standard of care

This chapter shows the results of the RCT. Detailed methodology was explained in Chapter 3 and is registered in https://doi.org/10.1186/ISRCTN92567676. A brief and specific methodology will be explained in this section.

5.3 Specific Materials and Methods

5.3.1 Modification after the pilot study

After the initial experience with the pilot study reported in Chapter 4, some minor modifications were made. 6MWT was conducted twice instead of once to avoid a learning effect. Carers were invited to attend all education sessions. A home exercise log was developed to monitor patients' adherence to exercises (Appendix. Home exercise log).

5.3.2 Subject selection

Subjects were identified from the regional ILD clinic by respiratory consultants or a senior ILD nurse. An initial conversation was conducted on the importance of PR and a patient information sheet was provided. Subjects were selected if an ILD diagnosis was available from the MDT and they had an MRC score from 2–5 and they were aged 40 or older. Patients were excluded

if they had uncontrolled cardiovascular disease or were unable to follow or attend exercise sessions.

5.3.3 Randomisation

After selection, subjects were randomised 1:1 into two groups: IMT and PRP or PRP only (Figure 28)Randomisation was performed by entering the subjects' study IDs into the online randomisation service (https://sealedenvelope.com/). This website randomly distributed patients to study groups and researchers were blinded to sequence allocation. All randomisations are saved on the website.

5.3.4 Pulmonary rehabilitation programme

Both groups received PR, but the IMT and PRP group received inspiratory muscle training (IMT) at 40% MIP X 30 BID using a PowerBreathe device. The MIP was assessed weekly and IMT pressure adjusted accordingly. The PRP involved aerobic training targeted and modified using the mBORG scale, resistance training, and education and relaxation sessions.

5.3.5 Outcomes

The primary outcome for this study was the feasibility of conducting a hybrid (home and in clinic settings) PR in a hospice care clinic setting for subjects with ILD, and the feasibility of adding IMT to the PR programme. Secondary outcomes involved FVC, MIP, 6MWT, K-Bild, HADS, FSS, iPos measurements, peripheral muscle strengths, physical activities, MMP7 levels, and assessment of polymorphisms of the MUC5B gene.

5.3.6 Statistical analysis

Since this is a proof-of-concept pilot study, no formal sample size calculation was performed. In keeping with the common practice of recruitment for pilot trials of 20–30 subjects, the plan was to recruit 36 subjects with an estimated possible loss to follow up of 20% of subjects. Statistical analysis involved basic description using R, SPSS, and Excel. In accordance with a proof-of-concept pilot RCT, no statistical hypothesis testing was done.

5.4 Results

Despite the plan to recruit 36 subjects with an estimated possible loss of 20%, limited time and the Covid-19 pandemic meant that 20 subjects were recruited and four were lost to follow up, a loss rate of 20%. Figure 28 shows a flow chart summarising the journey through the trial.

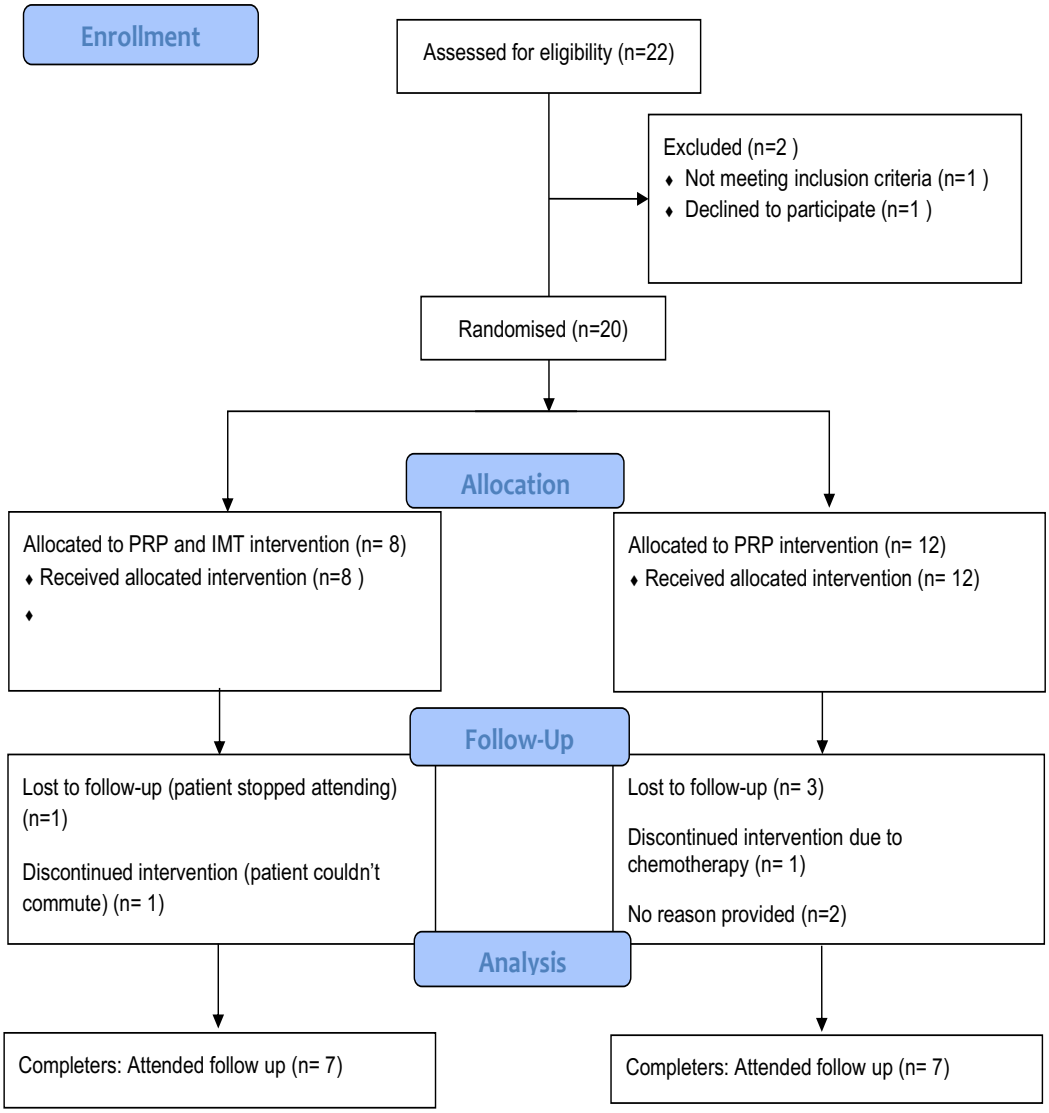


Figure 28. Flow diagram for the study, showing allocation, follow up and analysis distribution

Patient	Gender	Height	Weight	BMI	IMT	Dx
S001	male	175	82	26.7755102	NO	IPF
S004	male	177	96	30.6425357	NO	CHP
S006	male	183	103.4	30.87581	NO	IPF
S008	male	168	87.6	31.037415	NO	IPF
S009	female	161	102.7	39.620385	NO	CHP
S011	male	177	99	31.6001149	NO	CPFE
S013	female	177	85	27.1314118	NO	IPF
S017	male	185	102.7	30.0073046	NO	IPF
S019	male	174	92	30.3871053	NO	IPF
S020	male	168	92	32.5963719	NO	IPF
S021	male	170	66.6	23.0449827	NO	IPF
S022	female	158	70.6	28.2807242	NO	CHP
S002	male	168	67.2	23.8095238	YES	IPF
S003	male	175	87	28.4081633	YES	IPF
S005	male	172	92	31.0978908	YES	IPF
S007	male	170	88	30.449827	YES	CPFE
S012	male	164	87.7	32.6070791	YES	Unclassified
S015	female	152.5	99	42.5692018	YES	NSIP
S016	male	168	77.2	27.3526077	YES	Unclassified

Table 10. patient baseline characteristics

Variable	PRP (mean and SD)	PRP + IMT(mean and SD)	Sig
Height	172 +8	167 + 7	0.14
Weight	89 + 12	85 + 10	0.40
BMI	30 + 3.9	30 + 5	0.78

Table 11. Patients' baseline characteristics, comparison between PRP + IMT and PRP groups

Outcome	PRP group, n=12			PRP and IMT, n=8		
n **Median (Min, Max)**	Baseline	Follow up after PRP	Change from baseline to follow up	Baseline	Follow up after PRP	Change from baseline to follow up
Age in years	65 (54, 79)			73 (56, 81)		
Sex	9 M, 3 F			7M, 1 F		
	12	9	9	8	7	7
MIP in cm H_2O	53 (23, 117)	53 (13, 118)	9 (-40, 30)	47 (24, 84)	74 (35, 127)	28 (-1, 75)
	12	9	9	8	7	7
FVC in litres	2.43 (1.31, 3.21)	2.78 (1.29, 3.65)	0.1 (-0.02, 0.53)	2.49 (2, 3.2)	2.33 (2.04, 3.46)	-0.12 (-1.08, 0.93)
	12	9	9	7	7	6
6 MWT in metres	340.00 (177, 480)	380 (207, 471)	30 (-17, 68)	394 (350, 508)	367 (50, 465)	-1.5 (-33, 12)
	9	8	8	7	7	7
K-BILD	58 (34, 99)	75 (51, 102)	10.5 (-15, 31)	70 (53, 94)	75 (60, 93)	2 (-19, 23)
	9	8	8	7	7	7
HADS-D	6 (0, 10)	4.5 (1, 10)	-5 (-7, 3)	4 (2, 10)	4 (1, 10)	2 (-19, 23)
	9	8	8	7	7	7
HADS-A	6 (1, 14)	3.5 (0, 10)	-1.5 (-5, 1)	5 (0, 6)	4 (0, 8)	2 (-2, 3)
	9	8	8	7	7	7

FSS	5.22 (1, 9)	3.56 (1, 6)	-1.1 (-7.4, 3.33)	4.89 (2, 6)	5.44 (4, 6)	-0.1 (-1.1, 2)
	9	8	8	7	7	7
FSS-V	3 (1, 10)	5.5 (4, 9)	1 (-2, 5)	7 (3, 9)	5 (4, 7)	0 (-4, 3)
	11	9	8	8	7	7
R-Quads in kg	13.5 (5.4, 43.6)	12.5 (7.9, 21.7)	1.1 (-30, 6)	13.2 (4.8, 18.1)	13.7 (9.3, 39)	2.7 (-1.3, 27.1)
	11	9	8	8	7	7
L-Quads in kg	12.8 (5.0, 29.5)	12.6 (8, 22)	1.8 (-21.43, 4.08)	12.6 (7.1, 21)	13.4 (5, 31)	0.6 (-3, 19)
	11	9	8	8	7	7
R-Biceps in kg	20.2 (6, 28)	19.29 (14, 31)	-3.1 (-8.67, 4.9)	16.2 (3, 22)	17.8 (5, 40)	1.5 (0, 24)
	11	9	8	8	7	7
L-Biceps in kg	17.5 (8.7, 28.6)	19.4 (10.5, 28.1)	1.3 (-9.37, 4.9)	16.6 (3.5, 19.7)	18.6 (3.6, 48.1)	3.9 (0, 31)
	11	9	8	8	7	7
R-Deltoid in kg	14.6 (5.2, 21.4)	14 (8, 24)	0.8 (-7.9, 3.16)	13.4 (2.6, 17.6)	15.4 (2, 26)	0.3 (-3, 15.1)
	11	9	8	7	7	6
L-Deltoid in kg	15.2 (5.8, 20.9)	13.8 (8.3, 24.3)	-1.5 (-9, 3.4)	12 (8.7, 16.8)	15.2 (2.8, 23.1)	1.4 (-2.2, 13.6)
	12	9	9	7	7	6
MMP7 levels in ng/ml	1.82 (1.48, 4.3)	2.09 (1.53, 2.57)	-0.17 (-2.76, 0.93)	2.28 (1.77, 5.24)	1.82 (1.52, 2.21)	-0.50 (-3.63, 0.13)
	12	7	7	7	6	5

Average moderate and vigorous activities in minutes/day	4.25 (0.2, 9.6)	2.6 (0, 16)	-1.46 (-7, 8.6)	0.5 (0, 30)	3 (0.17, 7)	0 (-30, 6.7)
	12	7	7	7	6	5
Average sedentary time in minutes/day	775 (564, 939)	798 (680, 966)	10 (-854, 175)	828 (696, 959)	813 (784, 864)	-80 (-959, 865)
	12	11	11	8	7	7
iPOS total	14.5 (5, 44)	16 (1, 33)	-4 (-14, 8)	13.5 (9, 28)	11 (3, 31)	-3 (-6, 5)

Table 12: Median, minimum, and maximum of variables at baseline and after PRP. PRP (pulmonary rehabilitation programme) IMT (inspiratory muscle training) MIP (maximum inspiratory pressure) FVC (forced vital capacity) 6MWT (Six-minute walk test), K-Bild (King's Brief Interstitial Lung Disease)

	Study ID	Pre	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Post	Attendance rate
1	001S											100%
2	002S											100%
3	003S											100%
4	004S											90%
5	005S											80%
6	006S											70%
7	007S											80%
8	008s											100%
9	009s											60%
10	011s											100%
11	012s											80%
12	013s											80%
13	015s											80%
14	016s											90%
15	017s											80%
16	018s											20%
17	019s											70%
18	020s											100%
19	021s											100%
20	022s											40%
	Average											81%

Table 13. Attendance of subjects to rehabilitation sessions. Green = attended; red n = missed session

Outcome	MIP	PFT	6MWT	K-Bild	HADS	FSS	Muscle strength	MMP7	Physical activity
No. of missing data	4	4	1	1	1	1	4	7	7

Table 14. Summary of missing data before or after the PRP in the study

5.4.1 Maximum inspiratory pressure

Maximum inspiratory pressure (MIP) tests assess the strength of breathing muscles. In healthy subjects aged 50–83 years, the normal MIP is between 58–118 cm H_2O. This study provides the first such data on MIP in ILD, to my knowledge. In our cohort, the PRP and IMT group had better improvement in MIP compared to the PRP only group. Six out of seven either improved or maintained their MIP compared to five out of eight; this was expected since the PRP and IMT group performed the IMT training for eight weeks. That being said, some subjects from the PRP group had some improvement in MIP, possibly due to the other form of exercises or reflecting variability in the end point. Iwakura et al. (2020) looked at the MCID in MIP in older adults with COPD and found it to be 17.2–17.6 cm H_2O, which was achieved by eight subjects, five from the PRP and IMT group; however, two from the PRP only group recorded a reduced MIP by the MCID (Figure 29).

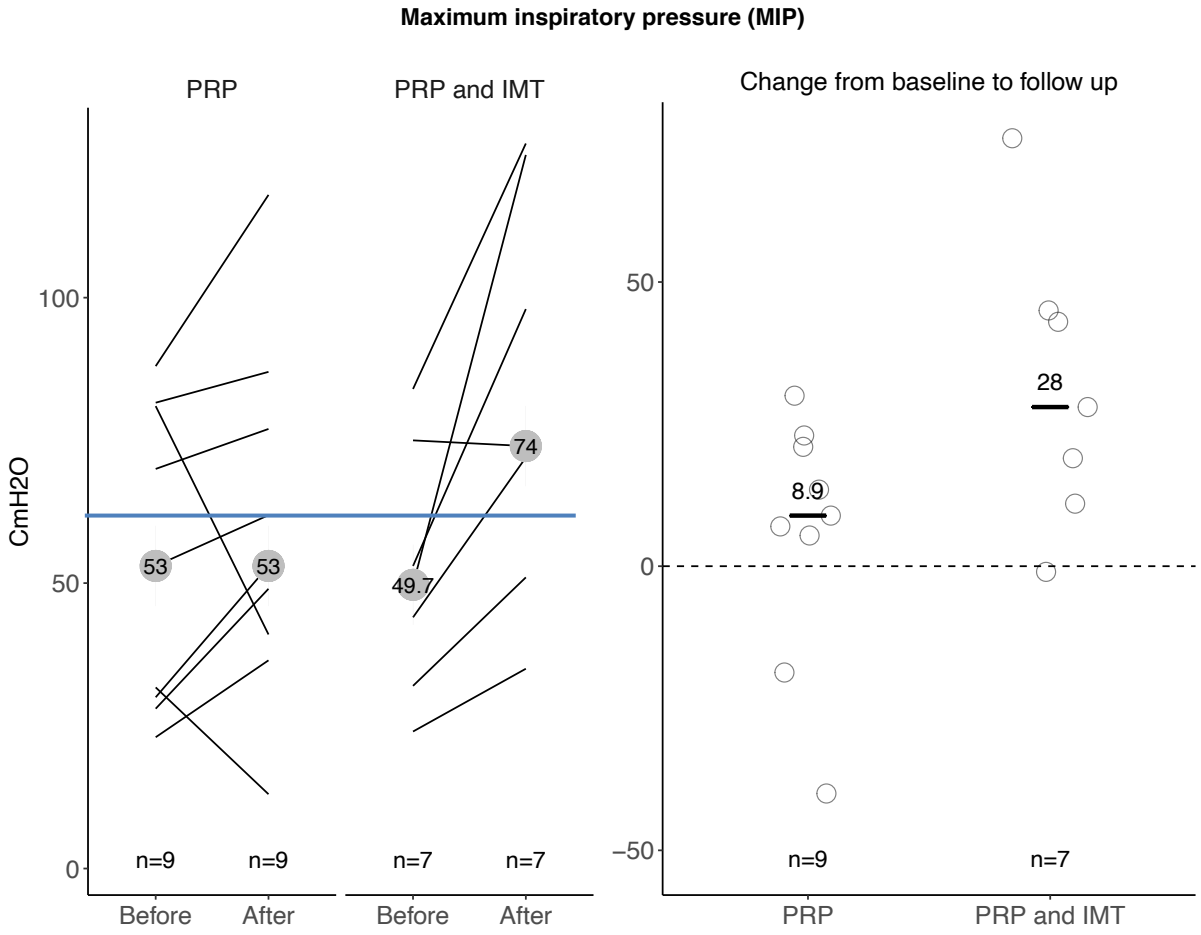


Figure 29. Maximum inspiratory pressure (MIP) before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in MIP. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement. *The horizontal blue line of the left plot represents 60 cm H_2O, above which there is an association of 100% survival in NMD

In neuromuscular disease (NMD), MIP above 60 cm H_2O was associated with a 100% 18 month survival rate and improvement in QOL (Schoser et al., 2017). Kabitz et al. (2006) compared inspiratory muscle strength in 24 subjects with sarcoidosis and matched them with healthy controls. They found inspiratory muscle strength correlated negatively with the Borg dyspnoea scale (BDS) (r=-0.575, p=0.012), and the mean and the SD of MIP was 114 (30) cm H_2O and 149 (29) for patients with sarcoidosis and the healthy control, respectively. Karadalli et al. (2016) conducted an RCT on 30 subjects with sarcoidosis. The intervention group received IMT at 40% maximum MIP for six weeks and the placebo group received 5% MIP. Although there was a significant improvement in dyspnoea perception, exercise capacity, and respiratory muscle strength, QOL, FVC, and peripheral muscle strength were not significantly different.

MIP improved in the intervention group from a mean and SD of 92.3 (28) cm H_2O to 139.4 (21) cm H_2O. The discrepancy between these two studies and our study can be explained by the heterogenous diagnosis in our study and the severity of disease. While FVC was normal or close to normal in the Karadalli et al. (2016) and Kabitz et al. (2006) studies, in our study this was not the case. Most (12 of 16) subjects had predicted FVC of below 80%.

5.4.2 Six-minute walk test (6MWT)

The 6MWT is a commonly used outcome in rehabilitation to assess patients' exercise capacity. In our cohort, there were five subjects who dropped their 6MWT after eight weeks of PRP. This could be related to worsening in disease conditions. However, the majority of patients (10 out of 15) either improved or maintained their 6MWT. Du Bois et al. (2011) have looked at 6MWT in (n=822) patients with IPF in two intervals and found that the change of 6MWT was a strong predictor of mortality and a decline of more than 50 meters in 24-weeks was associated with a four times increased risk of death in one year. They estimated the minimal clinically important difference (MCID) for 6MWT to be 24-45. In our cohort, none of the subjects dropped their 6MWT below 30 meters, this could lead to less mortality risk in those subjects, however, our measurements were 10 weeks apart and in Du Bois et al study they were 24 weeks apart (Figure 30).

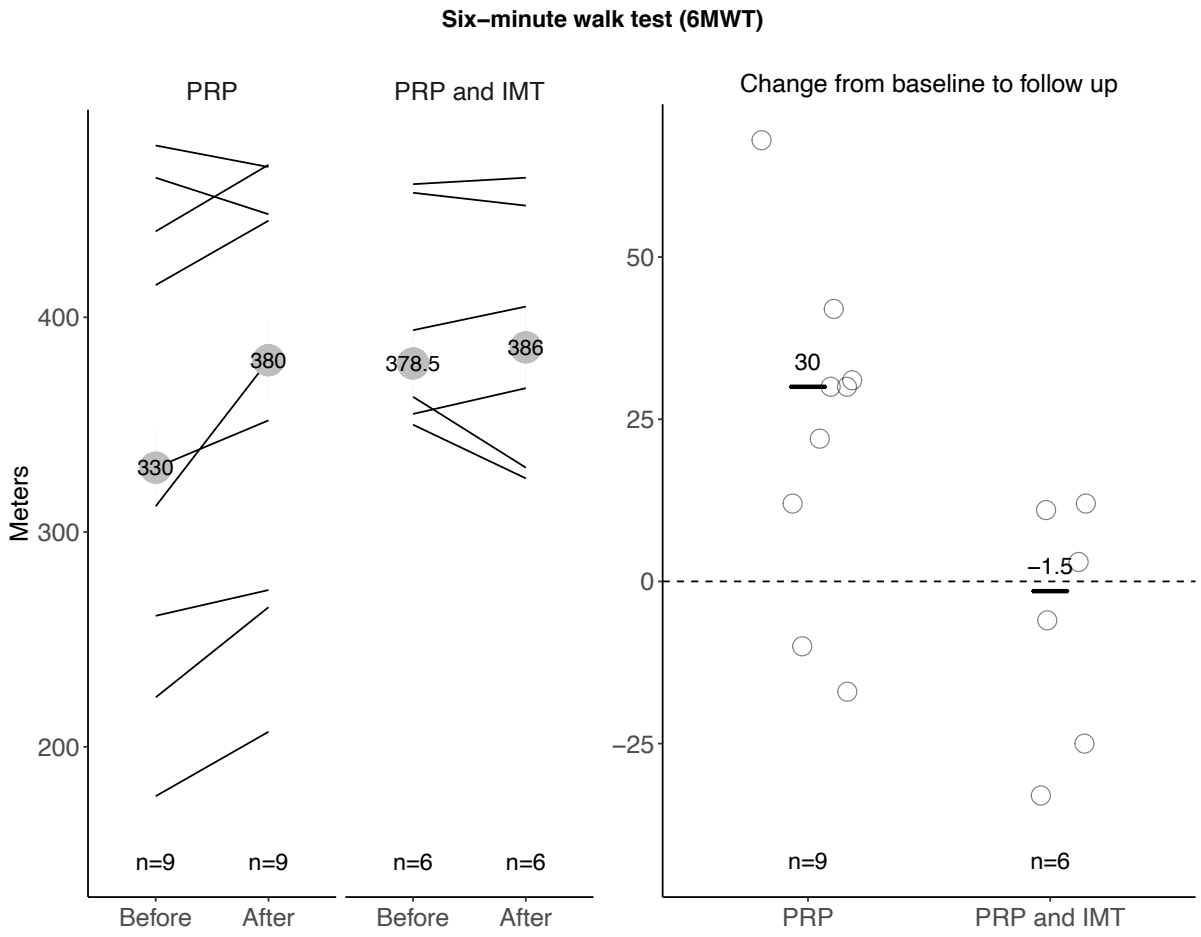


Figure 30. Six-minute walk test (6MWT) before/after 8-week PRP or PRP and IMT. Left: individual subjects represented by black lines. Right: changes in 6MWT (after being minus before). The grey circles on the left plot and the horizontal black lines on the right plot represent median values. The grey dotted line on the right plot represents zero, below which there is a deterioration in the variable and above which improvement

5.4.3 Forced vital capacity (FVC)

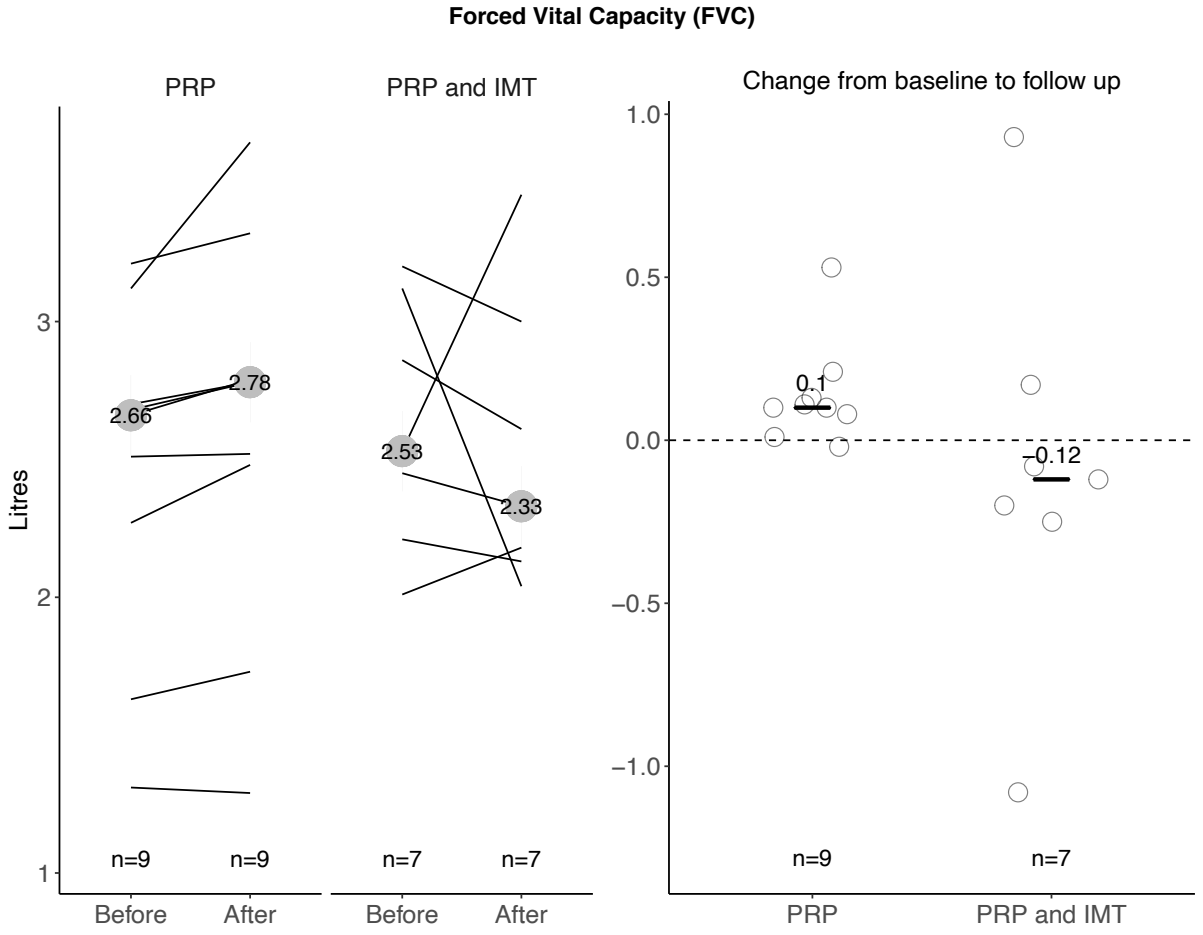


Figure 31. Forced vital capacity (FVC) before/after 8-week PRP or PRP and IMT.Left: individual subjects represented by black lines. Right: changes in 6MWT (after being minus before). The grey circles on the left plot and the horizontal black lines on the right plot represent median values. The grey dotted line on the right plot represents zero, below which there is a deterioration in the variable and above which improvement

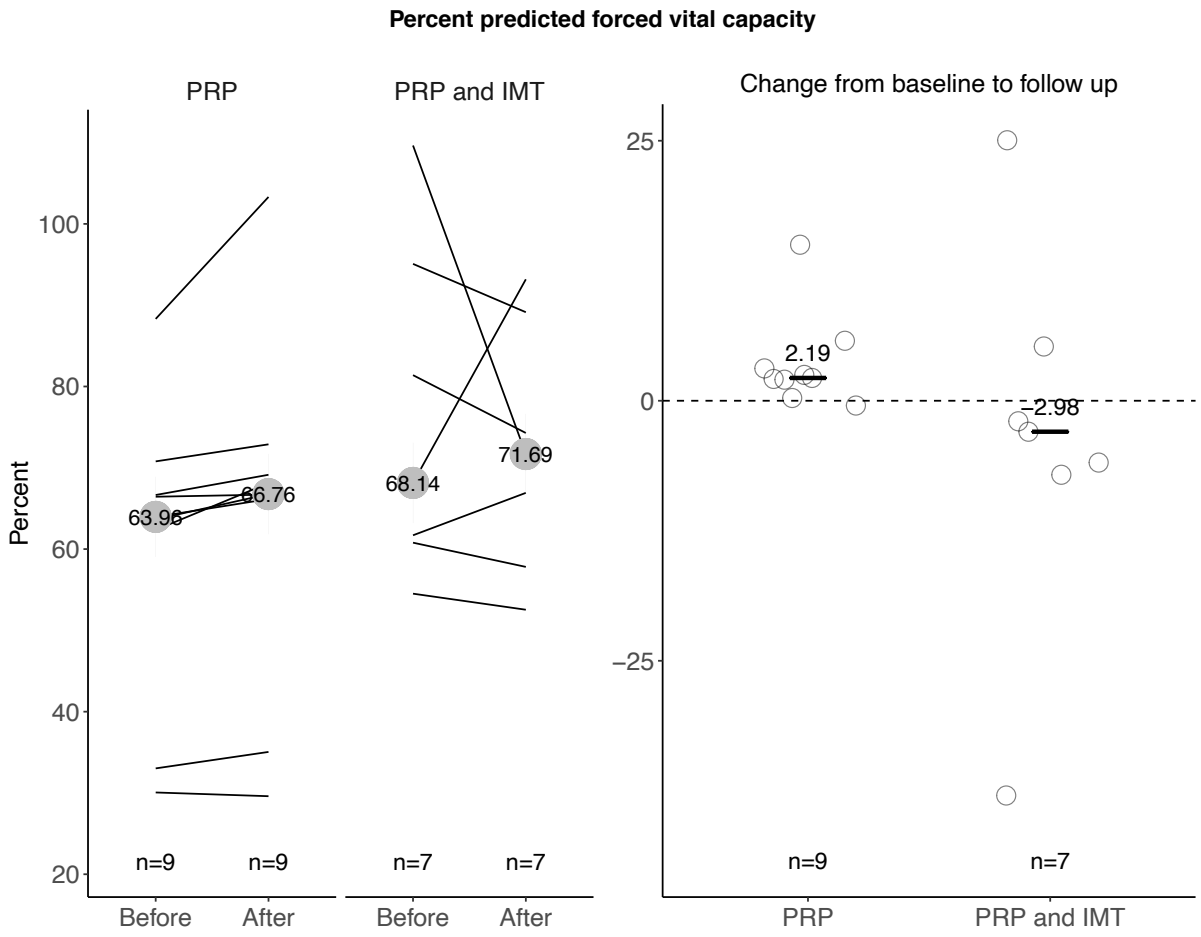


Figure 32. Percent predicted forced vital capacity (FVC%) before/after 8-week PRP or PRP and IMT. The left plot shows individual subjects represented by black lines while the right plot shows subjects' changes in 6MWT (after minus before). The grey circles on the left plot and the horizontal black lines on the right plot represent median values. The grey dotted line on the right plot represents zero, below which there is a deterioration in the variable and above which improvement

Predicted forced vital capacity is based on age, height, gender, and race. The Global Lung Function Initiative (GLI) produced the referencing for spirometry which was used in this study Quanjer et al. (2012). Figure 31 and Figure 32 show FVC and FVC% for the groups in this study. Since our study invited patients with ILD, a large portion of them seemed to have a restrictive pattern and an FVC% of less than 80, below which antifibrotics are recommended in UK in people with IPF. Usually, IPF patients either maintain or lose their FVC% over the course of the disease, but in our study some patients gained between 5–20%. We are unable to find a clear explanation for this gain, especially with this study design and sample size, but conclude that this finding warrants further study.

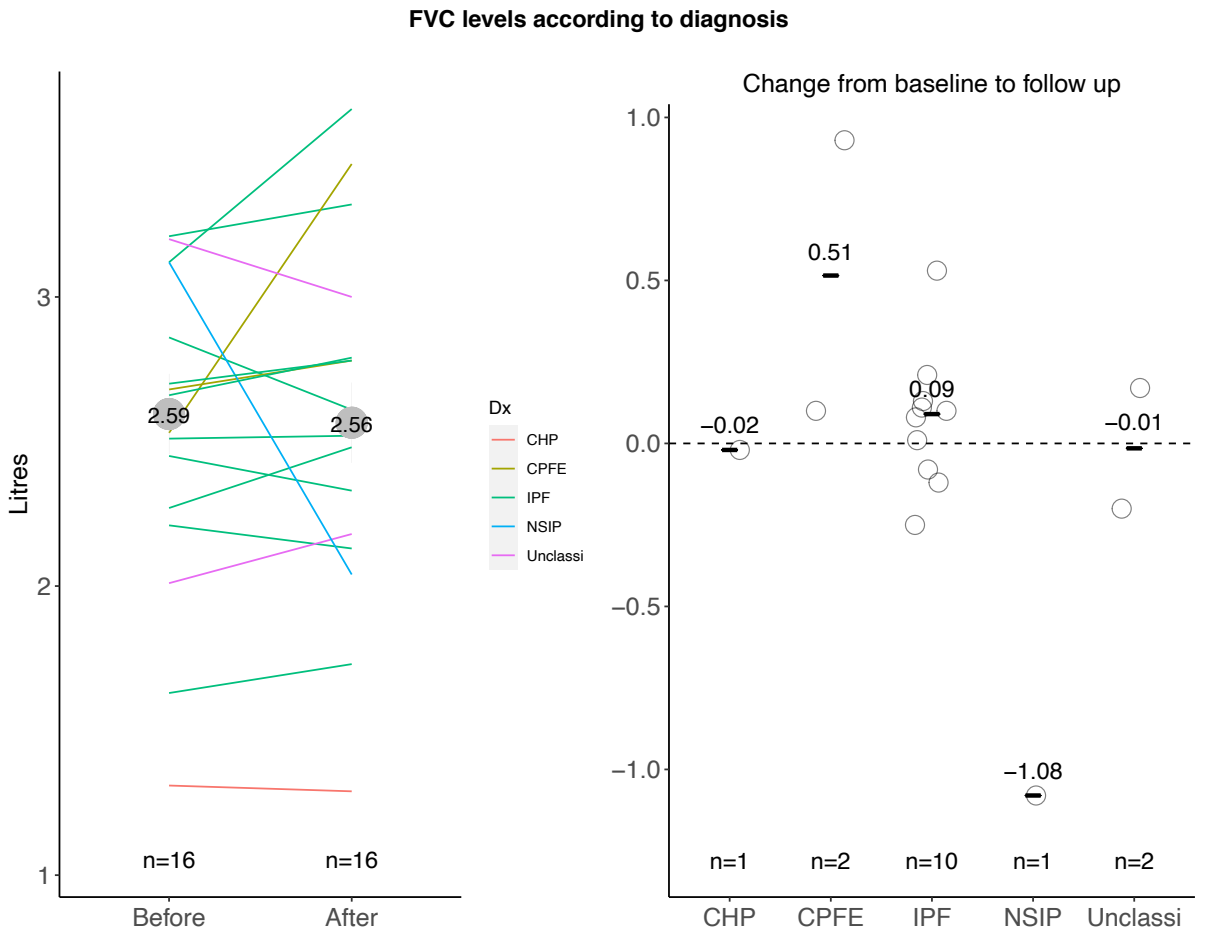


Figure 33. Forced vital capacity (FVC) according to subjects' diagnosis before/after 8-week PRP. Left: coloured lines represent individual subjects and the median is inside the grey circles. Right: subjects' changes. In the same plot, horizontal black lines represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement. CHP: Chronic hypersensitivity pneumonitis; CPFE: Combined pulmonary fibrosis and emphysema; IPF: Idiopathic pulmonary fibrosis; NSIP: Nonspecific interstitial pneumonia

In Figure 33, an outcome is displayed according to subjects' diagnosis to show the response in different diseases and to combine both groups' results (PRP only and IMT plus PRP) in one graph. This was implemented for selected outcomes in the figure. Five out of 15 patients lost some volume from their FVC while others (ten out of 15) either maintained or improved their volume. FVC is a very essential biomarker in IPF, and it guides the clinicians about response to antifibrotic treatments.

5.4.4 Left bicep strength

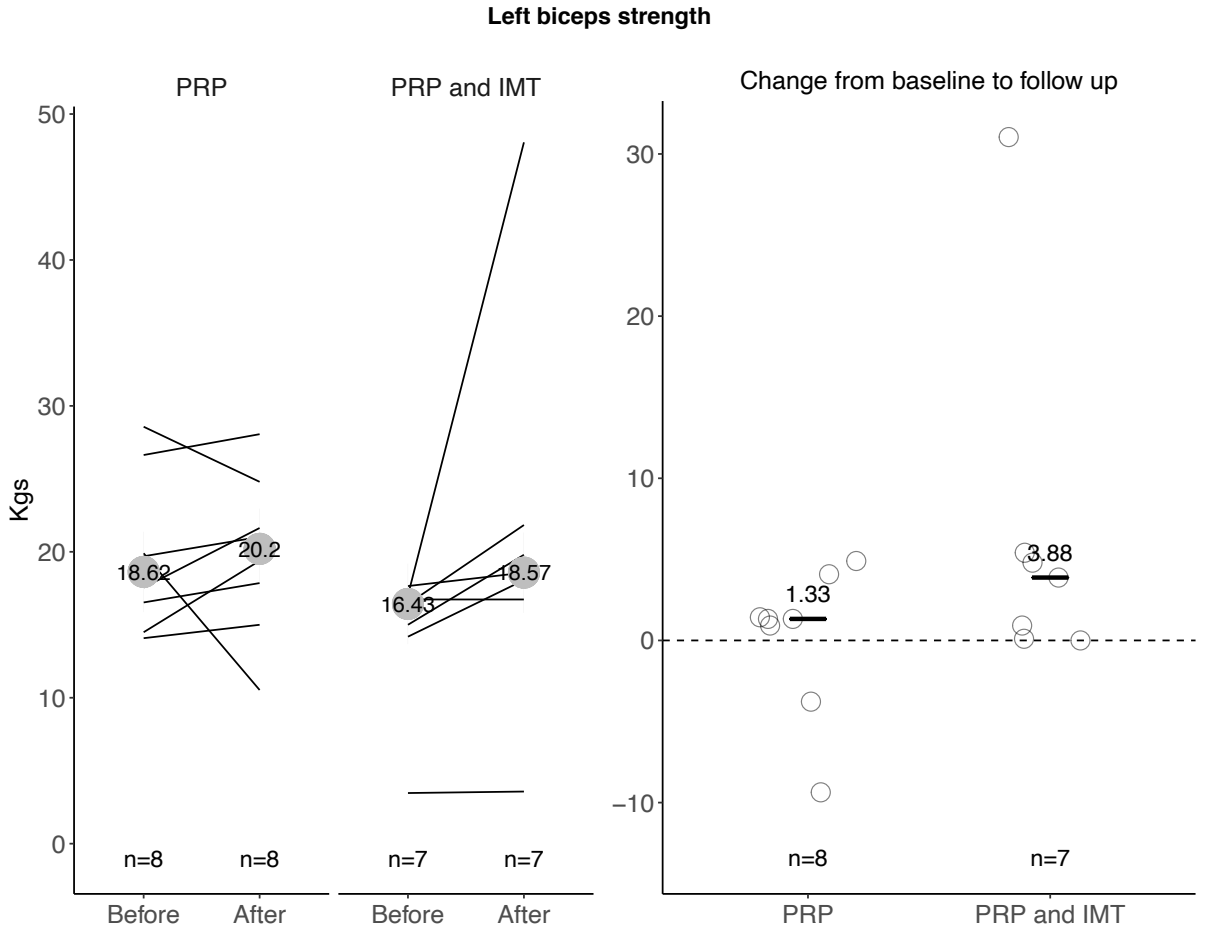


Figure 34. Left bicep strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left bicep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Left bicep strength is a recognised representative index of skeletal muscle capability. Left biceps were assessed by the same evaluator using an HHD, before and after the intervention, as described in (Dowman et al., 2016). In this study, mean strength was about 16 kg without rehabilitation, which is close to the median strength in the intervention group at baseline in our cohort. In general, there was an improvement or maintenance in the muscle strength of both groups and only two subjects lost strength. There was a trend for more improvement in the PRP and IMT group compared to the PRP only. In another study, Silva et al. (2018) compared QOL, muscle strength, and aerobic capacity in two groups of COPD patients. The intervention group did upper limb training in addition to standard rehabilitation and the control group did only standard rehabilitation. Both groups did IMT at 50% MIP. The intervention group had

significantly more improvement of MIP compared to the control. The authors concluded that there was a significant improvement in QOL, measured by SGRQ and upper muscle strength in the intervention group. Additionally, the intervention group had significant improvement in MIP. This could show a relationship between upper limb training and IMT.

5.4.5 Left deltoid strength

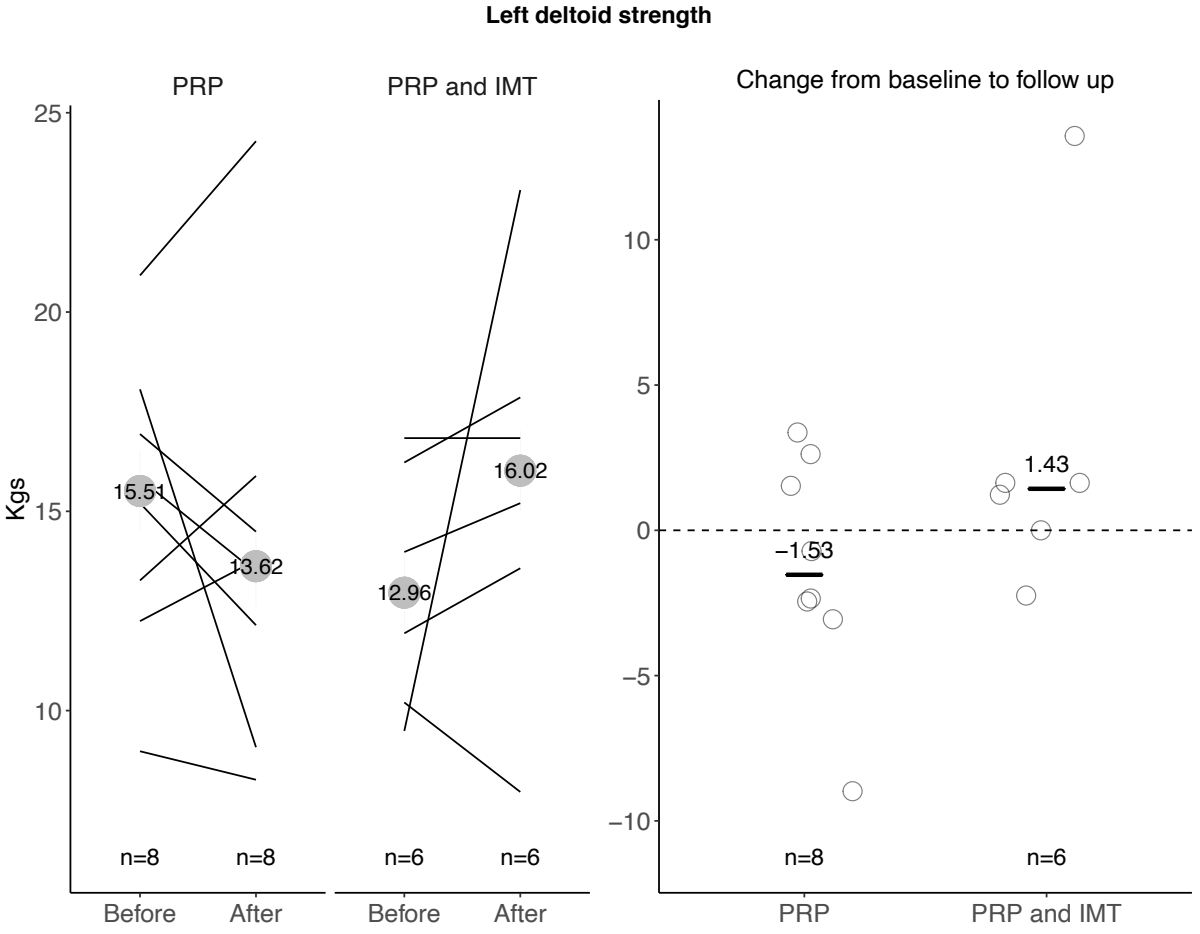


Figure 35. Left deltoid strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left deltoid strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Left deltoid strength was assessed by same person before and after rehab while subjects sat on the side of the bed, starting from a 90-degree position elbow flexed and the HHD placed on the superior side to the elbow. Subjects were asked to lift their arm upwards. To my knowledge, this is the first study to look at deltoid strength in ILD. As shown in Figure 35, our study

indicates better improvement in the intervention group, where five out of six either improved or maintained compared to three out of eight for the PRP only group. This could mean there is a positive relation between upper limb exercise and IMT, as seen in Silva et al. (2018).

5.4.6 Left quadricep strength

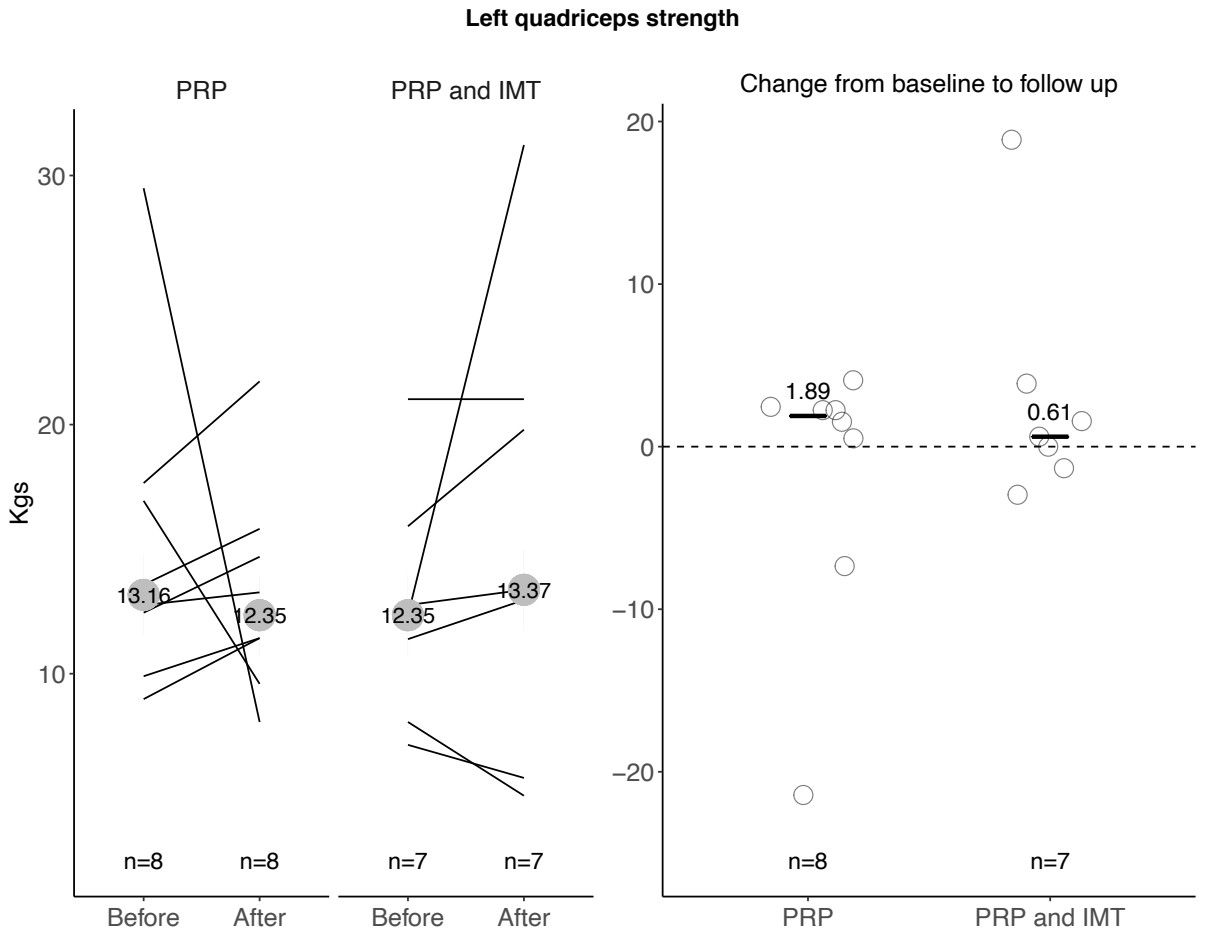


Figure 36. Left quadricep strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in left quadricep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

Peripheral muscle function is a contributor to exercise capacity in ILD and it has been reported that quad strength is a predictor of VO_2 peak. In our study, we exercised the peripheral muscle directly, in supervised and unsupervised sessions, and indirectly, during four targeted walking sessions per week. Our patients demonstrated different responses in left quad strength, where the median showed no to little improvement (3 out of 15), some worsened (4 out of 15), and some improved (8 out of 15). This could be related to heterogeneity in disease progression.

Dowman et al. (2016) have reported quad strength with a mean of about 20 kg using an HHD. They had 41 patients with ILD divided into two groups and rated by different raters. In the current study, median muscle strength was 12.35 and 13.37 after rehabilitation, which is less than in Dowman's study. This discrepancy could be due to the level of severity. The median FVC% in our cohort was 64% and 68% in PRP only and PRP and IMT, respectively, prior to rehabilitation; mean FVC% were 74% for PRP only and 78% for PRP and IMT, meaning our patients had more severe disease compared to Dowman et al. (2016).

5.4.7 Right bicep strength

Upper limb function is important for daily life. Bicep strength was measured using an HHD, when patients were supine, if tolerated, and their elbow was placed and stabilised on a bed. The patients were asked to flex their elbow starting from 90 degrees against the HHD and the rater, as explained in Dowman et al. (2016). As shown in Figure 37, the PRP and IMT group improved strength compared to the PRP only group. Five out of eight in the PRP group lost strength compared to no drop in the PRP and IMT group. However, the PRP group had a higher median before and after the study. Therefore, the PRP and IMT group may have had more room for improvement from baseline. Dowman et al. (2016) looked at elbow flexor strength in 30 subjects with ILD and the mean was 16.8 (+-6.5) kg, which seems very close to ours.

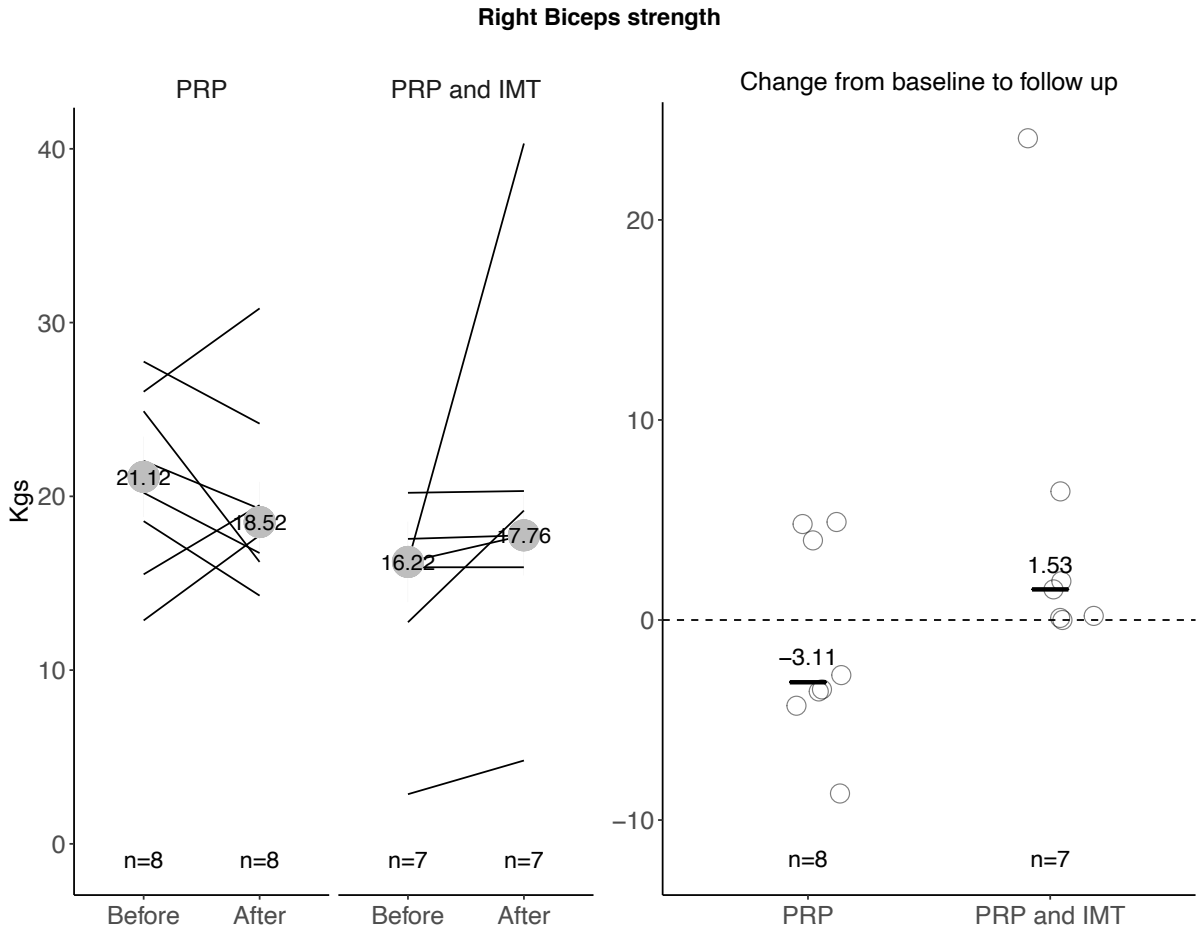


Figure 37. Right bicep strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in right bicep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

5.4.8 Right deltoid strength

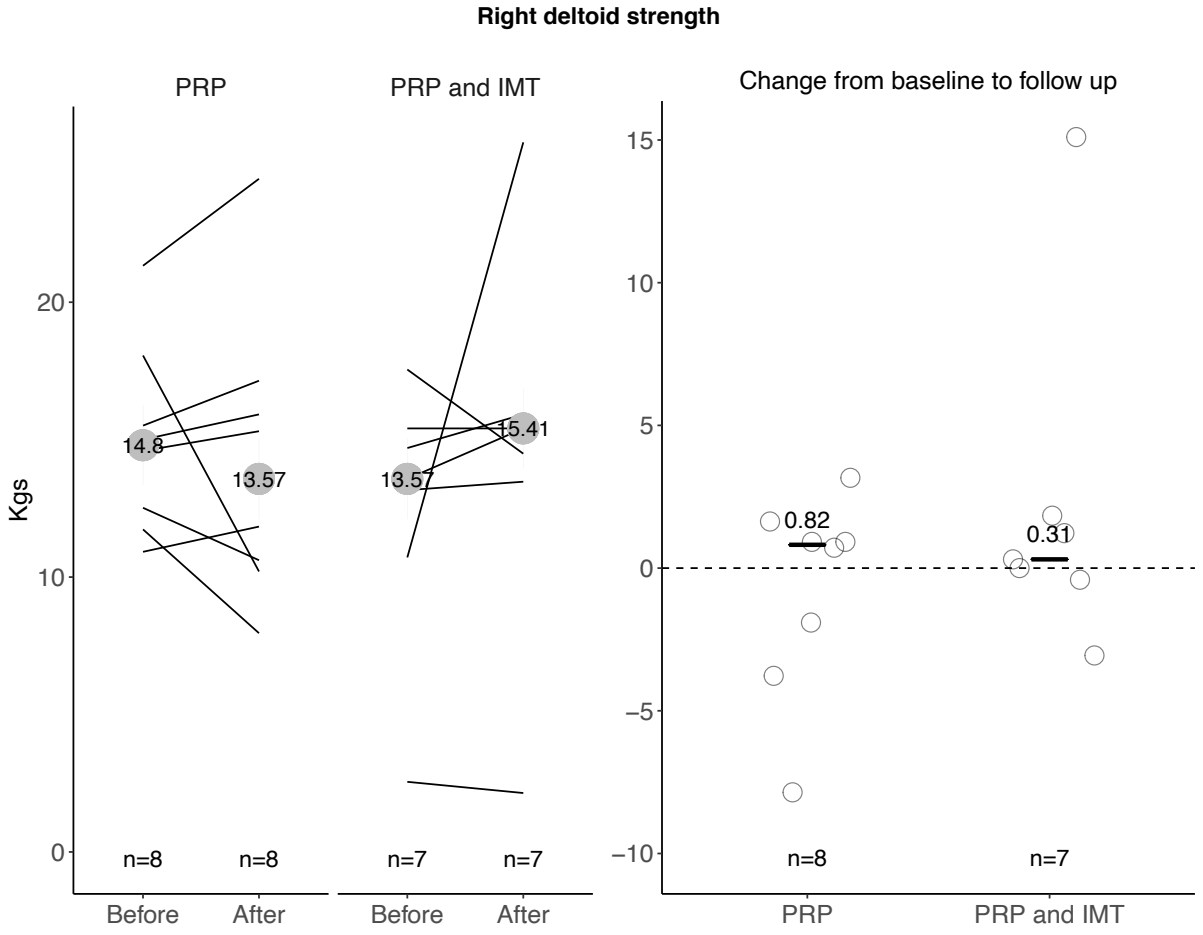


Figure 38. Right deltoid strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in right deltoid strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

As can be seen in Figure 38, in the right deltoid muscle similar changes occurred in both groups, where three out of eight lost strength in the PRP group compared to two out of seven in the PRP and IMT group. To my knowledge, no study has previously looked at deltoid muscle in ILD.

5.4.9 Right quadricep strength

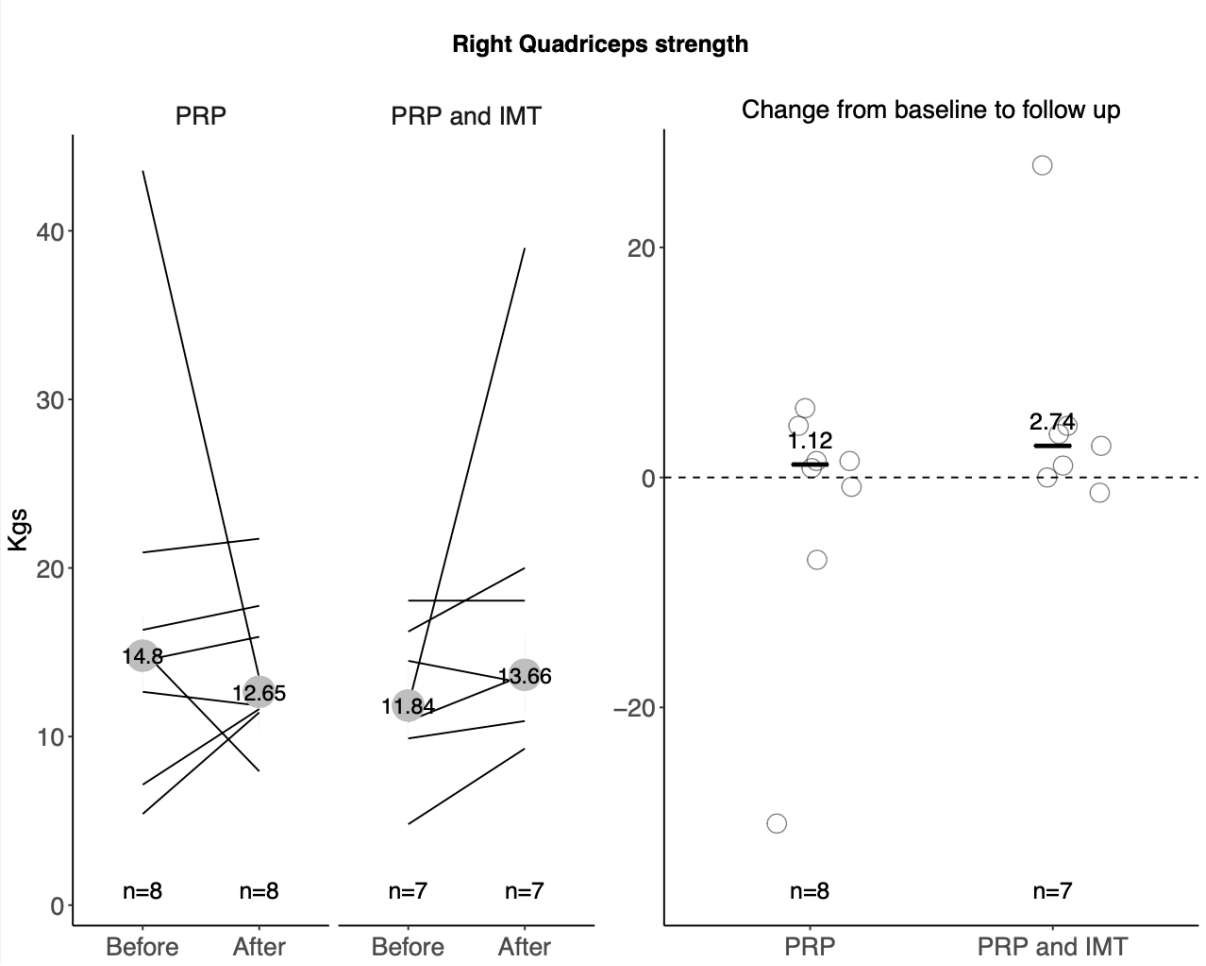


Figure 39. Right quadricep strength before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in right quadricep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

As Figure 39 shows, right quadricep muscle was assessed by the same assessor before and after using an HHD on the anterior side of the leg, just above the foot joint, as described in Dowman et al. (2016). In general, the median strength was better in the PRP and IMT group compared to the PRP only group. Six out of seven in the PRP and IMT group improved or maintained strength while five out of eight improved or maintained in the PRP only group. When Dowman et al. (2016) looked at knee extensor strength over two sessions, they found mean scores of 18.3

(4.8) and 19.0 (5.6), which seems higher than our medians after rehabilitation (12.65 in the PRP only group and 13.66 in the PRP and IMT group); however, their subjects (n=30) had almost normal FVC% at 74% (17%), and our cohort had a median of less than 70%, with two subjects having less than 40%.

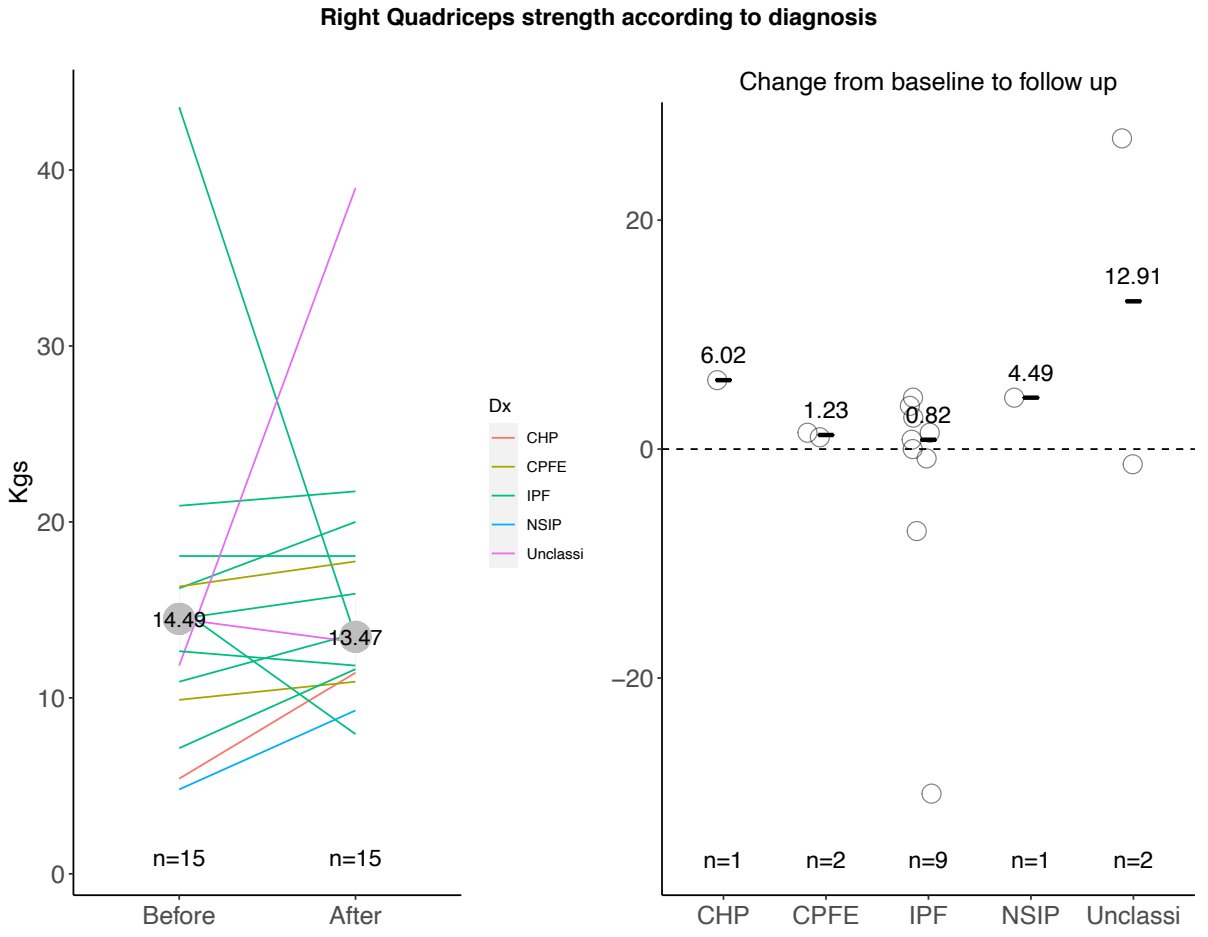


Figure 40. Right quadricep strength according to subjects' diagnosis before/after 8-week PRP. Left: black lines represent individual subjects. Right: changes in right quadricep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement. CHP: Chronic hypersensitivity pneumonitis, CPFE: Combined pulmonary fibrosis and emphysema, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia

Figure 40 shows right quadricep strength in all subjects according to their diagnosis, without considering the IMT. In general, there was an improvement or maintenance in muscle strength.

The MCID for quad strength in ILD is unavailable to our knowledge, but for COPD it is estimated to be 5.2 kg (Oliveira et al., 2021). Two of our patients exceeded this level of MCID.

5.4.10 Fatigue severity scale

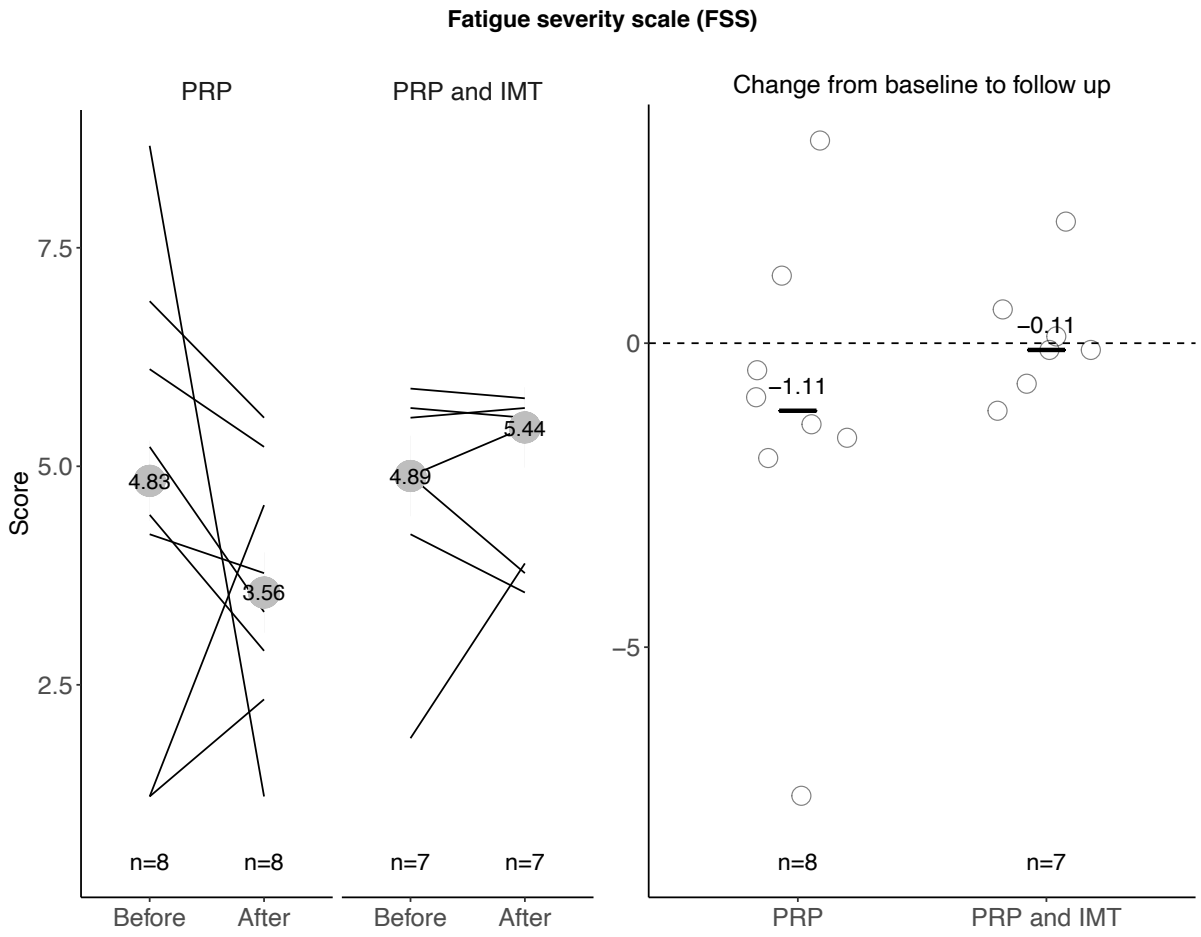


Figure 41. Fatigue severity scale before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in fatigue severity scale. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

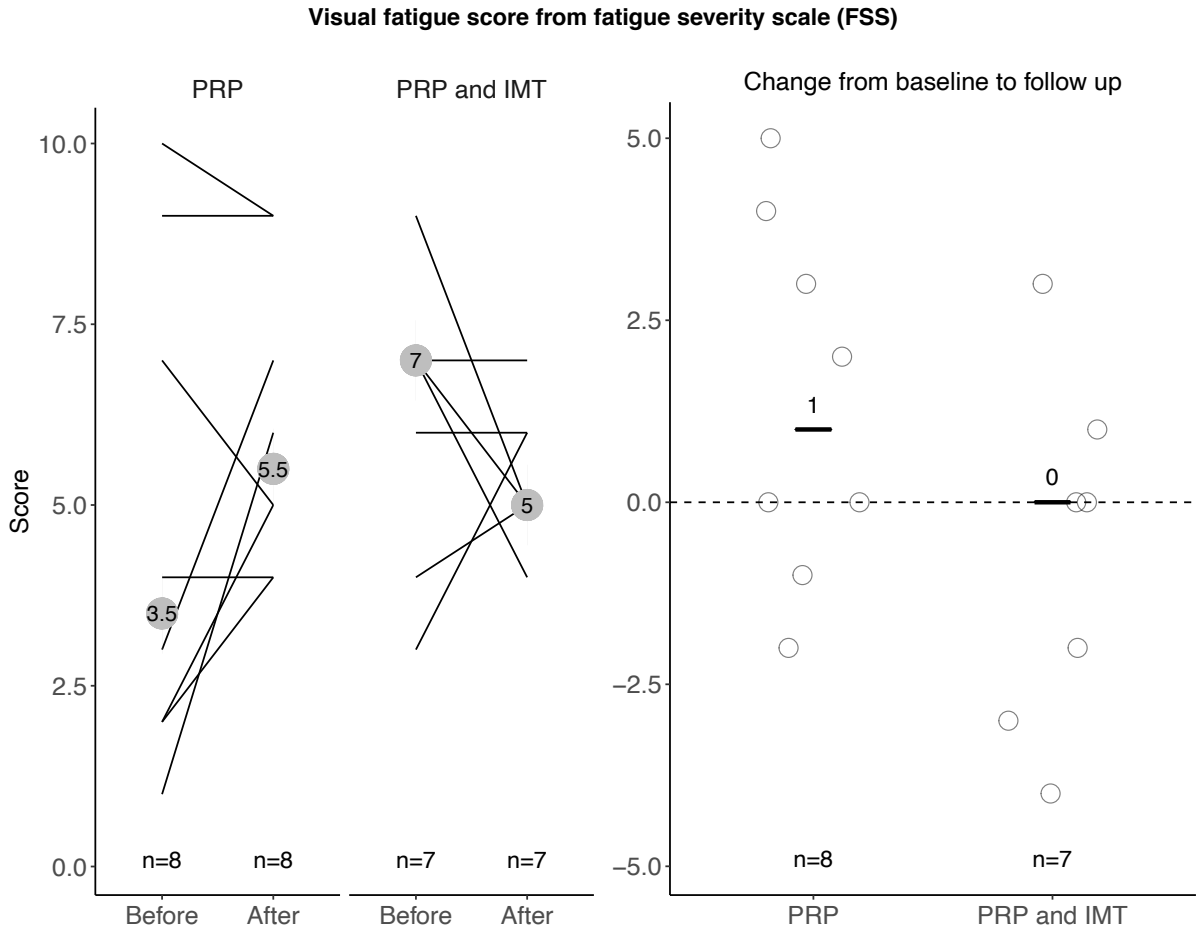


Figure 42. Visual fatigue score before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in visual fatigue score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement.

According to eurIPFreg, the second most common reported symptom in 525 subjects with IPF is fatigue (70%), with the first ranked symptom being dyspnoea (90%) (Guenther et al., 2018). The FSS is a subjective questionnaire used to evaluate fatigability in different diseases; it has nine questions, and each question can be answered on a scale from 1–7, where one is strongly disagree and seven strongly agree. It also includes a visual fatigue score, which has been reported to correlate with FSS. After answering the questions, the total is divided by nine to obtain the average. Higher scores indicate more fatigue. In our study, changes in both groups showed a reduction in median scores, but some patients' FSS increased (4 out of 15) (Figure 41 and Figure 42). This could be related to different responses from different patients to PRP or worsening in condition. Keyser et al. (2015) conducted a training programme three times a week for at least 30 minutes on 13 subjects with ILD. The mean FSS was 4.1 + - 1.2 before,

and 3.5 + - 0.9 after. In their study, FSS improved significantly after rehabilitation but did not correlate with time to anaerobic threshold. It could be that change can be seen in FSS as a patient-centred outcome not entirely based on the physiological outcomes measured.

5.4.11 Depression score

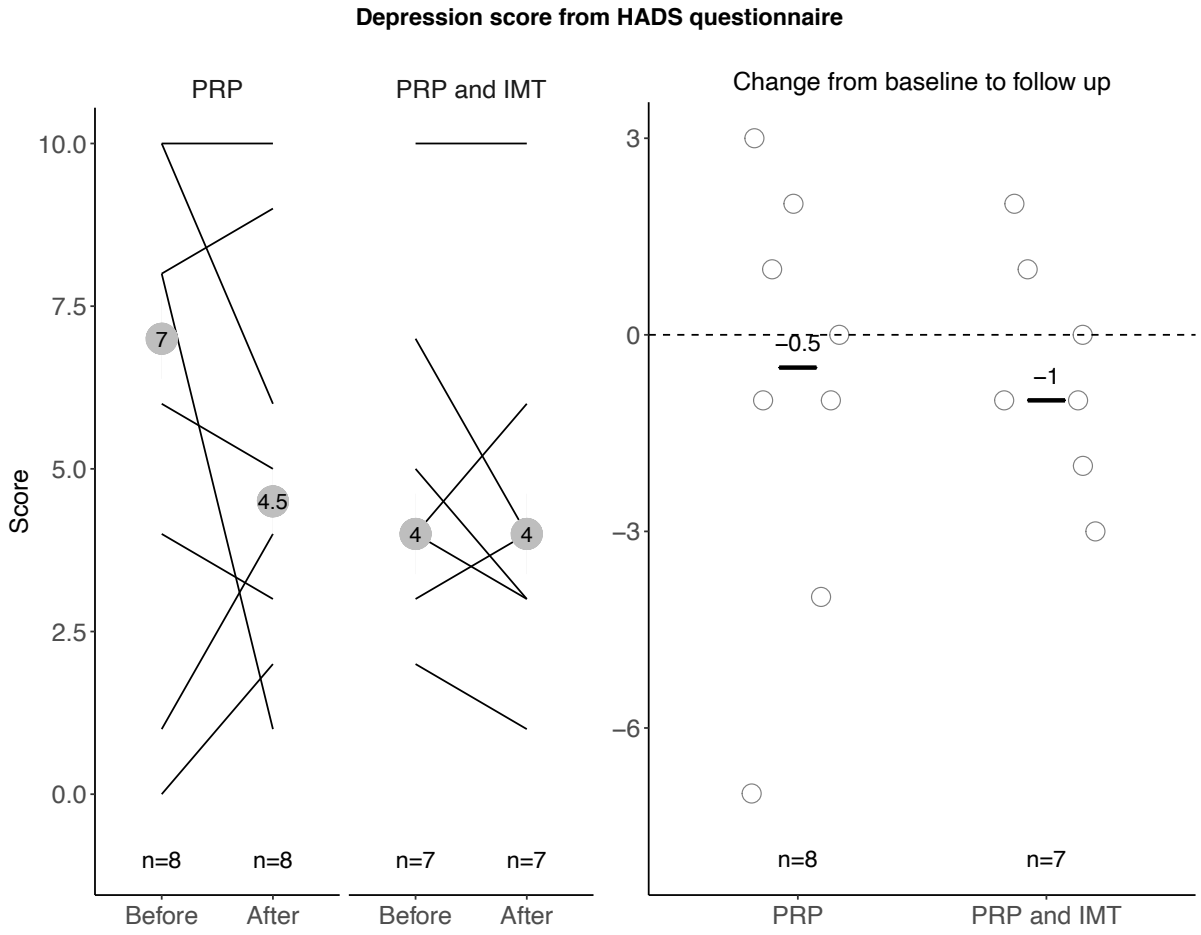


Figure 43. Depression score from the Hospital Anxiety and Depression Scale before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in depression score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is an improvement in the variable and above which a deterioration

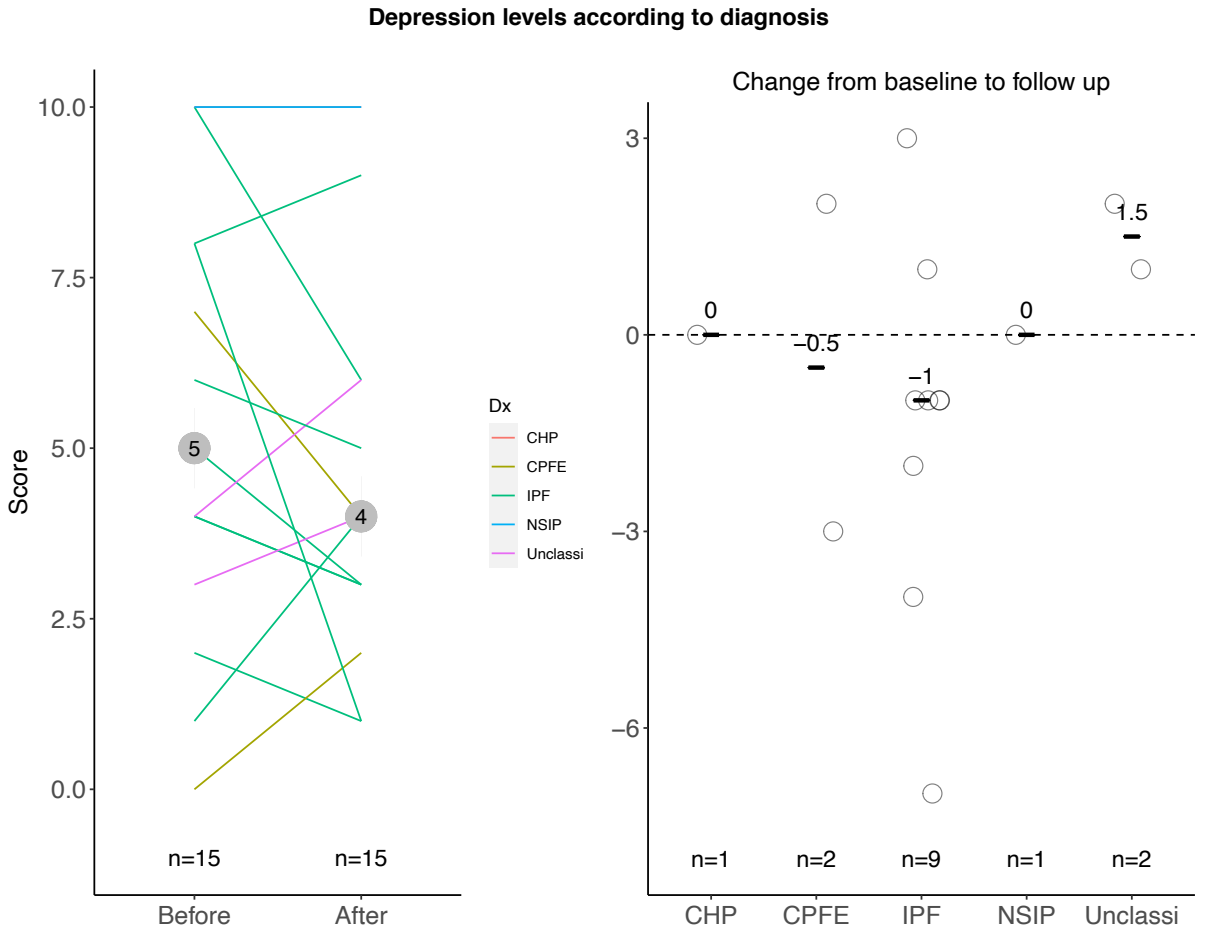


Figure 44. Depression levels according to subjects' diagnosis before and after 8 weeks of pulmonary rehabilitation programme. Left: black lines represent individual subjects and the median is inside the grey circles. Right: changes in right quadricep strength. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement. CHP: Chronic hypersensitivity pneumonitis, CPFE: Combined pulmonary fibrosis and emphysema, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia

For the HADS instrument, a score under seven is not considered depression, while 8–10 is mild depression, 11–14 moderate, and 15–21 severe (Stern, 2014). In our cohort, most subjects scored below seven and after rehabilitation there was a general reduction in their score. In a study published by Holland et al. (2014a), the prevalence of depression was 23%, with 7% having significant depression. In our cohort, ten out of 15 either maintained or improved their depression score (Figure 43 and Figure 44). The discrepancy between our cohort and Holland's could be explained by those who attended the rehabilitation programme in a research format being more motivated. The median improvement in the PRP and IMT group was more than in the PRP only group and we cannot explain this difference.

5.4.12 Anxiety score

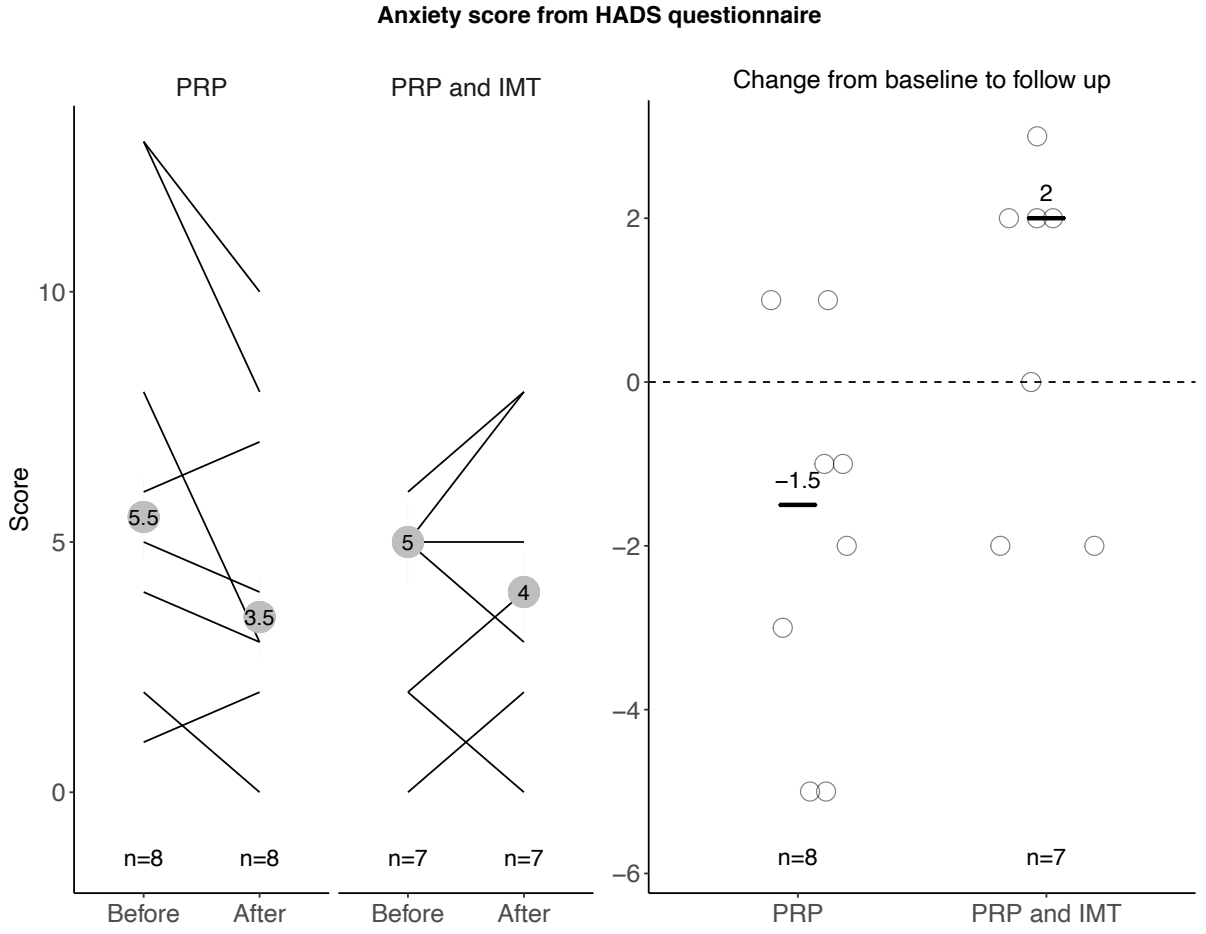


Figure 45. Anxiety score from Hospital Anxiety and Depression Scale (HADS) before/ after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in anxiety score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

A score of under seven is not considered to show anxiety, while 8–10 is considered mild, 11–14 moderate, and 15–21 severe depression (Stern, 2014). Holland et al. (2014a) looked at the prevalence of anxiety in 124 subjects with ILD and found that anxiety was present in 31%, and significant anxiety in 12%, correlating with mMRC (Modified Medical Research Council) dyspnoea scale. In our cohort, two subjects scored above ten but improved after PRP. Surprisingly, the median change (right plot in Figure 45) in the PRP and IMT group increased after the programme, possibly because there was more subjective awareness of breathing when

using the IMT device. During the education programme on palliative care, one subject stated that the talk scared them and did not want to listen to similar talks.

5.4.13 King's brief interstitial lung disease (K-Bild) score

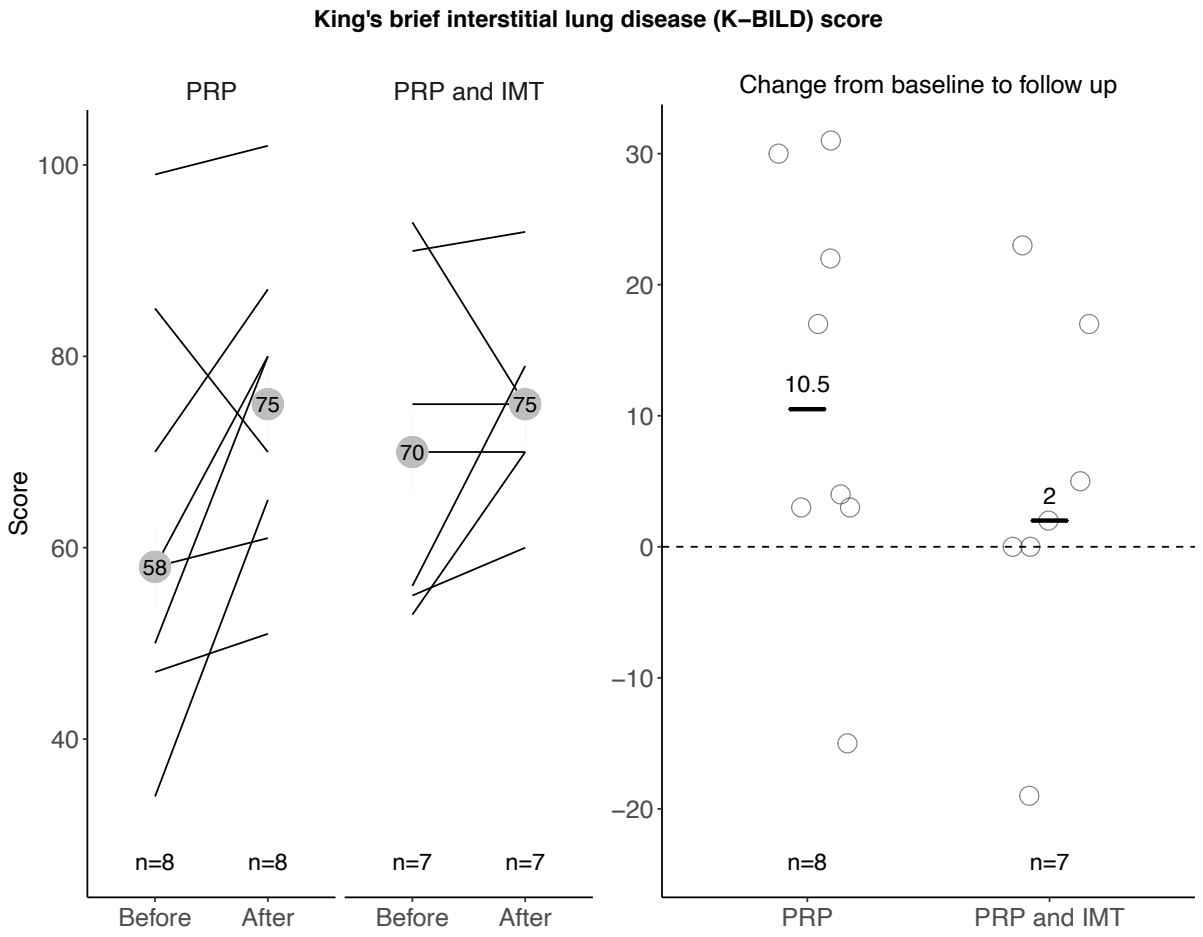


Figure 46. King's brief interstitial lung disease (K-Bild) score before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in K-Bild score. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

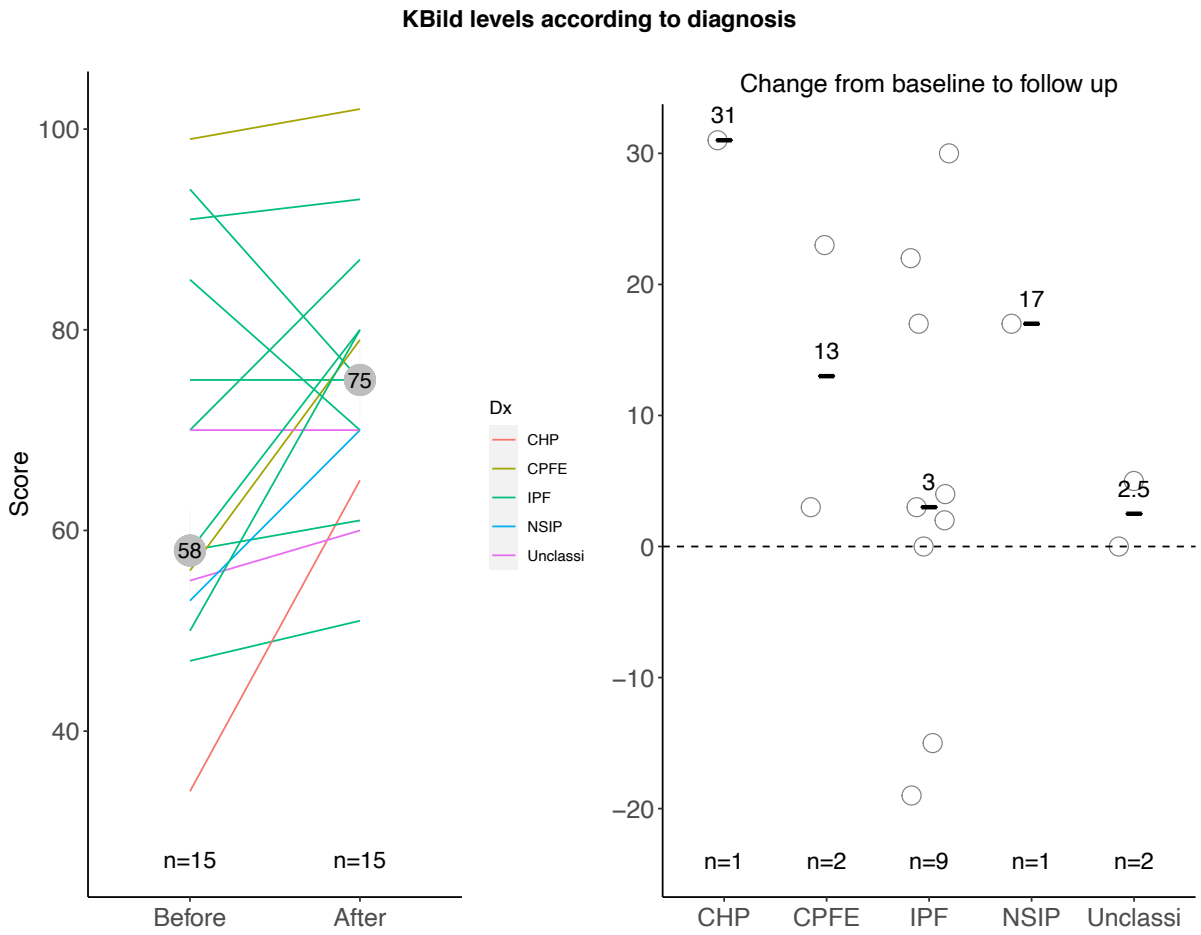


Figure 47. K-Bild levels according to subjects' diagnosis before/after 8-week PRP. Left: black lines represent individual subject and the median is inside the grey circles. Right: changes in K-Bild. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement. CHP: Chronic hypersensitivity pneumonitis, CPFE: Combined pulmonary fibrosis and emphysema, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia

K-Bild is a 15-item questionnaire specific for ILD, where 0 is the worst and 100 the best. Its items involve symptoms and QOL, and it was developed and validated for subjects with ILD in 2012 (Patel et al., 2012). In our study, the medians at base line for PRP only and PRP and IMT were 58 and 70, respectively (Figure 47). Our medians are slightly higher than the mean total score (54.3) that was reported in Nolan et al. (2019), who also reported that the MCID of K-Bild was 3.9. This was achieved in eight out of 15 of our patients, and two had an improvement of about 30 in the K-Bild score.

5.4.14 Integrated Palliative Care Outcome Scale (iPOS)

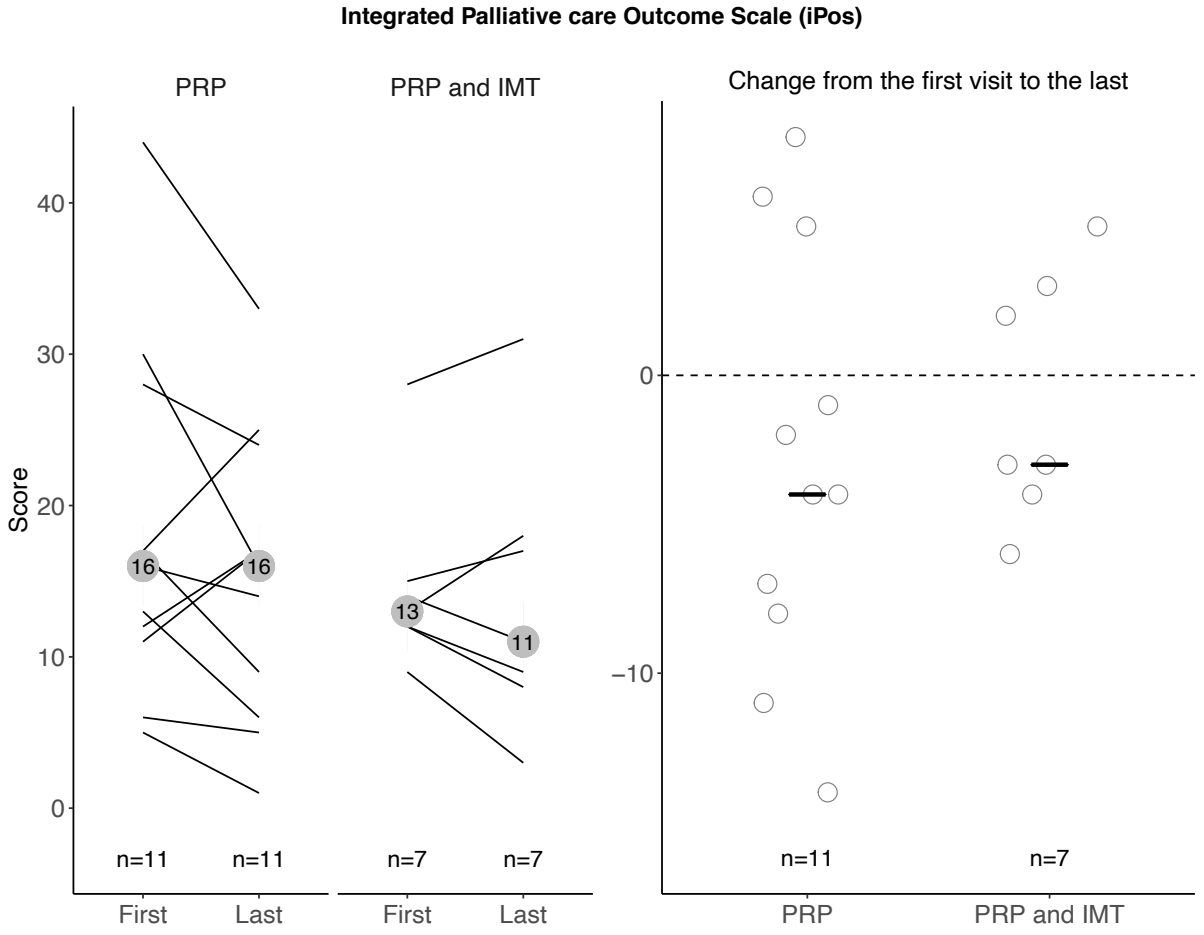


Figure 48. Integrated Palliative Care Outcome Scale levels (iPOS) before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in iPOS level. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is an improvement in the variable and above which deterioration

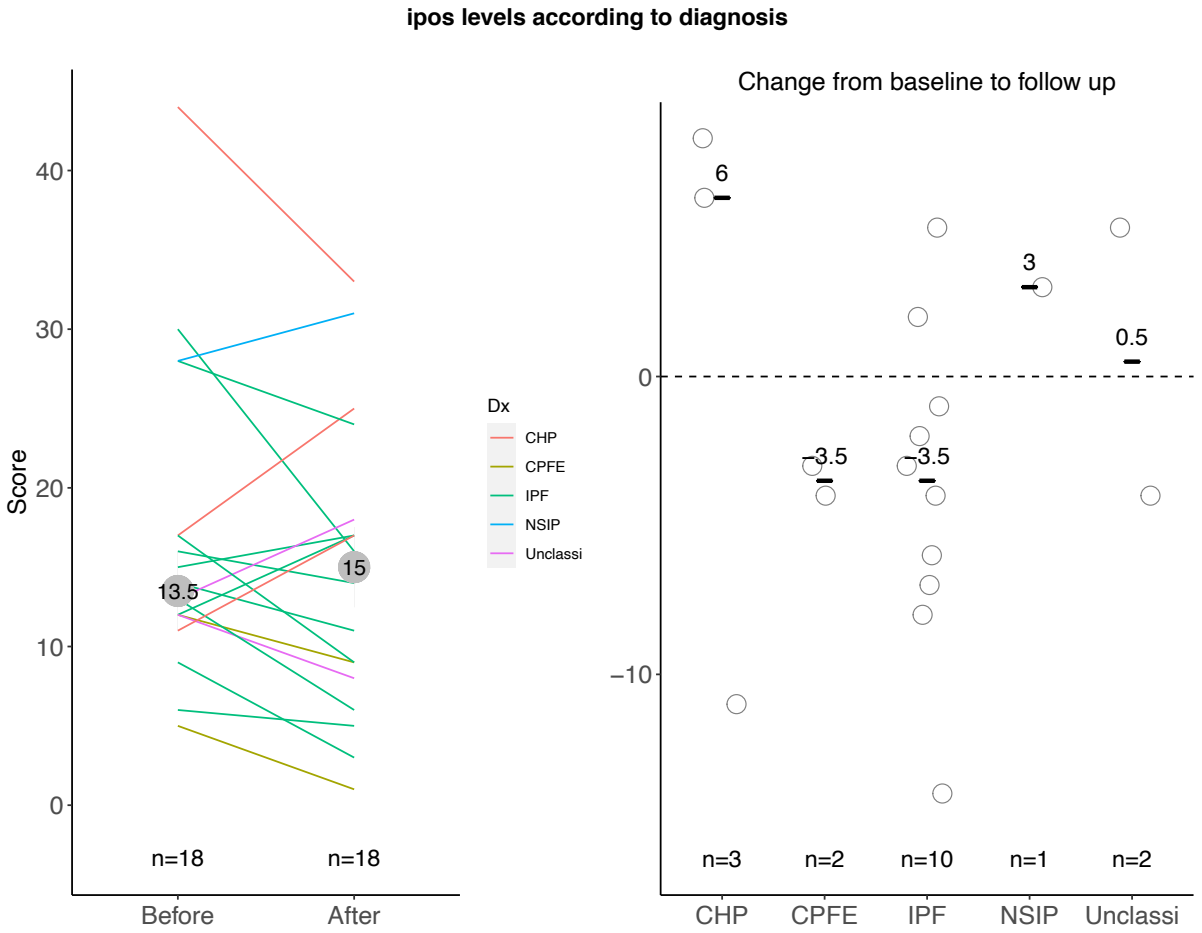


Figure 49. iPOS levels according to subjects' diagnosis before/after 8-week PRP. Left: black lines represent individual subjects. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is an improvement in the variable and above which deterioration. CHP: Chronic hypersensitivity pneumonitis, CPFE: Combined pulmonary fibrosis and emphysema, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia

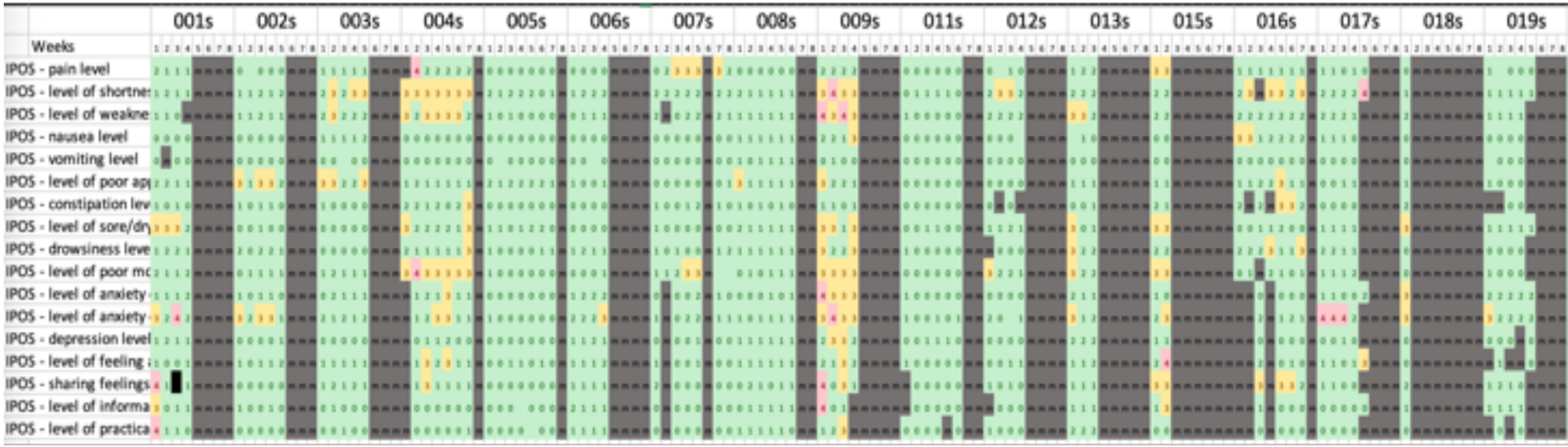


Figure 50. iPOS values across all subjects and weeks. The number in the top row corresponds to subjects' study ID. Higher numbers mean worsening in the variable. Green=0=Not at all; Green=1=Slightly; Green=2=Moderately; Yellow=3=Severely; Red=4=Overwhelmingly; Grey=m=missing

The iPOS is an assessment tool used to monitor and manage palliative care of different conditions. Subjects answer questions related to their symptoms so that these can be managed or minimised by the healthcare provider. Each question can be answered on a scale from 0–5, where 0 equals ‘none’ and 5 ‘overwhelming’. ILD is a condition that often requires palliative care to manage symptoms and difficulties associated with the disease. Nine out of 15 of our patients showed improvement in their symptoms and six showed deterioration (Figure 49 and Figure 50). When looking at different diseases, CHP showed worsening in their symptoms. Thus, could be related to chemotherapy, which could worsen some symptoms, in addition to the side effects of the treatment. In future studies, it might be worth excluding subjects who are in chemotherapy from pulmonary rehabilitation, or targeting themes identified by iPOS, either in PRP or other aspects of ILD patient care.

5.4.15 Matrix metalloproteinase 7 (MMP7)

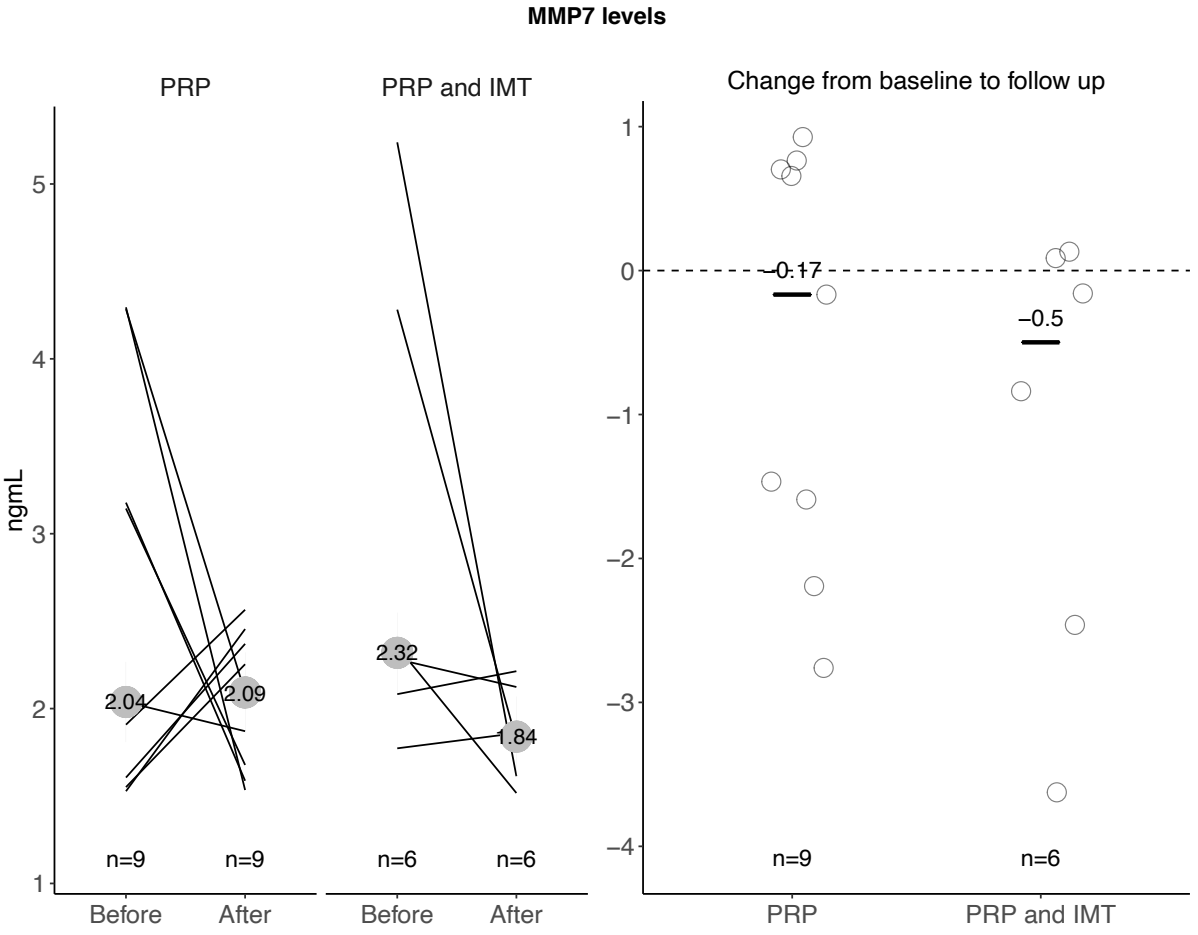


Figure 51. Matrix metallopeptidase 7 (MMP7) levels before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in MMP7 levels. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is an improvement in the variable and above which deterioration

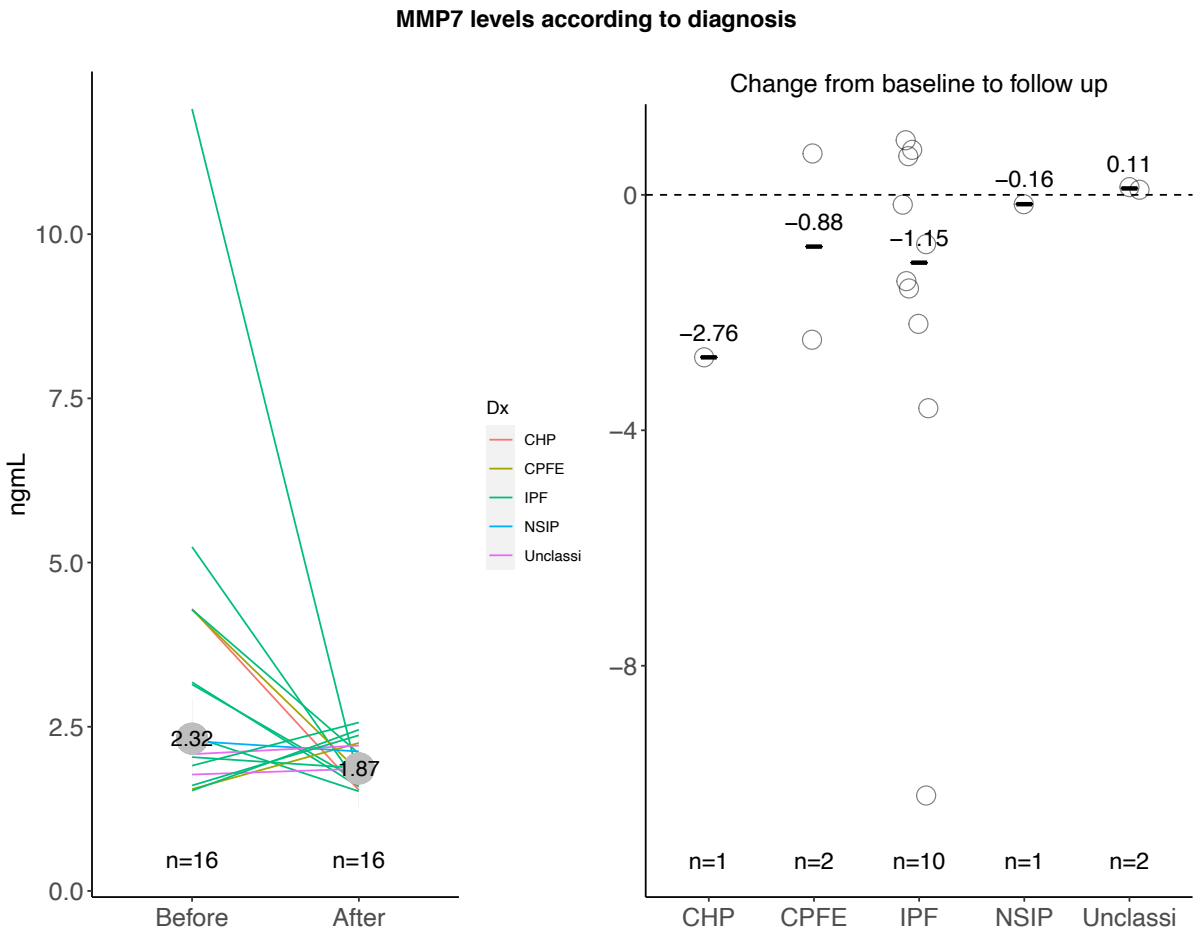


Figure 52. Matrix metallopeptidase 7 (MMP7) levels before/after 8-week PRP according to subjects. Left: coloured lines represent individual subjects. Right: changes in MMP7 according to disease. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. CHP: Chronic hypersensitivity pneumonitis, CPFE: Combined pulmonary fibrosis and emphysema, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia

MMP7 is a protein generated by a number of cell types including epithelial cells of the alveoli and airways in the human lungs. Along with other biomarkers, its expression is increased in IPF and many other ILD diseases, and it plays a potential role in disease pathophysiology as it is present in the extra cellular matrix (ECM) and bronchi alveolar lavage (BAL) of IPF patients (Bauer et al., 2017). In our cohort, there was a general reduction of MMP7 in some subjects regardless of the intervention, which was seen in nine out of 15 subjects (Figure 51 and Figure 52). When MMP7 was looked at according to diagnosis, it was also reduced across all diseases in some patients.

MMP7 has been used as a serum biomarker which can predict disease progression and mortality in people with IPF (Bauer et al., 2017). It was found to correlate negatively with FVC% and diffusing capacity of the lungs for carbon monoxide (DLCO). In a meta-analysis by (Khan et al., 2021), from 3,950 IPF participants, MMP7 levels were associated with increased mortality and disease progression. In the analysis, the authors reported that MMP7 levels of more than 5.7 ng/ml were associated with increased mortality (aHR 2.18 95% CI 1.1; 4.32) over a median follow up of 19 months in a study of 438 subjects. However, another smaller study of 57 subjects found MMP-7 levels were not predictive of death (Khan et al., 2021). Recently, COVID-19 is considered as a new cause for ILD as a long-term consequence and MMP7 will be utilized for those cases (Wild et al., 2021).

Adegunsoye et al. (2020) investigated prediction of transplant-free survival (TFS) using MMP7 and other biomarkers, finding that MMP7 can be used to predict TFS in addition to other biomarkers. Interestingly, there was no significant difference in MMP7 levels between IPF patients who received antifibrotics and those who did not. The inclusion of biomarkers in PRP studies in ILD is rare to my knowledge and I am not aware of studies that have examined MMP-7 in this setting.

Studies of tailored PRP in ILD are not common and work integrating PRP and potential biomarker analyses are often not included. Koczulla et al. (2020) have looked at the effect of vibration as a tool for rehabilitation on a serum biomarker (myostatin) on subjects with ILD. Myostatin is a protein that can negatively impact skeletal muscle growth. In their study, myostatin was significantly reduced in the intervention group after three months of rehabilitation. The improvement of MMP7 in our cohort, without modification of medication, is an interesting and novel finding associated with PRP. In the literature, there tend to be two types of biomarkers studies done on drugs and medication. There are also some interests in studies looking at PRP and patient cantered outcome. It is a novel approach to look at biomarker in PRP conducted by health care providers. The integration of biomarkers measurement it has been suggested because of the robots of MC4B it has suggested the collection of these markers should be used in routine clinical service. The collection of blook samples can be used for stratification of subjects based on a particular biomarker or genotype. All of that information and could contribute to a definitive RCT In theory, PRP in ILD can improve mortality when added to usual care. This can be explored further in future studies

5.4.16 Physical activity results

Data on physical activities were collected using an accelerometer worn on the right wrist for 5–7 days prior to PRP, and then after PRP. These data were then analysed using GENEActiv and GENEA data in R (GGIR) package version 2.0-0.

5.4.17 Moderate and vigorous activity time

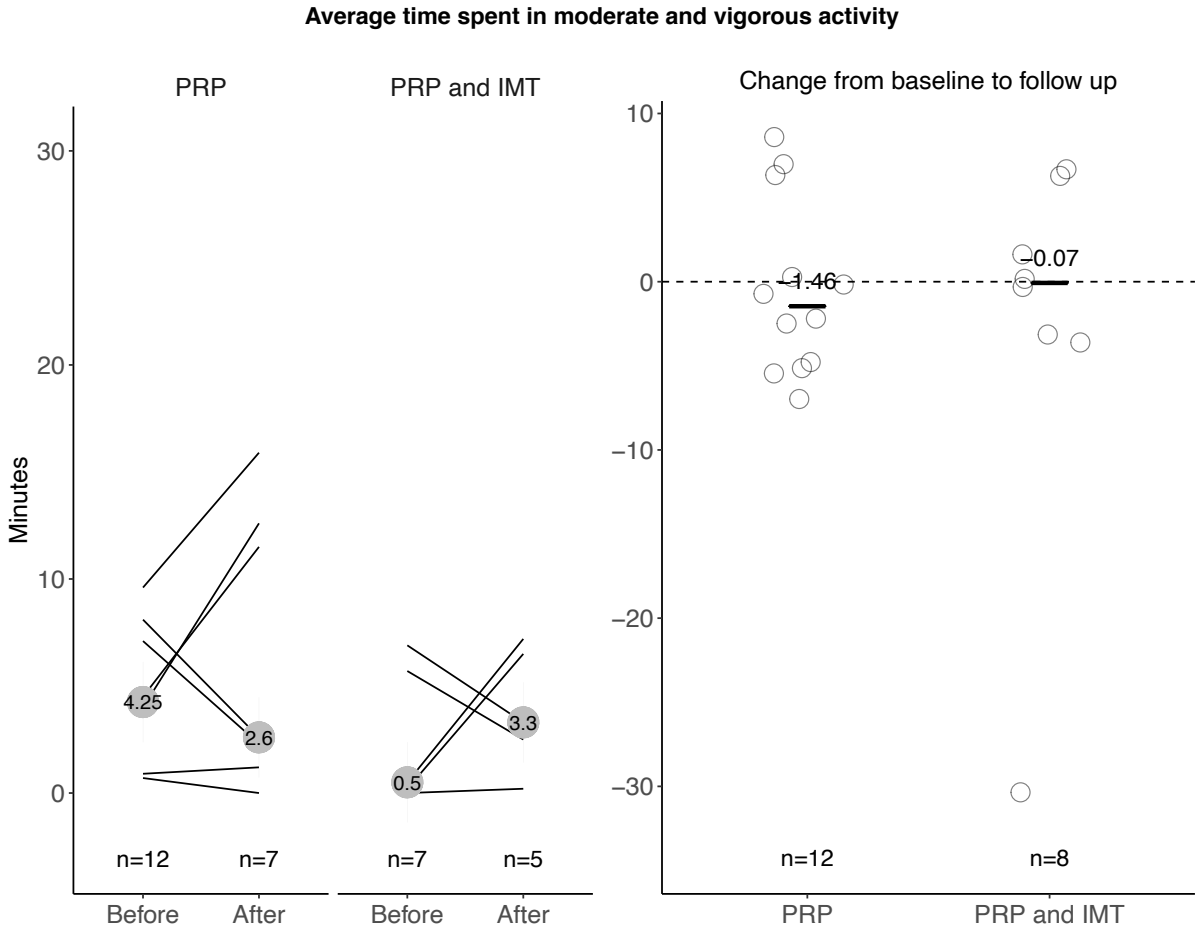


Figure 53. Average moderate and vigorous activities time in minutes per day before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in the sum of moderate and vigorous activities time. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is a deterioration in the variable and above which improvement

The time spent performing moderate and vigorous activity is a cornerstone of physical activity. The NHS recommends 150 minutes of moderate or 75 minutes of vigorous activity per week. This can be calculated as about 21 minutes of moderate activity per day, and this figure has been used to assess the level of impairment in ILD. A summary of reported time can be found in **Table 15.** Summary of time spent Table 15.

Time in moderate activity	n	Reference	Link
9 (2, 21)	N= 16 ILD and n=10 control	(Aguiar et al., 2018)	https://erj.ersjournals.com/content/52/suppl_62/PA5428.figures-only
About 9 and 4 for males and females	24 ILD	(Wickerson et al., 2013)	https://pubmed.ncbi.nlm.nih.gov/23403914/

Table 15. Summary of time spent in moderate activity

5.4.18 Sedentary time

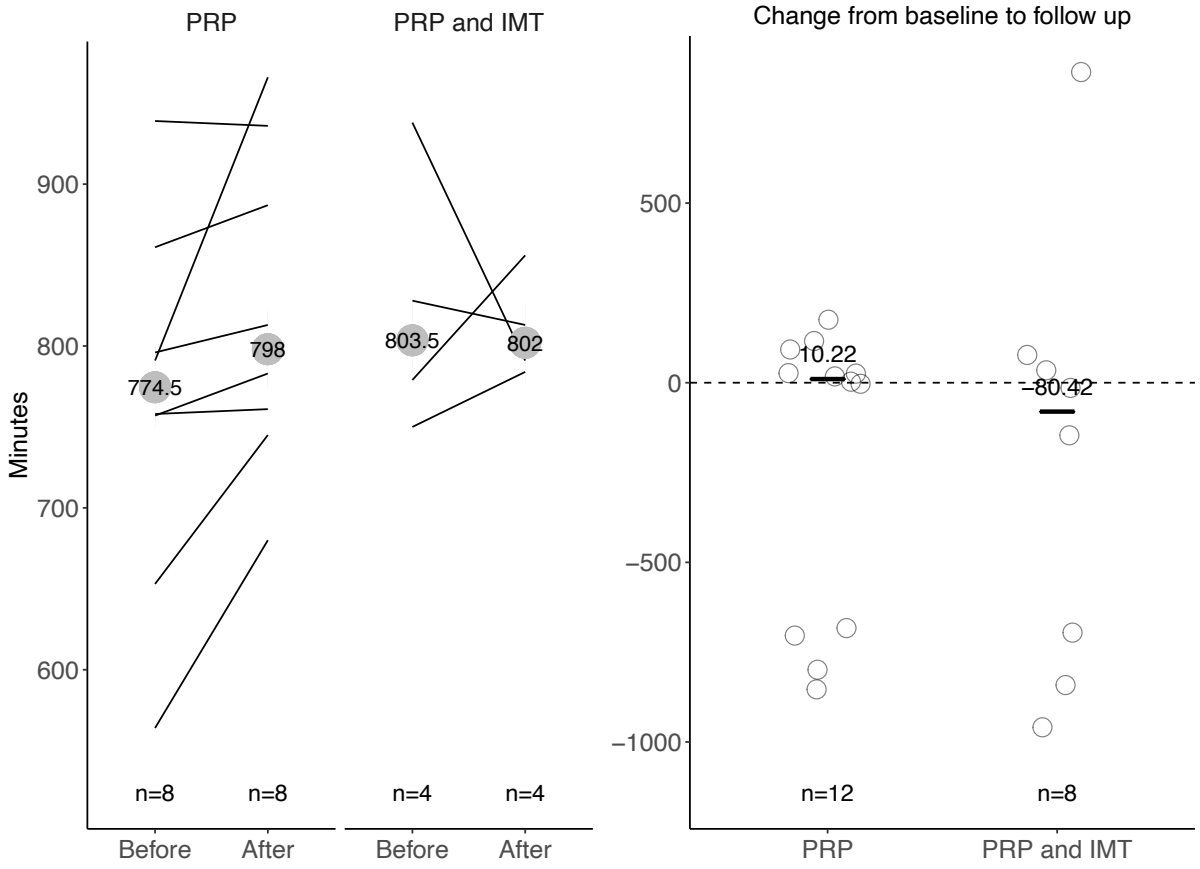


Figure 54. Inactivity time in minutes before/after 8-week PRP or PRP and IMT. Left: black lines represent individual subjects. Right: changes in inactivity. The horizontal black lines on the right plot and the grey circles on the left plot represent median values. The grey dotted line represents zero, below which there is an improvement in the variable and above which deterioration

Our participants' inactivity time (sedentary time) was higher than what was reported by Atkins et al. (2018), who found that mean sedentary time was 551.7 minutes per day. The authors also reported that no parameter was able to predict sedentary time, including the 6MWT, DLCO, and FVC. There was also a trend toward higher mortality with increased sedentary time.

5.4.19 Results from genetic analysis

Three ml of blood were obtained by venesection then stored under -80° after collection, and then genetic analysis was conducted using rs35705950 SNP on 20 blood samples. It has been consistently shown that that the minor (T) allele of a single nucleotide polymorphism (SNP) located upstream of the MUC5B gene transcription start site on chromosome 11p15 (rs35705950) is a risk factor for IPF. Notably, this is a functional polymorphism with increased expression of MUC5B shown in IPF lung. The risk of disease development also increases with the number of copies of the T allele present. An odds ratio of 9 has been described for heterozygous carriers of the T allele (GT) rising to 22 for the homozygous carriers (TT)(Seibold et al., 2011)

This is consistently found to be a risk factor for IPF, but also potentially with protective features for those with a disease diagnosis (Yang et al., 2015). A meta-analysis conducted by Lee and Lee (2015) on 2,733 IPF patients and 5,044 controls, MUC5B with T or G polymorphism confirmed susceptibility to IPF in Europeans and Asians (2015).

Genotype	Sample
GT	001S
G	002S
GT	003S
GT	004S
GT	005S
GT	006S
GT	007S
GT	008S
T	009S
G	011S
G	012S
GT	013S
G	015S
G	016S
G	017S
GT	018S
T	019S
GT	020S
GT	021S
GT	022S

Table 16: Genotype alleles for each subject

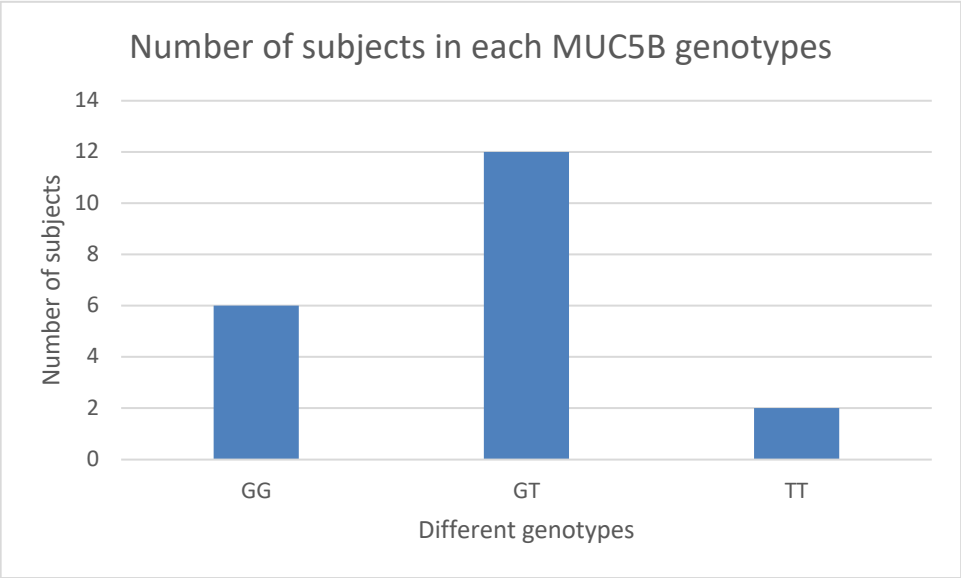


Figure 55: Distribution of MUC5B rs35705950 polymorphism

MUC5B has been identified as a potential single nucleotide polymorphism (SNP) in ILD and IPF with a role in the progression of fibrotic diseases. In our cohort, the GT type was the most common (Figure 55). A recent study found that MUC5B allele is associated with honeycomb appearance in HRCT and it is present across African American, White, and Hispanic ancestries (Garcia et al., 2021). Previously Seibold et al (2012) showed that the T allele was present in 38% people with IPF, 34% of subjects with familial interstitial pneumonia and 9% among controls. Interestingly the T allele presence seemed potentially higher in our group, at 70%

5.5 Overall Discussion

The main aim of this study was to test the feasibility of conducting pulmonary rehabilitation on subjects with ILD in a hospice care and home setting with or without inspiratory muscle training. This study showed that this was feasible for most patients, with a 20% drop out. There was positive feedback from patients and healthcare professionals involved and the study showed it was possible to integrate the collection of serum biomarkers for study. However, there is a limited number of such studies in ILD in general. In my study, the responses of subjects with ILD varied considerably between PRP only or PRP and IMT, possibly due to the heterogeneity of progression and the different types of diseases in ILD.

To summarise the outcomes, in MIP, six out of seven subjects in the PRP and IMT group showed an improvement and this was not the case for the PRP only group. However, the

remaining subject maintained MIP. This could potentially be explained by the direct exercise of inspiratory muscles using the IMT device. Both groups behaved similarly with the 6MWT, where more than ten out of 15 subjects showed improvement. In FVC, both groups behaved similarly as some subjects worsened and some maintained FVC, while a few improved. It is important to mention that, in ILD, maintaining function is considered a positive outcome because, in general, subjects lose FVC over time. One subject gained 1 litre FVC and was in the PRP and IMT group. For peripheral muscles, anxiety, and depression measures, about two thirds of our cohort either improved or maintained their values. For K-BILD, a specific patient-reported outcome measure for ILD, only two subjects had reduced scores, while eight subjects improved more than the MCID (3.9). Regarding the iPOS score, six out of 15 had worsened scores, possibly due to a worsening of symptoms. However, the other nine either improved or maintained their score. Having a senior palliative care nurse within the team was helpful in dealing with some cases and in improving the scores overtime. In MMP7, there was a trend toward reduction of this candidate biomarker. MMP7 levels have been shown to correlate with death in published studies (higher MMP7 levels mean greater risk of death) (Yunt et al., 2019). In my study there was a trend of improvement in nine out of 15 subjects, but some did not improve. Our sample size was limited (n=20) and the study was not powered to examine differences in MMP7 levels. However, given the importance of MMP7 in the literature, our results would indicate future powered studies could examine this end point, which in IPF is a recognised and consistant predictive of morbidity and mortality.

In clinical trial, simple randomisation can lead to unmatched groups at baseline. The difference in the group may invalidate the trial results. Alternatively, researcher can use stratification or minimization to improve groups equalness. In stratification, researcher divides the sample into blocks based on a covariate or covariates. Then simple randomisation is performed within each block (Suresh, 2011).While in minimization, the first subject is assigned to a group then a hypothetical allocation is done on the following subject in both groups, after that, an imbalance score is calculated. The aim is to allocate the subject based on the lowest possible imbalance score. The minimization method is preferred in clinical trial because it can work for ongoing recruitment (Saghaei, 2011). In our study we used simple randomization because of the study design and aim being a proof-of-concept study with no sample size calculation or inferential statistics.

5.6 Limitations

Although as stated our study was conducted on a relatively small sample size (n=20), this number is common in pulmonary rehabilitation studies. We did not do a formal sample size calculation because it was a proof-of-concept study aiming to provide preliminary information that could inform future studies and provide information for power calculations. The number of patients recruited (n=20) was therefore pragmatic and consistent with the performance of meaningful descriptive analyses. Peripheral muscle testing, MIP test, randomisation, and serum ELISA for MMP7 were all assessed by the same assessor, which could lead to bias toward the intervention group. However, a strict protocol was followed to improve accuracy and reliability.

5.7 Future studies

The results of this study indicate that pulmonary rehabilitation for subjects with ILD is feasible and it paves the way for studies with larger powered sample sizes. It can also be focused on one disease instead of the general group of ILD. The main intervention was inspiratory muscle training of 40% IMT 30 breaths/twice a day. Further work could test different IMT levels or a different number of interventions per day.

5.8 Conclusion

I conducted this trial with the aim of testing the feasibility of a pulmonary rehabilitation programme for ILD patients using a hybrid approach in a hospice care and home setting. This included two arms, with and without inspiratory muscle training. The programme was found to be feasible and was appreciated and liked by patients, their carers (detailed feedback in Chapter 7) and healthcare professionals. On average, the attendance rate was 81% and there were three complications. Two related to desaturation in a combined pulmonary fibrosis and emphysema (CPFE) patient, who was on 6L per minute oxygen. The other complication was a panic attack, which was managed nonpharmacologically by a senior ILD nurse using distraction techniques.

This RCT was able to test and involve variables not usually measured together in pulmonary rehabilitation studies. This combined approach using ILD relevant biological markers, subjective, and physiological measures could lead to better, personalised medicine in this patient group. In our results, outcome measures responded variably, with some outcomes improving, some remaining unchanged, and some deteriorating. The results obtained will be useful for planning subsequent studies. Preliminary data suggesting that MMP-7 levels, FVC and assessments of symptoms by K-Bild may change in association with a PRP are the first that

we are aware of and, for example, could be followed up in formal powered studies in people with IPF/ILD.

Chapter 6. Investigating the Usefulness of UK Biobank Data in Local ILD Research

6.1 Chapter Overview

The UK Biobank is a large-scale national level data set that contains health-related data for 500,000 subjects with different conditions. A successful application was made to acquire UK Biobank data, which were then downloaded. The aim of acquiring the data was to establish a foundation for the study, including physiological information about patients with ILD. Data were labelled and manipulated using R and RStudio. ILD subjects were selected for analysis based on a positive answer to questions on doctor diagnosed idiopathic pulmonary fibrosis, fibrosing alveolitis unspecified alveolitis, or asbestosis. The UK Biobank data were then analysed for FVC, FEV1, hand strength, Townsend deprivation index, and physical activity, and 122 subjects with ILD were identified. The subjects identified seem to have fairly normal FVC, grip strength, moderate vigorous activity, and Townsend index. However, sedentary time was higher, and there were significant correlations between sedentary time and weight (positive correlation, r=0.39, n=122 p=0.004), and between sedentary time and moderate-vigorous activity (negative correlation, r= -0.32, n= 122, p=0.021). In summary, the UK Biobank data on FVC and muscle strength is not similar to the experience of the regional ILD clinical service, possibly because the subjects in the data set are fit, and early in their disease course. The UK Biobank resource might be helpful in future blood biomarkers and genetic research, and for the collection of comparison data from other chronic lung diseases, in terms of promoting healthy diet and physical activity as important in subjects with ILD. The UK Biobank data indicate that this could be an area for preventative intervention.

6.2 Introduction

According to the UK Biobank's website, "the UK Biobank is, a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants. The database, which is regularly augmented with additional data, is globally accessible to approved researchers and scientists undertaking vital research into the most common and life-threatening diseases. UK Biobank's research resource is a major contributor to the advancement of modern medicine and treatment and has enabled several scientific discoveries that improve human health. Since 2006, UK Biobank has collected an unprecedented amount of biological and medical data on half a million people, aged between 40 and 69 years old and living in the UK, as part of a large-scale prospective study. With their

consent they regularly provide blood, urine and saliva samples, as well as detailed information about their lifestyle which is then linked to their health-related records to provide a deeper understanding of how individuals experience diseases" (UK Biobank, 2021).

6.3 Specific Materials and Methods

The UK Biobank raw data set contained more than 5,000 variables quantified in over 500,000 subjects. ILD cases were selected in subjects who had a diagnosis of IPF, fibrosing alveolitis unspecified alveolitis, or asbestosis. This resulted in the identification of 122 subjects (34 females and 88 males). This rate of approximately 20 per 100,000 in the UK Biobank sample population compares with the NICE 2015 prevalence estimate for IPF of 15–25 per 100,000. COPD subjects were selected based either on answering the question about doctor diagnosis or chronic bronchitis, emphysema, and or COPD and no other lung diagnosis. Healthy subjects were selected based on answering 'no' to all lung diagnosis questions (Figure 56).

In the UK Biobank, physical activity was objectively measured by the Axivity AX3 triaxial accelerometer worn on subjects' dominant wrist over a 7-day period (Doherty et al., 2017). Physical activity data were downloaded as raw data from the UK Biobank server using DOS command (ukbfetch -ak27844.key -binput.txt), after preparing the IDs for subjects identified as ILD with matching physical activity measurement in the biobank data. This resulted in 58 out 122 subjects with ILD who had physical activity data. All raw data were then downloaded and analysed using GENEActive and GENEA data in R (GGIR) package version 2.0-0, running on R and the RStudio software. This is open source and available for researchers. GGIR is a package that enables researchers to analyse raw accelerometer data.

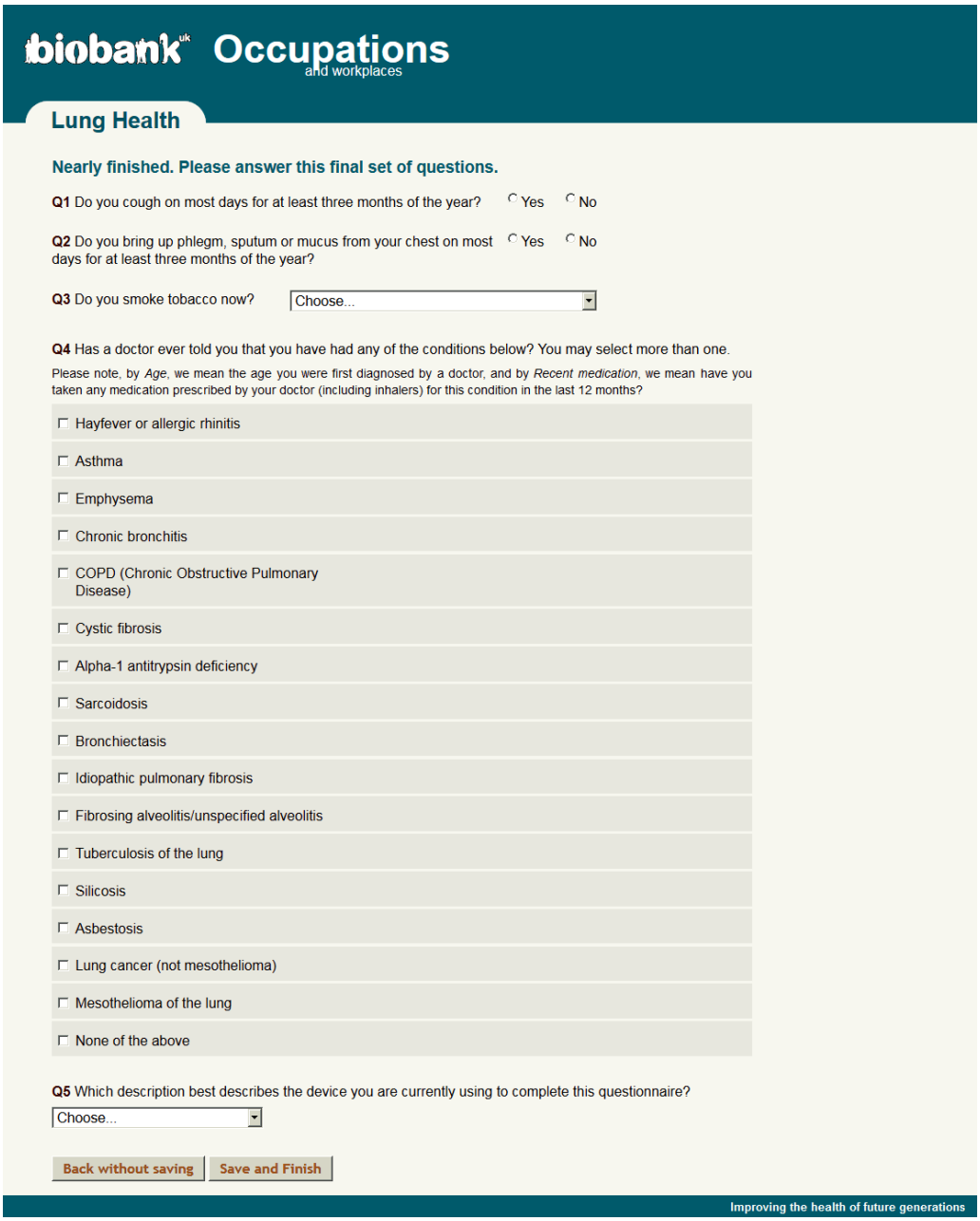


Figure 56. Screenshot of lung diagnosis questions from the UK Biobank database

6.4 Results

Disease and Sample Size	ILD, n=122	COPD, n=1,595	Healthy, n=82,153
Variable	Mean and standard deviation where appropriate		
Gender **Males (M)** **Females (F)**	M=88 F=34	M=875 F=720	M= 36899 F= 45254
Weight in kgs	82 ± 14.3	80.5±17	76 ± 15.3
Mean age in years	62.4± 5.0	59.5 ±6.6	56.3 ±7.6
FVC in litres	3.67±0.90	3.54 ±0.99	3.86 ± 1.0
FEV1 in litres	2.8 ±0.69	2.47± 0.83	2.97 ± 0.75
FEV1 %	96.0± 14.7	78.8± 21	99±15

Table 17: Selected UK Biobank data for interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and healthy subjects

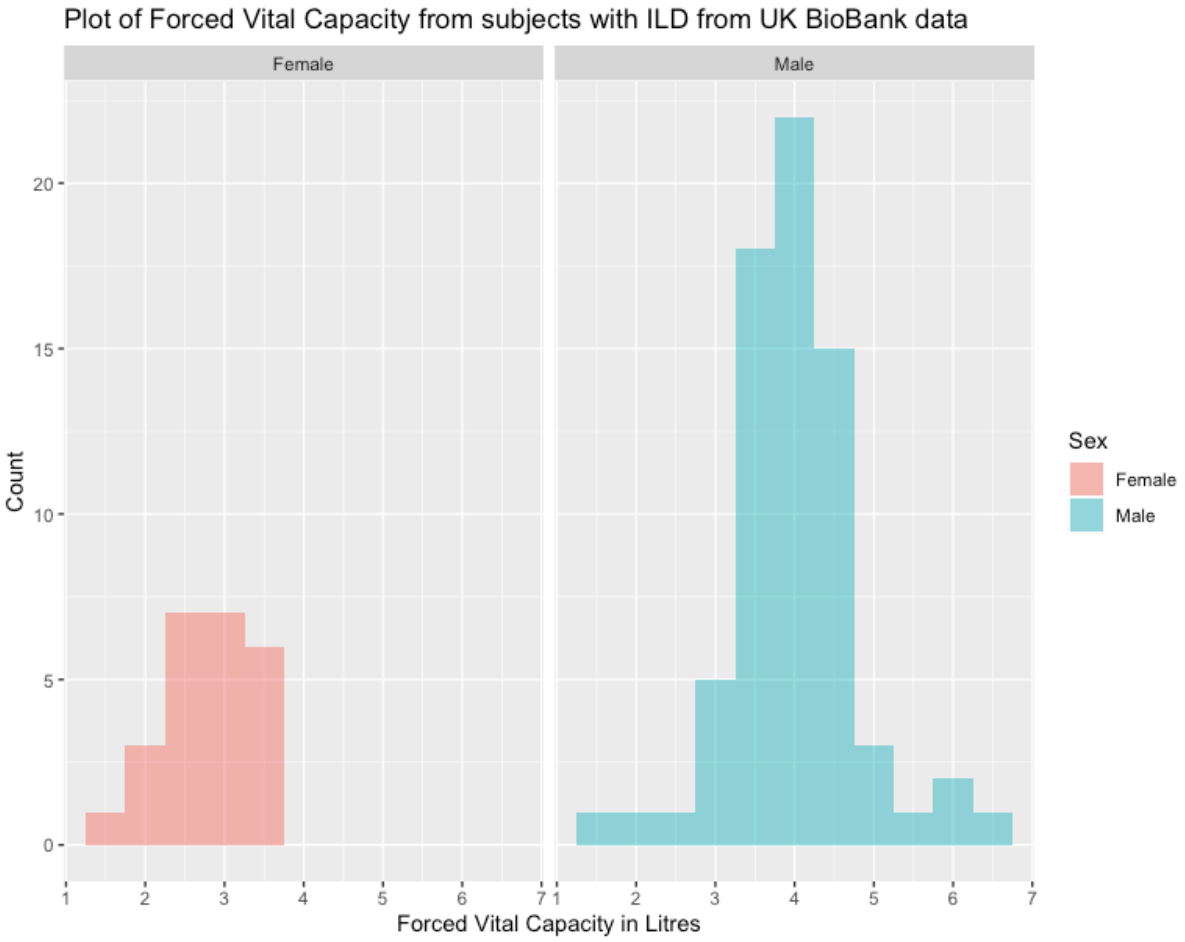


Figure 57. UK Biobank data comparing FVC in males and females with ILD

FVC in the UK Biobank is preserved, with a mean value of 3.67 SD (0.90), but in IPF/ILD it is expected that FVC will drop significantly as the disease progresses. In our RCT, the mean FVC was 2.40 litres with an SD of 0.58, and in our clinical service the mean was 2.48 litres and SD of 0.55 (Figure 57).

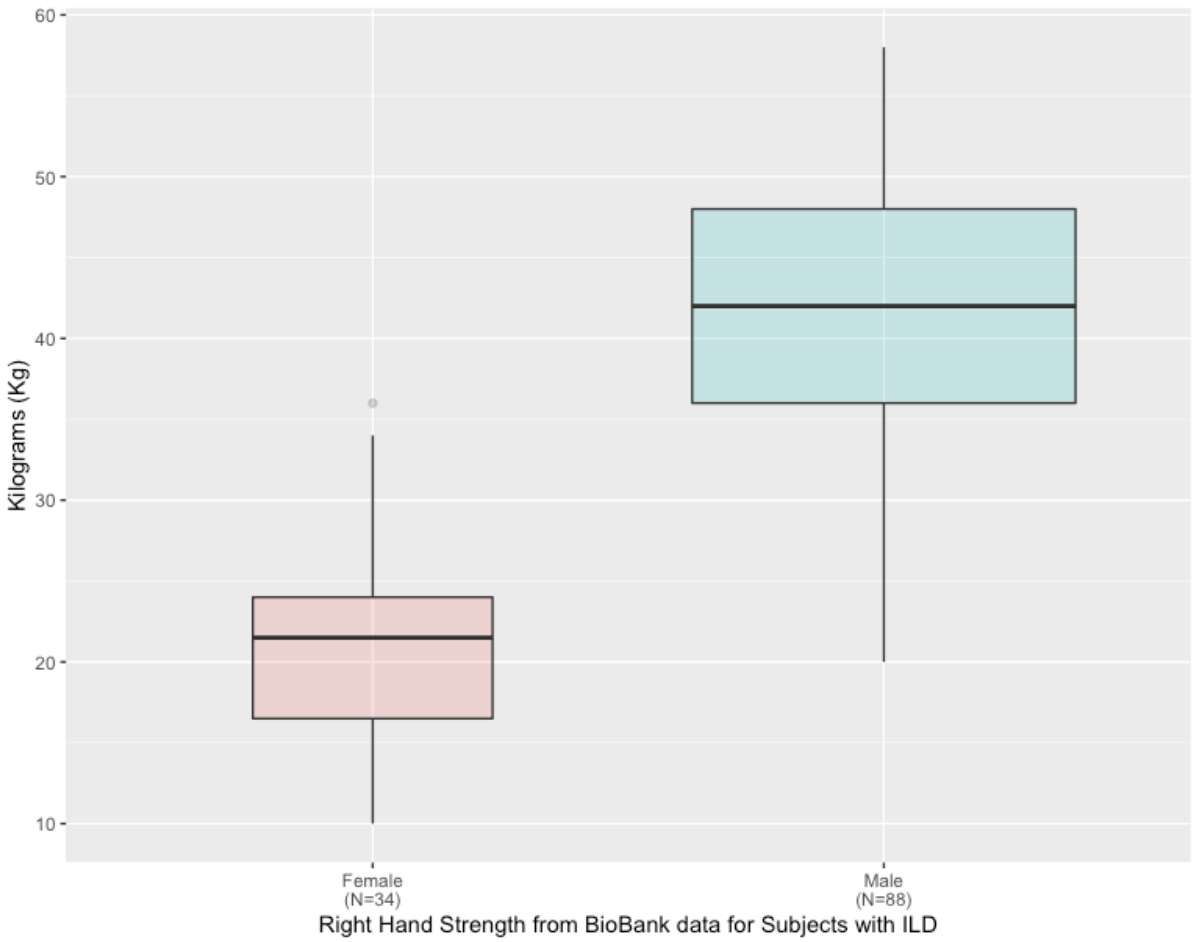


Figure 58. UK Biobank data comparing right hand strength in male and female ILD subjects

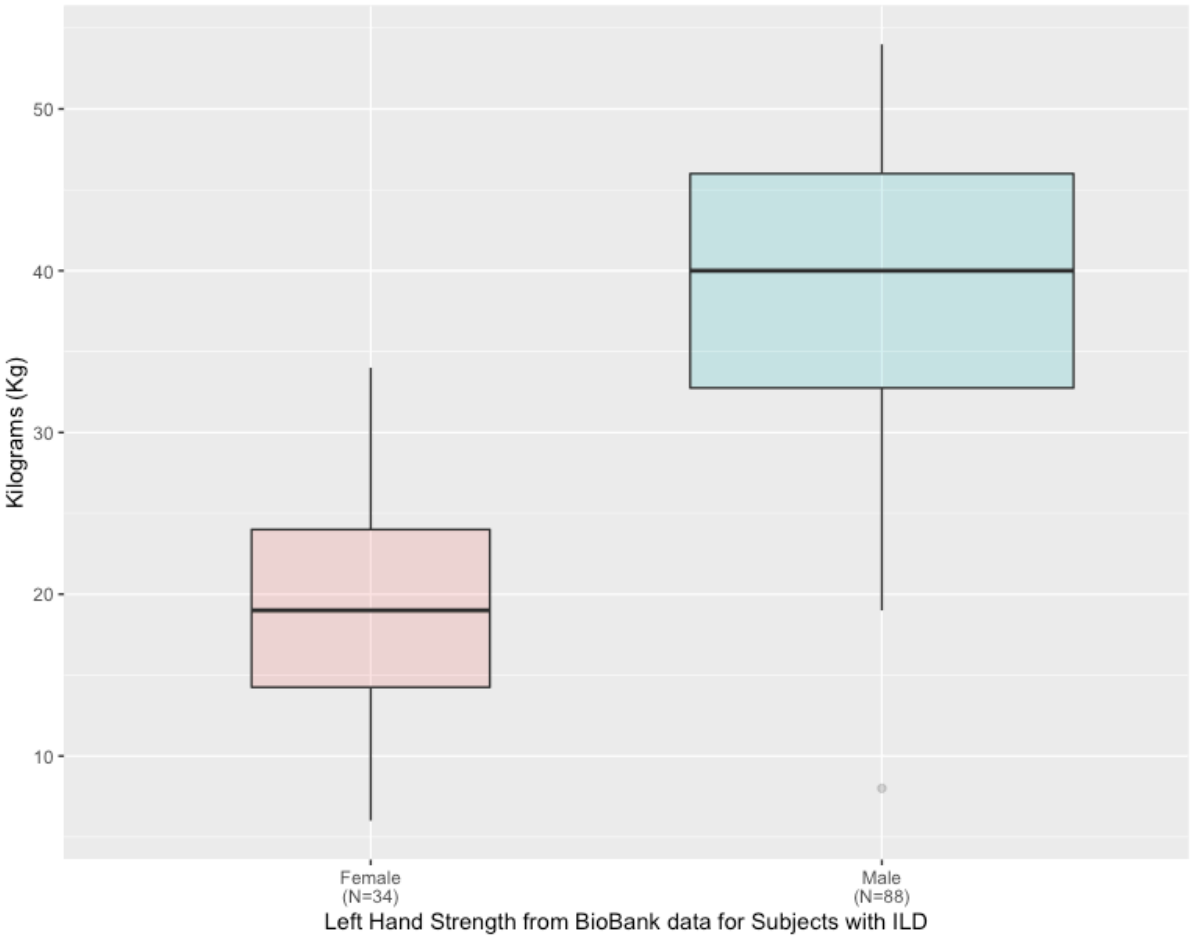


Figure 59. UK Biobank data plot comparing left hand strength in male and female ILD subjects

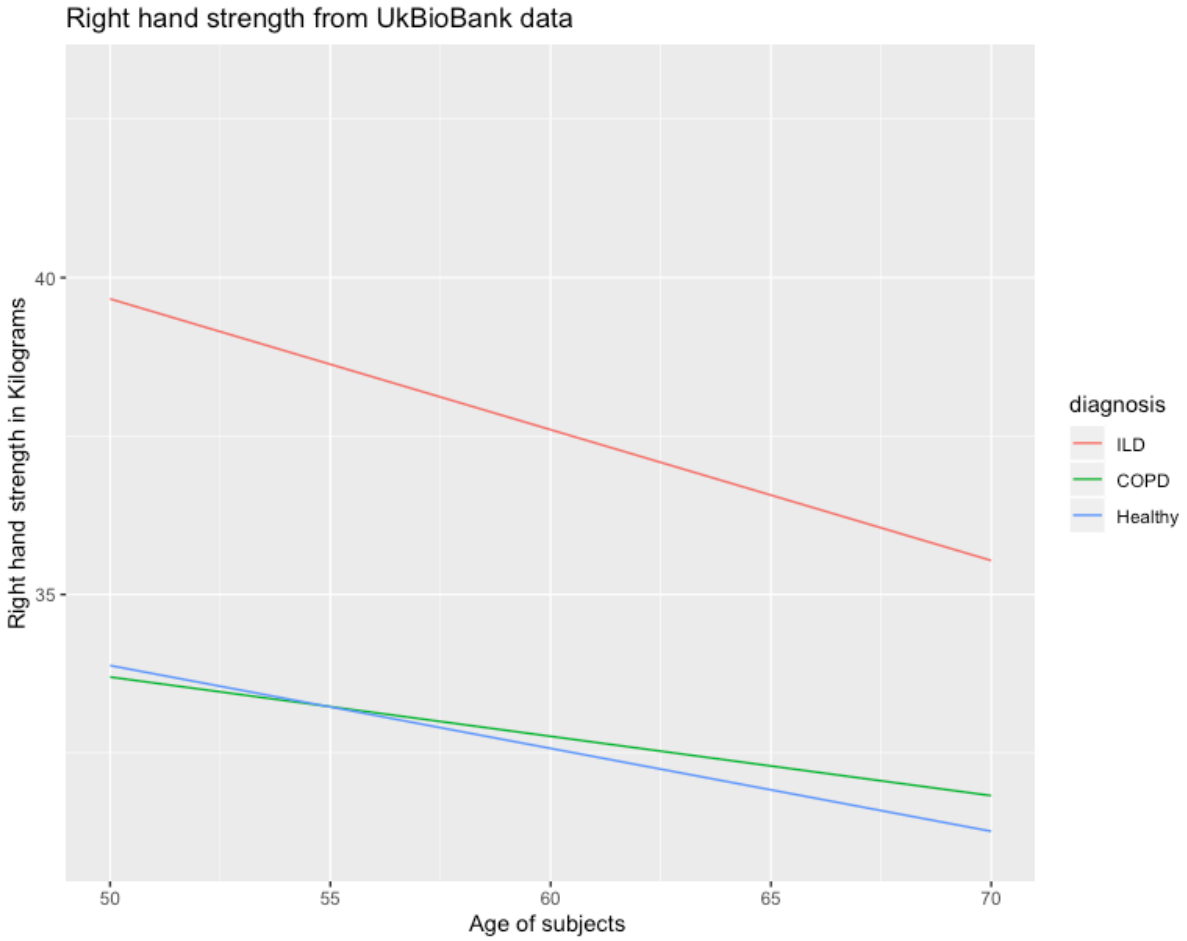
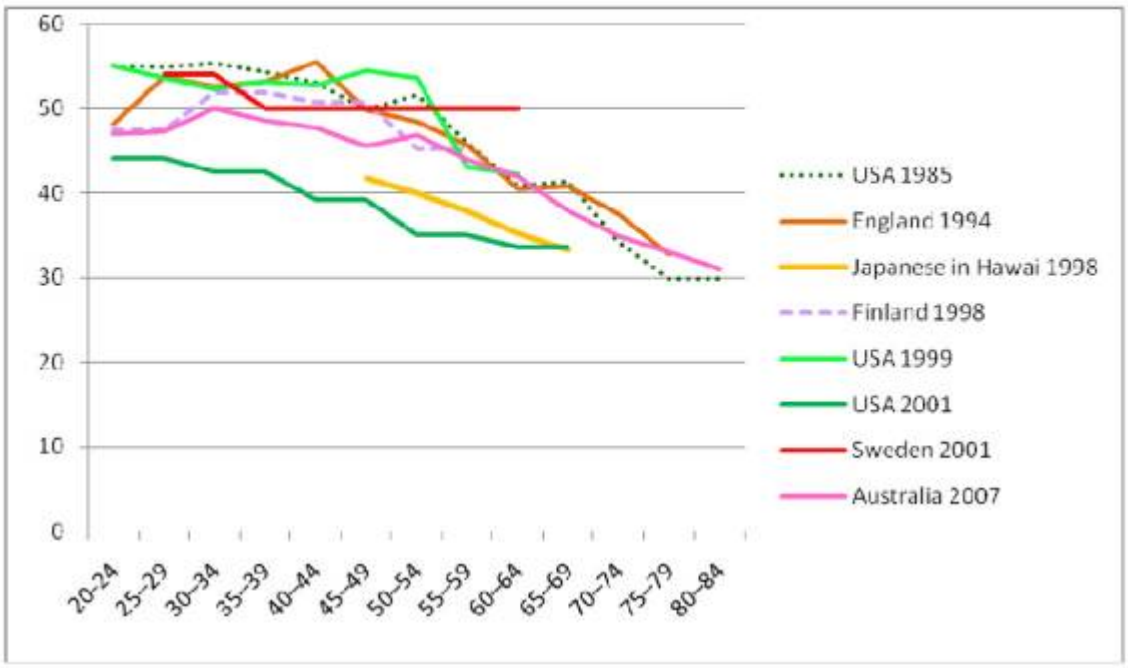


Figure 60. Comparison of right hand strength in healthy, ILD or COPD subjects relative to age



USA 1985
England 1994
Japanese in Hawai 1998
Finland 1998
USA 1999
USA 2001
Sweden 2001
Australia 2007

Figure 61. Population-based comparison of healthy subjects' hand strength relative to age

Massy-Westropp et al. (2011) compared normal hand grip strength in adults in seven countries (Figure 61), and their results are slightly higher than those we found in ILD, but much higher than for COPD and healthy individuals. It is expected that subjects with COPD will have lower grip strength, but this is not the case for healthy subjects.

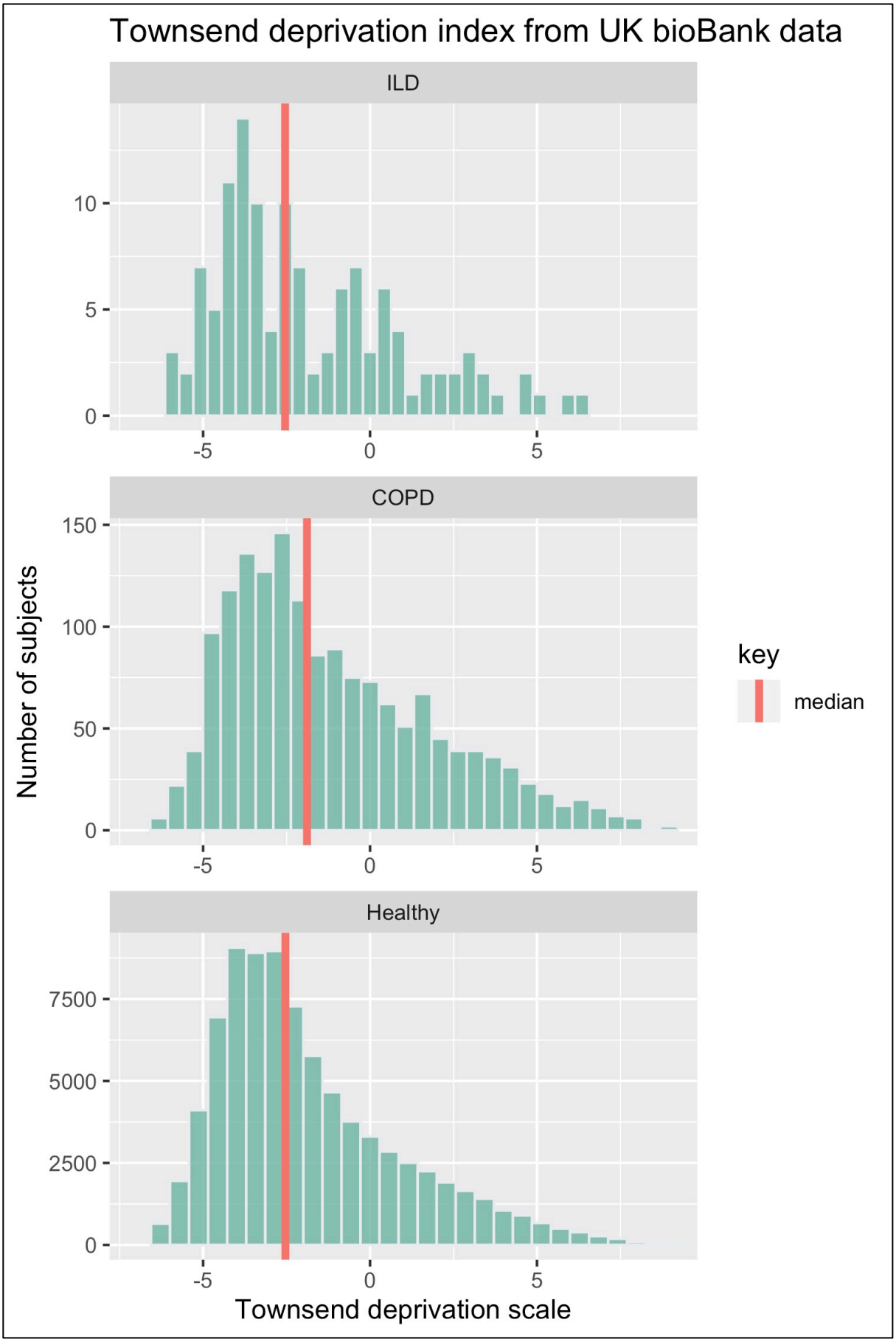


Figure 62. Townsend deprivation index: comparison of ILD, COPD, and healthy subjects

The Townsend deprivation index can be used to assess the economic burden of a specific group of people or disease, and a higher Townsend deprivation index score indicates more deprivation. The median Townsend deprivation index scores for ILD, COPD, and healthy subjects are -2.5, -1.89, and -2.5, respectively. According to these medians, the most deprived group is COPD, and the same group contains more deprived subjects compared to ILD or healthy subjects.

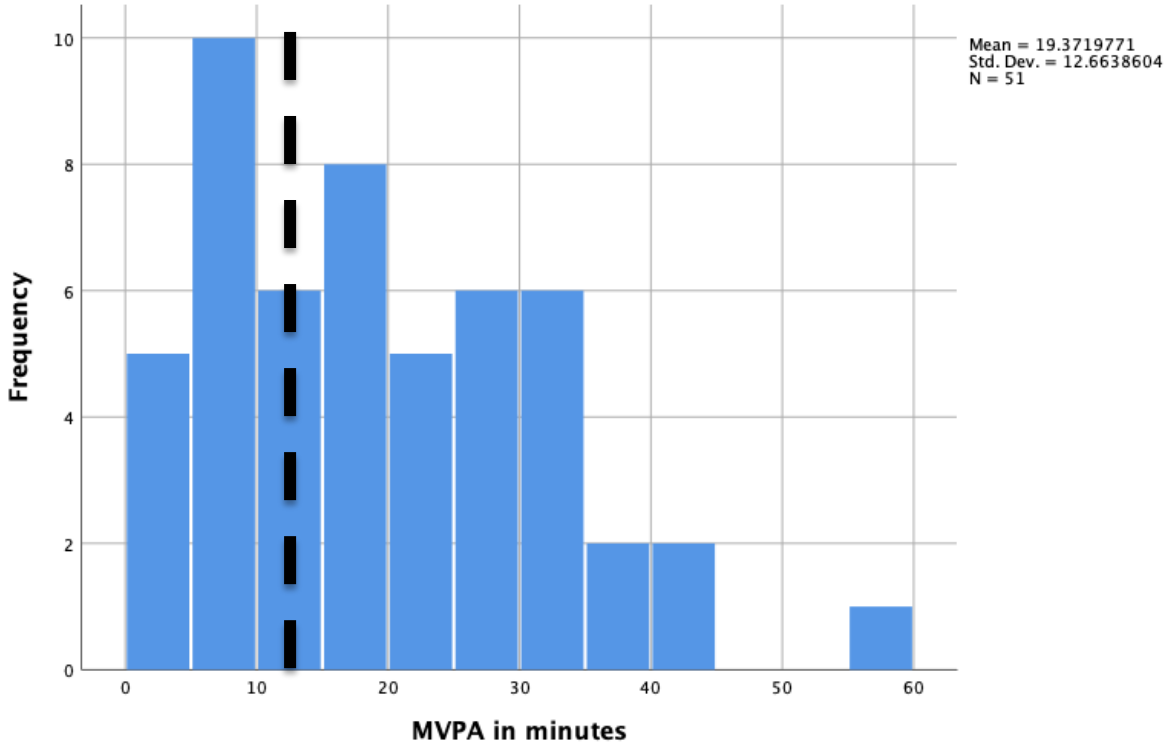


Figure 63. Moderate and vigorous activities in UK ILD subjects from UK Biobank data. The dashed line represents a normal level of MVPA in older healthy Dutch adults

Figure 63 shows the distribution of daily moderate to vigorous physical activity (MVPA) time in subjects with ILD from UK Biobank data (n=51). Van Ballegooijen et al. (2019) studied physical activity in older healthy Dutch adults with a mean age of 71 (SD 8) and found the MVPA time to be 14 (5–28) minutes. In the UK, the NHS (2019) recommends a moderate activity time for adults older than 65 to be 150 minutes a week, which is about 21 minutes a day. In Figure 63, we can see that about 70% of subjects spent more than 14 minutes per day undergoing MVPA. This is consistent with the suggestion that these subjects are relatively healthy as indicated by the fairly normal FVC data observed.

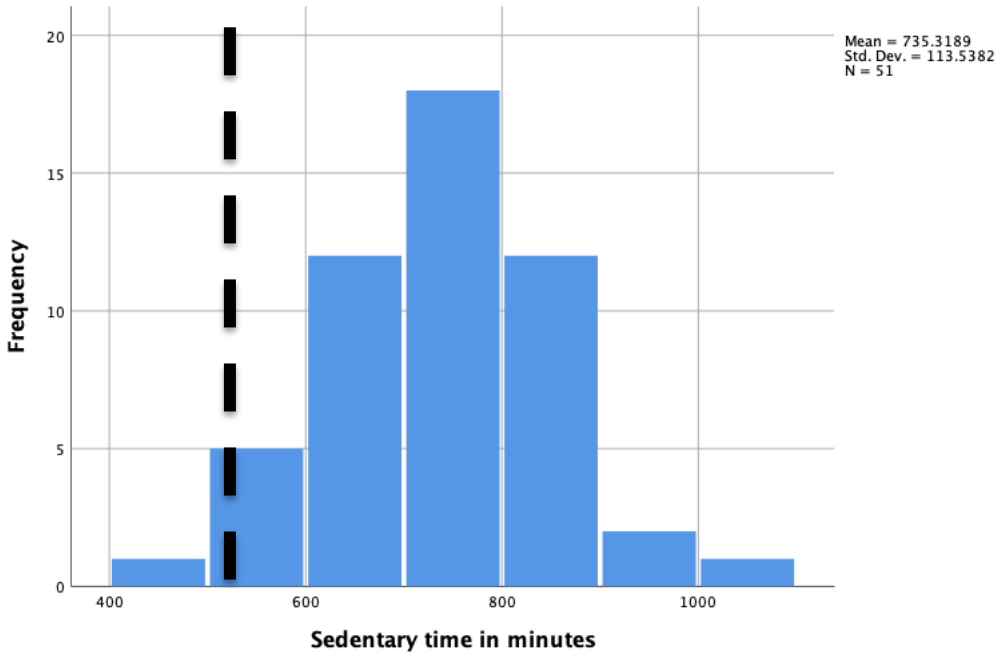


Figure 64. Sedentary time for ILD subjects from UK Biobank data. The dashed vertical black line represents normal sedentary time in older adults

Figure 64 shows the distribution of sedentary time in subjects with ILD from the UK Biobank data (n=51). Van Ballegooijen et al. (2019) investigated physical activity in older healthy Dutch adults (n=1,201) with a mean age of 71 (SD 8), and found the mean sedentary time to be 552 (90 SD) minutes. The UK Biobank subjects, with self-reported ILD, therefore had higher levels of sedentary time mean 735 (51 SD).

Correlations

		FVC	Weight	Age	MVPA	Sed time
FVC	Pearson Correlation	1	.14	.08	.16	.07
	Sig. (2-tailed)		.33	.59	.28	.64
	N	47	47	47	47	47
Weight	Pearson Correlation	.14	1	-.11	-.02	.39**
	Sig. (2-tailed)	.33		.43	.89	.004
	N	47	51	51	51	51
Age	Pearson Correlation	.08	-.11	1	.13	-.19
	Sig. (2-tailed)	.59	.43		.37	.19
	N	47	51	51	51	51
MVPA	Pearson Correlation	.16	-.02	.13	1	-.3
	Sig. (2-tailed)	.28	.89	.37		.021
	N	47	51	51	51	51
Sed time	Pearson Correlation	.07	.4**	-.19	-.32*	1
	Sig. (2-tailed)	.64	.00	.19	.02	
	N	47	51	51	51	51

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 18. Correlations between FVC, weight, age, time spent in moderate and vigorous physical activity (MVPA), and sedentary (sed) time

Table 18 shows the correlations between FVC, weight, age, MVPA, and sedentary time. Two significant correlations can be seen between weight and sedentary time (positive correlation, r=0.39, n=51, p=0.004), and between MVPA and sedentary time (negative correlation, r=-0.32, n=51, p=0.021); the other correlations were not significant.

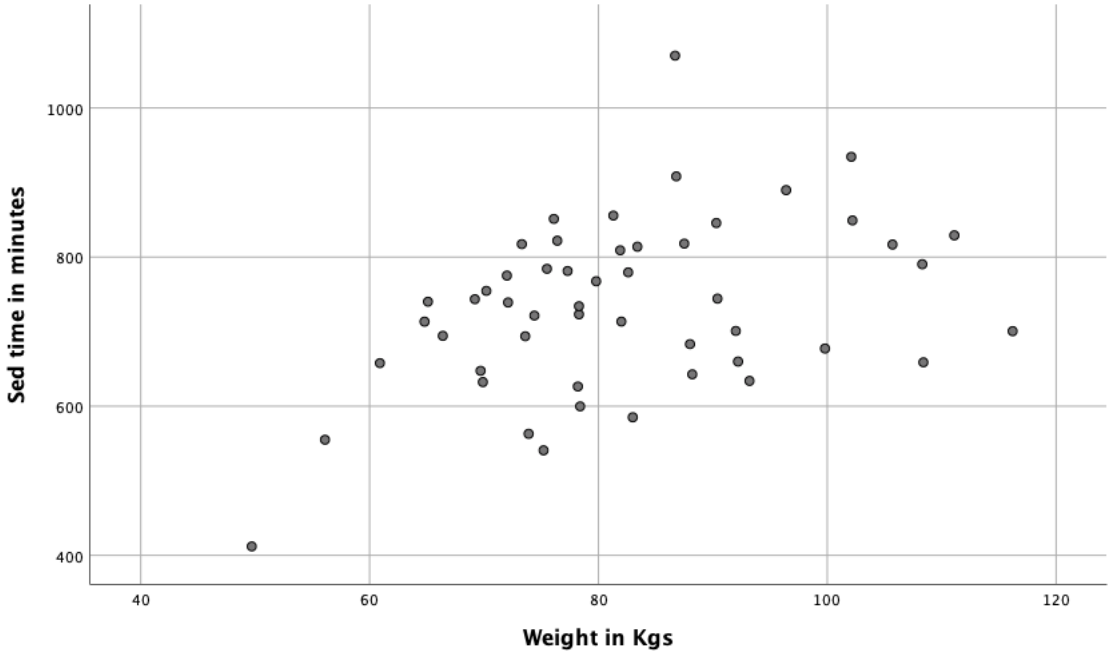


Figure 65. Correlation plot between weight in kilograms and sedentary (sed) time in minutes

Figure 65 shows broadly that as weight increases, sedentary time increases, which is logically expected. Ramakrishnan et al. (2021) have looked at accelerometer physical activity in (n= 96,675) subjects without prior cardiovascular disease and have found subjects with lowest PA had higher body mass index, smoked more, and were diagnosed with hypertension. These findings stress the importance of nutritional support, especially for subjects with obesity.

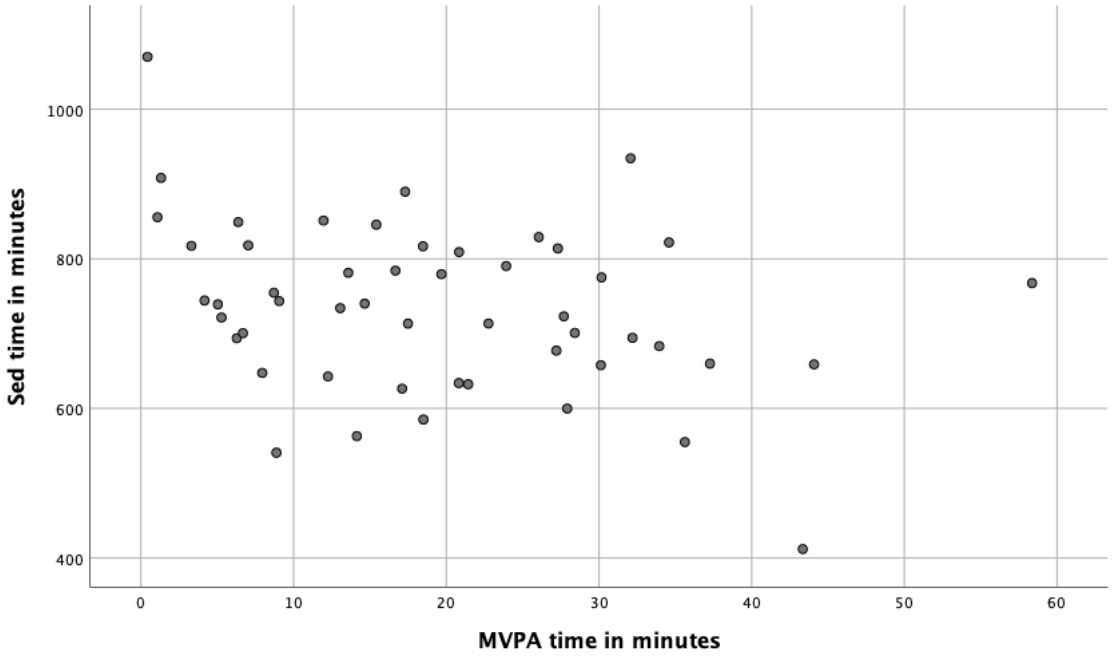


Figure 66. Correlation plot between moderate and vigorous activities time in minutes (MVPA) and sedentary (sed) time in minutes

Figure 66 broadly shows that as MVPA increases, sedentary time decreases, which is the expected relation between the two. However, the correlation, r=-0.32, is weak relation, which might indicate that other factors contribute to the observed increase in sedentary time in subjects with ILD.

6.5 Discussion

This chapter has explored the possibility of looking at an interesting, important, and helpful data set to inform research in ILD. In general terms the exploration of UK Biobank data collected at the national level from multiple centres and cities in the UK has provided insights into the methodological development of this concurrent project on providing PRP for ILD. Learning from UK Biobank methodologies was helpful in the setup of the clinical service and in designing the clinical trial (Chapters 3 and 4). The methodology we used locally for the collection of accelerometer and muscle strength therefore used the same methods employed in the UK Biobank and this experience was vital for the project. Browsing and analysing the big data set from the UK Biobank provided knowledge, skills, and experience for me as a researcher and PhD student. A big data set requires specific sets of skills and expertise in comparison with smaller data sets. Working on a real world large and complicated data set offered me experience of dealing with data at scale, and to relate this to my own local work in the region.

ILD cases were selected from the UK Biobank subjects was based on their affirmative answer to a question on a doctor's diagnosis of IPF, fibrosing alveolitis, unspecified alveolitis, or asbestosis. This rate of approximately 20 per 100,000 in the UK Biobank sample population compares with the NICE 2015 prevalence estimate for IPF of 15–25 per 100,000. This suggests that while the security of diagnosis in the UK Biobank is not the same as an ILD service MDT, our results have broad plausibility for the number of patients picked up by the novel biobank approach I used. There were also more males than females identified with ILD.

According to our analyses, the subjects who volunteered to attend UK Biobank centres were not severely ill compared to our samples from the clinical service and RCT. Also, the UK Biobank ILD subjects were younger than ours. The mean age of ILD subjects is 62.4 while the median age for our subjects in the clinical service was 74 years. The UK Biobank data seemed relatively fit and healthy based on lung function, showing preserved FVC in the UK Biobank data ILD subjects. This could be due to that fact that these subjects volunteered to attend to UK Biobank centres and spent effort and time for their data to be collected, while our subjects were actual patients coming to our regional ILD clinic with symptoms. It is also plausible that the subjects in the UK Biobank are early in the disease progression and their health may not have deteriorated and been detected by the physiological measures that were conducted. Another possibility is that the UK Biobank diagnosis was not accurately made, while our subjects' diagnoses were potential more secure as they were made via an MDT approach.

For the above reasons, the UK Biobank data may not be most helpful concerning physical activities, PFT, or muscle strength comparisons with subjects from ILD clinics. Nevertheless, two areas explored in our projects with UK Biobank data may be of interest. MMP7, for example, is an important, relevant, and targeted blood serum biomarker for ILD research that I have explored in my PhD (Chapter 5). Since blood was collected from some patients in the UK Biobank, this could be a valuable test to have conducted as, when we looked at the available blood biomarkers in the UK Biobank, MMP7 was not included. Another type of data that could be looked at is the genetic data collected by the UK Biobank, but due to limited time and the need for specific high computational specifications, such a genetic analysis was not performed with the UK Biobank data we had. However, an analysis was made for our patients in the RCT (Chapter 5). The gene that we examined was MUC5B, which is a targeted gene for ILD/IPF research.

Due to the limited number of IPF cases, studies are often conducted in collaboration with multiple centres. Future studies may need to examine the stratification and minimisation of

RCT. From the biobank study, it is obvious that there are patients who are not restrictive. A stratification of IPF patients would ensure the equality of the control and the intervention groups.

The collection of the physical activity and muscle strength data before and after PRP in my local studies of patients (Chapters 4 and 5) used the same or similar approaches used in the UK Biobank. This similarity indicates the possibility of conducting our protocol at the national level. Also, winning the NHS best practice award placed our project within NICE guidelines, along with recommended management for IPF.

It is interesting that the UK Biobank data showed a relationship between weight and sedentary time in subjects with ILD. As discussed in subsequent chapters, we included a session about nutrition ILD in our education programme. Our subjects valued this session and participated actively in the discussion about the importance of a proper and healthy diet. The UK Biobank data would also seem to confirm that this is a logical approach, based on national level data.

It is recognised that chronic lung disease can be associated with economic deprivation and this has been shown in COPD (Collins et al., 2018).The UK Biobank data for ILD showed that the median Townsend deprivation index was -1.89 in COPD and -2.5, in people with self-reported ILD. This information may be important when designing clinical trials and providing the PRP for subjects on lower incomes. Plans should thus consider all logistics and be tailored to subjects' needs in terms of transportation and other expenses; therefore, in our clinical PRP service and RCT (Chapters 4 and 5), taxi support was made available from the local chest clinic research fund.

6.6 Conclusion

I explored the UK Biobank data aiming to gain experience, skills, and knowledge about this valuable large data set to inform research in ILD. After several trials, courses, and consultations, I was able to browse, analyse, and ease the complicity of the data. Although the data was not directly helpful in detecting physiological abnormalities, found in my clinical ILD group, it may be helpful in the future e.g., for blood biomarker and genetic testing.

Chapter 7. Feedback from the Clinical Service and Randomised Clinical Trial

7.1 Chapter Overview

Feedback is an important aspect of improving the quality of healthcare services (Decorte et al., 2019). We felt this was a particularly important part of developing our novel clinical service of PRP tailored for ILD. It also provided formative information which contributed to the subsequent design of a pilot, randomised trial. A single page survey was developed with three open-ended questions, given to every patient at the end of their programme. After transcribing the answers, a word map was developed for each question. In general, patients liked the 'information' being provided in a friendly atmosphere, with topics specific for ILD. They also liked the 'socialisation' with others from the same condition and the inclusion of carers was appreciated. In summary, this feedback highlights the importance of tailoring PRP for ILD by providing education topics specific for ILD, as well as the benefit of grouping people with similar conditions. The feedback suggested useful areas in which to make modifications and improvements as experience of the clinical service was gained. This benefited the design of the subsequent pilot, randomised trial.

7.2 Introduction

Feedback is key to the development of healthcare services (Decorte et al., 2019). Following the establishment and implementation of this PRP for ILD, we therefore sought feedback to suggest ongoing improvements for our programme. This was also used to provide formative information which contributed to the subsequent design of a pilot, randomised trial.

Although different styles of feedback can be obtained, open-ended question feedback has the advantage of allowing subjects to write freely, without having to rank on a scale or choose between true or false options to questions which may reflect what the investigators want to know about, but which may not necessarily capture the thoughts of patients (Decorte et al., 2019). In a study on n=75,769 patients, open-ended questions were viewed as 'useful' and 'very useful' by 80% of the department management (Riiskjær et al., 2012).

7.3 Specific Materials and Methods

A short survey was developed which had three open-ended questions, and this was distributed to all subjects at the end of the programme. Subjects wrote their answers anonymously and were given the chance to write either in the rehabilitation centre or at home. The three questions were:

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

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

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

After collecting the answers to the three questions, word cloud figures were generated for each question using (https://www.jasondavies.com/wordcloud/) website.

7.4 Results

7.4.1 Answers to question 1: as a participant in the programme, what is/are the thing(s) you liked the most?

- Friendly and efficient staff
- Social respect
- Fantastic and meeting lovely people
- Motivation and working in a group
- The exercise and the talks
- Exercise, social interaction, support from staff
- Information
- Group talks and information from visiting specialists
- Interesting but tiring
- All the advice and physio
- Everything
- Meeting new friends and lovely staff and the activities
- The chats and the gym, the camaraderie

- With others with the same condition as myself
- Relaxed and pleasant atmosphere in depth explanation and advice feeling the difference the exercise makes
- Everything suited me and the talks gave more confidence and reduce the things that caused me to panic
- Motivation of the things you don't do. Confidence. Social aspects. Informal. Small group. Treat as a person. Motivated. Do exercise then relaxation great
- Meeting together with other people who have IPF. The talks on various subjects to do with the condition
- 1:1 training. Camaraderie. Exercise very good. Relaxation very good
- Information gathering, exercise routines, relaxation time. This really covers everything

Figure 67. Word cloud generated from patients' answers to the first question of the feedback form. The size of the word correlates with its frequency

Exercise, information, meetings, socialising, and talks were the most frequent words, as shown in (Figure 67), highlighting the importance of educational talks. Also, subjects used different synonyms such as 'group', 'people', 'camaraderie', 'social', highlighting the importance of

group therapy in pulmonary rehabilitation. In our programme, all subjects had ILD and could talk to each other about their symptoms, feelings, and/or treatments.

7.4.2 Answers to question 2: as a participant in the programme, what is/are thing(s) you hated the most?)

- None
- None
- Loved everything
- None
- None
- Breathing tests
- None
- Nothing
- Some of the exercises
- None
- Nothing
- None. Enjoyed the 8 weeks
- Didn’t hate anything
- Nothing I dislike
- None
- Nothing
- Noting to dislike

Figure 68. Word cloud generated from patients' answers to the second question of the feedback form. The size of the word correlates to its frequency

'None' and 'nothing' were the most frequent words, as shown in Figure 68, and this was very encouraging.

7.4.3 Answers to question 3: as a participant in the programme, what is/are the thing(s) that would like us to change or improve

- None
- None
- Nothing
- Longer programme
- None
- Not qualified to comment
- No suggestion
- Not really
- None
- Nothing

- Nothing
- Making the programme longer, i.e. three months
- OT education. Oxygen talk
- The programme requires me to do exercise. To perhaps a longer period for exercises
- Gave up on pedometer—could not get it work properly
- Perhaps a little more exercise of the chest cavity
- Nothing

Figure 69. Word cloud from the patients' answers to the third question of the feedback form. The size of the word correlates with its frequency

'None', 'nothing', 'longer', and 'programme' are the most frequent words, as shown in Figure 70. The word 'more' was also used in response to question 3. Similar to what is presented in the figure, some of our subjects had no suggestions for improving the programme, but some patients suggested having a longer programme.

7.4.4 Feedback from a carer of a patient with ILD

Feedback from carers is also important and helpful in managing a support group around a patient and can provide related, complimentary information to the feedback from patients. Carers' feedback was not collected formally in our PRP, but feedback from a single carer was

received during the PRP, which highlights the experience from a carer's viewpoint. The carer provided feedback to the same three questions described above, as follows. The feedback for the first question was 'better understanding of the illness', 'able to ask', 'helpful staff that are willing to listen'. For the second question, the feedback indicated that knowing the level of exercise that the patient was capable of would be useful. For the third question, the feedback was 'using quizzes after an education session, to test subjects' acquired knowledge about a topic'.

7.5 Overall Discussion

As stated, feedback is essential to the provision of better quality healthcare. While quantitative methods might be an attractive method of collecting feedback, it is not ideal for healthcare. It is in the nature of healthcare that it is a complex system with many variables that can alter patients' experiences. Qualitative methods can examine patients' feelings about a service or a provider more deeply, looking at subjective and broad assessment. Different qualitative approaches have been used in healthcare, and depending on the research question and feasibility, different methods can be used. In brief, individual face to face interviews have the advantage of providing detailed information about an issue that might have been missed by the researcher. Focus groups can also help identify shared experiences and provide a rich environment and platform for argument and discussion. Another type of qualitative method is the quality circle, which can be used to develop a hypothesis or action point to develop the quality of healthcare. We collected the feedback about our service via open ended questions, which is a subtype of individual face to face questions. We used this method based on my limited experience with qualitative data and the feasibility of collecting this type of data along with other data (Pope et al., 2002). The feedback that was received stressed the importance of providing the PRP to a specific group of patients, in our case, ILD. It was felt that this consolidated the experience of group therapy. There was a feeling that patients were learning from each other as well as from the healthcare professional education and PRP structured programme. This emphasises the broad importance of education as part of PRP. There was an informal suggestion to include carers in the education session, which was implemented. No major suggestions were given for the programme, but a suggestion for a longer programme was raised. This suggestion is very important to consider in the future, although it might be difficult to implement due to logistics.

Upon development of the programme, patients from the regional ILD support group were included. This might be why there were few negative words associated with the programme.

Although the surveys were completed anonymously, the researcher and or healthcare providers involved in the study collected them. This could have altered the accuracy of the answers and subjects might have hesitated to express weaknesses in the programme. I used the phrase 'hated', which could have masked some potentially helpful feedback.

Due to the Covid-19 situation, it was difficult to access the full data for the survey and calculate the response rate, but it is believed that we had at least 14 responses.

7.6 Conclusion

In conclusion, the feedback was helpful to learn the strengths and weaknesses of the PRP, and suggested potential for improvement. Monitoring PRP from a patient point of view is very important to the completeness of any PRP. Longer PRP might be considered and future work which collects feedback from carers and clinic staff would also be useful. In future work more extensive, academic qualitative methodology could be applied to patient feedback to further the understanding of PRP. This could be complimented by qualitative study of feedback from carers and clinical staff.

Chapter 8. My Personal Journey with COVID-19

I just want to shed some light on some of the challenges that I had and still have during this Covid-19 pandemic, based entirely on my personal experience.

Since starting the lockdown in March 2020, it was stressful to hear about the deaths around the world. Nothing was normal, shopping was difficult, and I had to go to Tesco before opening time to shop for groceries. I was worried about my small family; however, I was reassured to learn that early data did not show Covid-19 infects children. My family in my home country were worried about me and my kids in the UK. After a few weeks, our Saudi government announced an evacuation of students and asked us to be prepared to travel. We were not sure when we would travel and this uncertainty added stress to the situation. I decided to end my contract with the house that I was living in, which was one of the best decisions that I made during the pandemic because I spent more than a year in Saudi Arabia, and I would be paying for that house if the contract was ongoing. We started to hear about people from my home country leaving the UK and staying in hotels in Saudi Arabia for two weeks in quarantine. After a few months, we received a text message about our flight for June 4th, 2020. The flight was from London, so I had to travel by car from Newcastle to London. We managed to travel in a van with a driver and we had only one stop. I cleaned the inside of the van with sanitiser, which was very difficult to find. I had a mask over my face and my kids'. Nothing was the same, the road, the gas station, the rest area, and the airport. All looked and functioned in a different way compared to my pre-pandemic experience.

After arrival in Saudi Arabia, I had to prepare a new living place for my family and get my kids to school. Due to their primary language being English, I had to put them in private school and pay for it. I could not relax and do nothing in the pandemic, and felt a responsibility to do something as a trained respiratory therapist. I was reading a lot about the disease and tried to educate people around me or on Twitter, but still I felt the need to do something else. So, I took a job in a hospital as a frontline respiratory therapist. We were very busy during the pandemic with many challenges in the hospital. CPR with chest compression was performed daily. There were times when we had limited beds, staff, or equipment. I have participated in many CPR and proning of patients. Working on the hospital during the Covid-19 crisis affected me emotionally and physically. Many patients were dying, and many were suffering. We could not stop working and we had to work more if a co-worker got the infection and needed to stay at home. I had severe pain and had to take pain medication to keep working. However, I was

happy to introduce an important change in the hospital. I developed a protocol to care for patients with Covid-19 suitable for the Saudi Arabian setting of healthcare, I also developed a project to improve standard operating procedures for tidal volume settings in the critical care units, which worked very well (see Appendix. Detailed studies summary). I served as a resource and trainer for fresh graduates. I gave a whole day teaching session about mechanical ventilation for physicians and anaesthesia technicians. I was attending daily rounds and gave input on critical patients. In addition to all these mentioned difficulties, my wife fell down the stairs and hurt her hip. She needed many visits to the hospital and multiple scans. I had to help her by taking care of her and my kids. I also had eye correction surgery and had to be away from computer and phone. I was trying to work on my PhD but, truth to be told, I was not focused, and my progression was very limited. Because of the pandemic, it was difficult to meet with experts in respiratory conditions, especially frontline healthcare providers. My supervisor, Professor Chris Ward, was extremely helpful throughout this difficult time. He was supportive and happy that I worked as a frontliner. He responded to emails quickly and was always available for online meetings. Newcastle University was supportive in giving me emotional, financial, technical, and academic support whenever needed. I am proud and honoured to be a student and, hopefully, a graduate of Newcastle University.

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Appendix. Letters of Approval

North East - Newcastle & North Tyneside 2 Research Ethics Committee
NHS BT Blood Donor Centre
Holland Drive
Newcastle upon Tyne
Tyne and Wear
NE2 4NQ

Telephone: 0207 104 8087

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

03 April 2018

Mr Maher AlQuaimi
Cookson 1.072, Floor1, Cookson Building Medical School
Newcastle University
Newcastle upon Tyne
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**
IRAS project ID:	**211628**

Thank you for your letter of 29 March 2018. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 28 March 2018

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Letters of invitation to participant [Invitation letter]	2.0	29 March 2018

Health Research Authority

Skipton House
80 London Road
London SE1 6LH

Email: hra.approval@nhs.net

Dr Ian Forrest
Consultant Respiratory Physician
Newcastle upon Tyne Hospitals NHS Foundation Trust
Department of Respiratory Medicine
Royal Victoria Infirmary Newcastle upon Tyne
NE1 4LP

04 April 2018

Dear Dr Forrest

Letter of HRA Approval

Study title:	**The feasibility of respiratory muscle training as part of an interstitial lung disease pulmonary rehabilitation programme**
IRAS project ID:	**211628**
Protocol number:	**n/a**
REC reference:	**18/NE/0037**
Sponsor	**Newcastle upon Tyne Hospitals NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further from the HRA.

How should I continue to work with participating NHS organisations in England?
You should now provide a copy of this letter to all participating NHS organisations in England, as well as any documentation that has been updated as a result of the assessment.

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA Approval.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland, Scotland and Wales?
HRA Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland, Scotland and Wales.

If you indicated in your IRAS form that you do have participating organisations in one or more devolved administration, the HRA has sent the final document set and the study wide governance

Appendix. Home exercise log

Name: *ID:* *Date of the first day:*

Exercise	W1		W2		W3		W4		W5		W6		W7		W8		
																	Achieved
																	Target
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																	Achieved
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Please, write down how many counts you did and which colour band you used in abbreviations. Y: Yellow, R: Red, G: Green, B: blue, BL: black

Appendix. Detailed studies summary

Appendix protocols in Saudi Arabia during the Covid-19 pandemic

Data collection and planning

Data were collected from current patients in ICU1 and ICU2. Data were collected by independent respiratory therapist on Sunday 12 July 2020. The tables below show the results of the data.

From the results of n=17 , 9 males ICU patients on MV only one patient non-covid. Average tidal volume per kg is (6.4 ml/kg) range (4.07 to 10.13) with 41% above 6.5 ml/kg. 17% of subjects were in PRVC mode and the rest were an PC mode.

RT staff were asked to take an online course in addition to bedside instruction by senior staff to implement strict 6 ml/kg tidal volume in COVID-19/ARDS patients. This was discussed with Dr.Taleb (ICU consultant) and he is very comfortable with the VC+ and has used it before in KFSH-D.

VC+ and or 6ml/kg strict policy mode

VC+ or PRVC is a way of delivering the breath where the ventilator will guarantee to deliver the volume with minimal possible pressure. In theory, this method of breathing could minimize the risk of barotrauma, volutrauma, and multiple mechanical ventilation changes and or blood gases. In our data collected from our hospital on Sunday 12 July 2020, only 17% (n = 3) subjects were on this mode. This could be due to lack of knowledge or experience of hospital staff about this mode of ventilation or choice of mode preference by RT or ICU doctor. If there is difficulty in setting the mode, beside RT can sit subjects on pressure control (PC) but it should be 6ml/kg ideal body weight.

.

VAP protocol

It is not uncommon for patients in ICU to develop hospital acquired infection. One of the common infections in the ICU for intubated patients is Ventilator associated pneumonia. Currently, the rate of VAP in our hospital is ****. VAP bundle is one of the best strategies to minimize rate of VAP. Currently, we use a VAP bundle but maybe it is not strictly applied or utilized. We propose to use a strict VAP bundle where a page of VAP bundle is attached in the front of patient's door and the bundle is checked every shift by in charge or head nurse. RT supervisor will also check if time allows.

The Dr. Nurse

A confident student will be a successful nurse!

THE VENTILATOR BUNDLE

Nursing interventions aimed at the prevention of ventilator associated pneumonia.

ELEVATE THE HOB

Keep HOB 30-45 dgrees. This facilitates drainage of secretions.

DAILY SEDATION "VACATIONS"

Assess the patient's mental status daily. This facilitates earlier extubation.

GI PROPHYLAXIS

GI prophylaxis medication such as Protonix prevents stress ulcers and aspiration.

DVT Prophylaxis

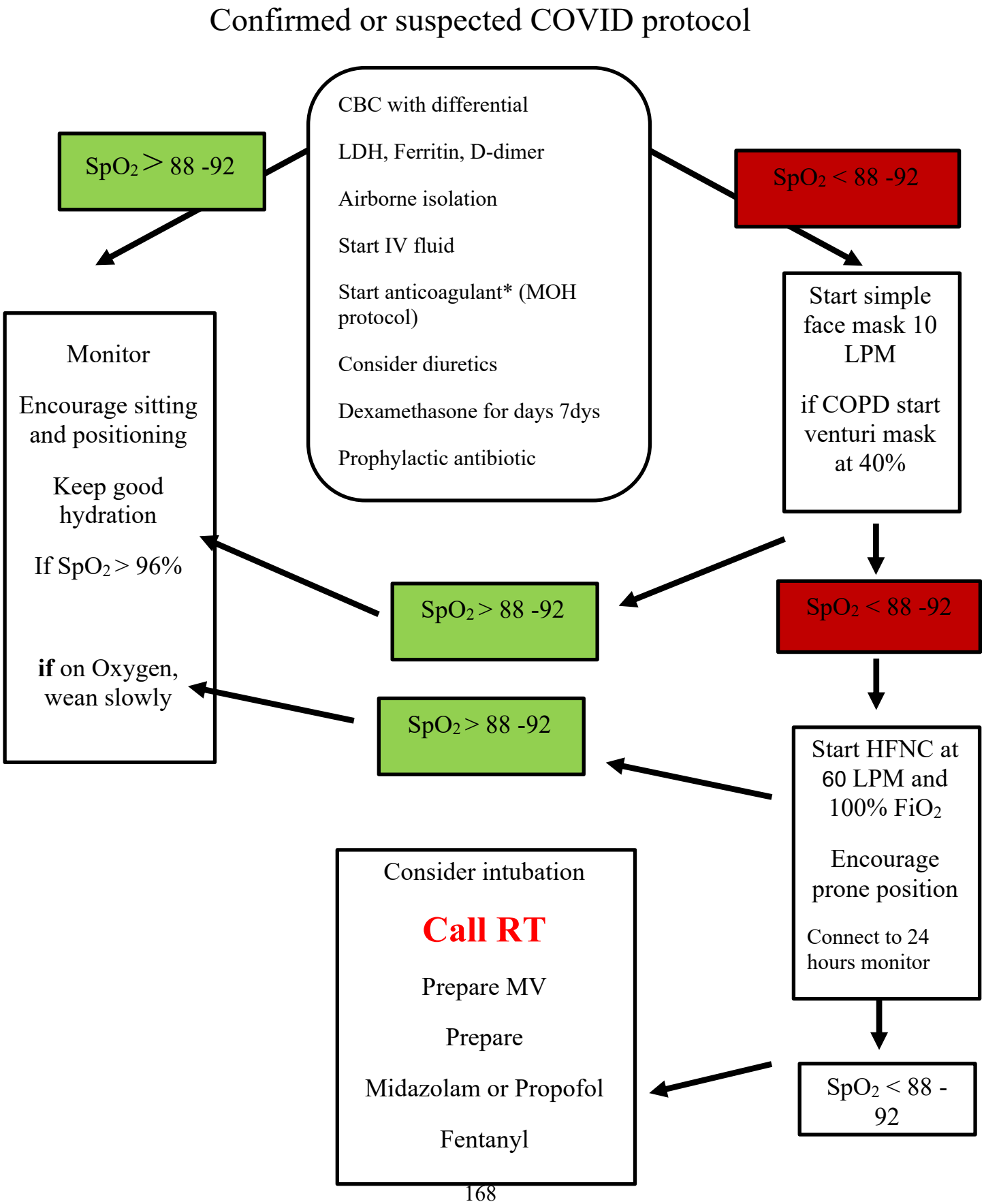
All ventilated patient's should have some form of DVT prophylaxis in place.

Oral care

Oral care should be performed at least every 2 hours.

www.thedrnurse.com

Ward COVID protocol



This protocol has been developed by Maher AlQuaimi, RT lecturer and PhD student and it was reviewed by two senior RTs from King Fahad Medical City. Also Dr.Taleb consultant ICU has reviewed it. We chose to use HFNC because it is easier and quicker to setup and use. We did not include NIV in the protocol because it takes longer time and harder to setup and could lead to more aerosol production. However, if the hospital is more comfortable, it could replace HFNC or it can be tried if HFNC failed.

Since this protocol depends heavily on SpO2, proper reading and interpretation is really essential for the success of this protocol. To improve SpO2 reading, consider the following:

Connect SpO2 to the opposite hand of patient BP cuff.

Make sure finger is straight

Make sure hand is warm, cover it if needed.

Compare HR from Spo2 to HR from ECG. It needs to be the same.

Check wave forms. It has to be large and sinusoidal waveforms.

If all fails, consider ABG.