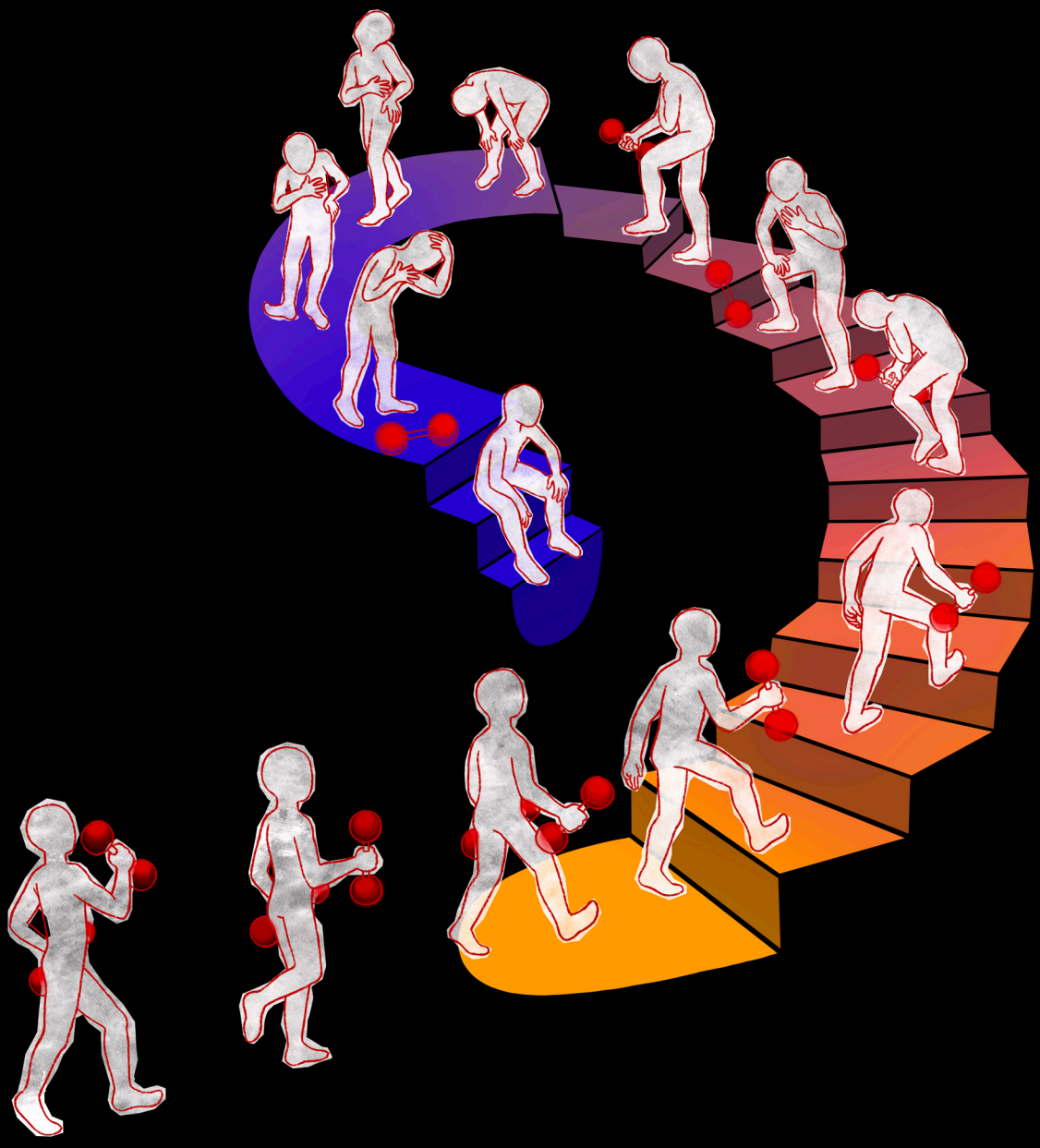
Patient-reported outcomes and functional capacity in patients with ILD



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Patiëntgerapporteerde uitkomsten en functionele capaciteit in patiënten met ILD

PROEFSCHRIFT

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‘It has long been an axiom of mine that the little things
are infinitely the most important.’

- Sherlock Holmes -

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Chapter 1

General Introduction

Introduction

Interstitial lung disease (ILD) is an umbrella term that encompasses a broad spectrum of lung diseases, most of which primarily affect the pulmonary interstitium.[1,2] ILDs exhibit a distinctive pathophysiology compared to the more commonly known obstructive lung diseases such as chronic obstructive pulmonary disease (COPD) or asthma.[3,4] However, ILD is also viewed as a large, heterogeneous group of diseases that affect the lung parenchyma via inflammation and/or fibrosis with a considerable heterogeneity in life expectancy.[5] Progressive scarring of lung tissue eventually affects ability to breathe, and exercise-induced hypoxemia affects the ability to perform physical activity.[6] As a result, patients with ILD often suffer from progressive, burdensome shortness of breath (SOB), known as dyspnoea on exertion, persistent coughing, fatigue and reduced physical function that affects both daily life and quality of life.[5,7]

Since the 19th century, knowledge about the extent, causes and consequences of human diseases and deaths worldwide has been reported via the International Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization's (WHO).[8,9] An individual's functioning and disability always takes place in a context, thus in 2001 the WHO presented the International Classification of Functioning, Disability and Health (classification of health and health-related domains), better known as ICF.[10] A person's functioning and disability were conceptualized as a dynamic interaction between health problems (diseases, disorders, etc.) and the factors that influence that functioning (medical and personal factors, and a person's physical and social environment). In short, the 'consequences of diseases' classification (1980 version) has evolved over the years into a 'components of health' classification (WHO 2001). Information on functioning and disability is essential for everyday clinical routine, for example for diagnosis, assignment to interventions, intervention management, and evaluation of treatment outcomes.[11] In today's healthcare it is important to focus on function in addition to the disease itself. This is in line with the advisory plans published by the Dutch Healthcare Institute in 2016 'Naar nieuwe zorg en zorgberoepen: de contouren'.[12]

This thesis focuses on the functioning of patients with ILD, in particular how they perceive or cope with various symptoms and perceived limitations in physical exercise capacity that affect their quality of life. The care for these patients should be based on the best available evidence, which is known as Evidence Based Practice (EBP).[13,14] EBP involves epidemiologic methods to answer a clinical question to improve practice

relevant to patient care, and is intended to improve clinical decision making in everyday healthcare.[13]

The research questions underlying this thesis are intended to support healthcare providers in more evidence informed strategies, and to better tailor care to the individual patient with ILD by adding knowledge about patients functioning and symptom burden.

Background

Interstitial lung diseases

Patients with ILD often suffer from progressive distressing dyspnoea on exertion, exercise intolerance, persistent cough, and fatigue which affects quality of life. On examination inspiratory crackles can be heard on auscultation, and impaired lung function is frequently observed.[5] The umbrella term ILD encompasses more than 200 different types of disease, from ultra rare such as Pulmonary Alveolar Proteinosis to relatively common such as sarcoidosis.[5] ILDs include diseases associated with other diseases (also connective tissue disease-related interstitial lung disease, CTD) or with environmental exposure, as well as ILDs in which the cause is unknown, the idiopathic interstitial pneumonias (IIP). In some cases, ILD is a feature of an underlying autoimmune disease, such as CTD associated ILD (e.g., rheumatoid arthritis, systemic sclerosis or Sjögren's syndrome). Also there is a subset of exposure related pulmonary interstitial disorders, such as asbestosis, silicosis and drug-induced lung injury.

ILDs can vary in clinical course from completely reversible to self-limiting to a progressive, irreversible and often fatal course in patients with pulmonary fibrosis.[1,6,15] The two most common types of ILDs of unknown etiology are IPF[16] and sarcoidosis.[17] Idiopathic pulmonary fibrosis (IPF) is the most common disease in IIP, and is characterized by chronic irreversible progressive fibrosis of the lung with a fatal outcome. Sarcoidosis is an inflammatory ILD characterized by the formation of non-caseating granulomas in potentially any organ, usually transient but variable in course, potentially leading to organ dysfunction in a minority of patients. In summary, IPF and sarcoidosis have a different underlying pathophysiology and expected disease course. As sarcoidosis is a predominant inflammatory driven disease affecting multiple organs, pulmonary fibrosis is less prominent and the disease course more heterogeneous compared to the fatal outcome in patients with IPF, if not suitable for lung transplantation.[18] However, a subgroup of patients with sarcoidosis is also characterized by progressive fibrosis.[19]

Idiopathic pulmonary fibrosis

IPF is a chronic, fibrosing interstitial pneumonia of unknown cause that is characterized by radiological and histologic pattern of usual interstitial pneumonia (UIP).[20] It occurs primarily in adults older than 50 years (the median age at diagnosis is 65 years) and is more common in men.[21] A widely supported model of IPF pathogenesis is the combination of repetitive injury and an aberrant repair of the injured alveolus leading to the formation of interstitial fibrosis resulting in progressive fibrosis, and a deterioration of lung function.[22,23] Patients with IPF report progressive breathlessness, dry cough, fatigue and worsening of dyspnoea on exercise, resulting in a declining physical functional capacity over time.[21] The disease course is variable and unpredictable and has a poor prognosis, with a median survival time from diagnosis of 2 to 4 years if untreated.[16,24] The prevalence of IPF in Europe is 10-40 cases per 100,000 with an incidence of 1-9 cases per 100,000 per year.[22] Before the era of antifibrotic medication, starting in 2014, there were no effective medical treatment options for most patients with IPF other than lung transplant. However, lung transplant is only an option for a minority of patients with IPF.[21] In 2014 the US Food and Drug Administration and European Medicines Agency (EMA) approved two antifibrotic agents for the treatment of IPF, which slow down the rate of decline in lung function and show an increase in median survival in patients with IPF.[25-28]

Sarcoidosis

Sarcoidosis is an inflammatory systemic disease of unknown etiology that is characterized by the formation of non-necrotizing granulomas.[29] Although granulomas can occur in any organ, there is a predilection for lungs and intrathoracic lymph nodes.[30,31] Pulmonary sarcoidosis is the most common manifestation of sarcoidosis (more than 90% of patients with sarcoidosis) and the most established diagnosis in the group of ILDs.[32] Sarcoidosis can affect people of all ages but mostly develops in young and middle-aged adults before the age of 50 years.[33] Worldwide it is estimated to affect 2-160/100,000 people and has 5 year mortality rate of approximately 7%.[34,35] In the Netherlands the prevalence is estimated to be 50 per 100,000 with an incidence of 10 to 20 per 100.000 persons a year.[36] Unfortunately, some patients with sarcoidosis develop sarcoidosis-associated pulmonary fibrosis.[37] The prognosis of sarcoidosis varies enormous, partly dependent on clinical presentation, extent of disease and genetic profile.[29,38] Patients may experience organ-related symptoms, such as in pulmonary sarcoidosis, for example persistent cough and shortness of breath that become more common as the disease progresses, in cardiac sarcoidosis, for example abnormal heart rhythms, fainting and chest pain, and in neurosarcoidosis, for example, symptoms of

loss of control, resulting in problems speaking, swallowing or moving limbs.[17,39,40] Apart from organ-related symptoms patients may suffer from a wide range of non-organ specific symptoms such as depressive symptoms, anxiety and stress, cognitive and/or physical impairments and lack of energy.[39] A prominent reported complaint in sarcoidosis is fatigue with a prevalence of 50-90%.[41,42] Fatigue is often persistent even in the absence of evidence of disease activity.[43] The etiology is poorly understood and likely to be multifactorial (encompassing possible active inflammation, cytokine release, physical and/or psychosocial status, comorbidities and overall health).[41,44] Fatigue next to exercise intolerance and muscle weakness can substantially influence patient's daily activities and affect quality of life (QoL).[39,45,46] Also not organ specific symptoms were reported by patients with sarcoidosis in three European countries (n >1000) associated with small fiber neuropathy (SFN).[42,47,48] Prevalence of SFN in patients with sarcoidosis ranges between 60-86% and may contribute to a poor health-related quality of life (HRQL).[42,49]

This thesis has a two-fold structure with two main research paths. We examine the functioning of patients with ILD using original patient data. One path draws particular attention to the symptoms experienced in patients with IPF or sarcoidosis, with special attention to fatigue and fatigue perceptions and whether these patients are activated to self-management strategies. This path uses health outcomes reported directly by the patient, so-called patient-reported outcomes (PROs which will be discussed in the next paragraph). The other path focuses on exercise capacity tested by the 6-minute walk test (6MWT) and performance tests in patients with pulmonary fibrosis, also discussed in the next paragraph.

Symptom burden in IPF or sarcoidosis

A PRO is defined as: "Any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else".[50] Self-report questionnaires are instruments to measure PROs.[51] Physicians traditionally deal with the physical health related aspects of IPF or sarcoidosis, assessing disease activity and severity with imaging, lung function and blood tests. The patients' input is important for understanding the effect of disease and its treatment on patients' daily lives. What matters most to patients are measures to express their symptom burden, improve survival and QoL.[52] In IPF, the reduced QoL is closely associated with the worsening of shortness of breath, fatigue and/or coughing, which gradually limits the ability to perform even routine physical activities.[53] In addition,

patients deal with uncertain future expectations. Patients with sarcoidosis can also exhibit fatigue, social dysfunction, depression and emotional problems, all of which impact the QoL.[54] To provide a complete assessment of patients' needs, it is important to measure PROs in addition to traditional outcomes.[55] The use of information from PROs in both clinical practice and research leads to better communication and decision making between physicians and patients, provides more insight in the patients' needs and improves patient satisfaction with care.[56,57]In our research within the PROs, we focused on symptom burden, in particular the prevalence of burdensome fatigue.

Fatigue: prevalence and perceptions

Patients with IPF or sarcoidosis frequently complain of fatigue, even patients with sarcoidosis in clinical remission.[43,58] Although breathlessness and cough are the main symptoms of pulmonary fibrosis patients, fatigue is another bothersome, yet often overlooked, non-respiratory symptom in clinical practice and research.[59] Thus, fatigue, defined as the subjective feeling of tiredness or exhaustion[60], may be a common and clinically relevant symptom in patients with pulmonary fibrosis or sarcoidosis.[41,61]Across chronic disease conditions, patients consistently described fatigue as persistent overwhelming tiredness, severe lack of energy, and physical weakness that worsened over time.[62] Fatigue differs from tiredness, which is a common symptom experienced by everyone and includes both physical and mental components.[60] However (comparatively), the impact of persistent and severe fatigue in (chronic) clinical conditions can be pervasive, difficult and disabling for patients.[62]

Fatigue in sarcoidosis has previously been studied, and prevalence varies between 50-80% of patients.[58,63] The prevalence of severe fatigue in patients with IPF had not been studied extensively until the last decade. In 2014, the Food and Drug Administration held a public meeting to hear perspectives from people living with pulmonary fibrosis about their disease, its impact on their daily life, and currently available therapies.[64] More than 50% of the patients with pulmonary fibrosis identified fatigue as being one of their most significant symptoms, manifesting in a variety of ways such as physical fatigue, muscle fatigue, persistent lack of energy, and overall malaise. One participant identified fatigue as being a constant difficulty for her, saying, "the fatigue really weighs on you you're completely exhausted".[65] Fatigue is associated with a lower QoL, the perceived seriousness of illness, exercise intolerance and symptoms of depression.[65-67] Fatigue is associated with physical inactivity, irrespective of the degree of lung function impairment. Furthermore, exercise capacity and fatigue are the stron-

gest independent predictors of physical inactivity in patients with pulmonary fibrosis.[68] Particularly given the limited efficacious pharmacological therapies for pulmonary fibrosis, improvement in QoL is an important focus in management of patients with pulmonary fibrosis.[1,69] Fatigue reduction in patients with pulmonary fibrosis is one of the most important aspects to consider to improve quality of life.

In addition to the prevalence of fatigue, the perception of fatigue can vary from person to person. Healthy individuals use a variety of adjectives to describe fatigue such as normal, pleasant, relaxing, fulfilling and temporary.[70] Patients with chronic conditions often use negative adjectives such as frustrating, exhausting, upsetting and frightening.[62,70] When managing fatigue in patients with IPF or sarcoidosis, it is necessary to know more about the different perceptions of fatigue to enable a more targeted approach to fatigue management. In addition to fatigue, patients with IPF or sarcoidosis may also suffer from other non-respiratory symptoms.[39,61] However, most studies lack a control group and no previous studies made the comparison between the patient and the control subjects for a broad range of respiratory and non-respiratory symptoms.

Patient activation for self-management

The impact of a serious chronic illness and the obstacles associated with it change the way the patient copes with the disease and adjusts his or her daily activities accordingly.[71] Living with IPF or sarcoidosis significantly affects QoL, with negative consequences for general health and social and psychosocial well-being.[5,39,66] The challenge for the individual is to deal with the consequences inherent to the disease. The individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent to living with their chronic condition is all part of the patient's self-management to try to maintain a satisfactory quality of life.[72,73] To manage one's health, one must have the knowledge, skills and confidence to become an activated patient to meet the challenges of self-management.[74] Patient activation indicates the level of involvement in self-management. Knowing patients' level of activation for self-management seems clinically relevant, as self-management increasingly becomes part of their own disease management.[12,74] The Patient Activation Measure (PAM) was designed to assess this level of patient activation.[75] The PAM can be used to determine which stage of patient activation applies to the individual patient: believe that an active role is important, have confidence and knowledge to take action, take action and continue healthy behavior under tension. In patients with IPF or sarcoidosis there is a lack of information about the level of activation for self-management. Therefore, it is necessary to understand which factors may play a role in patient activation in self-management.

Exercise field tests

In patients with pulmonary fibrosis associated symptoms, an exercise test can be used to provide insight into shortness of breath on exertion at an early stage of the disease and to quantify possible exercise limitation.[68,76] The cardiopulmonary exercise test (CPET) is able to accurately determine the maximum exercise capacity (Wmax) of the individual patient and to establish exercise-limiting factors and pathophysiologic mechanisms.[77] Specific indications for CPET in ILD are detection of early (occult) gas exchange abnormalities, magnitude of exercise-induced hypoxemia and determination of potential exercise limiting factors.[78,79]Alteration of gas exchange is a major abnormality which is thought to reflect the severity of fibrotic process, and abnormal values for arterial blood gases during exercise are likely to be the most sensitive manifestations of lung disease with impaired oxygenation uptake.[80,81] Although CPET was recommended in the ATS/ERS guidelines for pulmonary rehabilitation[82], it is not recommended in the guidelines of management of patients with IPF.[20] CPET measurements are often time-consuming and costly, and significant functional exercise capacity and/or exercise-induced gas exchange can also be readily identified by the 6MWT.[83,84] Assessment of functional capacity has gained importance in understanding the impact of disease and development of disease management strategies as pulmonary rehabilitation for patients with ILD. The 6MWT is currently one of the most widely used clinical tests of functional exercise capacity in people with pulmonary fibrosis.[87]

The 6MWT is subject to the execution protocol of the test: The result of the 6MWT depends on the protocol as the distance walked is highly sensitive to variations in methodology (tester encouragement, patient use of supplemental oxygen and/or walker use, changes in track layout and length).[84] Due to a learning effect on repetition, two measurement procedures are necessary[80,86], however the test-retest reliability of the 6MWT performed on one day in patients with pulmonary fibrosis remained unknown. The functional performance tests, the 4-meter-gait-speed (4MGS)[87] test and the 5-repetitions-sit-to-stand (5STS)[88,89] test have measuring protocols that are simple to implement, reliable and inexpensive. Both tests have been validated in healthy adults and patients with COPD.[90,91] The 4MGS test and 5STS test have not been studied in patients with pulmonary fibrosis and might be valid in pulmonary fibrosis for objectifying functional exercise capacity. If more practical and shorter performance tests could serve as a simple replacement for the regular 6MWT, this could potentially reduce the burden for a patient with pulmonary fibrosis compared to performing a 6MWT. In addition it would put less strain on the limited capacity of the healthcare system. These simple functional performance tests could then be introduced into daily general practice.

Prognostic value of 6MWT

Next to the dynamic CPET, the 6MWT also contains exercise parameters that predict survival within the IPF population.[92] Tests that are predictive of adverse outcomes can aid clinical decision-making, such as lung transplant referral, the need for oxygen therapy, or starting palliative care. Known predictors of mortality from the 6-minute walk test-derived characteristics in patients with IPF are exercise-induced desaturation of ≤88%[93], or a maximum walk distance in 6 minutes less than 250 m.[94] However, the treatment of patients with IPF changed substantially when antifibrotic drugs, a disease-modifying therapy, were introduced in 2014.[95] These antifibrotic drugs have shown to slow the rate of lung function decline and meant a longer life expectancy for the patients with IPF.[25,28,95] At present, antifibrotic treatment is seen as standard of care in patients with IPF.[96,97] In 2012, a negative recommendation was made for a widely used treatment for IPF, a combination therapy of prednisone, azathioprine and N-acetylcysteine (NAC). This was a result of a randomized, double-blind, placebo-controlled trial which showed an increased risk of death and hospitalization in patients with IPF treated with this drug combination as compared with placebo.[98] Chronic corticosteroid treatment is now known to contribute to muscle weakness in ILD patients.[99,100] However, the aforementioned predictive values established for the 6MWT in IPF were all determined before the change in clinical practice regarding the use of antifibrotic drugs instead of immunosuppressive drugs.[94,101] Furthermore, the two-year mortality prediction of 6MWT has never been established in a large, well-defined IPF cohort in the era of antifibrotics and has never been done before in a Dutch cohort. Predicting mortality is important for the patient with IPF to enable appropriate life planning decisions and for clinical management when referral to a transplant center is considered.[102] Well-known predictors of prognosis are gender, age and lung physiology variables such as Forced Vital Capacity (FVC) and diffusion capacity (DLCO) which can be combined in a prediction model such as the gender-age-physiology (GAP) index.[103] For the prognostic assessment, the reduced exercise capacity and exercise-induced hypoxemia measured at the 6MWT could be complementary. [94,104]

Scope and outline of this thesis

This thesis addresses two important themes regarding patients with ILD. First of all, prevalence and symptom burden are studied in patients with IPF and sarcoidosis with a specific focus on fatigue and the capability of self-management in these patients. Second, different aspects of the 6MWT in patients with IPF are studied such

as reliability and prognostic value and the correlation with less time consuming tests (validity) such as 4MGS and 5STS.

This dissertation therefore has a twofold structure. The first part, **chapter 2-5**, outlines the patient-reported outcomes fatigue prevalence and perceptions, symptoms burden, and activation for self-management in patients with pulmonary fibrosis or sarcoidosis. The second part, **chapter 6-8**, outlines exercise capacity in patients with IPF, in terms of content, the test-retest reliability of the 6MWT, the validity of performance tests 4MGS or 5STS and the prognostic values of the 6MWT.

The specific research objectives were formulated as follows:

- to determine the prevalence of severe fatigue in patients with IPF or pulmonary sarcoidosis, and to evaluate the association between fatigue and clinical parameters **(Chapter 2)**;
- to assess the different perceptions of fatigue in IPF or pulmonary sarcoidosis, to evaluate the association between the different perceptions of fatigue and clinical parameters, and to assess determinants related to general health **(Chapter 3)**;
- to assess a wide range of respiratory and non-respiratory symptoms in patients with IPF or pulmonary sarcoidosis, and to compare these with control subjects with normal spirometric values **(Chapter 4)**;
- to determine the level of patient activation for self-management in patients with IPF or sarcoidosis, to compare clinical characteristics between patients with low or high levels of patients activation for self-management per disease, and to investigate the association between patient activation levels, clinical characteristics and health-related outcomes **(Chapter 5)**;
- to assess the test–retest reliability of the 6MWT when performed within one day in patients with pulmonary fibrosis **(Chapter 6)**;
- to determine the validity of the 4MGS and the 5STS patients with pulmonary fibrosis, and to assess whether these performance tests, alone or with other office-available performance tests, contribute to explain the variances in the 6MWD in patients with pulmonary fibrosis **(Chapter 7)**;
- to assess the prognostic value of 6MWT-derived attributes on 2-years-transplant-free survival in a real-world cohort of well-defined patients with IPF, and
- to investigate whether and to what extent 6MWT-derived attributes contribute to the predictive value of GAP-model in patients with IPF **(Chapter 8)**.

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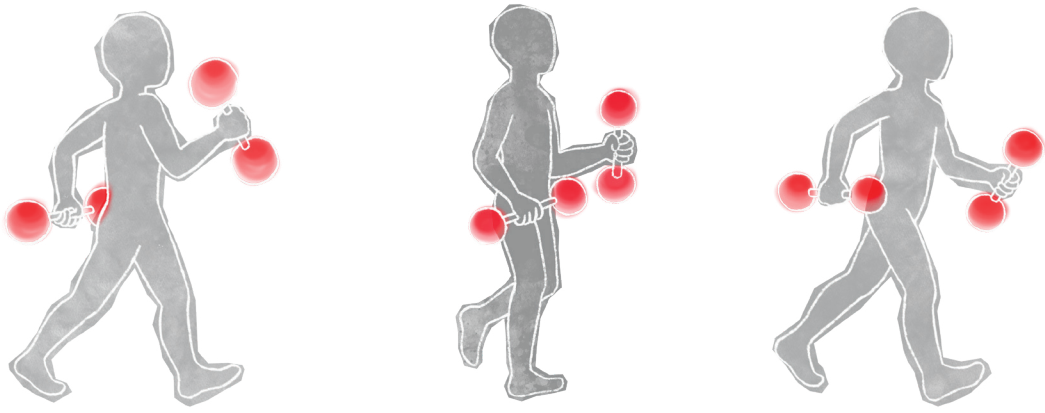

Chapter 2

Severe fatigue is highly prevalent in patients with IPF or sarcoidosis

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Abstract

In patients with interstitial lung disease (ILD) next to dyspnoea, fatigue is expected to be the most prevalent symptom. Surprisingly, the prevalence of severe fatigue has been scarcely studied in ILD patients and limited information on its associated factors is available.

This study aimed to determine the prevalence of severe fatigue in patients with idiopathic pulmonary fibrosis (IPF) or pulmonary sarcoidosis and to identify the relationship between fatigue, patient characteristics, and clinical parameters.

In this cross-sectional study, fatigue (checklist individual strength-fatigue (CIS-Fat)), demographics, lung function, dyspnoea (modified-Medical Research Council (mMRC)), sleepiness (Epworth Sleepiness Scale), anxiety/depression (hospital anxiety and depression scale (HADS-A/HADS-D)), catastrophizing (fatigue catastrophizing scale (FCS)), functional activity impairment (respiratory illness quality-of-life (QoL-RIQ-Activity)), and health status (EuroQol five-dimensional descriptive system (EQ-5D-5L)) were assessed in outpatients with ILD.

Mean CIS-Fat scores were 34.1 (SD ± 11.2) in 59 IPF patients and 40.0 (12.3) in 58 sarcoidosis patients. Severe fatigue (SD ± ≥36 points) was present in IPF patients (47.5%) and sarcoidosis (69%). In IPF, CIS-Fat correlated strongly ($\rho > 0.5$; $p < 0.01$) with FCS, QoL-RIQ-Activity, and EQ-5D-5L-Health and moderately ($0.3 < \rho < 0.5$; $p < 0.01$) with EQ-5D-5L-Index, mMRC, and HADS-D. In sarcoidosis, CIS-Fat correlated strongly with EQ-5D-5L-Health, QoL-RIQ-Activity, EQ-5D-5L-Index, HADS-D, and mMRC and moderately with FCS and hospitalization <12 months.

Severe fatigue is highly prevalent in ILD patients and is associated with dyspnoea, depression, catastrophizing, functional activity impairments, and QoL.

Keywords: fatigue; interstitial lung disease; idiopathic pulmonary fibrosis; sarcoidosis

Introduction

Patients with interstitial lung disease (ILD) experience common and distressing respiratory symptoms, e.g., dyspnoea on exertion and a cough.[1,2] Moreover, fatigue, which is defined as the subjective feeling of tiredness or exhaustion[3], is assumed to be present and affects ILD patients' quality of life (QoL) significantly. [4–6]

Two common forms of ILD are idiopathic pulmonary fibrosis (IPF) and sarcoidosis. More than 50% of the patients with IPF reported fatigue as being one of their most significant symptoms, which can manifest in a variety of ways, such as physical fatigue, including muscle fatigue, persistent lack of energy, and overall malaise.[7] The prevalence of severe fatigue in patients with IPF has not been studied extensively. A previous study in patients with sarcoidosis demonstrated that severe fatigue occurred in 47.9% of the patients, of which about two-thirds of the patients had pulmonary sarcoidosis.[8] A similar percentage of severe fatigue was present in patients in clinical remission of sarcoidosis in another study. [9]

The etiology of severe fatigue is poorly understood and likely to be multifactorial. Fatigue is significantly associated with a patient's health status, reduced physical condition, and functional impairments, irrespective of the degree of lung function impairment. [4,10–12] Fatigue may be affiliated by dyspnoea[13,14], daytime sleepiness[14,15] (characterized by difficulty staying awake and alert during the day)[16], symptoms of anxiety and/or depression, and fatigue-related catastrophizing.[4,7] Fatigue might be an adverse event of systemic medication used to treat ILD.[17,18] Severe fatigue can have many different causes and is assumed to negatively affect QoL. Severe fatigue will most probably require patient-tailored treatment due to the (combination of) many perpetuating factors.[19] Hence, it is necessary and clinically relevant to study the relationship between severe fatigue and possible underlying factors in patients with ILD.

Therefore, the aims of the present study were (1) to determine the prevalence of severe fatigue in patients with ILD and (2) to evaluate the association between fatigue and clinical parameters.

Materials and Methods

Study Design and Participants

This cross-sectional prospective clinical study took place in the outpatient clinic of the Department of Respiratory Medicine, Zuyderland Medical Centre Heerlen (The Netherlands) between May 2018 and March 2019. Patients (age ≥18 years) were eligible to participate with a confirmed diagnosis of IPF [2,20] or pulmonary sarcoidosis [21,22], visiting the outpatient department of the chest physician for usual care. Exclusion criteria were insufficient understanding of the Dutch language and/or inability to complete questionnaires because of cognitive impairment or participating at the same time in an intervention study that may have impacted the outcome of this study. Eligible participants were invited by the chest physician (RM) and received a written explanation of the study. Subsequently, the nurse practitioner (NS) informed participants about the research protocol, including instructions to fill in the forms and the data extraction from patient electronic medical records. After giving written informed consent, participants received paper-based questionnaires to be filled out. The study protocol was approved by the Medical Research Ethics Committee of the institution (METCZ20180027) and registered at the Netherlands Trial Register (Trialcode7201).

Measures

Fatigue

Experience of fatigue was assessed by the subscale fatigue of the checklist individual strength-fatigue (CIS-Fat).[23] The CIS-Fat is a standardized and validated questionnaire that has been used in healthy subjects and among various patient populations. [24–26] The CIS-Fat consists of eight items scored on a seven-point Likert scale, with a total range from 8 to 56 points. A score of points ≤26 indicates normal fatigue, between 27–35 mild fatigue, and a score of ≥36 severe fatigue.[23,26]

Medical Information

Data extracted from the electronic medical record were: age (years), diagnosis, comorbidities, smoking pack-years, medication, resting transcutaneous oxygen saturation (SpO_2; %), oxygen supplementation (yes/no), last available (within the preceding three months) spirometry (forced vital capacity, forced expiratory volume in one second; Liter, % predicted), static lung volumes (total lung capacity, residual volume; Liter, % predicted), and diffusing capacity for carbon monoxide (TLCO; % predicted).[27]

Demographic Data

All participants provided information on their gender (man/woman), height (m), weight (kg), partner (yes/no) and living status (alone/cohabiting), education level ("low educated" meaning maximum preparatory vocational education and "educated" meaning minimal secondary or higher), diagnosis history of the lung disease (years) and hospitalization in the past year (yes/no), working history in the previous two years (yes/no), a history of psychological support (yes/no), smoking status (never, former smoker, current smoker), and the amount of caffeine and alcohol (units per day) consumption.

Symptom and Limitation Measures

The modified Medical Research Council (mMRC) dyspnoea scale was used to classify the severity of dyspnoea. The categorizing levels ranged from 0 ("normal") to 4 ("too breathless to leave the house")[28,29] Daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS).[30] The ESS consists of eight questions with a score from 0 (never) to 3 (always), with a total score ranging from 0–24 points; a score of 11 points or higher represents excessive daytime sleepiness (EDS) and normative values are known.[31] From the Quality-of-Life for Respiratory Illness Questionnaire, the general activities of the domain "functional impairment" were assessed (QoL-RIQ/activity).[32] This activity list contains four questions presenting the impairment in activity due to breathing problems. A higher score in the 7-level score (between "no burden at all" to "a lot of burden") indicated more impairment.

Psychological Measures

Symptoms of anxiety and depression were scored using the well-validated Hospital Anxiety and Depression Scale (HADS).[33,34] This scale is divided into a subscale anxiety (HADS-A) and a subscale depression (HADS-D), both containing seven intermingled items. Each item is rated on a four-point scale, ranging from 0 to 3 points, with 3 points indicating higher symptom frequency. Total scores for each subscale range from 0 to 21 points, categorized as: normal/mild (0–10 points) and moderate/severe (11–21 points, meaning a clinically significant case of anxiety or depression).[33]

Catastrophizing has been defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience"[35], The fatigue catastrophizing scale (FCS) was used as a measure of fatigue-related catastrophizing. The FCS was modified from the pain catastrophizing scale (PCS)[36–38] by replacing the term "pain" with "fatigue" where relevant. The FCS consists of 13 items scored from 0 to 4 points (ranging from 0, "Not at all", to 4, "All the time") with a total possible score of 52 points. The higher the score, the more catastrophizing of fatigue was present. The cutoff >30 points has been shown to be associated with clinical relevance.[39]

The attribution of possible causes from the patient point-of-view was assessed with the causal attribution list (CAL).[40] The CAL comprises two subscales of "physical" (5 items) and "non-physical" (6 items) causes. Scoring items were divided into "not agree", "slightly agree", "strong agree", and "totally agree". Item scores were combined into one total score and one score for each of the subscales, whereby a stronger causal attribution was indicated by a higher score.

Health Status

The EuroQol five-dimensional descriptive system (EQ-5D-5L) comprises two forms; a 5-dimension list (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with a 5-level classification (no problems, slight, moderate, severe, extreme problems) and the EQ-visual analogue scale (EQ-VAS). The patient was asked to indicate his health state in each dimension (1-digit number). The total result was reported as a 5-digit number that describes the patient's health state. The digit number IIIII indicated no problems in each dimension. Additionally, the results were converted into an index value (EQ-5D-5L-Index). The EQ-VAS recorded the patient's self-rated health on a vertical visual analogue scale, where the endpoints were labelled from O ("worst imaginable health") to 1OO points ("best imaginable health").[41–43]

Statistical Analyses

Statistical analysis was performed using IBM SPSS Statistics (Version 25). Patients' characteristics were presented with appropriate measures of central tendency and dispersion. Numerical data were tested for normality by a mean-median ratio, SD-mean ratio, and judging histogram.[44] Differences between groups for continuous data were analyzed by an unpaired t-test or the non-parametric pendant (Mann–Whitney U test) where appropriate. Categorical data were analyzed with the Chi-square or Fisher Exact test. A p-value of ≤0.05 was considered as statistically significant. Correlations were calculated by Pearson's r or when the assumptions were violated by Spearman's rho. In case of missing values, cases were excluded pairwise. The range for what constitutes a weak, moderately strong, strong, or very strong correlation was respectively $0.1 \leq r < 0.3$, $0.3 \leq r < 0.5$, $0.5 \leq r < 0.7$, and $0.7 \leq r < 1.0$[46,47] (level of significance $p < 0.05$). A multivariable model was conducted to assess the associations between the dependent variable QoL-RIQ/activity and independent in univariate analysis significant variables ($p < 0.01$). In case of multicollinearity, identified variables (variance inflation factor (VIF) > 5) were removed from the model.[47]

Results

Patient Characteristics

A total of 121 Patients with ILD volunteered to participate (92% of invited patients with IPF, 42% of invited patients with sarcoidosis). Four participants were excluded due to the absence of a fully completed CIS-Fat questionnaire. Participants (n = 117) were diagnosed with IPF (n = 59, 50%), of which 26% were classified as a severe disease (forced vital capacity (FVC) <50% and/or TLCO <40% predicted[48]) or sarcoidosis (n = 58, 50%). In this ILD sample, there was a male predominance (62%), the median age was 66 years, and the mean body mass index (BMI) was slightly elevated (27.6 kg/m2). Overall, the patients were well educated (64% secondary level education or higher), had a partner (74%), and a smoking history (59%; 8.5 pack-years). A total of 50% reported a daily coffee consumption of ≥3 cups per day, and 42% reported ≥1 units of daily alcohol consumption. Most patients had one or more comorbidity but had no differences after stratification for degree of fatigue severity. For detailed differences between patients with IPF or sarcoidosis see **Table 1 and 2**.

Prevalence of Severe Fatigue

Patients with ILD (n = 117) had a mean CIS-Fat score of 37.0 (SD12.1) points, of which 58% had severe fatigue (CIS-Fat ≥36 points, n = 68). Patients with IPF had a significantly lower mean CIS-Fat score (34.1 points, SD11.2) compared to patients with sarcoidosis (40 points, SD12.3) (p < 0.01). In addition, severe fatigue was prevalent in 48% of patients with IPF (n = 28) and in 69% of patients with sarcoidosis (n = 40) **(Table 1)**.

Factors Associated with Severe Fatigue in Patients with IPF

The group of IPF patients with severe fatigue had a significantly higher proportion of men (89.3% vs 64.5%), higher daily coffee consumption (71.4% vs 40.0% ≥3 cups a day), lower mean diffusion capacity (45.0% vs 53.0% TLCO % predicted), and reported more dyspnoea (64.3% vs 37.9% mMRC grade ≥2) **(Figure 1a)** compared to IPF patients with normal/mild fatigue **(Table 1)**. Spirometry results were not related to fatigue severity **(Table 1)**. The depression score on the HADS (5.0 vs 3.0 points) and the result of the FCS (21.0 vs 5.0 points) were different between patients with and without severe fatigue, respectively. Patients with severe fatigue versus normal/mild fatigue felt more impaired in functional activities (15.0 vs 11.0 points QoL-RIQ/activity),

and QoL scores were lower (0.67 vs 0.80 points EQ-5D-5L-Index, 55.0 vs 71.0 points EQ-5D-5L-Health-today; indication IIIII was not reported) **(Table 3)**.

Factors Associated with Severe Fatigue in Patients with Sarcoidosis

Patients with sarcoidosis and severe fatigue compared to those with sarcoidosis and normal/mild fatigue were significantly ($p < 0.05$) less educated (30% vs 0% school level "low"), had visited a psychologist more often (42.5% vs 11.1%), and had a higher average of smoking pack-years (5.7 vs 0.9 pack-years), but no significant differences in lung function results were present **(Table 1)**. Sarcoidosis patients with severe fatigue reported significantly more severe dyspnoea (49.0% vs 6.3% mMRC) **(Figure 1b)** and excessive sleepiness (21.1% vs 0% EDS) **(Table 2)**. Anxiety and depression scores were significantly higher in sarcoidosis patients with severe fatigue compared to those with normal-to-mild fatigue (5.0 vs 3.0 points HADS-A, 6.0 vs 1.0 points HADS-D). In addition, scores on catastrophizing were significantly higher (11.5 vs 4.0 points FCS). Moreover, patients with severe fatigue versus normal/mild fatigue felt more impaired in activities (15.0 vs 6.0 points QoL-RIQ/activity), and QoL scores were lower (0.68 vs 0.89 points EQ-5D-5L-Index, 55.3 vs 81.2 points EQ-5D-5L-Health-today; indication IIIII was reported by 8% of the patients).

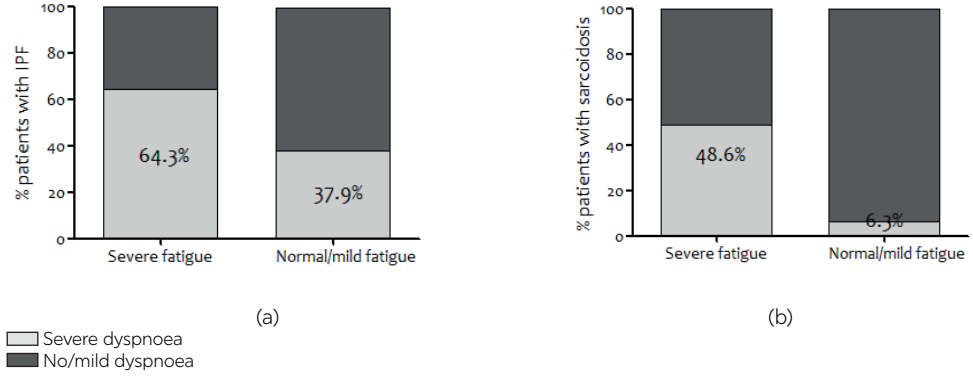

Figure 1: *(a) Prevalence of patients with idiopathic pulmonary fibrosis (IPF) with no/mild dyspnoea (Modified-Medical Research Council (mMRC) <2) or severe dyspnoea (mMRC ≥2) after stratification for the degree of fatigue (checklist individual strength-fatigue (CIS-Fat) mild/moderate <36 and severe >35). (b) Prevalence of patients with sarcoidosis with no/mild dyspnoea (mMRC <2) or severe dyspnoea (mMRC ≥2) after stratification for the degree of fatigue (CIS-Fat mild/moderate <36 and severe >35).*

Table 1: General characteristics of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF), and sarcoidosis, stratified for fatigue severity in normal/mild or severe fatigue based on the checklist individual strength-fatigue (CIS-Fat) questionnaire

Variables	Patients with ILD (Total group)	Patients with IPF	Fatigue Severity in IPF Patients			Patients with Sarcoidosis	Fatigue Severity in Sarcoidosis Patients			IPF – Sarcoidosis
			Normal/Mild Fatigue <36	Severe Fatigue Fatigue ≥36 p	p-Value		Normal/Mild Fatigue <36 p	Severe Fatigue Fatigue ≥36 p	p-Value	p-Value
n (%)	117	59 (50.4)	31 (52.5)	28 (47.5)		58 (49.6)	18 (31.0)	40 (69.0)		
CIS-Fat	37.0 ± 12.1	34.1 ± 11.2	25.5 ± 7.2	43.5 ± 5.8	p < 0.01	40.0 ± 12.3	24.9 ± 8.5	46.7 ± 6.2	p < 0.01	p < 0.01
General Characteristics										
Gender (male, %)	73 (62.4)	45 (76.3)	20 (64.5)	25 (89.3)	p < 0.05*	28 (48.3)	12 (66.7)	16 (40.0)	ns	p < 0.01*
Age (years, IQR)	66.0 (53.5–74)	73.0 (70.0–78.0)	72.0 (70.0–77.0)	73.0 (70.3–78.8)	ns	53.5 (45.8–62.0)	55.5 (48.8–66.0)	51.5 (43.8–59.8)	ns	p < 0.01
Weight (kg)	82.2 ± 14.7	81.4 ± 14.8	82.7 ± 16.1	80.0 ± 13.4	ns	83.0 ± 14.6	84.5 ± 9.5	82.3 ± 16.5	ns	ns
BMI[a] (kg/m2)	27.6 ± 4.2	27.6 ± 4.1	28.1 ± 4.4	27.0 ± 3.8	ns	27.6 ± 4.2	27.2 ± 3.1	27.7 ± 4.7	ns	ns
Partner (n, %)	86 (73.5)	43 (72.9)	23 (74.2)	20 (71.4)	ns	43 (74.1)	15 (83.3)	28 (70.0)	ns	ns
Living together (n, %)	80 (68.4)	39 (66.1)	21 (67.7)	18 (64.3)	ns	41 (70.7)	15 (83.3)	26 (65.0)	ns	ns
Education[b] ≥secondary level (n, %)	73 (63.5)	27 (47.4)	13 (41.9)	14 (53.8)	ns	46 (79.3)	18 (100.0)	28 (70.0)	p < 0.05#	p < 0.01
Diagnosis time ≤1 year (n, %)	36 (31.3)	21 (36.2)	12 (40.0)	9 (32.1)	ns	15 (26.3)	4 (23.5)	11 (27.5)	ns	ns
Hospitalization ≤1 year (n, %)	24 (20.7)	14 (23.7)	7 (22.6)	7 (25.0)	ns	10 (17.5)	1 (5.6)	9 (22,5)	ns	ns
Work last 2 years (n, %)	48 (41.0)	12 (20.3)	7 (22.6)	5 (17.9)	ns	36 (62.1)	13 (72.2)	23 (57.5)	ns	p < 0.01
Psychological support (n, %)	27 (23,1)	8 (13.6)	5 (16.1)	3 (10.7)	ns	19 (32.8)	2 (11.1)	17 (42.5)	p<0.05#	p < 0.05
Smoking[a] current/former (n, %)	68 (58.6)	46 (78.0)	23 (74.2)	23 (82.1)	ns**	22 (38.6)	5 (29.4)	17 (42.5)	ns**	p < 0.05**
Pack-years[+] (n)	8.5 ± 15.1	13.5 ± 18.1	12.2 ± 16.4	15.1 ± 20.3	ns	4.0 ± 9.8	0.9 ± 2.6	5.7 ± 11.8	p < 0.05	p < 0.01
Coffee[++b] cup ≥3 (n, %)	58 (50.4)	32 (55.2)	12 (40.0)	20 (71.4)	p < 0.05*	26 (45.6)	9 (52.9)	17 (42.5)	ns	ns
Alcohol[++b] glass ≥1 (n, %)	48 (41.7)	24 (41.4)	12 (40.0)	12 (42.9)	ns	24 (42.1)	9 (52.9))	15 (37.5)	ns	ns
Spirometry, static lung volumes, and diffusing capacity										
TLC[e] (liter)	5.2 ±1.4	4.6 ± 1.1	4.4 ± 1.1	4.7 ± 1.1	ns	6.0 ± 1.3	6.3 ± 1.2	5.8 ± 1.3	ns	p < 0.01
TLC[f] (% predicted)	85.3 ± 20.8	73.3 ± 14.3	72.6 ± 12.9	74.1 ± 16.0	ns	98.6 ± 18.8	96.5 ± 12.6	99.6 ±21.2	ns	p < 0.01
RV[d] (liter)	1.8 ± 0.5	1.6 ± 0.4	1.5 ± 0.4	1.7 ± 0.3	ns	2.0 ± 0.6	2.0 ± 0.6	2.0± 0.5	ns	p < 0.01
RV[h] (% predicted)	80.3 ± 26.6	64.4 ± 13.8	63.3 ± 14.5	65.6 ± 13.3	ns	98.0 ± 26.2	90.8 ± 18.0	101.3 ± 28.9	ns	p < 0.01
FVC (liter)	3.4 ± 1.1	2.9 ± 0.8	2.8 ± 0.8	3.0 ± 0.9	ns	3.9 ± 1.1	4.1 ± 1.1	3.8 ± 1.1	ns	p < 0.01
FVC (% predicted)	90.7 ± 21.6	83.2 ± 19.6	83.5 ± 18.7	82.9 ± 20.8	ns	98.2 ± 21.1	100.9 ± 16.3	97.0 ± 23.1	ns	p < 0.01
FEV1 (liter)	2.6 ± 0.8	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	ns	3.0 ± 0.9	3.1 ± 0.9	2.9 ± 0.9	ns	p < 0.01

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Table 1: General characteristics of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF), and sarcoidosis, stratified for fatigue severity in normal/mild or severe fatigue based on the checklist individual strength-fatigue (CIS-Fat) questionnaire *(Continued)*

FEV1 (% predicted)	89.5± 20.7	87.3 ± 20.9	89.3 ± 22.1	84.9 ± 19.5	ns	91.9 ± 20.5	94.1 ± 17.6	90.9 ± 21.8	ns	ns
TLCO [c] (liter)	5.5 ± 2.4	3.9 ± 1.3	4.2 ± 1.5	3.6 ± 1.0	ns	7.3 ± 2.0	7.8 ± 2.0	7.1 ± 2.0	ns	p < 0.01
TLCO [d] (% predicted)	65.1 ± 23.2	49.1 ± 14.7	53.0 ± 15.4	45.0 ± 12.8	p < 0.05	82.2 ± 18.0	86.6 ± 17.2	80.1 ± 18.2	ns	p < 0.01
Comorbidities										
Comorbidity (n, %)					ns**				ns**	p < 0.05**
none	44 (37.6)	15 (25.4)	9 (29.0)	6 (21.4)		29 (50.0)	10 (55.6)	19 (47.5)		
1	42 (35.9)	25 (42.4)	13 (41.9)	12 (42.9)		17 (29.3)	3 (16.7)	14 (35.0)		
>1	31 (26.5	19 (32.2)	9 (29.0)	10 (35.7)		12 (20.7)	5 (27.8)	7 (17.5)		
Medication										
IPF: antifibrotic (n, %)		51 (86.4)	27 (87.1)	24 (85.7)		0 (0.0)	0 (0.0)	0 (0.0)		p < 0.01*
Nintenadib (n, %)		17 (33.3)	9 (33.3)	8 (33.3)	ns					
Pirfenidon (n, %)		34 (66.7)	18 (66.7)	16 (66.7)	ns					
Immunosuppressant[+++] (n, %)	27 (23.1)	5 (8.5)	0 (0.0)	5 (17.9)	p < 0.05#	22 (37.9)	5 (27.8)	17 (42.5)	ns	p < 0.01*
Heart rate-lowering medication (n, %)	23 (19.7)	15 (25.4)	9 (29.0)	6 (21.4)	ns	8 (13.8)	3 (16.7)	5 (12.5)	ns	ns
Antidepressant medication (n, %)	6 (5.1)	5 (8.5)	1 (3.2)	4 (14.3)	ns	1 (1.7)	0 (0.0)	1 (2.5)	ns	ns
Antihypertensive medication (n, %)	37 (31.6)	25 (42.4)	16 (51.6)	9 (32.1)	ns	12 (20.7)	4 (22.2)	8 (20.0)	ns	p < 0.05*
Other medication for pulmonary conditions (n, %)	38 (32.5)	7 (11.9)	2 (6.5)	5 (17.9)	ns	31 (53.4)	7 (38.9)	24 (60.0)	ns	p < 0.01*

Data is presented as mean ± SD, median (IQR) or number (%). p-value in bold indicates p < 0.05: Pearson Chi-square; # Fisher's exact test; **Mann–Whitney U Test. [+] Pack-year, number of years smoking x average number of cigarettes smoked per day/20. [++] number of consumed cups/glasses a day. [+++] Immunosuppressant including prednisone (corticosteroids). Alphabetic characters in superscript indicates a sample size deviant from n = 117, in the order: [a] n = 116, [b] n = 115, [c] n = 112, [d] n = 110, [e] n = 109, [f] n = 108,. Abbreviations: arbitrary units (au); body mass index (BMI; kg/m2); checklist individual strength (CIS); forced expiratory volume in one second (FEV1); forced vital capacity (FVC); interstitial lung disease (ILD); included (incl.); idiopathic pulmonary fibrosis (IPF); interquartile range (IQR); number of subjects (n); not significant (ns); residual volume (RV); residual volume to total lung capacity ratio (RV/TLC Ratio); total lung capacity (TLC); transfer factor of the lung for carbon monoxide (measured in ml/min/mm Hg) (TLCO).*

Table 2: Comorbidities of patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis, stratified for fatigue severity.

Variables	Patients with ILD (Total group)	Patients with IPF	Fatigue Severity in IPF Patients			Patients with Sarcoidosis	Fatigue Severity in Sarcoidosis Patients			IPF – Sarcoidosis
			Normal/Mild Fatigue <36	Severe Fatigue Fatigue ≥36 p	p-Value		Normal/Mild Fatigue <36 p	Severe Fatigue Fatigue ≥36 p	p-Value	p-Value
n (%)	117	59 (50.4)	31 (52.5)	28 (47.5)		58 (49.6)	18 (31.0)	40 (69.0)		
CIS (p, 8–56	37.0 ± 12.1	34.1 ± 11.2	25.5 ± 7.2	43.5 ± 5.8	p < 0.01	40.0 ± 12.3	24.9 ± 8.5	46.7 ± 6.2	p < 0.01	p < 0.01
General Characteristics										
Comorbidity										
Comorbidity (n, %)					ns**				ns**	p < 0.05**
none	44 (37.6)	15 (25.4)	9 (29.0)	6 (21.4)		29 (50.0)	10 (55.6)	19 (47.5)		
1	42 (35.9)	25 (42.4)	13 (41.9)	12 (42.9)		17 (29.3)	3 (16.7)	14 (35.0)		
>1	31 (26.5)	19 (32.2)	9 (29.0)	10 (35.7)		12 (20.7)	5 (27.8)	7 (17.5)		
Comorbidity ≥1 (n, %)	73 (62.4)	44 (74.6)	22 (71.0)	22 (78.6)	ns*	29 (50.0)	8 (44.4)	21 (52.5)	ns*	p < 0.01*
Comorbidities										
Hypertension (n, %)	22 (18.8)	17 (28.8)	9 (29.0)	8 (28.6)	ns*	5 (8.6)	1 (5.6)	4 (10.0)	ns#	p < 0.01*
Pulmonary hypertension (n, %)	2 (1.7)	2 (3.4)	0 (0.0)	2 (7.1)	ns#	0 (0.0)	0 (0.0)	0 (0.0)	-	n s#
COPD/asthma (n, %)	6 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	-	6 (10.3)	1 (5.6)	5 (12.5)	ns#	p < 0.05#
Cardiac failure (n, %)	12 (10.3)	6 (10.2)	3 (9.7)	3 (10.7)	ns#	6 (10.3)	4 (22.2)	2 (5.0)	ns#	ns*
Cardiac sarcoidosis (n, %)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	-	1 (1.7)	1 (5.6)	0 (0.0)	ns#	ns#
Cardiac surgery CABG and/or Heart Valve (n, %)	8 (6.8)	6 (10.2)	4 (12.9)	2 (7.1)	ns#	2 (3.4)	1 (5.6)	1 (2.5)	ns#	ns#
Diabetes Mellitus (n, %)	12 (10.3)	8 (13.6)	3 (9.7)	5 (17.9)	ns#	4 (6.9)	2 (11.1)	2 (5.0)	ns#	ns#
OSAS (n, %)	4 (3.4)	3 (5.1)	1 (3.2)	2 (7.2)	ns#	1 (1.7)	1 (5.6)	0 (0.0)	ns#	ns#
Eyes-Uveitis (n, %)	5 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	-	5 (8.6)	2 (11.1)	3 (7.5)	ns#	p < 0.05#
TIA/CVA (n, %)	7 (6.0)	5 (8.5)	1 (3.2)	4 (14.3)	ns#	2 (3.4)	1 (5.6)	1 (2.5)	ns#	ns#
Carotid artery stenosis/sPAD (n, %)	6 (5.1)	5 (8.5)	2 (6.5)	3 (10.7)	ns#	1 (1.7)	0 (0.0)	1 (2.5)	ns#	ns#
Other comorbidities (n, %)	36 (30.8)	20 (33.9)	13 (41.9)	7 (25.0)	ns*	16 (27.6)	4 (22.2)	12 (30.0)	ns#	ns*

*Data is presented as mean ± SD, number (%). p-value in bold indicates a significant difference: * Pearson Chi-square; # Fisher's exact test; **Mann–Whitney U Test. Abbreviations: coronary artery bypass grafting (CABG); checklist individual strength (CIS); chronic obstructive pulmonary disease (COPD); cerebrovascular accident (CVA); idiopathic pulmonary fibrosis (IPF); interquartile range (IQR); number of subjects (n); obstructive sleep apnea syndrome (OSAS); symptomatic peripheral arterial disease (sPAD); transient ischemic attack (TIA).*

Table 3: Questionnaire results of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF) or sarcoidosis, stratified for fatigue severity.

Variables	Patients with ILD (Total group)	Patients with IPF	Fatigue Severity in IPF Patients			Patients with Sarcoidosis	Fatigue Severity in Sarcoidosis Patients			IPF – Sarcoidosis
			Normal/Mild Fatigue <36	Severe Fatigue Fatigue ≥36 p	p-Value		Normal/Mild Fatigue <36 p	Severe Fatigue Fatigue ≥36 p	p-Value	p-Value
n (%)	117	59 (50.4)	31 (52.5)	28 (47.5)		58 (49.6)	18 (31.0)	40 (69.0)		
CIS (p, 8–56	37.0 ± 12.1	34.1 ± 11.2	25.5 ± 7.2	43.5 ± 5.8	p < 0.01	40.0 ± 12.3	24.9 ± 8.5	46.7 ± 6.2	p < 0.01	p < 0.01
Dyspnoea										
mMRC-Dyspnoea grade [g] range 0–4 (p, IQR)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	2.0 (1.0–3.0)	ns**	1.0 (1.0–2.0)	0.5 (0.0–1.0)	1.0 (1.0–2.0)	p < 0.05**	p < 0.05**
mMRC [g] grade ≥2 (moderate-severe dyspnoea) (n, %)	48 (43.6)	29 (50.9)	11 (37.9)	18 (64.3)	p < 0.05	19 (35.8)	1 (6.3)	18 (48.6)	p < 0.05	ns
Sleepiness										
ESS [i] (p, IQR, 0–24)	5.0 (4.0–8.0)	5.0 (4.0–8.0)	4.0 (3.0–7.0)	5.5 (4.0–8.3)	ns	5.0 (4.0–8.0)	5.0 (3.8–6.0)	6.5 (3.8–10.0)	ns	ns
ESS > 10 excessive [i] (n, %)	9 (8.4)	1 (2.0)	0	1 (4.5)	ns	8 (14.3)	0	8 (21.1)	p < 0.05#	p < 0.05#
Anxiety and Depression										
HADS anxiety [e] range 0–21 (p, IQR)	5.0 (2.0–7.8)	5.0 (2.0–8.0)	4.0 (2.0–7.8)	6.0 (4.0–8.0)	ns	4.0 (2.0–7.0)	3.0 (2.0–5.3)	5.0 (3.0–8.0)	p<0.05**	ns
(HADS anxiety ≥11points) [e] (n, %)	12 (10.7)	5 (9.1)	2 (7.1)	3 (11.1)	ns	7 (12.3)	2 (11.1)	5 (12.8)	ns	ns
HADS depression [c] range 0–21 (p, IQR)	4.5 (2.0–7.0)	5.0 (2.0–7.0)	3.0 (2.0–6.5)	5.0 (4.0–8.0)	p< 0.05**	4.0 (1.0–7.0)	1.0 (1.0–3.5)	6.0 (3.0–8.0)	p<0.01**	ns
(HADS depression ≥11 points) c (n, %)	9 (7.9)	5 (8.9)	2 (6.9)	3 (11.1)	ns	4 (6.9)	0	4 (10.0)	ns	ns
Fatigue-related Catastrophizing										
FCS f (p, IQR)	11.0 (3.0–23.0)	11.0 (2.0–26)	5.0 (0.3–14.5)	21.0 (11.0–28.5)	p < 0.01**	10.0 (3.8–18.0)	4.0 (0.0–11.5)	11.5 (6.5–23.0)	p < 0.01**	ns
FCS [f] grade >30 (n, %)	13 (11,7)	7 (13.2)	2 (7.1)	5 (20)	ns	6 (10.3)	0	6 (15.0)	ns	ns
Causal Attributions of Fatigue										
CAL[g] Sum score (p, 11–44)	18.3 ± 5.1	18.4 ± 4.5	17.8 ± 4.5	19.2 ± 4.5	ns	18.3 ± 5.6	17.6 ± 6.8	18.6 ± 5.0	ns	ns
CAL Physical Sum [d] (p, 5–20)	9.4 ± 3.4	9.7 ± 3.1	9.1 ± 3.0	10.4 ± 3.1	ns	9.1 ± 3.7	7.9 ± 4.0	9.6 ± 3.5	ns	ns
CAL Non-Physical Sum [e] (p, 6–24)	8.9 ± 2.9	8.6 ± 2.4	8.7 ± 2.6	8.5 ± 2.1	ns	9.2 ± 3.3	9.6 ± 4.1	9.0 ± 3.0	ns	ns
Quality of Life Respiratory Illness (Functional Impairment)										
QoL-RIQ/activity [h] (p, IQR)	13.0 (8.0–17.0)	14.0 (10.3–17.0)	11.0 (8.0–15.0)	15.0 (13.0–20.0)	p < 0.01**	10.5 (7.0–16.8)	6.0 (4.0–9.0)	15.0 (9.0-18.0)	p < 0.01**	p < 0.05**
Quality of Life, Health Status										
EQ-5D-5L [a], index values (p, 0–1)	0.74 ± 0.20	0.74 ± 0.18	0.80 ± 0.16	0.67 ± 0.17	p < 0.01	0.75 ± 0.23	0.89 ± 0.14	0.68 ± 0.23	p < 0.01	ns
EQ-5D-5L[b], VAS (p, 0–100)	63.1 ± 18.1	63.3 ± 16.5	71.0 ± 15.6	55.0 ± 13.4	p < 0.01	63.0 ± 19.7	81.2 ± 11.5	55.3 ± 17.2	p < 0.01	ns

*Data is presented as mean ± SD, median (IQR), or number (%). p-value in bold indicates a significant difference: * Pearson Chi-square; # Fisher's exact test; **Mann–Whitney U Test. Alphabetic characters in superscript indicate a sample size deviant from n = 117, in the order: [a] n = 116, [b] n = 115, [c] n = 114, [d] n = 113, [e] n = 112, [f] n = 111, [g] n = 110, [h] n = 108, [i] n = 107. [1] IIIII. [2] Answer option "not applicable" is out of score. Abbreviations: Acceptance of Disease and Impairments Questionnaire (ADIQ); checklist individual strength (CIS); EuroQol, 5 dimensions, 5 levels (standardized measure of health status) (EQ-5D-5L); Epworth Sleepiness Scale (ESS); fatigue catastrophizing scale (FCS); hospital anxiety and depression scale (HADS); interstitial lung disease (ILD); included (incl.); idiopathic pulmonary fibrosis (IPF); interquartile range (IQR); modified Medical Research Council (mMRC) dyspnoea scale; number of subjects (n); points (p); Quality of Life for Respiratory Illness Questionnaire (QoL-RIQ/activity), domain "functional activity impairment", list "general activities".*

Correlations of Fatigue

Significant correlations (moderately strong or strong) with the CIS-Fat score were found in patients with IPF for drinking coffee (cups a day) ($r = 0.269$; $p < 0.05$), forced expiratory volume in one second (FEV1)% predicted ($r = -0.329$; $p < 0.05$), TLCO% predicted ($r = -0.324$; $p < 0.05$), mMRC ($\rho = 0.374$; $p < 0.01$), HADS-A ($\rho = 0.281$; $p < 0.05$), HADS-D ($\rho = 0.369$; $p < 0.01$), FCS ($\rho = 0.572$; $p < 0.01$), QoL-RIQ/activity ($\rho = 0.544$; $p < 0.01$), EQ-5D-5L-Index value ($\rho = -0.414$; $p < 0.01$), EQ-5D-5L-Health today ($\rho = -0.529$; $p < 0.01$).

In patients with sarcoidosis from significant moderate to strong correlations with the CIS-Fat score were found with hospitalization <12 months ($\rho = 0.359$; $p < 0.01$), mMRC ($\rho = 0.535$; $p < 0.01$), ESS ($\rho = 0.282$; $p < 0.05$), HADS-A ($\rho = 0.264$; $p < 0.05$), HADS-D ($\rho = 0.556$; $p < 0.01$), FCS ($\rho = 0.481$; $p < 0.01$), CAL-physical ($\rho = 0.392$; $p < 0.01$), QoL-RIQ/activity ($\rho = 0.604$; $p < 0.01$), EQ-5D-5L-Index value ($\rho = -0.577$; $p < 0.01$), EQ-5D-5L-Health today ($\rho = -0.710$; $p < 0.01$) were found.

Determinants of Functional Impairment QoL-RIQ/Activity

The following significant correlations ($p < 0.01$) with the QoL-RIQ/activity for patients with IPF or sarcoidosis were identified: mMRC ($\rho = 0.608$; $\rho = 0.667$), HADS-D ($\rho = 0.582$; $\rho = 0.611$), FCS ($\rho = 0.639$; $\rho = 0.533$), CIS-Fat ($\rho = 0.544$; $\rho = 0.604$), causal attribution list (CAL)-physical ($\rho = 0.490$; $\rho = 0.650$).

The stepwise multiple regression model in IPF explained 65.7% of variance in QoL-RIQ/activity (adjusted $R2 = 0.657$; Std Error of the Estimate 3.245; $p < 0.01$), whereby significant predictors were: FCS (50.1%), CIS-Fa (10.1%), and mMRC (5.5%) (regression equation QoL-RIQ/activity = 2.438 + 0.161*FCS + 0.182*CIS-Fat (scale) + 1.403* mMRC).

In sarcoidosis, multiple regression modelling explained 66.8% of variance in QoL-RIQ/activity (adjusted R2 0.67, Std Error of the Estimate 3.533; $p < 0.01$), with the significant predictors mMRC (43.7%), CAL-Physical (17.4%), and FCS (5.7%) (regression equation QoL-RIQ/activity = −0.086 + 1.965*mMRC + 3.620*CAL-Physical + 0.156*FCS).

Discussion

This study clearly shows that severe fatigue was present in a substantial proportion of patients with ILD; in 48% of patients with IPF and 69% of patients with pulmonary sarcoidosis. Furthermore, fatigue was significantly associated (ρ > 0.3) with dyspnoea, depression, fatigue-related catastrophizing, activity impairments, and quality-of-life.

Severe Fatigue in Patients with IPF or Sarcoidosis

Severe fatigue has been observed frequently in patients with chronic obstructive pulmonary disease (COPD) (ranging between 41 to 75%)[49–51], asthma (62%)[52], or cancer survivors (range from 7% to 52%).[53] The current findings of severe fatigue of 48% and 69% in patients with IPF or sarcoidosis, respectively, fit well. This is significantly higher compared with elderly non-COPD subjects, of which 10% report severe fatigue.[54,55] Interestingly, severe fatigue was more prevalent in the sarcoidosis patients than in the IPF patients, despite the fact that the sarcoidosis group consisted of fewer men, was younger of age, was higher educated, had worked the last two years, had more psychological support, had more never smokers, and had less comorbidities.

Factors Associated with Fatigue in Patients with IPF or Sarcoidosis

Overall, the sarcoidosis patients had a mildly impaired lung function, which did not correlate with fatigue. Previous findings in patients with sarcoidosis[56], COPD[50], or asthma[52] showed that the forced vital capacity was not different between patients with and without severe fatigue, suggesting that the degree of lung function impairment does not play a major role in the development and/or maintenance of severe fatigue. In contrast, FEV1% predicted and TLCO% predicted were moderately correlated with CIS-Fat in the IPF patients, and severely fatigued patients had a significant lower diffusion capacity (p < 0.05) vs no/mild fatigue. Sheth et al.[57] found in patients with IPF that a low diffusion capacity and a higher fatigue score were independent predictors of frailty. Frailty was not assessed in the current study. However, these data may suggest that patients with IPF with a low diffusion capacity and who report severe fatigue are at risk of becoming frail.

Similar to patients with COPD, more patients with IPF or sarcoidosis with severe fatigue experienced severe dyspnoea (mMRC ≥2) than those with normal/mild fatigue.[13] Indeed, in IPF, severe dyspnoea was present in 64% of the patients with severe fatigue and in 49% of the patients with sarcoidosis.

Although the terms "fatigue" and "sleepiness" are often used interchangeably, both phenomena are distinct.[58] Bosse-Henck[14] studied excessive daytime sleepiness (defined as ESS ≥ 16) and severe fatigue (Fatigue Assessment Scale ≥35 points) in sarcoidosis patients and found sleepiness and/or fatigue in 27% of their sample. In the current study, ESS values were not different to the normative value[31], although EDS (ESS > 10) was more present in sarcoidosis patients with severe fatigue (21%) than in IPF patients with severe fatigue (5%). However, severe fatigue was obviously more present in both groups (58%) compared to EDS (8%), which suggests poor sleep quality may not be the main driver of severe fatigue in ILD patients.

It is known that in patients with chronic respiratory diseases, symptoms of anxiety and depression are common.[59,60] In the current study, the patients with severe fatigue had significantly higher anxiety (sarcoidosis) and depression (IPF, sarcoidosis) scores vs normal/mild fatigue. These findings affirmed the findings of respectively 12% and 7% in a tertiary referral clinic for ILD.[60]

The current study shows that catastrophizing is moderate to strong, correlated to fatigue, which is a novel finding. Indeed, the relation of catastrophizing to fatigue has not been investigated before in patients with ILD. Catastrophizing may contribute to increased intensity of symptom experience[35] and, in chronic pain, catastrophizing is a prospective marker for the risk of severe disability.[61] Catastrophizing can influence the experience of fatigue and seems to be a good predictor of fatigue severity.[62] Catastrophizing might be of great importance to consider, because if patients avoid activity by negative attention, this might decrease their physical functioning. Moreover, patients with IPF or sarcoidosis experienced high subjective impairments in activity and significantly more in those patients with severe fatigue.

Although objective measurements of functional capacity in this study are lacking, different aspects (both cognitive as perceptive) were pointed out to play an important role of this experienced impairment in activity. Indeed, dyspnoea (IPF, sarcoidosis), fatigue (IPF), fatigue-related catastrophizing (IPF, sarcoidosis), and causal attributions scores (sarcoidosis) explained 66% (IPF) and 67% (sarcoidosis) of the variance of the perceived impairment in activity (QoL/RIQ-activity).

Limitations and Strength

This study had several methodological considerations. First, the sample group of patients with ILD was restricted to patients with IPF and pulmonary sarcoidosis only, and only patients were included who were visiting the outpatient consultation of an ILD-specialized pulmonologist (RM). This may limit the external validity of the current findings. The reason of the lower response rate on the invitation letter of patients with sarcoidosis (42%) vs patients with IPF (92%) is unknown. Second, as is known, predictors of physical activity are the exercise capacity and fatigue in patients with ILD[56,63], but the study setting and funding did not allow us to assess physical functioning, such as a 6 min walk distance and peak aerobic capacity. Therefore, it remains unknown whether and to what extent a lower level of physical functioning may explain, at least partially, the presence of severe fatigue in patients with ILD. Third, in patients with COPD only receiving usual care, the proportion of patients with severe fatigue doubles over a period of 4 years.[49] The current cross-sectional study design did not allow us to assess possible changes in fatigue over time. Fourth, the generic EQ-5D-5L is not an ILD-specific questionnaire for QoL and consequently it does not capture disease-specific effects of ILD. However, the EQ-5D-5L is validated in patients with different lung diseases (COPD, ILD) and will make comparisons between patients with different lung diseases and the general population possible.[64,65]

The strength of the study was the sample size of 117 patients with IPF or sarcoidosis. Next to dyspnoea, severe fatigue has now been indicated highly prevalent in patients with IPF or sarcoidosis. A broad range of patient characteristics, psychological, behavioral, and health factors, including dyspnoea, sleepiness, anxiety, depression, fatigue-related catastrophizing, functional impairment, and quality-of-life, were collected, which provided unique new insights into severe fatigue. For clinical management, it is important to know about this.

Finally, fatigue is a multidimensional phenomenon and just a part of all possible associated factors were investigated, consequently a patient-tailored treatment advice to reduce fatigue based on this study is not possible. Longitudinal prospective studies, including patient characteristics, psychological aspects, and physical functioning, are required for a better understanding of severe fatigue in IPF and sarcoidosis and to explore its long-term impact on quality-of-life.

Conclusions

To conclude, fatigue is an important symptom in patients with ILD, and ILD patients with severe fatigue experienced more severe dyspnoea, sleepiness, anxiety, depression, fatigue-related catastrophizing, functional activity impairments, and a lower QoL. In clinical management of patients with ILD, it is recommended to assess fatigue, catastrophizing thoughts, and causal attributions of fatigue, because these elements together with dyspnoea are related to the functional impairments in activities of the patients.

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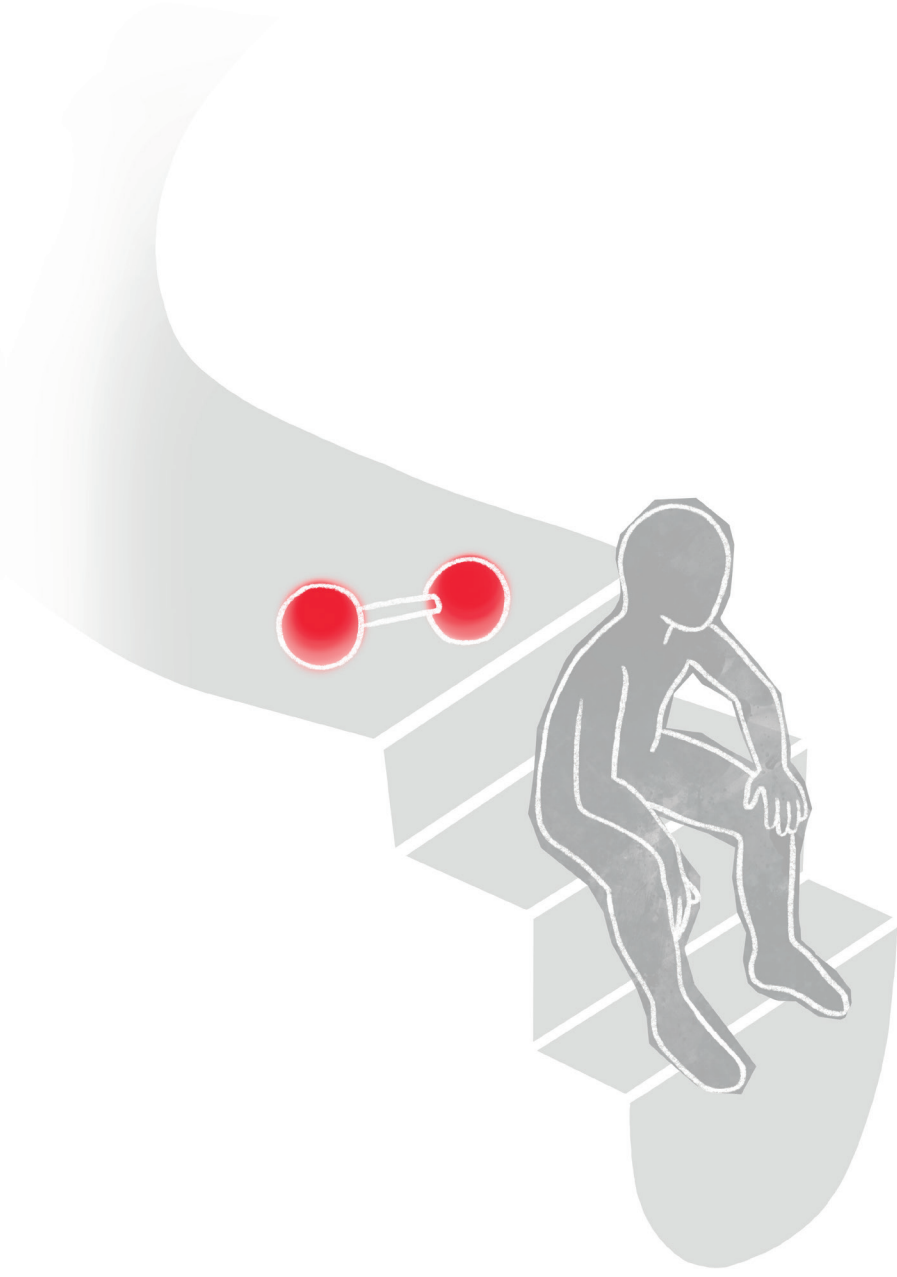

Chapter 3

Perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis

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Abstract

Background: Fatigue is highly prevalent in patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis. However, the difference in fatigue perceptions for these patients is unknown and this may be important to better understand what fatigue means to the individual patient.

Methods: This cross-sectional quantitative study aims to determine the different perceptions of fatigue as 'frustrating', 'exhausting', 'pleasant', 'frightening' using the Fatigue Quality List and to assess determinants related to these perceptions of fatigue. Beside the fatigue quality connotations, demographics, lung function, fatigue severity (Checklist Individual Strength subscale Fatigue), dyspnoea (modified-Medical Research Council), fatigue catastrophizing (Fatigue Catastrophizing Scale), anxiety/depression (Hospital Anxiety and Depression Scale) and general health status (EuroQoL 5-dimension 5-level) were assessed.

Results: Mean frequency score of fatigue-related perceptions in patients with IPF was 3.4 points and in patients with sarcoidosis 4.0 points. Severely fatigued patients with IPF reported their fatigue less 'pleasant' significantly more often than patients without severe fatigue. Fatigue severity, dyspnoea, catastrophizing and general health were significantly correlated with the negative connotations categories of the Fatigue Quality List in patients with IPF. Severely fatigued sarcoidosis patients reported their fatigue perceptions significantly more often as 'frustrating', 'exhausting', 'frightening' and less 'pleasant' than patients without severe fatigue. Moreover, in patients with sarcoidosis fatigue severity, dyspnoea, catastrophizing and depression were significantly associated with all four categories of the Fatigue Quality List that describe the experienced fatigue ($p<0.05$).

Conclusions: The current findings of experiences of fatigue in patients with IPF or pulmonary sarcoidosis provide insights for professionals treating these patients. Although similarities were found in the several experiences of fatigue across non-severely and severely fatigued patients, differences were also evident and could be mapped for IPF and sarcoidosis.

Keywords: Idiopathic pulmonary fibrosis (IPF); sarcoidosis; fatigue; perceptions

Introduction

Idiopathic pulmonary fibrosis (IPF) and sarcoidosis are diseases belonging to the interstitial lung diseases (ILDs). ILDs comprise a large group of respiratory disorders affecting the interstitium of the lungs.[1, 2] Although ILDs include diseases with different pathophysiology and prognostics, most patients with ILD experience similar symptoms as shortness of breath, fatigue, dry cough and impaired exercise tolerance. It is known that fatigue is highly prevalent in patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis.[1,2,3,4,5,6] To date, no data are available about the different perceptions of fatigue in these patients. This, however, may be important to create a better understanding of what fatigue means to the individual patient, and to determine whether or not it is a possible target for intervention.

The perception of fatigue can differ between individuals. For example, healthy individuals use adjectives such as normal, pleasant, relaxing, fulfilling and temporary to describe fatigue.[7] Contrary, patients with different chronic conditions (i.e., chronic fatigue syndrome, neuromuscular diseases, pancreatitis, post-cancer fatigue, rheumatoid arthritis and chronic obstructive pulmonary disease) more often use negative adjectives such as frustrating, exhausting, upsetting and frightening.[7, 8, 9]

The degree of fatigue severity may, at least partially, influence the perception of fatigue. Indeed, patients with severe fatigue describe their fatigue more often as frustrating or exhausting, whereas non-severely fatigued patients perceived their fatigue as normal.[7, 8] Additionally, symptoms of breathlessness, anxiety/depression and catastrophic thoughts of fatigue may also have contributed to the different experiences of fatigue. [9, 10] IPF and sarcoidosis are two different chronic pulmonary diseases in pathophysiological perspective, in which IPF is an fatal disease with progressive fibrosing of the lung with only some delay by antifibrotic medication and sarcoidosis is characterized by granulomatous inflammation with possible immunosuppressant therapy.[1, 2] Severe fatigue was present 48% of patients with IPF and 69% in patients with sarcoidosis, but the differences in perceptions remained unclear.

To find out more about the perceptions of fatigue in patients with IPF or sarcoidosis, the aims of this study were: (I) to assess the different perceptions of fatigue in IPF or pulmonary sarcoidosis; (II) to evaluate the association between the different perceptions of fatigue and clinical parameters; and (III) to assess determinants related to general health. We present the following article in accordance with the SURGE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-462).

Methods

Study design and participants

In the period between May 2018 and March 2019, patients (age ≥18 years) with a confirmed diagnosis of IPF [2, 11] or pulmonary sarcoidosis [12, 13] were invited to participate in this cross-sectional clinical fatigue study.[6] The study setting was at the outpatient clinic of the Department of Respiratory Medicine, Zuyderland Medical Centre Heerlen (The Netherlands). Patients were excluded if one of the following issues occurred: insufficient understanding of the Dutch language and/or inability to complete questionnaires due to cognitive impairment, or simultaneous participation in a potentially conflicting intervention study. Before this study (no funding) started, Medical Ethical Committee approval was granted (METCZ20180027) and registration with the Netherlands Trial Register (Code 7201) was established. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The study protocol was in short: The chest physician (RM) invited eligible patients during the regular outpatient visit to participate in the study and he provided them with the written explanation. After that, patients met the nurse practitioner (NS) for complementary information of study participation and, if partaking, written informed consent; All participations were given a unique code (NS). Study participation involved completing the paper-and-pencil questionnaires directly or at home after a reflection period; The one-time participation was on a voluntary basis. Data were collected from medical records (NS) to provide information on: age (years), gender (man/woman), diagnosis, comorbidities, smoking pack-years (average packs smoked per day × duration of smoking, in years), medication, last available (within the preceding three months) spirometry (forced vital capacity, forced expiratory volume in one second; Liter, % predicted), static lung volumes (total lung capacity, residual volume; Liter, % predicted), and diffusing capacity for carbon monoxide (TLCO; % predicted).[14]

Measures

Experiences of fatigue

The primary outcome measure was the difference in the experiences of fatigue. For the multidimensional perceptions of fatigue inventory the Fatigue Quality List (FQL) was used. The short form FQL consists of single choice questions (yes/no) for 18 adjectives (FQL-Adjectives) belonging to one of the FQL-categories 'frustrating', 'exhausting', 'pleasant' or 'frightening'. Patients were instructed to indicate which of the

adjectives suited their experienced fatigue; multiple answers were allowed.[7] Then the adjectives were divided into one of four fatigue description categories (FQL-Categories) with a score range of 0-100 points within each category. Adjectives belonging to the category frustrating (FQL-Frustrating) are discouraging, incessant, annoying, persistent and frustrating. Adjectives belonging to the category exhausting (FQL-Exhausting) are exhausting, wearisome, extreme and unbearable. In the category pleasant (FQL-Pleasant) are temporary, relaxing, fulfilling, normal and pleasant. And in the category frightening (FQL-Frightening) are upsetting, frightening, inexplicable and insuperable. [7]

Demographic characteristics

Participants self-reported the following demographic data on partner (yes/no), living situation (alone/cohabiting), education ("low education level" meaning maximally preparatory school and "high education level" meaning minimally secondary vocational education), height (m), weight (kg), hospitalization last year (yes/no), working situation last 2 years (yes/no), psychological support (yes/no) and smoking (former/current, never).

Self-reported questionnaires

Fatigue severity was assessed by the Checklist Individual Strength subscale fatigue (CIS-Fatigue). The subscale CIS-Fatigue (eight items) investigates the patients' severity of fatigue of the previous two weeks.[15, 16] Each item was scored on a seven-point Likert scale with a total item score range of 8-56 points. A score of points ≤26 indicates normal fatigue, between 27–35 moderate fatigue (called together non-severe fatigue <36 points), and a score of ≥36 indicates severe fatigue.[17, 18]

Activity-related dyspnoea was measured with the modified medical research council scale for dyspnoea (mMRC). The severity of dyspnoea is indicated on a 5-point scale (0-4 score; higher level reflects more activity limitation due to dyspnoea).[19]

To investigate catastrophizing thoughts related to fatigue the Fatigue Catastrophizing Scale (FCS) was used. The FCS was adapted from the pain catastrophizing scale (PCS) by replacing the term "pain" with "fatigue" where relevant.[20] This scale consists of 13 items measuring the relation of catastrophizing to fatigue on a 5-point scale from 0 (not at all) to 4 (always), with a total maximum of 52 points. Higher scores are indicative for more fatigue catastrophizing.[21]

The Hospital Anxiety and Depression Scale (HADS) is a self-reporting instrument to estimate emotional distress, consisting of two subscales for anxiety (HADS-Anxiety) and depression (HADS-Depression) in somatically ill patients.[22, 23] Total scores for each subscale range from 0 to 21 points, categorized as: normal/mild (0–10 points) and moderate/severe (11–21 points, meaning a clinically significant case of anxiety or depression).[22]

The patients' self-rated general health (score of today) was recorded with the visual analog scale of the European Quality of Life-5 Dimensions (EQ-5D-5L VAS) and the 5-dimension list (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).[24] The vertically situated VAS had labelled endpoints from 0 (worst imaginable health) to 100 points (best imaginable health). The 5-dimension list results were converted into an index value (EQ-5D-5L index value).[25]

Statistical analyses

Data were presented with appropriate measures of central tendency and dispersion, as mean ± standard deviation (SD), median and interquartile range, or frequencies and proportions. Numerical data were tested for normality by Shapiro-Wilkinson test, a mean-median ratio, SD-mean ratio, and judging the histogram.[26] Differences between groups for continuous data were analyzed by an unpaired t-test or the non-parametric pendant (Mann–Whitney U test) where appropriate. Categorical data were analyzed with the Chi-square or Fisher Exact test. A p-value of ≤0.05 was considered as statistically significant. Univariate differences between non-severely (mild/moderate fatigue) and severely fatigued patients were tested with independent t-tests, Mann–Whitney U-tests and chi-square-tests were performed as appropriate. Pearson's r or Spearman's rho were used to study correlations between the continuous data FQL-Categories or EQ-5D-5L (VAS or index value) and patient characteristics or psychosocial factors. In case of missing values, cases were excluded pairwise. The range for what constitutes a weak, moderately strong, strong, or very strong correlation was respectively $0.1 \leq r < 0.3$, $0.3 \leq r < 0.5$, $0.5 \leq r < 0.7$, and $0.7 \leq r < 1.0$ (level of significance $p < 0.05$). Stepwise multiple linear regression with backward selection procedure was performed to investigate the associations between the EQ-5D-5L VAS or EQ-5D-5L index value and independent in univariate analysis significant variables ($p < 0.05$). In case of multicollinearity, variables were identified (variance inflation factor (VIF) >5) and removed from the model[27] IBM SPSS Statistics (Version 25) was used for statistical analysis.

Results

General characteristics

Of the 170 patients invited to participate in this fatigue study, 61 patients with IPF responded (92% response rate) and 60 patients with sarcoidosis (58% response rate). General characteristics of the patients with IPF or sarcoidosis are shown in **Table 1**. Most patients with IPF were elderly men, with a low education level, a smoking history and a slightly increased body mass index (BMI). They had an impaired lung function, most of these patients were diagnosed with one or more comorbidities, and 87% used anti-fibrotic medication. Severe fatigue was prevalent in 48% of the patients with IPF and 51% had more severe scores on activity-related dyspnoea (mMRC ≥2). Moreover, moderate/severe anxiety or depression was present in 9% of the patients with IPF, patients had a mild degree of catastrophic thoughts related to fatigue, and 52% scored VAS general health at 60 points or less (data not shown).

The patients with sarcoidosis were middle aged and had an increased mean BMI. Patients mainly used medication such as immuno-suppressants (39%) and divers medication for lung conditions (56%). 69% of patients with sarcoidosis were severely fatigued and 36% were more impaired in walking due to dyspnoea (mMRC ≥2). Also, moderate/severe anxiety and depression was reported by 12% and 8% of the patients with sarcoidosis. They had a mildly elevated score of catastrophizing, and 46% self-rated general health at 60 points or less (data not shown).

Perceptions of fatigue in patients with IPF

Patients were allowed to report as many adjectives for fatigue as they found appropriate. In patients with IPF the mean score was 3.4 adjectives (3.2 SD). The distribution of the frequency of adjectives is depicted in **Figure 1A**. The mean number of adjectives was similar between IPF patients with or without severe fatigue (4 versus 3 respectively, p >0.05). IPF patients with severe fatigue reported significantly more adjectives as upsetting, incessant, wearisome and persistent than the non-fatigued patients. Not one patient stated fatigue as normal. With respect to the categories of the FQL, severely fatigued patients with IPF only scored significantly less on FQL-Pleasant than non-severe fatigued patients **(Table 2)**.

Table 1: General characteristics of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF) or sarcoidosis

Variables	Patients with IPF (n=61)	Patients with Sarcoidosis (n=60)
General Characteristics		
Gender, male, n (%)	47 (77.0)	29 (48.3)
Age, years [IQR]	73.0 [70-78]	53.5 [46.3-62.0]
Partner, n (%)	45 (73.8)	44 (73.3)
Living together, n (%)	41 (67.2)	42 (70.0)
Education, low <secondary level, n (%) [b]	30 (50.8)	13 (21.7)
Diagnosis time, ≤1 year, n (%) [b]	21 (35.0)	16 (27.1)
Hospitalization, ≤1 year, n (%) [a]	14 (23.0)	10 (16.9)
Work, last 2 years, n (%)	12 (19.7)	37 (61.7)
Psychological support, n (%)	9 (14.8)	20 (33.3)
Smoking, current/former, n (%) [a]	48 (78.7)	23 (39.0)
Pack-years[+], smoking current/former [j]	19.5 ± 19.4	10.6 ±13.9
Physiological		
BMI (kg/m2) [a]	27.5 ±4.1	27.6 ±4.2
TLC (liter) [h]	4.6 ±1.1	6.0 ±1.3
TLC (% predicted) [i]	73.3 ±14.1	98.5 ±18.5
RV (liter) [g]	1.6 ±0.4	2.0 ±0.5
RV (% predicted) [i]	64.8 ±14.2	97.9 ±25.7
FVC (liter)	2.9 ±0.8	3.9 ±1.1
FVC (% predicted)	82.8 ±19.4	98.1 ±20.8
FEV1 (liter)	2.3 ±0.6	2.9 ±0.9
FEV1 (% predicted)	87.0 ±20.7	91.5 ±20.3
TLCO (liter) [e]	3.8 ±1.3	7.3 ±2.0
TLCO (% predicted) [e]	48.7 ±15.2	81.6 ±18.3
Comorbidity 1 ≤, n (%) [b]	45 (75)	30 (51)
Medication		
IPF - antifibrotic, n (%)	53 (86.9)	0 (0.0)
Immunosuppressant incl. prednisone (corticosteroids), n (%) [c]	5 (8.5)	23 (39.0)
Heart rate-lowering medication, n (%) [c]	16 (27.1)	7 (11.9)
Antidepressant medication, n (%) [c]	5 (8.5)	1 (1.7)
Antihypertensive medication, n (%) [c]	26 (44.1)	11 (18.6)
Medication for pulmonary conditions, n (%) [c]	7 (11.9)	33 (55.9)
Fatigue		
CIS-Fatigue1 (p, 8-56) [d]	34.1 ±11.2	40.0 ±12.3
CIS, Severe >35 points, n (%) [d]	28 (47.5)	40 (69.0)

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Table 1: General characteristics of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF) or sarcoidosis *(Continued)*

Dyspnoea		
mMRC[2] (p, 0-4) [g]	1.9 ±1.2	1.4 ±1.1
Fatigue Catastrophizing		
FCS[3] (p, 0-52) [f]	14.7 ±13.4	13.1 ±11.2
Anxiety and Depression		
HADS-Anxiety[4] (p, 0-21) [e]	5.4±3.8	5.1±3.7
HADS-Anxiety, ≥11points (n, %)	5 (8.8)	7 (11.9)
HADS-Depression4 (p, 0-21) [c]	5.0±3.3	4.7±3.7
HADS-Depression, ≥11points (n, %)	5 (8.6)	5 (8.3)
Quality of Life, General Health		
EQ-5D-5L VAS[5] (p, 0-100) [b]	63.8 ±16.6	62.7 ±19.6
EQ-5D-5L index value[6] (p, 0-1) [b]	0.7 ±0.2	0.7 ±0.2

Data are presented as mean ±SD, median [IQR] or n (%). [+] Pack-year, number of years smoking x average number of cigarettes smoked per day/20. Alphabetic characters in superscript indicates a sample size deviant from n=121, in the order: [a] n=120, [b] n=119, [c] n=118, [d] n=117, [e] n=116, [f] n=115, [g] n=114, [h] n=113, [i] n=112, [j] n=52. [1], CIS-Fatigue scores range from 8 to 56; high scores indicate more fatigue; [2], mMRC score range from 0 to 4; high scores indicate more activity related dyspnoea; [3], FCS score range from 0 to 52; high scores indicate more catastrophizing of fatigue; [4], HADS-Anxiety or 4HADS-Depression score range from 0 to 21; high scores indicate more experience of anxiety or depression; [5], EQ-5D-5L VAS score range from 0 to 100; high score indicate better general health (today); [6], EQ-5D-5L index value score range from 0 to 1; score 1 mean full health. BMI, Body Mass Index (kg/m^2); CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L, EuroQol, 5 dimensions, 5 levels (standardised measure of health status); FCS, Fatigue Catastrophizing Scale; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HADS-Anxiety: Hospital Anxiety and Depression Scale subscale Anxiety; HADS-Depression: Hospital Anxiety and Depression Scale subscale Depression; IPF, Idiopathic Pulmonary Fibrosis; IQR, interquartile range; mMRC, modified Medical Research Council dyspnoea scale; p, points; RV, residual volume; RV/TLC, residual volume to total lung capacity; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; VAS, Visual Analog Scale

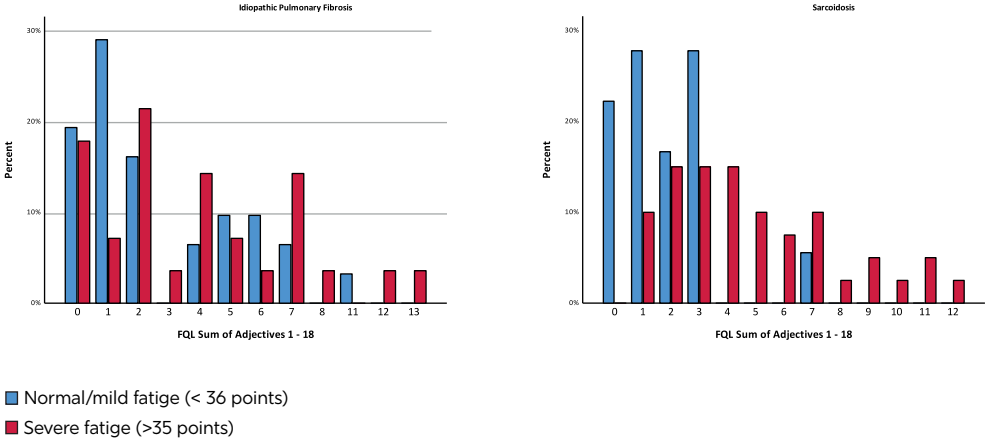

Figure 1: *Frequency of adjectives for fatigue stratified for fatigue severity in patients with idiopathic pulmonary fibrosis or sarcoidosis. (A) Frequency of adjectives for fatigue stratified for fatigue severity in patients with idiopathic pulmonary fibrosis; (B) Frequency of adjectives for fatigue stratified for fatigue severity in patients with sarcoidosis. CIS Fatigue, Checklist Individual Strength subscale Fatigue; FQL, Fatigue Quality List*

Perceptions of fatigue in patients with sarcoidosis

The mean of the sum of adjectives reported by patients with sarcoidosis was 4.0 (3.0 SD). Severely fatigued patients with sarcoidosis used a higher number of adjectives to describe their experience of fatigue than the non-severe fatigued patients: 5 versus 2 adjectives, respectively ($p < 0.05$; **Table 3, Figure 1.B**). The severely fatigued patients more often reported the following adjectives of fatigue: discouraging, temporary, exhausting, incessant, wearisome, annoying, extreme, persistent, frustrating, inexplicable and normal **(Table 3)**. With respect to the categories of the FQL, patients with severe fatigue significantly scored higher on FQL-Frustrating, FQL-Exhausting and FQL-Frightening, and significantly less on the FQL-Pleasant than patients with non-severe fatigue.($p < 0.05$; **Table 2**.)

Perceptions of fatigue in patients with IPF or sarcoidosis with severe fatigue

Severely fatigued patients with IPF or sarcoidosis generally used the same percentage of adjectives to express their fatigue experience. However, the adjectives exhausting and frustrating were reported by a significant higher number of severely fatigued patients with sarcoidosis as compared to severely fatigued patients with IPF. Moreover, there were no significant differences between both groups with respect to the categories FQL-Frustrating, FQL-Exhausting, FQL-Pleasant and FQL-Frightening, and the highest scores were seen in the category FQL-Frustrating in both patient groups (IPF 34 points, sarcoidosis 48 points).

Univariate correlations of perceptions of fatigue

Table 4 gives an overview of all significant correlations ($p < 0.05$) between the four FQL-Categories and fatigue severity (CIS-Fatigue), dyspnoea (mMRC), fatigue catastrophizing (FCS), anxiety (HADS-Anxiety), depression (HADS-Depression) and general health status (EQ-5D-5L VAS). In patients with IPF catastrophizing fatigue correlated strongly ($0.5 \leq \rho < 0.7$) with the three categories of the FQL representing negative adjectives and not one of these concepts correlated with the experience of pleasant fatigue. In patients with sarcoidosis strong correlations were found between FQL-Frustrating and fatigue severity, catastrophizing, depression and general health, and in FQL-Exhausting the same traits supplemented with dyspnoea and anxiety. FQL-Pleasant was strongly correlated with general health and FQL-Frightening with catastrophizing **(Table 4)**.

Table 2 : Categories perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis, stratified for fatigue severity

Categories	IPF (n=61)	Fatigue Severity in Patients with IPF			Sarcoidosis (n=60)	Fatigue Severity in Patients with Sarcoidosis			IPF - Sarcoidosis Severe Fatigue
		Non-severe Fatigue (n=31)	Severe Fatigue (n=28)	p-Value		Non-severe Fatigue (n=18)	Severe Fatigue (n=40)	p-Value	p-Value
Frustrating (p, 0-100)	26.2 ±30.9	18.1 ±24.4	33.6 ±34.9	ns	36.3 ±32.6	7.8 ±14.0	48 ±30.0	p<0.05	ns
Exhausting (p, 0-100)	17.6 ±27.5	10.5 ±21.2	23.2 ±28.8	ns	22.5 ±29.0	4.2 ±12.9	31.3 ±30.9	p<0.05	ns
Pleasant (p, 0-100)	12.1 ±19.4	17.4 ±24.1	7.1 ±11.2	p<0.05	10.7 ±15.4	20.0 ±18.2	7.0 ±12.4	p<0.05	ns
Frightening (p, 0-100)	18.4 ±28.1	13.7 ±27.3	24.1 ±29.3	ns	17.5 ±25.3	6.9 ±18.8	21.3 ±26.9	p<0.05	ns

Data are presented as mean ± SD; p-value (Student's t-test) in bold indicates a significant difference <0.05; Fatigue severity is based on the Checklist Individual Strength subscale Fatigue (CIS-Fatigue): 'Non-severe Fatigue' CIS-Fat <36 points, 'Severe Fatigue' CIS-Fat ≥36 points. In case of missing data of CIS-Fatigue cases were excluded analysis by analysis. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; IPF, Idiopathic Pulmonary Fibrosis; ns, not significant; p, points. FQL scores range from 0 to 100; higher scores in each category indicate fatigue is frustrating, exhausting, pleasant, or frightening to a higher degree.

Table 3: Perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis, stratified for fatigue severity

Fatigue Quality List	IPF (n=61)	Fatigue Severity in Patients with IPF			Sarcoidosis (n=60)	Fatigue Severity in Patients with Sarcoidosis			IPF - Sarcoidosis Severe Fatigue
		Non-severe Fatigue (n=31)	Severe Fatigue (n=28)	p-Value		Non-severe Fatigue (n=18)	Severe Fatigue (n=40)	p-Value	p-Value
Upsetting, n (%)	14 (23.0)	4 (12.9)	10 (35.7)	<0.05*	11 (18.3)	2 (11.1)	9 (22.5)	NS**	NS*
Discouraging, n (%)	13 (21.3)	4 (12.9)	8 (28.6)	NS*	15 (25.0)	1 (5.6)	13 (32.5)	<0.05**	NS*
Temporary, n (%)	16 (26.2)	10 (32.3)	6 (21.4)	NS*	18 (30.0)	9 (50.0)	9 (22.5)	<0.05*	NS*
Exhausting, n (%)	15 (24.6)	6 (19.4)	8 (28.6)	NS*	22 (36.7)	1 (5.6)	21 (52.5)	<0.05*	NS (p=0.05) *
Incessant, n (%)	12 (19.7)	3 (9.7)	9 (32.1)	<0.05*	20 (33.3)	1 (5.6)	18 (45.0)	<0.05*	NS*
Wearisome, n (%)	17 (27.9)	4 (12.9)	12 (42.9)	<0.05*	15 (25.0)	1 (5.6)	14 (35.0)	<0.05**	NS*
Frightening, n (%)	11 (18.0)	6 (19.4)	5 (17.9)	NS*	8 (13.3)	1 (5.6)	6 (15.0)	NS**	NS**
Annoying, n (%)	20 (32.8)	8 (25.8)	11 (39.3)	NS*	20 (33.3)	1 (5.6)	18 (45.0)	<0.05*	NS*
Extreme, n (%)	7 (11.5)	2 (6.5)	4 (14.3)	NS**	10 (16.7)	0 (0.0)	10 (25.0)	<0.05**	NS*
Persistent, n (%)	11 (18.0)	2 (6.5)	8 (28.6)	<0.05**	21 (35.0)	1 (5.6)	19 (47.5)	<0.05*	NS*
Frustrating, n (%)	24 (39.3)	11 (35.5)	11 (39.3)	NS*	33 (55.0)	3 (16.7)	28 (70.0)	<0.05*	<0.05*
Relaxing, n (%)	5 (8.2)	2 (6.5)	3 (10.7)	NS**	1 (1.7)	0 (0.0)	1 (2.5)	NS**	NS**
Inexplicable, n (%)	10 (16.4)	3 (9.7)	6 (21.4)	NS**	15 (25.0)	1 (5.6)	13 (32.5)	<0.05*	NS*
Fulfilling, n (%)	2 (3.3)	2 (6.5)	0 (0.0)	NS**	3 (5.0)	2 (11.1)	1 (2.5)	NS**	NS**
Insuperable, n (%)	10 (16.4)	4 (12.9)	6 (21.4)	NS**	8 (13.3)	1 (5.6)	6 (15.0)	NS**	NS*
Unbearable, n (%)	4 (6.6)	1 (3.2)	2 (7.1)	NS**	7 (11.7)	1 (5.6)	5 (12.5)	NS**	NS**
Normal, n (%)	9 (14.8)	9 (29.0)	0 (0.0)	<0.05**	10 (16.7)	7 (38.9)	3 (7.5)	<0.05*	NS**
Pleasant, n (%)	5 (8.2)	4 (12.9)	1 (3.6)	NS**	0 (0.0)	0 (0.0)	0 (0.0)	NS**	NS**
Total descriptions, (p, 0-18)	3.4 ±3.2	2.7 ±2.8	3.9 ±3.5	NS~	4.0 ±3.0	1.8 ±1.7	4.9 ±3.0	<0.05~	NS~

*Data are presented as n (%) or mean ± SD, p-value in bold indicates a significant difference <0.05. *, Pearson Chi-Square test; **, Fisher's Exact Test; ~, Student's T-test. Fatigue severity is based on the Checklist Individual Strength subscale Fatigue: 'Non-severe Fatigue' CIS-Fatigue <36 points, 'Severe Fatigue' CIS-Fatigue ≥36 points. In case of missing data of CIS-Fatigue cases were excluded analysis by analysis. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; IPF, Idiopathic Pulmonary Fibrosis; ns, not significant; p, points*

Table 4: Correlations of the categories of the FQL with fatigue, dyspnoea, catastrophizing, anxiety, depression and general health in patients with idiopathic pulmonary fibrosis or sarcoidosis

	FQL-Frustrating		FQL-Exhausting		FQL-Pleasant		FQL-Frightening	
	ρ	p	ρ	p	ρ	p	ρ	p
Idiopathic Pulmonary Fibrosis								
Fatigue (CIS-Fatigue)	0.322	<0.05	0.258	<0.05	-0.231	ns	0.351	<0.01
Dyspnoea (mMRC)	0.350	<0.01	0.343	<0.01	0.235	ns	0.445	<0.01
Fatigue catastrophizing (FCS)	0.551	<0.01	0.504	<0.01	0.000	ns	0.642	<0.01
Anxiety (HADS-Anxiety)	0.228	ns	0.252	ns	-0.054	ns	0.466	<0.01
Depression (HADS-Depression)	0.172	ns	0.195	ns	0.141	ns	0.438	<0.01
General health (EQ-5D-5L VAS)	-0.355	<0.01	-0.369	<0.01	-0.021	ns	-0.350	<0.01
Sarcoidosis								
Fatigue (CIS-Fatigue)	0.597	<0.01	0.583	<0.01	-0.404	<0.01	0.320	<0.05
Dyspnoea (mMRC)	0.393	<0.01	0.556	<0.01	-0.469	<0.01	0.296	<0.05
Fatigue catastrophizing (FCS)	0.608	<0.01	0.643	<0.01	-0.486	<0.01	0.650	<0.01
Anxiety (HADS-Anxiety)	0.250	ns	0.530	<0.01	-0.237	ns	0.484	<0.01
Depression (HADS-Depression)	0.531	<0.01	0.584	<0.01	-0.389	<0.01	0.421	<0.01
General health (EQ-5D-5L VAS)	-0.525	<0.01	-0.531	<0.01	0.537	<0.01	-0.169	ns

P, statistically significant; ρ Spearman rank correlation coefficient. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L: EuroQol, 5 dimensions, 5 levels (standardised measure of health status); FCS, Fatigue Catastrophizing Scale; FQL, Fatigue Quality Scale; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale Anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale Depression; mMRC, modified Medical Research Council-Dyspnoea; VAS, Visual Analogue Scale

Table 5: Correlations of general health (EQ-5D-5L-VAS and EQ-5D-5L-Index Value) in patients with idiopathic pulmonary fibrosis or sarcoidosis

General Health								
	Idiopathic Pulmonary Fibrosis				Sarcoidosis			
	EQ-5D-5L VAS		EQ-5D-5L IV		EQ-5D-5L VAS		EQ-5D-5L IV	
	ρ	p	ρ	p	ρ	p	ρ	p
Fatigue severity (CIS-Fatigue)	-0.529	<0.01	-0.414	<0.01	-0.710	<0.01	-0.577	<0.01
FQL-Frustrating category	-0.355	<0.01	-0.339	<0.01	-0.525	<0.01	-0.633	<0.01
FQL-Exhausting category	-0.369	<0.01	-0.377	<0.01	-0.531	<0.01	-0.703	<0.01
FQL-Pleasant category	-0.021	NS	0.013	NS	0.537	<0.01	0.604	<0.01
FQL-Frightening category	-0.350	<0.01	-0.485	<0.01	-0.169	NS	-0.415	<0.01
Dyspnoea (mMRC)	-0.564	<0.01	-0.620	<0.01	-0.508	<0.01	-0.666	<0.01
Fatigue catastrophizing (FCS)	-0.537	<0.01	-0.672	<0.01	-0.327	<0.05	-0.574	<0.01
Anxiety (HADS-Anxiety)	-0.398	<0.01	-0.521	<0.01	-0.292	<0.05	-0.380	<0.01
Depression (HADS-Depression)	-0.414	<0.01	-0.625	<0.01	-0.489	<0.01	-0.656	<0.01
Age (years)	-0.157	NS	0.006	NS	0.026	NS	-0.070	NS
Gender	-0.100	NS	-0.012	NS	-0.171	NS	-0.297	<0.05
Comorbidity frequency	-0.361	<0.01	-0.245	NS	-0.223	NS	-0.340	<0.01
TLCO%Pred	0.417	<0.01	0.488	<0.01	0.168	NS	0.232	NS

P, statistically significant; ρ Spearman rank correlation coefficient. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L IV, EuroQol, 5 dimensions, Index Value; EQ-5D-5L VAS, EuroQol, 5 dimensions, Visual Analog Scale; FCS, Fatigue Catastrophizing Scale; FQL, Fatigue Quality Scale; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale Anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale Depression; mMRC, modified Medical Research Council-Dyspnea; VAS, Visual Analogue Scale; TLCO %Pred, Transfer Factor of the lung for carbon monoxide (measured in ml/min/mm Hg) percentage predicted.

Table 6: Regression equations for general health (EQ-5D-5L VAS or EQ-5D-5L index value) in patients with idiopathic pulmonary fibrosis or sarcoidosis

	Regression equation	R	R^2	SEE
IPF				
EQ-5D-5L VAS	80.700 – 0.529*CIS-Fatigue – 1.611*HADS-Anxiety – 5.440* Comorbidities + 0.339*TLCO%Pred	0.76	0.58	11.72
EQ-5D-5L index value	0.829 – 0.003*FQL-Exhausted – 0.032*mMRC – 0.011*HADS-Anxiety – 0.014*HADS-Depression + 0.003*TLCO%Pred	0.87	0.75	0.10
Sarcoidosis				
EQ-5D-5L VAS	98.672 – 0.815*CIS-Fatigue + 0.340*FQL-Pleasant – 1.387*HADS-Depression	0.77	0.59	12.73
EQ-5D-5L index value	0.986 – 0.002*FQL-Exhausted – 0.070*mMRC – 0.019*HADS-Anxiety	0.75	0.56	0.15

Regression equations with backwards analysis, dependent variable EQ-5D-5L VAS or EQ-5D-5L index value, independent variables in univariate analyses significant ($p < 0.05$) correlated; only equations are presented after the final backward regression analysis. CIS-Fatigue, Checklist Individual Strength subscale fatigue; EQ-5D-5L, EuroQol 5 dimensions 5 levels; FCS, Fatigue Catastrophizing Scale; FQL-Exhausted, Fatigue Quality List category exhausted; FQL-Pleasant, Fatigue Quality List category pleasant; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale depression; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council dyspnea scale; TLCO %Pred, Transfer Factor of the lung for carbon monoxide (measured in ml/min/mm Hg) percentage predicted; VAS, Visual Analog Scale.

Determinants of general health

Table 5 shows the associations for general health (EQ-5D-5L VAS and EQ-5D-5L index value) with fatigue severity (CIS-Fatigue), experience of fatigue (FQL-categories) and other clinical parameters. In patients with IPF moderately strong correlations with general health (EQ-5D-5L VAS or index value) were found with the FQL-Frustrating, FQL-Exhausting and FQL-Frightening, but no significant correlation with FQL-Pleasant. In patients with sarcoidosis general health (EQ-5D-5L VAS or index value) showed strong correlations with FQL-frustrating, FQL-Exhausting and FQL-Pleasant, and moderately strong correlation of the EQ-5D-5L index value with FQL-Frightening. The regression equations with the dependent variables EQ-5D-5L VAS or index value are presented in **Table 6**. The explained variance (R2) of the stepwise multiple regressions models for patients with IPF vs sarcoidosis was for EQ-5D-5L VAS 58% vs 59% and for EQ-5D-5L index value 75% vs 56%.

Discussion

This study shows that there are extensive variations in perceptions of fatigue in patients with IPF or sarcoidosis, in addition to the severity of fatigue. Patients expressed their perceived fatigue in a different number of adjectives, ranging from 0 to 13 adjectives. Also, severely fatigued patients with IPF perceived their fatigue (categories FQL) less as pleasant than non-severely fatigued IPF patients. Severely fatigued patients with sarcoidosis perceived their fatigue as more frustrating, exhausting, frightening and less pleasant compared to non-severely fatigued patients. Although a third of the patients without severe fatigue reported their fatigue as normal and temporary, some of these non-severely fatigued patients also had negative associations with fatigue, such as exhausting (14%), frightening (14%), annoying (18%) and frustrating (29%). The findings in this study for negative connotations of fatigue are in line with other chronic diseases.[7, 8, 9]

Negative connotations were mentioned in both diseases IPF or sarcoidosis and most prevalent were frustrating (39% IPF, 55% sarcoidosis), followed by exhausting (IPF 25%, sarcoidosis 37%) and annoying (IPF 33%, sarcoidosis 33%). In severely fatigued patients with IPF or sarcoidosis these percentages of negative connotations were even higher and also other negative connotations were substantially prevalent (>30%) as wearisome, incessant, upsetting, discouraging and inexplicable. Catastrophizing thoughts about fatigue are associated with higher rates of experiencing fa-

tigue as frustrating, exhausting, frightening and less rates of pleasant. So, for a better understanding of fatigue it is necessary to look at the severity of the fatigue on the one hand, and the perception of fatigue on the other hand. Moreover, patients without severe fatigue might experience negative associations concerning fatigue and patients with severe fatigue might not come up with very negative terms. In treatment of patients, it is useful to know how people view their fatigue, to connect with the perception of the patient and thus to find out what is desirable to change their cognitions and/or behavior. Treatment of fatigue can be recommended in many ways and one of the treatment options is cognitive behavioral therapy (CBT), a type of psychotherapy. CBT aims to influence cognitions and behaviors that are related to the experienced problems.[28,29] CBT could be an intervention for reducing fatigue in patients with sarcoidosis or IPF, as is already seen in patients with sarcoidosis[30,31], cancer[32], chronic fatigue syndrome[33] and multiple sclerosis.[34] CBT also aims at changing the patients' attitude towards fatigue and in that way changing the experience of fatigue. Patients with chronic conditions with more complex problematic conditions might be referred to pulmonary rehabilitation. In pulmonary rehabilitation, cognitive behavioral therapy is already integrated and considered for improving patients' physical, psychological and quality of life.[35,36] In addition to this known information, this study emphasizes the importance of taking into account the patients' different perceptions of fatigue in the rehabilitation of the patients. Further research is needed to investigate the most targeted approach to reduce negative experiences of fatigue.

It has been established that fatigue and depression are highly correlated and depression symptomatology and prevalence are significantly increased in fatigued individuals.[37] In patients with sarcoidosis the HADS-depression score is significantly related to negative expressions of fatigue, but, in patients with IPF only to frightening. In the current study severe fatigue was present in 48% of the patients with IPF and in 69% of the patients with sarcoidosis. The depression rate of moderate/severe level was present in 9% of the patients with IPF and in 8% of the patients with sarcoidosis. These data support that fatigue is a common symptom in many physical and psychological disorders, such as depression. But that doesn't mean that fatigue and depression are the same phenomenon. In other words, a fatigued patient does not necessarily have to be depressed.

The symptoms fatigue and sleepiness are often used intermingled, but the symptom excessive daytime sleepiness (ESS) describes the probability to fall asleep in various situations at daytime.[38] This study and a recent study of Bloem et al. [2020][6] showed a slight correlation between CIS-fatigue score and sleepiness (ESS >10) in patients with sarcoidosis ($\rho = 0.282$; $p < 0.05$) but not in patients with IPF. In the search for

different experiences of fatigue is sleepiness not included. Remarkable in the study of Bosse Henck[38] severe fatigue in patients with sarcoidosis was found in (only) 16% of the total sample while in the current study it is much higher (i.e., 69%). Both studies used a different fatigue questionnaire, Bosse Henck used the Fatigue Assessment Scale[39, 40,41] and current study used the CIS-Fatigue. The intracorrelation between the FAS and the CIS-Fatigue is to be expected seemly high. So differences in fatigue severity results is expected to be part of different sarcoidosis cohorts. The German cohort existed from members of the German Sarcoidosis Society in contrary of current study with a well-defined pulmonary sarcoidosis cohort.

A limitation of the current study is that all patients were recruited in an outpatient clinic of a respiratory medicine department. Therefore, these results may not be generalizable to patients with IPF or sarcoidosis in other settings. In addition, fatigued patients with negative perceptions of fatigue might not be willing to participate in a questionnaire-based fatigue study. Insights why patients were not responding have remained unknown due to inability to study non-participating patients. Strengths of the study are the cross-sectional design, the good distribution of patients between the non-severely and the severely fatigued groups and the relatively large sample size of the number of patients with IPF.

Conclusion

In conclusion, this is the first study investigating experiences of fatigue in patients with IPF or pulmonary sarcoidosis. Professionals treating patients with IPF or sarcoidosis not only should focus on fatigue severity, but also on the subjective experiences related to fatigue. In addition, not only severely fatigued patients may have negative fatigue-related experiences, but also non-severely fatigued patient may have these. Although similarities were found in the connotations of fatigue across non-severe and severe fatigued patients, differences were also evident and could be mapped for IPF and sarcoidosis.

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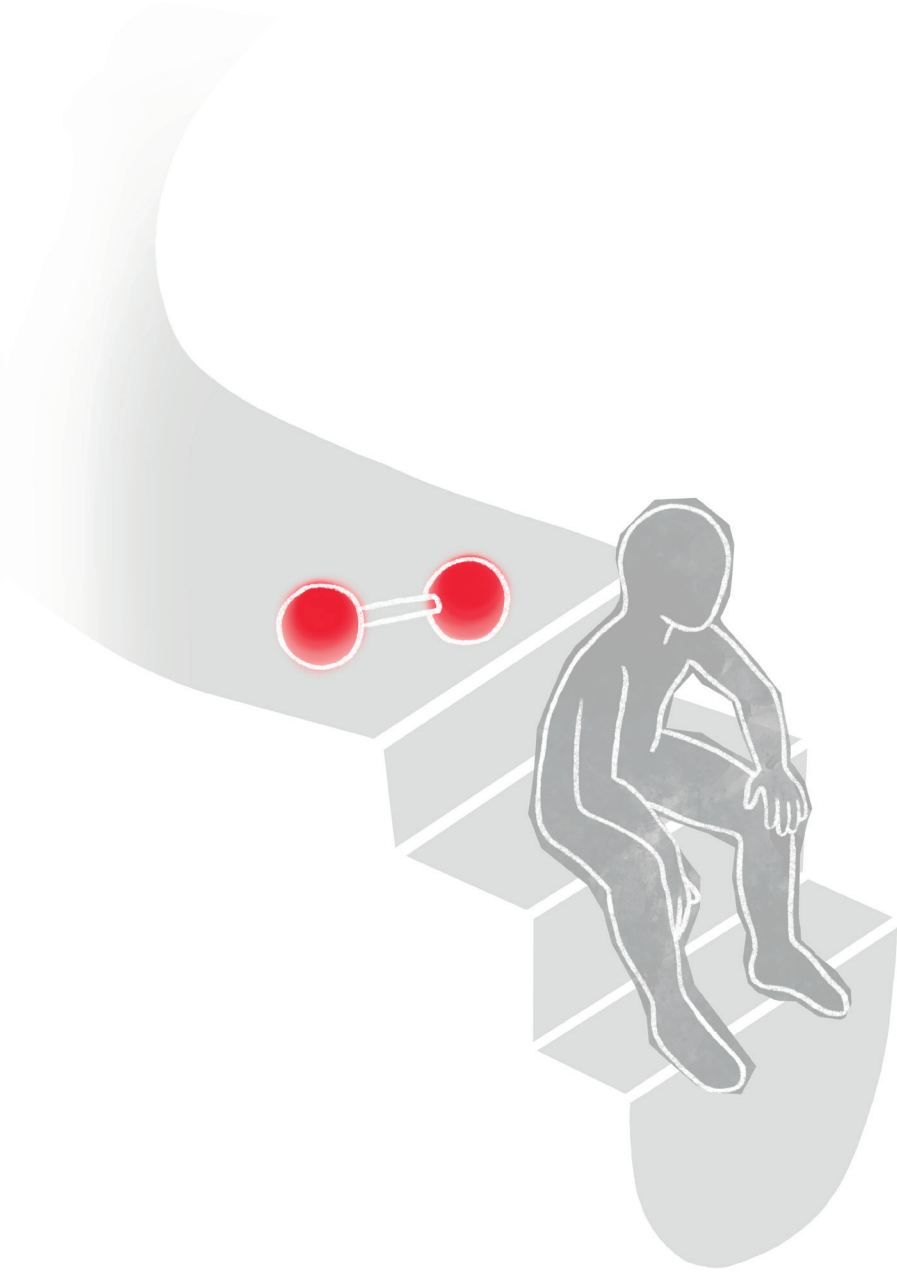

Chapter 4

Respiratory and non-respiratory symptoms in patients with IPF or sarcoidosis and controls

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Abstract

Introduction: Besides dyspnoea and cough, patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis may experience distressing non-respiratory symptoms, such as fatigue or muscle weakness. However, whether and to what extent symptom burden differs between patients with IPF or sarcoidosis and individuals without respiratory disease remains currently unknown.

Objectives: To study the respiratory and non-respiratory burden of multiple symptoms in patients with IPF or sarcoidosis and to compare the symptom burden with individuals without impaired spirometric values, FVC and FEV1 (controls).

Methods: Demographics and symptoms were assessed in 59 patients with IPF, 60 patients with sarcoidosis and 118 controls (age ≥ 18 years). Patients with either condition were matched to controls by sex and age. Severity of 14 symptoms was assessed using a Visual Analogue Scale.

Results: 44 patients with IPF (77.3% male; age 70.6±5.5 years) and 44 matched controls, and 45 patients with sarcoidosis (48.9% male; age 58.1±8.6 year) and 45 matched controls were analyzed. Patients with IPF scored higher on 11 symptoms compared to controls ($p<0.05$), with the largest differences for dyspnoea, cough, fatigue, muscle weakness and insomnia. Patients with sarcoidosis scored higher on all 14 symptoms ($p<0.05$), with the largest differences for dyspnoea, fatigue, cough, muscle weakness, insomnia, pain, itch, thirst, micturition (night, day).

Conclusions: Generally, respiratory and non-respiratory symptom burden is significantly higher in patients with IPF or sarcoidosis compared to controls. This emphasizes the importance of awareness for respiratory and non-respiratory symptom burden in IPF or sarcoidosis and the need for additional research to study the underlying mechanisms and subsequent interventions.

Keywords: Idiopathic Pulmonary Fibrosis, Sarcoidosis, Symptom burden, Interstitial Lung Disease

Introduction

The two most common types of interstitial lung diseases (ILDs) are idiopathic pulmonary fibrosis (IPF)[1,2,3] and pulmonary sarcoidosis.[4] Although these diseases have different pathophysiology and prognosis, patients with IPF or sarcoidosis usually experience distressing respiratory symptoms like dyspnoea and cough. In addition, non-respiratory symptoms, like fatigue, muscle weakness and depression[5,6,7], can also contribute to a severely reduced quality of life.[8,9] Most ILD research focused on a limited number of respiratory and/or non-respiratory symptoms. Despite multiple respiratory and non-respiratory symptoms coexisting in patients with ILD, the prevalence of multiple co-occurring symptoms has been studied scarcely.[10,11] Consequently, clinicians have to actively search for daily symptoms using appropriate tools to further personalized treatments.

To date, many different tools are used to measure respiratory and non-respiratory symptom burden[12-15] which complicates a comparison of symptom scores. Timely mapping of the broad symptom burden requires attention and requires a more in-depth understanding of symptoms. Assessing respiratory and non-respiratory symptoms using a visual analogue scale (VAS) allows assessment of not only the presence, but also the severity of symptoms and allows for comparisons. The advantage of VAS is that they are effectively classless, in other words, the respondent can choose their own gradations between the endpoints of the scale with the advantage of marking an interval. This makes it possible to calculate the arithmetic mean. Nominal or categorical measurements can only be interpreted in terms of their dissimilarity and rank; as such, the data are ordinal-scaled.[16,17] In summary, by using the VAS, one gets a first impression of whether the symptom is present and to what extent, and it is possible to query many items in the same way.[18] To the best of our knowledge, this has not previously been studied across a wide range of symptoms simultaneously. Furthermore, a control group is lacking in most studies about symptom burden in patients with IPF or sarcoidosis[8-10] which would provide a better understanding of the symptom burden.

Therefore, the aim of the present study was to assess a wide range of respiratory and non-respiratory symptoms in patients with IPF or pulmonary sarcoidosis and to compare these with individuals without impaired spirometric values, FVC and FEV1 (controls). A priori, we hypothesized, that patients with IPF or sarcoidosis have a significantly higher burden of respiratory and non-respiratory symptoms compared to controls.

Methods

Study design and participants

This study was conducted within a cross-sectional prospective clinical study concerning patient reported outcomes in patients (age ≥18 years) with confirmed IPF[3] or pulmonary sarcoidosis[4] at the outpatient clinic of the Department of Respiratory Medicine, Zuyderland Medical Centre Heerlen in the Netherlands (METC approved, METCZ20180027). Details of the methodology of this study have been published before.[19] Individuals without impaired spirometric values (FVC and FEV1) (controls) were obtained from the Chance study, an observational longitudinal study concerning the clinical, physiological and psychosocial determinants of health status in a broad sample of patients with COPD and controls recruited by general practitioners from the southern parts of The Netherlands (METC approved, METC 11-3-070).[20,21] Controls were eligible for the Chance study if they fulfilled the following criteria: age 40–85 years, postbronchodilator FEV1/FVC ≥ 70% and healthy, as judged by the investigator, and determined by medical history and physical examination.[20]

Demographic and clinical characteristics

Patients with IPF or sarcoidosis
The following data were extracted from electronic patient dossier: diagnosis (IPF / sarcoidosis), sex (man / woman), age (years), diagnosis history of the lung disease (diagnosed ≤ 1 year yes/no), static lung volumes (total lung capacity (TLC) and residual volume (RV)) (Liter, % predicted), spirometry (forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)) (Liter, % predicted), diffusing capacity for carbon monoxide (TLCO) (ml/min/mm Hg, %predicted)[22], medication, comorbidities, pack-years. Patients reported weight (kg), height (m), living status (living alone/cohabiting), hospitalization respiratory related ≤ 1 year (yes/no), a history of psychological support (yes/no) and tobacco use (never or current/former smoker).

Controls
The following data were collected: Demographics, weight (kg), height (m), living status (living alone/cohabiting), all cause hospitalization ≤ 1 year (yes/no), history of psychological support (yes/no) and tobacco use (never or current/former smoker), pack-years, medication, comorbidities. Postbronchodilator spirometry was done using a handheld SpiroPro Viasys (Jaeger/Cardinal Health, Hoechberg, Germany).[20]

Severity of symptoms was assessed using Visual Analogue Scales (VAS), a reliable tool for assessing patients experienced symptom burden and this measurement tool is validated in patients with ILD.[23-27] The following symptoms were assessed: dyspnoea, fatigue, cough, muscle weakness, loss of appetite, insomnia, gloom, anxiety, pain, mouth complaints, itch, thirst, frequent micturition during the night or during the day. The VAS ranged from 'none' at one end of the line and 'worst possible' at the other end of the line, resulting in a range from 0 to 100 mm. The patients had to mark on the line the point that represented the self-perceived severity of the symptom during the previous two weeks. The severity of symptom burden was classified as mild (VAS score ≤ 30 mm), moderate-to-severe (VAS score > 30 to ≤ 54 mm) or severe (VAS score > 54 mm).[23]

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics (Version 27). Categorial and continuous variables were presented with appropriate measures of central tendency and dispersion. Numerical data were tested for normality by a mean-median ratio, SD-mean ratio, and judging histogram.[28] Differences between groups for continuous data were analyzed by an unpaired t-test or Mann–Whitney U test, as appropriate. Categorical data were analyzed with the Chi-square or Fisher Exact test. A priori, a p-value of ≤0.05 was considered as statistically significant. Patients with IPF (n=59) and patients with sarcoidosis (n=60) were matched for age and gender to subjects from a pool of 118 individuals without respiratory disease using the case control matching technique in SPSS. Age tolerance was assessed for IPF or sarcoidosis separately, aiming for the largest possible sample size per group with a non-significant age difference. This resulted in an age tolerance of seven years in IPF and four years in sarcoidosis. Only cases with matched controls were included for analysis. For the current analysis, 44 patients with IPF and 44 matched controls as well as 45 patients with sarcoidosis and 45 matched controls were included. 16 of the 118 controls were part of both control groups. 45 of the 118 controls were not part of any control group.

Results

Patients with IPF versus controls

Characteristics
Patients with IPF and matched controls were mostly men (77.3 %) with a comparable mean age (70.6 ±5.5 years and 68.3 ±5.6 years, respectively). Patients had an impaired lung function compared to the controls (FVC %pred 82.2 ±19.2 vs 112.1 ±18.4; FEV1 %pred 85.7 ±20.8 vs 111.5 ±19.6). The vast majority of patients with IPF (91%) used antifibrotic medication. In general, compared to controls, patients were less often cohabiting and used more medication for purposes other than the defined drug groups. **(Table 1)**. No differences between groups (patients or controls) were observed in body mass index, psychological support, smoking history and pack-years. **(Table 1)** Correlations between pulmonary function tests and symptoms in dyspnoea in patients with IPF were moderate (FEV1 %pred, r =-0.41; TLCO %pred, r=-0.48). **(Table 2)**

Symptom burden
Patients with IPF had a significantly higher symptom burden in comparison to the control group (11 out of 14 symptoms, 79%), including dyspnoea, cough, fatigue, muscle weakness, loss of appetite, insomnia, gloom, pain, mouth complaints, itch, and micturition complaints during the day. **(Figure 1.A)** Moderate/severe symptom burden was most prominent in patients compared to controls for dyspnoea 58.1% vs 11.3%, fatigue 53.5% vs 13.6%, cough 55.8% vs 11.3%, muscle weakness 43.2% vs 9.1% and insomnia 29.5% vs 25.0%. **(Figure 2**; all $p<0.05$) The proportion of patients reporting ≥3 symptoms was significantly higher compared to the controls (70.4 vs 13.6%). **(Figure 3.A) Figure 4.A** shows that respiratory and non-respiratory symptoms co-occur frequently in patients with IPF. For example, almost 85% of all patients with muscle weakness also suffered from dyspnoea.

Patients with sarcoidosis versus controls

Characteristics
Almost half of the patients with sarcoidosis and matched controls were male (48.9%) with a comparable mean age of 58.1 ±8.6 years and 60.5 ±6.0 years, respectively. Compared to controls, patients received more often psychological support, were less frequently current or former smokers, had less packyears and medication use was higher for respiratory, immunosuppressive and medication for purposes other than

the defined drug groups **(Table 1)**. Pulmonary function tests were slightly but significantly lower in patients than in controls (FVC %pred 97.1 ±22.9 vs 116.8 ± 16.3; FEV1 %pred 91.1 ±21.4 vs 113.3 ± 15.0). In patients with sarcoidosis correlations between pulmonary function tests and the symptom dyspnoea were as follows: FVC %pred, r=-0.35; FEV1 %pred r=-0.41; TLCO %pred, r=-0.60. **(Table 2)**

Table 1: General characteristics of patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis and their matched non-respiratory controls

Variables	Patients with IPF (n=44)	Controls (n=44)	p-value IPF vs control	Patients with Sacoidosi (n=45)	Controls (n=45)	p-value sarcoidosis vs control
General Characteristics						
Gender, male, *n* (%)	34 (77.3)	34 (77.3)	1.000	22 (48.9)	22 (48.9)	1.000
Age, years	70.6 ±5.5	68.3 ±5.6	0.053	58.1 ±8.6	60.5 ±6.0	0.129
Living cohabiting, *n* (%)	33 (75.0)	42 (95.5)	0.007	35 (77.8)	41 (91.1)	0.081
Diagnosis time, ≤1 year, *n* (%)[1, a]	13 (30.2)	X	X	11 (25.0)	X	X
Hospitalization, previous year, n (%) *	10 (22.7)	6 (13.7)	0.459	6 (13.3)	2 (4.4)	0.289
Psychological support, *n* (%)	7 (15.9)	3 (6.8)	0.179	17 (37.8)	2 (4.4)	<0.001
Smoking, current/former, *n* (%)	37 (84.1)	33 (75.0)	0.564	16 (35.6)	28 (62.3)	0.026
Pack-years**, smoking current/former[3, e]	17.5 ±20.1	13.8 ±15.4	0.367	4.4 ±11.0	10.9 ±14.0	0.027
Physiological						
BMI (kg/m2)	27.9 ±3.9	27.1 ±3.9	0.366	27.7 ±4.2	26.3 (3.5)	0.081
TLC (liter)[1, c]	4.7 ±1.1	X	X	5.8 ±1.4	X	X
TLC (% predicted) [1, d]	73.5 ±14.0	X	X	97.0 ±20.4	X	X
RV (liter)[1, b]	1.6 ±0.4	X	X	2.0 ±0.5	X	X
RV (% predicted)[1, d]	65.8 ±15.0	X	X	94.2 ±26.0	X	X
FVC (liter)	3.0 ±0.8	4.1 ±1.0	<0.001	3.7 ±1.1	4.0 ±0.8	0.208
FVC (% predicted)	82.2 ±19.2	112.1 ±18.4	<0.001	97.1 ±22.9	116.8 ± 16.3	<0.001
FEV1 (liter)	2.4 ±0.6	3.2 ±0.8	<0.001	2.8 ±0.8	3.1 ±0.6	0.032
FEV1 (% predicted)	85.7 ±20.8	111.5 ±19.6	<0.001	91.1 ± 21.4	113.3 ± 15.0	<0.001
TLCO (ml/min/mm Hg)[b]	4.0 ±1.4	X	X	6.9 ±2.1	X	X
TLCO (% predicted)[b]	49.0 ±15.7	X	X	81.6 ±20.1	X	X
Comorbidity						
Myocardial infarction, Cardiac failure	6 (13.6)	5 (11.4) [a]	ns	0 (0.0)	1 (2.2) [a]	ns
TIA, CVA or Hemiplegia	3 (6.8)	4 (9.1) [a]	ns	2 (4.4)	4(8.9) [a]	ns
Peripheral vascular disease	4 (9.1)	2 (4.5) [a]	ns	1 (2.2)	0 (0.0)[a]	ns
COPD, Asthma	0 (0.0)	0 (0.0) [a]	ns	6 (13.3)	0 (0.0) [a]	p=0.011
Diabetes mellitus	6 (13.7)	4 (9.1) [a]	ns	4 (8.9)	1 (2.2) [a]	ns
Medication use (≥1)						
Pulmonarya, *n* (%)	3 (6.8)	8 (18.2)	0.125	24 (54.5)	2 (4.4)	<0.001
Cardiovasculara, *n* (%)	21 (47.7)	22 (50.0)	1.000	11 (25.0)	14 (31.1)	0.521
Immunosuppressivea, *n* (%)	3 (6.8)	2 (4.5)	0.607	17 (38.6)	0 (0.0)	<0.001
Antidepressanta, *n* (%)	4 (9.1)	3 (6.8)	0.646	1 (2.3)	2 (4.4)	0.570
Othera, *n* (%)	39 (88.6)	25 (56.8)	<0.001	27 (61.4)	16 (35.6)	0.015
Antifibrotic[2], *n* (%)	40 (91)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	ns

Controls consisted of individuals without impaired spirometric values, FVC and FEV1. Data are presented as mean ±SD or n (%). Numeric characters in superscript indicate a sample size deviant, in the order: [1] IPF n=43; [2] IPF n=42; [3] IPF n=32; [a] sarcoidosis n=44; [b] sarcoidosis n=41; [c] sarcoidosis n=40; [d] sarcoidosis n=39; [e] sarcoidosis n=35. Abbreviations: BMI, Body Mass Index (kg/m2); COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebrovascular Accident; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; IPF, Idiopathic Pulmonary Fibrosis; na, not applicable; p, points; RV, Residual Volume; TLC, Total Lung Capacity; TIA, Transient Ischemic Attacks; TLCO, Transfer Factor of the lung for carbon monoxide (measured in ml/min/mm Hg) Hospitalization, patients with IPF or sarcoidosis hospitalization respiratory related, non-respiratory controls all causes hospitalization ** Pack-year, number of years smoking x average number of cigarettes smoked per day/20 Charlson Comorbidity Index (CCI)*

Table 2: Relationship between pulmonary function tests and symptoms

Correlations	Patients with IPF (n=44)			Patients with sarcoidosis (n=45)		
	FVC %Pred	FEV1 %Pred	TLCO %Pred	FVC %Pred	FEV1 %Pred	TLCO %Pred
	r	r	r	r	r	r
Dyspnoea	-0,255^{-1}	-0.411^{-1}**	-0.483^{-1}**	-0.350*	-0.405**	-0.599^{-4}**
Fatigue	-0,159^{-1}	-0,263^{-1}	-0.310^{-1}*	-0,085	-0,056	-0.326^{-4}*
Cough	0,085^{-1}	0,030^{-1}	-0,047^{-1}	-0,198	-0,206	-0,286^{-4}
Muscle weakness	-0,045	-0,179	-0.342*	-0,212	-0,150	-0,006^{-4}
Loss of appetite	0,086	0,012	-0,109	-0,196	-0,211	0,090^{-4}
Insomnia	-0,233	-0,267	0,102	0,073	0,037	-0,095^{-4}
Gloom	-0,158	-0.298*	-0,061	0,010	0,015	-0,120^{-4}
Anxiety	-0,158	-0,281	0,070	-0,016	-0,122	-0,115^{-4}
Pain	-0,064	-0,154	-0,167	-0,235	-0,159	-0,279^{-4}
Mouth complaints	-0.378*	-0.394**	-0,067	-0,079	-0,072	-0,103^{-4}
Itch	0,202	0,071	-0,020	-0,060	-0,019	-0,129^{-4}
Thirst	-0,051	-0,042	-0,087	-0,033	-0,020	-0,228^{-4}
Micturition (night)	-0,150	-0,218	0,211	-0.341*	-0.301*	-0,136^{-4}
Micturition (day)	0,007^{-1}	-0,120^{-1}	-0,078^{-1}	-0.359*	-0,287	-0,146^{-4}

Correlations between pulmonary function tests and symptom burden; p= Pearson correlation coefficient. Numeric characters in superscript indicate a sample size deviant, in the order: $^{-1}$ n=-1, $^{-4}$ n=-4
*** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).*

Abbreviations: FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; IPF, Idiopathic Pulmonary Fibrosis; Pred, predicted; TLCO, Transfer Factor of the lung for carbon monoxide (measured in ml/min/mm Hg)

Symptoms burden

Patients with sarcoidosis reported for all respiratory and non-respiratory symptoms more symptoms burden in comparison to controls (14 out of 14 symptoms, 100%, p<0.05). **(Figure 1.B)** The proportion of moderate/severe symptom burden in patients vs controls was for the most prominent symptoms: dyspnoea 55.6% vs 4.4%, fatigue 75.6% vs 8.9%, cough 35.6% vs 4.4%, muscle weakness 57.8% vs 4.4%, insomnia 37.8% vs 15.6%, pain 53.3% vs 8.8%, itch 26.7% vs 2.2%, thirst 35.6% vs 0%, micturition night 37.8% vs 11.1% and micturition day 46.7% vs 9.1%. **(Figure 2)** More patients (73.7%) than controls (11.6%) reported 3 or more symptoms. **(Figure 3.B) Figure 4.B** shows that respiratory and non-respiratory symptoms also co-occur frequently in patients with sarcoidosis. For example, all patients suffering gloom also reported fatigue.

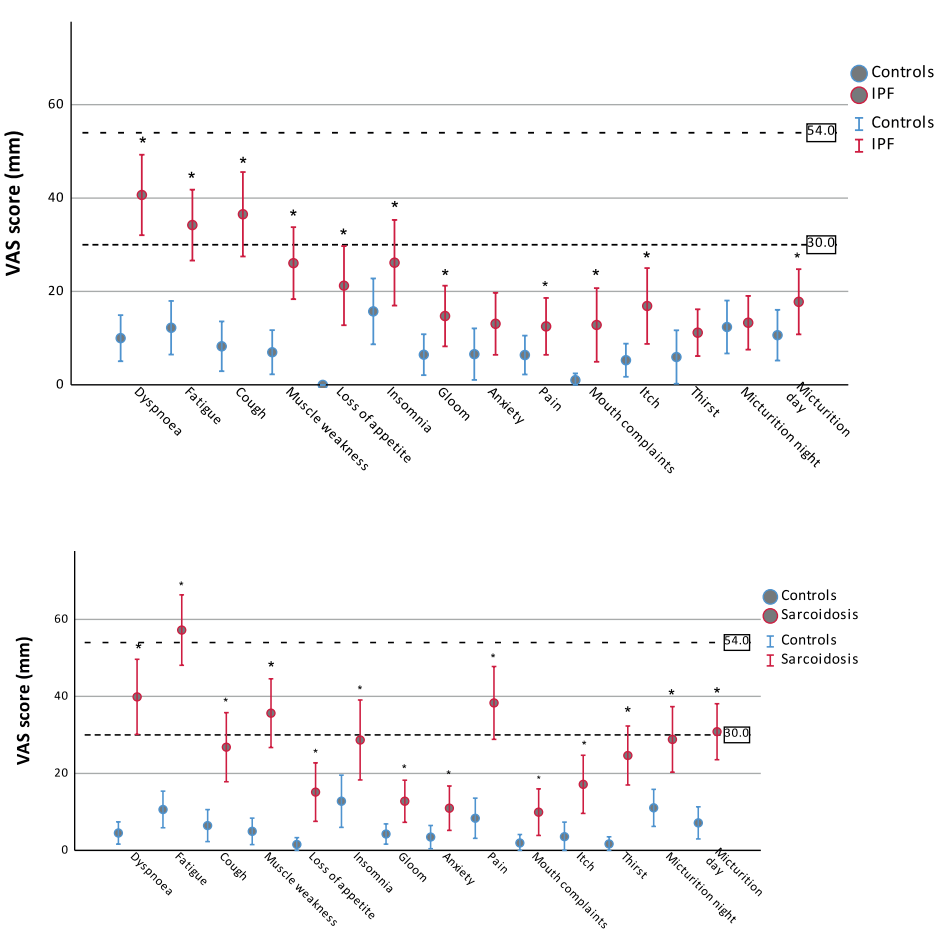

Figure 1:

A *Mean (standard deviation [SD]) visual analogue scale (VAS score) of symptoms in patients with idiopathic pulmonary disease (IPF) or controls without pulmonary disease. Mean VAS scores >30 mm (dotted line) represent moderate severity; Mean VAS scores >54 mm (dotted line) represent severe symptom burden. *p< 0.05 IPF vs control*

B *Mean (standard deviation [SD]) visual analogue scale (VAS score) of symptoms in patients with sarcoidosis or controls without pulmonary disease. Mean VAS scores >30 mm (dotted line) represent moderate severity; Mean VAS scores >54 mm (dotted line) represent severe symptom burden. *p< 0.05 sarcoidosis vs control*

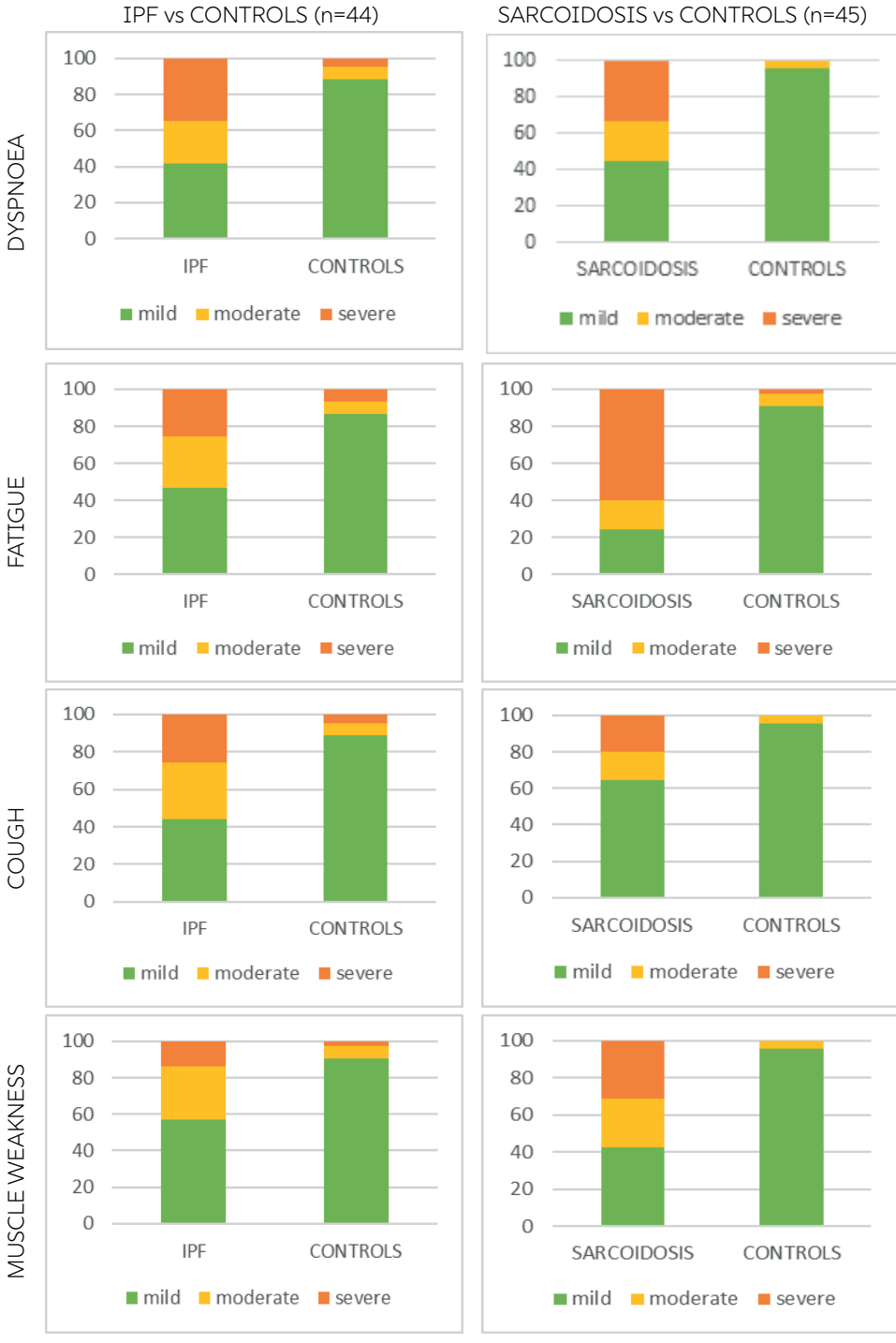

Figure 2

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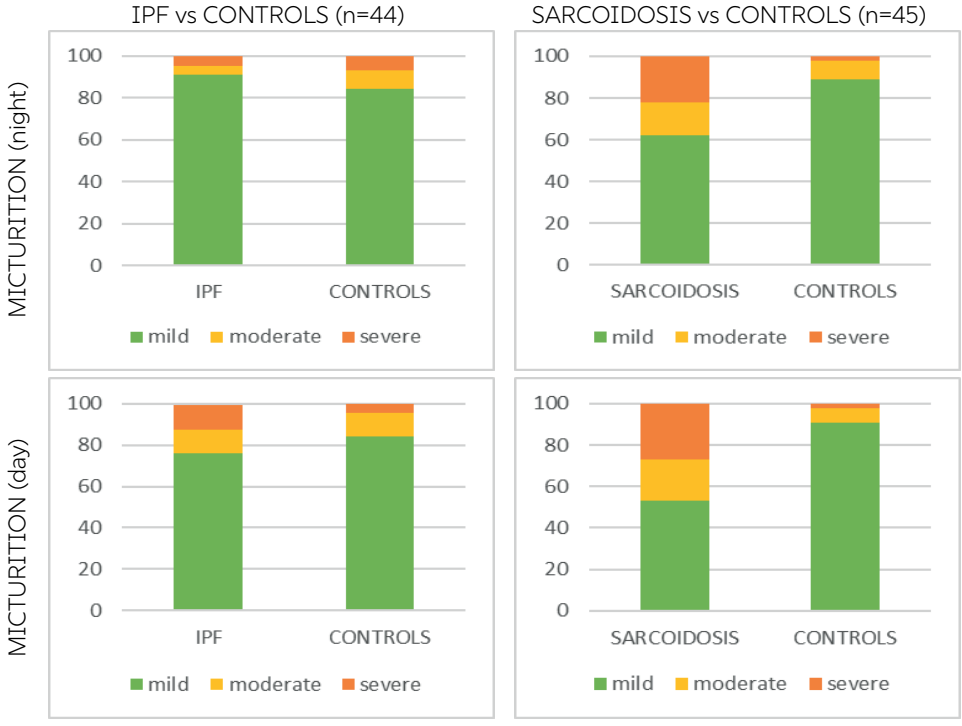
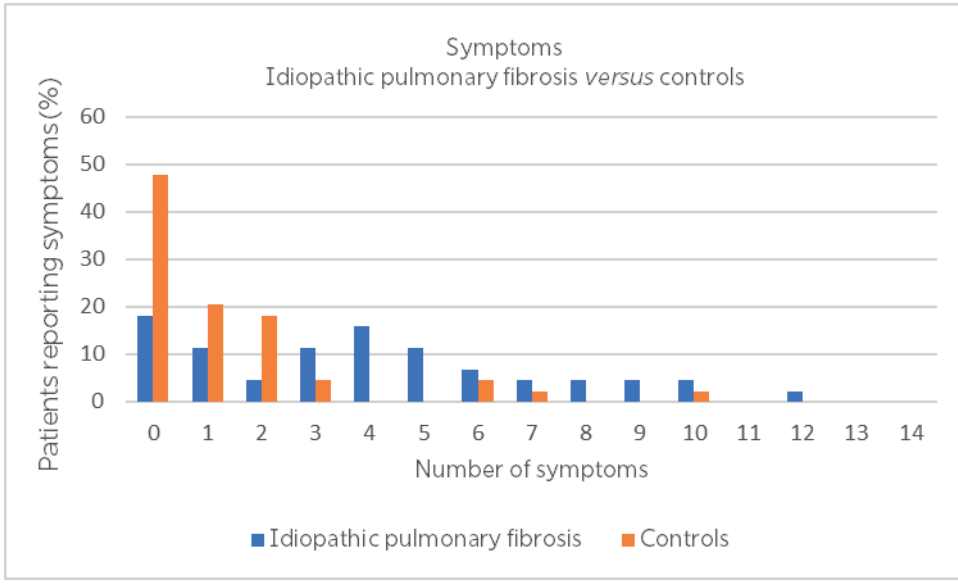


Figure 2: *Symptoms severity mild-moderate-severe on visual analogue scale (VAS score) in patients with idiopathic pulmonary disease (IPF) or sarcoidosis versus individuals without respiratory disease (controls). VAS score, symptom burden mild, moderate or severe: mild ≤ 30 mm, >30 mm moderate ≤54 mm, severe >54 mm.*

A



B

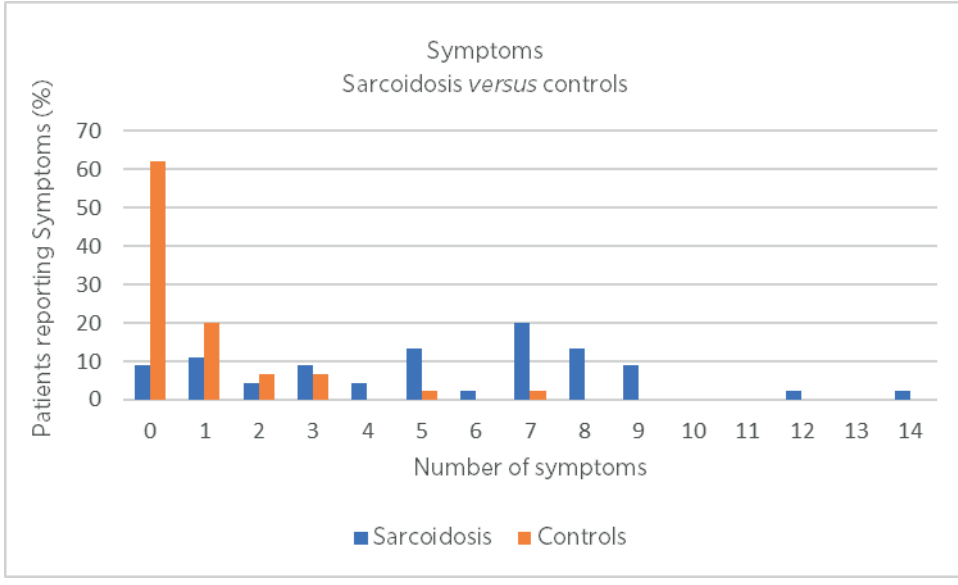


Figure 3 :

A: *Percentage of symptoms, with a symptom severity score >30 mm on Visual Analogue Scale (VAS), in patients with idiopathic pulmonary fibrosis (IPF) or individuals without respiratory disease (controls)*

B: *Percentage of symptoms, with a symptom severity score >30 mm on Visual Analogue Scale (VAS), in patients with sarcoidosis or individuals without respiratory disease (controls)*

A Figure 4

IPF Blue <20% Green 20-40% Yellow 40-60% Red ≥60%	n	% Dyspnoea	% Fatigue	% Cough	% Muscle weakness	% Loss of appetite	% Insomnia	% Gloom	% Anxiety	% Pain	% Mouth complaints	% Itch	% Thirst	% Micturition night	% Micturition day
Dyspnoea	37	X	81.1	56.8	61.1	35.1	40.5	24.3	10.8	18.9	21.6	22.9	16.2	21.6	37.8
Fatigue	34	88.2	X	52.9	69.7	41.2	41.2	32.4	17.6	23.5	26.5	21.9	23.5	29.4	44.1
Cough	27	77.8	66.7	X	55.6	33.3	48.1	29.6	14.8	29.6	22.2	26.9	14.8	18.5	33.3
Muscle weakness	26	84.6	88.5	57.7	X	42.3	42.3	30.8	19.2	23.1	30.8	29.2	11.5	23.1	42.3
Loss of appetite	16	81.3	87.5	56.3	73.3	X	43.8	25.0	12.5	18.8	25.0	6.3	18.8	25.0	50.0
Insomnia	18	83.3	77.8	72.2	61.1	38.9	X	38.9	27.8	38.9	27.8	33.3	11.1	27.8	33.3
Gloom	12	75.0	91.7	66.7	66.7	33.3	58.3	X	58.3	41.7	41.7	36.4	33.3	33.3	50.0
Anxiety	9	44.4	66.7	44.4	55.6	22.2	55.6	77.8	X	55.6	33.3	25.0	22.2	33.3	33.3
Pain	10	70.0	80.0	80.0	60.0	30.0	70.0	50.0	50.0	X	30.0	44.4	20.0	40.0	40.0
Mouth complaints	10	80.0	90.0	60.0	80.0	40.0	50.0	50.0	30.0	30.0	X	25.0	30.0	40.0	60.0
Itch	12	66.7	58.3	63.6	58.3	8.3	50.0	33.3	16.7	33.3	16.7	X	16.7	16.7	33.3
Thirst	9	66.7	88.9	44.4	33.3	33.3	22.2	44.4	22.2	22.2	33.3	25.0	X	33.3	66.7
Micturition night	10	80.0	100.0	50.0	66.7	40.0	50.0	40.0	30.0	40.0	40.0	25.0	30.0	X	90.0
Micturition day	16	87.5	93.8	56.3	73.3	50.0	37.5	37.5	18.8	25.0	37.5	28.6	37.5	56.3	X

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B Figure 4 *(Continued)*

Sarcoidosis Blue <20% Green 20-40% Yellow 40-60% Red ≥60%	n	% Dyspnoea	% Fatigue	% Cough	% Muscle weakness	% Loss of appetite	% Insomnia	% Gloom	% Anxiety	% Pain	% Mouth complaints	% Itch	% Thirst	% Micturition night	% Micturition day
Dyspnoea	34	X	85.3	44.1	70.6	29.4	41.2	26.5	17.6	64.7	23.5	38.2	50.0	50.0	50.0
Fatigue	43	67.4	X	39.5	69.8	27.9	46.5	23.2	14.0	60.5	18.6	37.2	51.2	46.5	48.8
Cough	20	75.0	85.0	X	70.0	30.0	55.0	15.0	10.0	60.0	35.0	50.0	65.0	40.0	55.0
Muscle weakness	33	72.7	90.9	42.4	X	36.4	45.5	27.3	15.2	75.8	24.2	36.4	48.5	54.5	60.6
Loss of appetite	13	76.9	92.3	46.2	92.3	X	61.5	38.5	23.1	84.6	38.5	30.8	46.2	69.2	76.9
Insomnia	23	60.9	87.0	47.8	65.2	34.8	X	21.7	21.7	60.9	26.1	39.1	47.8	47.8	47.8
Gloom	10	90.0	100.0	30.0	90.0	50.0	50.0	X	50.0	70.0	40.0	20.0	40.0	50.0	60.0
Anxiety	7	85.7	85.7	28.6	71.4	42.9	71.4	71.4	X	57.1	28.6	14.3	28.6	42.9	57.1
Pain	29	75.9	89.7	41.4	86.2	37.9	48.3	24.1	13.8	X	27.6	41.4	51.7	58.6	69.0
Mouth complaints	9	88.9	88.9	77.8	88.9	55.6	66.7	44.4	22.2	88.9	X	66.7	100.0	55.6	66.7
Itch	17	48.8	62.8	23.3	48.8	20.9	32.6	18.6	14.0	39.5	7.0	X	18.6	32.6	37.2
Thirst	23	73.9	95.7	56.5	69.6	26.1	47.8	17.4	8.7	65.2	39.1	65.2	X	47.8	56.5
Micturition night	22	77.3	90.9	36.4	81.8	40.9	50.0	22.7	13.7	77.3	22.7	36.4	50.0	X	68.2
Micturition day	24	70.8	87.5	45.8	83.3	41.7	45.8	25.0	16.7	83.3	25.0	33.3	54.2	62.5	X

Figure 4

A *The frequencies of symptoms identified as moderate or severe (VAS>30.0 mm) in patients with idiopathic pulmonary fibrosis (IPF) with concurrent presence of any of the other 14 symptoms. In subjects with the symptom listed in the row present, the prevalence of the other symptom mentioned in the column is shown. For interpretation, the table is colored: blue, less than 20% prevalence; green, 20–40% prevalence; yellow, 40–60% prevalence; and red, more than 60% prevalence.*

B *The frequencies of symptoms identified as moderate or severe (VAS>30.0 mm) in patients with sarcoidosis with concurrent presence of any of the 14 symptoms. In subjects with the symptom listed in the row present, the prevalence of the other symptom mentioned in the column is shown. For interpretation, the table is colored: blue, less than 20% prevalence; green, 20–40% prevalence; yellow, 40–60% prevalence; and red, more than 60% prevalence.*

Discussion

Generally, the burden of respiratory and non-respiratory symptoms is significantly higher in patients with IPF or sarcoidosis compared to individuals without respiratory disease. To the best of our knowledge, this is the first study assessing a wide range of respiratory and non-respiratory symptoms in both patients with IPF or sarcoidosis and controls, and subsequently also examined them in a unified manner using VAS.

We demonstrated that the observed symptom burden was experienced as more severe by patients with IPF compared to controls for 11 of the 14 symptoms and in patients with sarcoidosis for all 14 symptoms.

In patients with IPF, dyspnoea, fatigue, cough, muscle weakness, insomnia, pain, itch and micturition at daytime were the most severe symptoms. The prevalence of moderate-to-severe burden (>30 mm) of respiratory symptoms generally fell within the particular range of the findings of a systematic review for symptom prevalence in fibrotic ILD (dyspnoea 58.2% vs 54.7-98% and cough 55.8% vs 59-94 %, respectively).[10] Psychological problems such as depression or sadness also fell within the range (18.2% vs 10-49.2%), but anxiety was slightly less present in the current study (15.9% vs 22-58%). Although insomnia was comparable between the current cohort and the data presented in the review (29.6% vs 6-46%), the prevalence of fatigue was clearly higher in the current study (53.3% vs 7.6-29%). Whether these differences are due to the use of different outcome measures and/or the inclusion criteria of the different studies remains unknown. Surprisingly, for the outcome of fatigue of the six included studies in the review, only one study used the Fatigue Severity Scale[29], two studies used the Epworth Sleepiness Scale[30] and the other studies based the prevalence of fatigue on retrospective medical records studies with (qualitative) interviews.[10] This could also explain the difference with the higher perceived fatigue in the current study. Next to forementioned known symptoms, the current study added prevalent non-respiratory symptoms in IPF e.g. muscle weakness, loss of appetite, mouth complaints and itch.

Findings of symptom burden in a Dutch sample of patients with sarcoidosis as reported by Voortman and colleagues[11] and the current sample show similarities but also differences. For example, the prevalence of respiratory symptoms was comparable for dyspnoea (55.5% vs 61.1%) and cough (35.6% vs 38.1%) but fatigue and pain were less pronounced in our sample (65.6% vs 90.7% and 53.3% vs 62.5%, respectively). These differences might be partly explained by the different assessment methods used by

Voortman and colleagues who used the Fatigue Assessment Scale to assess fatigue and the Small Fiber Neuropathy Screening List[31] to assess pain. Also, the authors conducted a study with an online questionnaire tool among patients with sarcoidosis who were members of the Dutch Association for Sarcoidosis (388 participants out of 2000 members). In the current study, the sample of patients with sarcoidosis was selected from an outpatient respiratory medicine clinic who may represent a more defined population.

The comparison between patients with IPF or sarcoidosis and controls shows that a significantly higher symptom burden is present in both patient groups than in controls. Although the underlying factors have not been investigated in this study, the underlying causes are probably partly related to the disease itself but probably also to physical, psychological and emotional factors. In patients with COPD, physical deconditioning, pulmonary dysfunction, anxiety and depression are known to be associated with fatigue.[32] The cause of fatigue is poorly understood in ILD, but physiological, psychological, and behavioral factors certainly appear to play a role, with the cause of fatigue likely not appearing to be ILD-specific.[33] Correlation between pulmonary function tests and dyspnoea in patients with ILD appears to be low to moderate, and there is no significant correlation between pulmonary function tests and most other symptoms. So maybe the difference in lung function explains part of the difference between patients and controls, but certainly not all of it. Moreover, muscle weakness can be caused by a reduced physical activity levels in ILD as well as systemic inflammation and perhaps even common comorbidities.[34,35] Importantly, the daily symptoms of patients with ILD partly improve following an exercise-based rehabilitative intervention.[36,37] Indeed, pulmonary rehabilitation focuses on experienced symptoms and their treatment options from a broader perspective and has already proven itself as a safe and effective treatment method.[37-40] Subsequently, in this multidisciplinary and non-pharmacological treatment approach, various specialists are involved who can address experienced symptoms, such as a dietician (loss of appetite), a physiotherapist (exercise limitations and reducing fatigue and/or shortness of breath), and an occupational therapist (complaints during activities of daily living).

Methodological considerations

The present study used data from two robust cross-sectional studies. The symptom burden was assessed in the same way in both studies. The impact of age and gender on the results/comparisons was minimized by a case control matching procedure. Patients' lung function tests were performed in a clinical pulmonary setting, while

controls performed spirometry (FEV1 and FVC) with a portable SpiroPro device at home under the supervision of a trained investigator providing instructions. As a result, TLC, RV and TLCO were not available for the controls. The list of symptoms used in the current study in patients with IPF or sarcoidosis was in accordance with the list used in the controls.[20] Most symptoms investigated in the current study can occur in patients with different respiratory diseases. As a result, other possible existing symptoms, like anorexia, skin lesions, dry eyes and palpitations, were not investigated. The CCI may not include all comorbidities that may occur more specifically in patients with ILD. The differences in respiratory and non-respiratory symptoms could not be explained by these comorbidities studied. Whether and to what extent other comorbidities may partially explain these differences remains to be determined. Also, the limited sample size was a limitation for logistic regression or other sophisticated methods, and did not allow us to correct for all confounders. Future studies should include a larger sample size to arrive at a final answer. Therefore the current data are rather hypothesis generating than final. Lastly, only patients with IPF or sarcoidosis were included for the current study. Therefore, the current findings should not be extrapolated to other ILDs.

Conclusions

This study emphasizes the high prevalence of respiratory and non-respiratory symptoms in patients with IPF or sarcoidosis. Respiratory as well as non-respiratory symptom burden is significantly higher in patients with IPF or sarcoidosis in terms of severity and number of symptoms compared to matched individuals without respiratory disease. The results underline the importance to screen for respiratory and non-respiratory symptoms in patients with IPF and sarcoidosis. Future research is needed to study the underlying mechanisms and subsequent optimal treatment approach.

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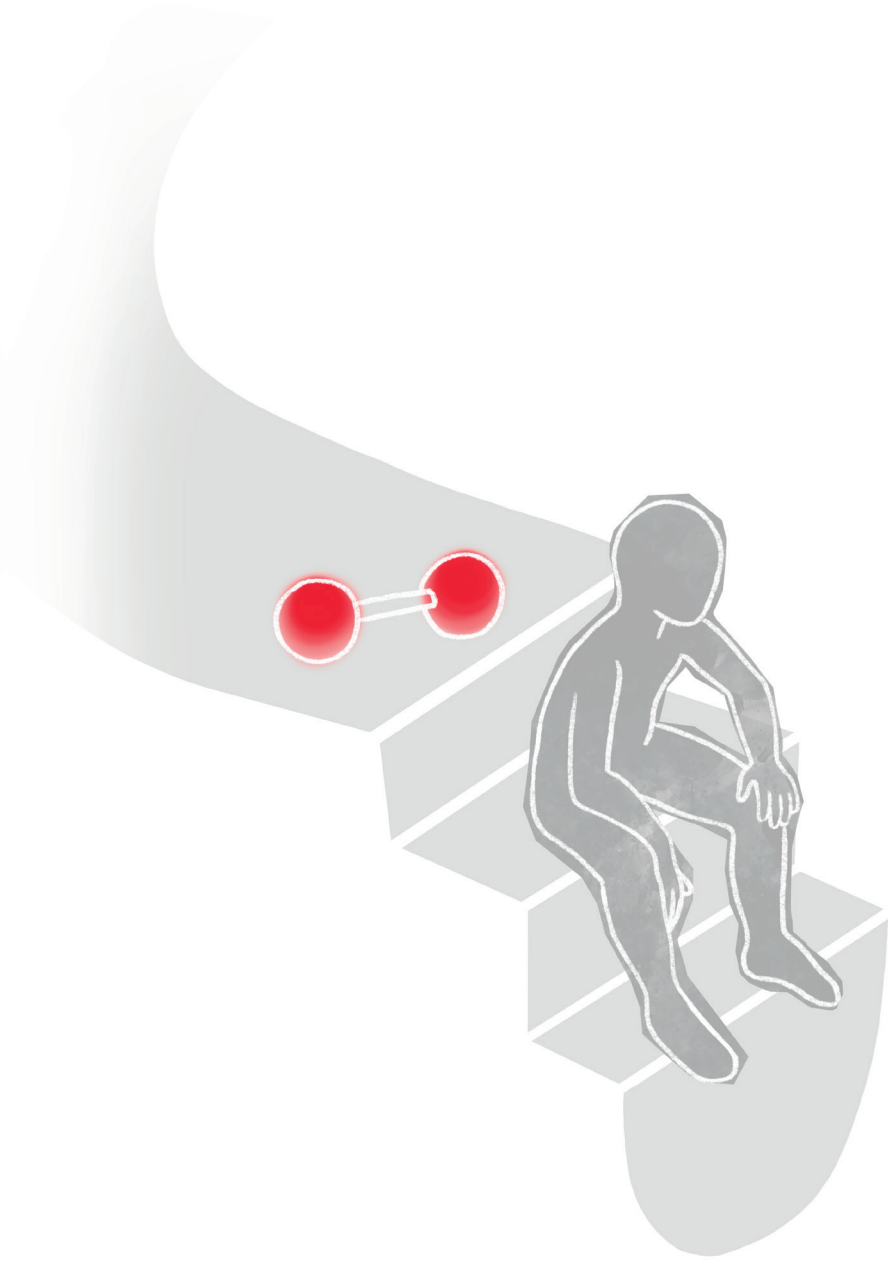

Chapter 5

Patient activation for self-Management in patients with idiopathic pulmonary fibrosis or sarcoidosis

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Abstract

Background: Self-management is considered important in the management of patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis. However, data about the degree of activation for self-management is lacking.

Objectives: The aim of the study was to determine the degree of activation for self-management in patients with IPF or sarcoidosis using the Patient Activation Measure (PAM) and to evaluate the association between PAM scores, clinical characteristics, and health-related outcomes.

Study Design and Methods: This cross-sectional prospective study assessed besides the PAM also demographics, lung function, dyspnoea (modified-Medical Research Council (mMRC)), fatigue (Checklist Individual Strength-Fatigue (CIS-Fatigue)), anxiety/depression (Hospital Anxiety and Depression Scale (HADS-A/HADS-D)) and generic health status (EuroQol five-dimensional-five-level (EQ-5D-5L)).

Results: Mean PAM was 55.0 (9.1) points in patients with IPF (n = 59), and low levels of patient activation for self-management (PAM ≤55.1 points) were present in 56% of the patients. PAM Scores correlated significantly (p <0.05) with mMRC (p=-0.476), HADS-A (p =-0.326), HADS-D (p =-0.459) and EQ-5D-5L (p =0.393). In patients with sarcoidosis (n=59) the mean PAM score was 55.7 (11.0) points, and 46% of the patients reported low PAM levels. Significant correlations were found with mMRC (p =-0.356), HADS-A (p=-0.394), HADS-D (p =-0.478) and EQ-5D-5L (p =0.313).

Conclusion: About half of the outpatients with IPF or sarcoidosis have a low degree of activation for self-management, and these patients generally report more dyspnoea, anxiety, depression and a lower health status. Whether patients with a low degree of activation can be successful in self-managing their disease remains to be determined.

Keywords: Interstitial lung disease, Idiopathic pulmonary disease, Sarcoidosis, Patient activation measure, Self-management

Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of diffuse parenchymal lung disorders, most of them chronic with different pathogenesis and prognosis. Two common forms of ILDs are idiopathic pulmonary fibrosis (IPF) and sarcoidosis.[1,2] Pharmacotherapy is a central part of the chronic management of these diseases to stabilize lung function and quality of life.[1] One may expect that patients should be activated and informed in health and disease management. They need to have the knowledge, the skills, confidence, and the essentials for an activated patient to self-manage their health challenges.[3] Self-management, which refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent to living with a chronic condition[4], is a key issue to increase patients' ability to deal with consequences of their disease to maintain a satisfactory quality of life (QoL).[4,5,6] Patient activation indicates the level of involvement in self-management. The activation levels range from disengaged and being over-whelmed up to taking action and control, maintaining behavior and pushing further.[3] Interestingly, there is a growing body of literature indicating that activated patients with chronic diseases have better self-management behaviors, better patient outcomes, and lower health-care costs compared to patients with low levels of activation for self-management.[7,8,9] So, the patient's level of activation for self-management may provide an indication of his/her tendency in positive health behaviors.

The Patient Activation Measure (PAM) was designed to assess the level of patient activation for self-management. By using pre-defined cutoffs, the PAM classifies patients into four levels: (1) passive and feeling overwhelmed, may not yet be willing to believe that the patient role is important, (2) lacking confidence and knowledge to manage their health, (3) beginning to take action but may still be lacking the confidence and skills, or (4) have already adopted many behaviors needed to support their health, but possibly still having difficulty maintaining behaviors over time.[3,10,11] Indeed, PAM scores have been shown indicative for self-management behaviors in patients with chronic health conditions.[12] Moreover, patients with higher PAM scores have better care experiences compared to patients with lower scores[13], are more likely to make use of online health information[14], and generate lower health care costs.[8]

To date, there is a lack of information about the level of activation for self-management in patients with IPF. Moreover, it is interesting to gain insight into which factors may play a role in this patient activation in self-management. Knowing patients' level

of activation for self-management seems clinically relevant, as self-management increasingly becomes part of their own disease management.[8,15,16] Therefore, the present study had three objectives: 1) to determine the level of patient activation for self-management in patients with IPF or sarcoidosis; 2) to compare clinical characteristics between patients with low or high levels of patients activation for self-management per disease; and 3) to investigate the association between patient activation levels, clinical characteristics and health-related outcomes.

Materials and Methods

Study design, participants and procedure

A cross-sectional study was performed. Ethical approval was obtained from the local Medical Research Ethics Committee (METCZ20180027) and the study was registered at the Netherlands Trial Register (Trialcode7201). Written informed consent was provided by all patients before study entry. Eligible patients were adults (age ≥18 years) with a confirmed diagnosis of IPF[2,17] or pulmonary sarcoidosis[18,19] visiting the outpatient clinic of the Department of Respiratory Medicine, Zuyderland Medical Centre Heerlen (The Netherlands) between May 2018 and March 2019. Exclusion criteria were insufficient understanding of the Dutch language and/or inability to complete questionnaires because of cognitive impairment or simultaneous participation in an intervention study that may have impacted the outcome of this study.

Measures

The primary outcome measure was the degree of patient activation for self-management, measured by the Dutch version of the PAM.[20] The PAM consists of 13-items with each 5 answering options; 4 options on a 4-point Likert scale ('totally disagree', 'disagree', 'agree', 'totally agree') and the 5th option 'non applicable'. Different stages of patient activation are assessed: believing an active role is important; having confidence and knowledge to take action; taking action; and continuing healthy behaviors under stress. The PAM is reliable, valid and psychometric properties of the Dutch PAM were generally good, also in an older, multimorbid population.[3,20,21,22] These findings were confirmed in patients with chronic cardiovascular or neurological diseases.[23] The raw data were presented to the independent organization Insignia Health, the official developers of the PAM, to calculate the standardised patient activation score.[24]

Subsequently, the levels of patient activation were determined in a conversion table based on the algorithms of Insignia Health. The PAM score ranged from 0 to 100 points (results o and 100 were considered as "missing data") and classified the respondents into four calibration levels: level 1 'not believing activation important' (≤47.0 points); level 2 'a lack of knowledge and confidence to take action'(47.1-55.1 points); level 3 'beginning to take action' (55.2-67.0 points); level 4 'taking action' (≥67.1 points). Self-management PAM calibration levels 1 and 2 together are defined as 'low levels of activation', while levels 3 and 4 are defined as 'high levels of activation'.

Demographic data were collected to provide information on gender, age (years), body mass index (BMI, kg/m2), partner (yes/no), living status (yes/no cohabiting), education level ("low educated" meaning maximally a preparatory vocational education and "educated" meaning at least secondary school or higher), diagnosis history of the lung disease (years) and hospitalization <1 year (yes/no), work <2 years (yes/no), a history of psychological support (yes/no), smoking status (never/former/current). Spirometry data (forced vital capacity, forced expiratory volume in one second; litre, % predicted), static lung volumes (total lung capacity, residual volume; liter, % predicted), and diffusing capacity for carbon monoxide (TLCO; % predicted)[25], the number of comorbidities and medication were obtained <3 months of completing the questionnaire.

Situational dyspnoea was measured with the modified Medical Research Council dyspnea scale (mMRC).[26,27] For measuring fatigue the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue) was used, consisting of 8 items scored on a 7-point Likert scale, with a range of score from 8 (normal fatigue) to 56 (most severe fatigue). A score of ≥36 points indicates severe fatigue.[28,29] Anxiety and depression were scored using the well-validated hospital anxiety and depression scale (HADS)[30], consisting of 14 items in the subscales anxiety (HADS-A) and depression (HADS-D). Total scores for each subscale range from 0 to 21 points, categorized as: normal/mild (0–10 points) and moderate/severe (11–21 points). A generic instrument to assess health-related quality of life (HRQoL) is the EuroQol five-dimensional descriptive system (EQ-5D-5L). The EQ-5D-5L is a 5-dimension list (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 levels of classification (no problems, slight, moderate, severe, extreme problems). The results are together converted into an index value (EQ-5D-5L-index): a higher score corresponds with a better HRQoL. Moreover, patients indicate a self-rated health on a visual analogue scale (EQ-5D-5L-VAS), where the end points were labelled from 0 ("worst imaginable health") to 100 points ("best imaginable health").[31,32 33]

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics (Version 25). Data were presented with appropriate measures of central tendency and dispersion. Numerical data were tested for normality by Shapiro-Wilkinson test, a mean-median ratio, SD-mean ratio, and judging the histogra.[34] Differences between groups for continuous data were analyzed by an unpaired t-test or the non-parametric pendant (Mann–Whitney U test) where appropriate. Categorical data were analyzed with the $\chi 2$ or Fisher Exact test. Correlations were analyzed with Pearson's r or Spearman's rho where appropriate. In case of missing values, cases were excluded pairwise. The range for what constitutes a weak, moderately strong, strong, or very strong correlation was respectively $0.1 \leq r < 0.3$, $0.3 \leq r < 0.5$, $0.5 \leq r < 0.7$, and $0.7 \leq r < 1.0$.[35,36] A multivariable model (backward regression) was conducted to assess the associations between the dependent variable PAM level and the independent, in univariate analysis significant, variables ($p < 0.05$). In case of multicollinearity, identified variables (variance inflation factor [VIF] > 5) were removed from the model.[37] A p value of ≤ 0.05 was considered as statistically significant.

Results

Characteristics

121 of the 170 (71%) invited patients consented to participate whereof three patients were excluded from the analysis due to absence of PAM data. This convenience sample consisted of 59 patients with IPF and 59 patients with sarcoidosis. Patients characteristics are presented in **Table 1, 2**. In general, patients with IPF differed significant ($p < 0.05$) from the patients with sarcoidosis in prevalence of men, age, education level, working in past 2 years, visiting a psychologist and smoking status, lung function and dyspnoea.

Patients activation in patients with IPF

Mean PAM score in patients with IPF was 55.0 points (SD 9.1) and 56% showed low levels of activation for self-management (shown in **Fig. 1**). Dyspnoea, anxiety, depression, and HRQoL differed significantly between the group with low versus high levels of activation for self-management (**Table 2**). Lung function, fatigue and the EQ-5D-5L-VAS were similar between groups.

Table 1: General characteristics of patients with interstitial lung disease, IPF or sarcoidosis, stratified for patient adequate self-management based on the PAM

Variables	Patients with IPF	Self-Management in Patients with IPF		p value	Patients with Sarcoidosis	Self-Management in Patients with Sarcoidosis		p value
		Level 1-2 PAM ≤55.1 points	Level 3-4 PAM ≥55.2 points			Level 1-2 PAM ≤55.1 points	Level 3-4 PAM ≥55.2 points	
N (%)	59 (50)	33 (56)	26 (44)		59 (50)	27 (46)	32 (54)	
PAM Score, points (0-100)	55.0 ± 9.1	48.8 ± 4.4	62.9 ± 7.1	<0.01	55.7 ± 11.0	46.6 ± 6.2	63.4 ± 7.8	<0.01
Gender, male	45 (76)	23 (70)	22 (85)	ns*	29 (49)	12 (44)	17 (53)	ns*
Age, years	73.0 [70-78]	72.0 [66.5-77.0]	74.5 [70.8-78.0]	ns	53.0 [46.0-62.0]	53.0 [47.0-60.0]	53.5 [45.3-62.0]	ns
BMI, kg/m2 [a]	27.4 ±4.1	28.1 ± 4.4	26.6 ± 3.6	ns	27.5 ± 4.2	27.6 ± 4.4	27.4 ± 4.1	ns
Partner	43 (73)	25 (76)	18 (69)	ns*	43 (73)	18 (67)	25 (78)	ns*
Living together	39 (66)	21 (64)	18 (69)	ns*	41 (70)	17 (63)	24 (75)	ns*
Education, ≥secondary level[b]	27 (47)	12 (39)	15 (58)	ns*	46 (78)	20 (74)	26 (81)	ns*
Diagnosis time ≤1 year[a]	21 (36)	11 (33)	10 (39)	ns*	16 (28)	10 (37)	6 (19)	ns*
Hospitalization ≤1 year[a]	13 (22)	10 (30)	3 (12)	ns*	10 (17)	6 (23)	4 (13)	ns*
Work last 2 years	11 (19)	6 (18)	5 (19)	ns*	37 (63)	17 (63)	20 (63)	ns*
Psychological support	8 (14)	5 (15)	3 (12)	ns*	19 (32)	10 (37)	9 (28)	ns*
Smoking current/former[a]	46 (78)	26 (79)	20 (77)	ns*	23 (40)	10 (39)	13 (41)	ns*
Pack-years+ [g]	13.8 ± 18.8	17.6 ± 20.9	8.4 ± 14.0	ns	4.0 ± 9.8	3.9 ± 9.6	4.0 ± 10.2	ns
TLC, L[e]	4.6 ± 1 .1	4.5 ± 1.1	4.6 ± .1	ns	6.0 ± 1.3	6.0 ± 0.9	6.0 ± 1.5	ns
TLC, % predicted[f]	73.4 ± 14.2	72.8 ± 13.0	74.1 ± 15.9	ns	98.8 ± 18.6	100.3 ± 13.1	97.7 ± 21.9	ns
RV, Ld	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	ns	2.0 ± 0.5	1.9 ± 0.5	2.0 ± 0.6	ns
RV, % predicted[f]	64.9 ± 14.3	65.8 ± 13.9	63.6 ± 14.9	ns	98.2 ± 25.9	98.4 ± 22.1	98.0 ± 28.7	ns
FVC, L	2.9 ± 0.8	2.8 ± 0.9	2.9 ± 0.8	ns	3.9 ± 1.1	3.9 ± 1.0	3.9 ± 1.2	ns
FVC, % predicted	82.9 ± 19.6	81.6 ± 19.8	84.5 ± 9.6	ns	98.3 ± 20.9	98.6 ± 18.8	98.2 ± 22.8	ns
FEV_1, L	2.3 ± 0.6	2.3 ± 0.6	2.4 ± 0.6	ns	3.0 ± 0.9	3.0 ± 0.9	2.9 ± 0.8	ns
FEV_1% predicted	87.0 ± 20.7	84.4 ± 21.3	90.2 ± 19.9	ns	91.6 ± 20.5	93.4 ± 19.6	90.0 ± 21.4	ns
TLCO, L[c]	3.8 ± 1.3	3.7 ± 1.5	3.8 ± 0.9	ns	7.3 ± 2.0	7.3 ± 2.2	7.3 ± 2.0	ns
TLCO, % predicted[c]	48.0 ± 14.8	47.0 ± 16.4	49.2 ± 12.5	ns	81.5 ± 8.4	81.0 ± 17.8	81.9 ± 19.1	ns
Comorbidity : None	14 (24)	6 (18)	8 (31)	ns*	29 (49)	15 (56)	14 (44)	ns*
1	25 (42)	14 (42)	11 (42)	ns*	18 (31)	5 (19)	13 (41)	ns*
>1	20 (34	13 (39	7 (27	ns*	12 (20)	7 (25.9)	5 (16)	ns*
IPF - antifibrotic	52 (88)	31 (94)	21 (82)	ns*	0 (0)	0 (0)	0 (0)	ns*
Immunosuppressant incl. prednisone (corticosteroids)	5 (9)	2 (6)	3 (12)	ns*	23 (39)	10 (37)	13 (41)	ns*
Heart rate-lowering medication	16 (27)	8 (24)	8 (31)	ns*	7 (12)	2 (7)	5 (16)	ns*
Antidepressant medication	5 (9)	2 (6)	3 (12)	ns*	1 (2)	1 (4)	0 (0)	ns*
Antihypertensive medication	26 (44)	16 (49)	10 (39)	ns*	11 (19)	5 (19)	6 (19)	ns*
Other medication for pulmonary conditions	7 (12)	5 (15)	2 (8)	ns*	33 (56)	15 (56)	18 (56)	ns*

*Data are presented as mean ± SD, median [interquartile range], or number (%). BMI, body mass index (kg/m2); FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Incl., included; IPF, idiopathic pulmonary fibrosis; PAM, Patient Activation Measure; RV, residual volume; RV/TLC ratio, residual volume to total lung capacity ratio; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide (measured in ml/min/mm Hg). * Pearson χ^2. + Pack-year, number of years smoking x average number of cigarettes smoked per day/20. Alphabetic characters in superscript indicates a sample size deviant from n = 117, in the order: [a] n = 117, [b] n = 116, [c] n = 113, [d] n = 112, [e] n = 111, [f] n = 110, [g] n = 92.*

Table 2: Questionnaire results of patients with interstitial lung disease, IPF or sarcoidosis, stratified for patient adequate self-management based on the PAM

Variables	Patients with IPF	Self-Management in Patients with IPF		p value	Patients with Sarcoidosis	Self-Management in Patients with Sarcoidosis		p value
		low levels PAM ≤55.1 points	high levels PAM ≥55.2 points			low levels PAM ≤55.1 points	high levels PAM ≥55.2 points	
N (%)	59 (50)	33 (56)	26 (44)		59 (50)	27 (46)	32 (54)	
PAM, points (0-100)	55.0 ± 9.1	48.8 ± 4.4	62.9 ± 7.1	p<0.01	55.7 ± 11.0	46.6 ± 6.2	63.4 ± 7.8	p<0.01
mMRC, points (0-4)[d]	1.9 ± 1.2	2.3 ± 1.3	1.3 ± 0.9	p<0.01	1.4 ± 1.1	1.8 ± 1.2	1.1 ± 1.0	p<0.05
mMRC grade ≥2 (moderate-severe dyspnoea)[d]	30 (53)	21 (66)	9 (36)	p<0.05*	20 (37)	11 (48)	9 (29)	ns
CIS-Fatigue, points (8-56)[b]	34.4 ± 10.9	35.7 ± 12.0	32.9 ± 9.5	ns	40.5 ± 11.7	42.5 ± 10.5	38.8 ± 12.6	ns
CIS Severe >35 points[b]	28 (48)	16 (50)	12 (46)	ns	40 (70)	20 (74)	20 (63)	ns
HADS anxiety range 0-21, points[c]	5.0 [2.3-8.0]	6.0 [3.3-8.0]	4.0 [1.3-6.8]	p<0.05**	4.0 [2.0-7.3]	6.0 [2.3-10.0]	3.5 [2.0-5.0]	p<0.05**
HADS anxiety ≥11points[c]	5 (9)	4 (13)	1 (4)	ns	7 (12)	5 (19)	2 (6)	ns
HADS depression range 0-21, points[b]	5.0 [2.3-7.0]	5.5 [4.0-8.0]	3.0 [1.3-5.8]	p<0.01**	4.0 [1.0-7.0]	7.0 [3.0-9.0]	2.0 [1.0-5.8]	p<0.01**
HADS depression ≥11points[d]	5 (9)	5 (16)	0 (0)	ns	5 (9)	4 (15)	1 (3)	ns
EQ-5D-5L index values, points (0-1)[a]	0.73 ± 0.18	0.68 ± 0.18	0.80 ± 0.16	p<0.01	0.74 ± 0.23	0.70 ± 0.25	0.78 ± 0.20	ns
EQ-5D-5L VAS, points (0-100)	63.3 ± 16.4	61.0 ± 14.7	66.3 ± 18.2	ns	62.7 ± 19.6	61.1 ± 20.3	64.1 ± 19.2	ns

*Data are presented as mean ± SD, median [interquartile range], or n (%). CIS, Checklist Individual Strength; EQ-5D-5L: EuroQol, 5 dimensions, 5 levels (standardized measure of health status); HADS, Hospital Anxiety and Depression Scale; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council dyspnoea scale; PAM, Patient Activation Measure. * Pearson χ^2. **Mann-Whitney U Test. Alphabetic characters in superscript indicates a sample size deviant from n = 118, in the order: [a] n = 117, [b] n = 115, [c] n = 114, [d] n = 111*

PAM scores correlated moderately strong with mMRC p= -0.48 (p<0.01), HADS-A p= -0.33 (p<0.05), HADS-D p= -0.46 (p<0.01), and EQ-5D-5L p= 0.39 (p<0.01). The explained variance (R^2) of the multivariable model was 34% (regression equation: PAM = 64.0 – 2.1*mMRC – 1.1*HADS-D; SEE 9).

Patient activation in patients with sarcoidosis

In patients with sarcoidosis the mean PAM score was 55.7 points (SD 11.0) and 46% showed low levels of activation for self-management (shown in **Fig. 1**). Dyspnoea, anxiety, and depression differed significantly between low levels versus high levels of patient activation for self-management. Lung function, CIS-Fatigue, HRQoL, and EQ-5D-5L-VAS were similar between groups (**Table 2**). PAM scores correlated moderately strong with the mMRC p= -0.36 (p<0.01), HADS-A p= -0.39 (p<0.01), HADS-D p= -0.48 (p<0.01), and EQ-5D-5L p= 0.31 (p<0.05). The explained variance (R2) of the multivariable model was 16% (regression equation: PAM = 62.3 – 1.3*HADS-D; SEE 10).

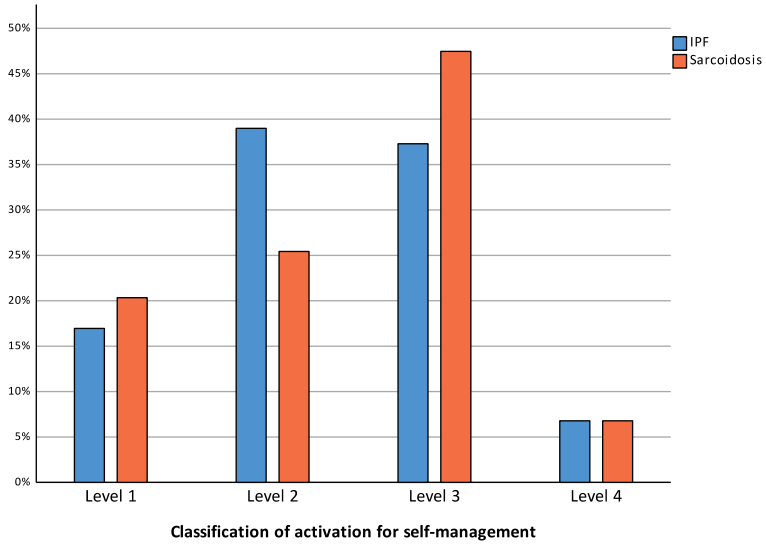

Figure 1: *Activation for self-management in patients with IPF or sarcoidosis according to the PAM. PAM, classification of the four calibration levels: level 1 'not believing activation important' (≤47.0 points); level 2 'a lack of knowledge and confidence to take action'(47.1-55.1 points); level 3 'beginning to take action' (55.2-67.0 points); level 4 'taking action' (≥67.1 points)*

Abbreviations: IPF Idiopathic Pulmonary Fibrosis; PAM Patient Activation Measure

Discussion

This is the first study to assess the level of patient activation for self-management in patients with ILD. About half of patients with IPF or pulmonary sarcoidosis attending the specialized ILD outpatient consultation had low levels of activation for self-management. These findings suggest that in about half of the patients their role in managing health, the knowledge and confidence for doing so may be insufficient for optimal health behaviors in self-management. Interestingly, levels of patient activation were not associated with the degree of lung function impairment. In contrast, lower levels of patient activation for self-management were associated with more dyspnoea, more anxiety, more depression and worse health status.

The level of patient activation for self-management varies considerably between populations. Low levels of patient activation were found in 22% of U.S. adults [9] and in 70% of frail older adults (median age 87 year, median PAM score of 51 points).[38] In patients with COPD (Chronic Obstructive Pulmonary Disease) an average PAM score of 59 points was found, in diabetes 55 points, in chronic heart failure 54 points, in chronic renal failure 51 points, in cancer survivors 56 points and in asthma 66 points.[16,39,40]
So, low PAM scores occur in different chronic diseases, suggesting a trans-diagnostic issue. This is confirmed by the fact that low PAM scores were associated with generic characteristics (such as a higher BMI, more financial distress, a higher comorbidity index score, a medium education level, a shorter disease duration, a more negative illness perception, living alone and being depressed) in a sample of patients with diabetes mellitus, COPD, chronic renal failure and chronic heart failure.[41] The current analyses shows significantly higher mean anxiety and depression scores on the HADS in the patients with low PAM scores (**Table 2**). This is in line with previous observations in patients with COPD[42] or atrial fibrillation.[43] This may suggest that the PAM score is partly biased by mood status. However, the current study design does not allow establishment of causality and directionality between the PAM scores and the HADS scores, if present at all. Indeed most patients with low PAM scores did not have high symptoms of anxiety and depression in the current study. The impact of a chronic disease on QoL is at least partially determined by the patient's degree of self-management capacity.[44,45] The significant association between PAM scores and EQ-5D-5L scores in the current study, corroborates this again. This also emphasizes the importance for these patients to take an active role in managing their health.[17,46]

Despite the clinical relevance of interventions aiming to support self-management of patients with ILD, this topic has been limited addressed in research, so far. Results from a recent, first-ever eHealth study in patients with IPF were disappointing with respect to overall HRQoL. Moor and colleagues found in a randomized clinical trial, that a comprehensive home monitoring program did not improve overall HRQoL, although it tended to improve psychological wellbeing.[15] Unfortunately, the level of patient activation for self-management was not assessed. Moreover, patients with a low activation for self-management may even have declined participation in an eHealth study. Low activation levels may explain, at least partially, the negative study results. Should such an effect modification exist than could the PAM be utilized as instrument in the selection of suitable candidates for this type of self-management tools.[6,47,48]

Key to self-management is that the patient gets more empowered, takes his responsibility and anticipates on different situations to manage his health. A patient's engagement and health outcomes can improve by intervening to increase activation.[8,11] Applying motivational interviewing techniques have shown to higher PAM scores in patients with chronic conditions.[49,50] To date, there are no studies aiming at enhancement of activation for self-management in patients with ILD.

Health care providers also have an important role to patients in their support self-management. This also requires further attention. Indeed, self-reported attitudes and the actual practices of healthcare professionals in the pulmonary rehabilitation setting showed that, despite they embrace patient self-management and value patient involvement in their care, they still need to improve their positive attitudes toward patient's participation.[51] This means that also healthcare professionals should be supported into their behavior to help the patient in self-management.

Limitations and Strengths

ILDs encompass a wide range of diseases. Inclusion for this study was restricted to patients with established IPF or pulmonary sarcoidosis, and only patients were included who were visiting the outpatient consultation of an ILD-specialized pulmonologist (RM). This may limit the external validity of the current findings. Second, the cross-sectional design did not allow to assess patient activation levels over time. It is widely recognized that patient activation is changeable and can be increased by targeted interventions.[11,52] Third, no insights were investigated into possible processes that already support in self-management activities. Fourth, it remains unknown why patients

declined participation from this study. Deselection of less activated patients could not be ruled out possibly resulting in underestimation of the proportion of patients with lower levels of activation.

The current study had three major strengths: First, the relatively large sample size of patients with IPF (an orphan disease) or pulmonary sarcoidosis. Second, the PAM questionnaire was administrated well (98%), only 3 questionnaires were incomplete. Third, all PAM data were calculated and registered by the conversion table of Insignia Health, so PAM data were presented using the uniform international manner.

Conclusion

To conclude, this is the first study investigating the level of patient activation for self-management in patients with IPF or pulmonary sarcoidosis. Low levels of patient activation for self-management were seen in about half of the patients. Further research is need to understand whether and to what extent these patients may not be able to self-manage their health and health care, or do not appear to take action or to manage their health and care.

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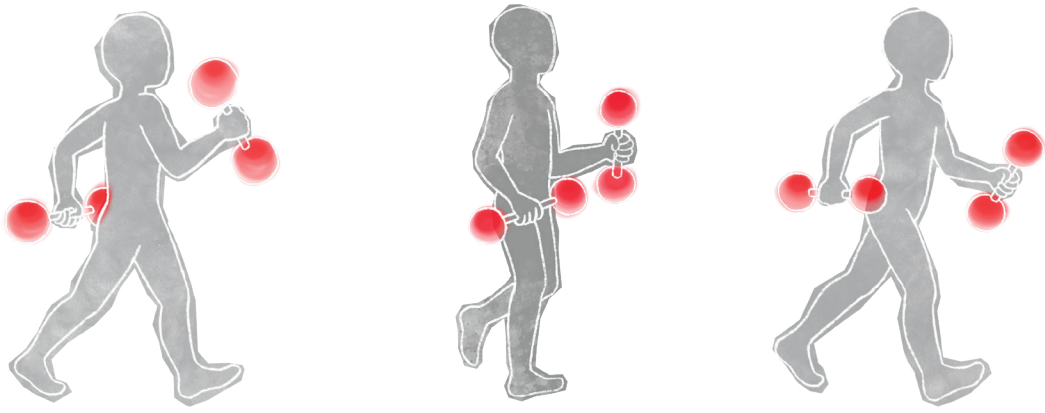

Chapter 6

Within-day test–retest reliability of the 6-min walk test in patients with pulmonary fibrosis

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To the Editor:

Interstitial lung diseases (ILDs) are a group of more than 150 different disorders characterized by inflammation of the lung parenchyma, or interstitium, often followed by the occurrence of pulmonary fibrosis. Patients with pulmonary fibrosis complain about exertional dyspnoea, exercise intolerance and reduced quality of life.[1] Poor exercise tolerance and oxygen desaturation during exercise are associated with poor survival.[2] Therefore, measuring exercise capacity in patients with pulmonary fibrosis is an important element of clinical management. The 6-min walk test (6MWT) is one of the most widely used clinical tests of functional exercise capacity in people with pulmonary fibrosis.[3,4]

The official European Respiratory Society (ERS)/American Thoracic Society (ATS) technical standard recommends that two 6MWTs should be performed as there is strong evidence of a learning effect on repetition.[3] Indeed, a mean improvement of 26.3 m during the second 6MWT has been found in patients with chronic obstructive pulmonary disease (COPD).[5] Whether, and to what extent, the 6MWT is reproducible in patients with pulmonary fibrosis has been studied scarcely and, in one example, Kozu et al.[6] reported a mean improvement of only 11 meters during the second 6MWT in 35 patients with idiopathic pulmonary fibrosis (IPF). Indeed, performing the 6MWT twice in 1 day may prove too burdensome for the patient and too time consuming as, during a 1-day visit to a specialized ILD clinic, patients are already asked to undergo routine clinical tests (such as spirometry and chest X-rays) and to have blood drawn. The aim of this study was to assess the test–retest reliability of the 6MWT when performed within 1 day in patients with pulmonary fibrosis.

Data were collected in a prospective clinometric validation study that took place at the ILD Centre of Excellence, St. Antonius Hospital, Nieuwegein, The Netherlands, from June to December 2015 (Medical Research Ethics Committees United, NL51679.100.15/PT-PF). Eligible for participation were patients aged 18 years or older with a confirmed pulmonary fibrosis diagnosis according to the diagnostic criteria laid out in the *ERS/ATS* consensus statement[1]. Subjects were excluded if they had known cardiovascular or musculoskeletal disease that would prevent them from completing the 6MWT so as to conform to the official *ERS/ATS* technical standard.[3] Statistical analysis was performed using IBM SPSS Statistics (Version 23). The correlation of the distance walked in the 6MWT between test and retest was calculated by intraclass correlation coefficient (ICC) of single measures and absolute agreement with random effect (95% CI; $p<0.05$).

Before the start of the first 6MWT, blood pressure (BP; mmHg), heart rate (HR; beats·min^{-1}), transcutaneous oxygen saturation (SpO_2; % measured by pulse oximetry using a Nellcor-N-20 pulse oximeter (Medtronic, Minneapolis, MN, USA)), body mass index (BMI; kg·m^{-2}) and body fat percentage (BFP; measured using an Omron HBF-306 body fat monitor (Omron Corp., Kyoto, Japan)) were assessed. Additionally, the medical research council (MRC) ratings[7] for situational perception of breathlessness were obtained.

Subjects performed the 6MWT according to the official *ERS/ATS* technical standards.[3] In brief, the 6MWT took place in a quiet 30-m corridor and only standardised instructions and encouragement were given. It was performed twice in 1 day with the interval between tests being a minimum of 1 h and with each test starting at baseline values of heart rate (HR_{rest}) and oxygen saturation (SpO_{2Rest}). Each test was supervised by one of two trained physiotherapists (who walked slightly behind the subjects to avoid setting the walking pace) and, if present, oxygen therapy was delivered at a constant flow rate during both tests. Both SpO_2 and HR were monitored continuously during the test (telemetry), including after test end to determine the degree of heart rate recovery (HRR). Patients were not stopped during the test when SpO_2 was below 80%, as this also occurs during daily activities.[8]

The primary outcome was the distance covered in 6 min (6MWD; m) while secondary outcomes included the lowest level of oxygen saturation (SpO_{2Low}), the peak heart rate (HR_{peak}), the chronotropic response (CR; where $CR=HR_{peak}-HR_{rest}$), and the degree of heart rate recovery between end of test and 1 min into recovery (HRR1; where $HRR_1=H_{Rend}-H_{Rend+1}$).[9] Ratings for dyspnoea and leg fatigue (using a modified 0–10 Borg scale) were also obtained before and after each 6MWT.[10]

The sample consisted of 51 pulmonary fibrosis patients with a median age of 68 years (interquartile range: 63–74), of which 73% were men. The patients' pulmonary fibrosis diagnoses were divided between IPF (37%), pulmonary fibrosis other than IPF (47%) and unclassified pulmonary fibrosis (16%). Supplemental oxygen was used by 11 subjects (22%) during their 6MWTs. Generally, the patients were slightly overweight (BMI 27.4 ±4.6 kg·m^{-2}; BFP 31 ±7%) and had impaired lung function as indicated by forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide (DLCO) predictions (FVC(predicted)=79.7 ±21.5%; FEV_1(predicted)=81.5 ±21.4%; DLCO(predicted)=46.1 ±16.4%). Moreover, 55% of patients endorsed the MRC dyspnoea scale at grade 3 while mean HR_{rest} was 76 ±12

beats·min−1 and mean SpO_{2Rest} was 97 ±2%. Nine patients (18%) did not perform a second 6MWT and were therefore excluded from the test–retest analysis. The mean 6MWD of these nine patients (394±166 m) was on average 57 m shorter than that of the remaining 42 patients (p=0.346).

The mean 6MWD of the test–retest group was 451±104 m (70±13% predicted) during the first 6MWT and 460±105 m (71±14% predicted) during the second 6MWT. Of this group, 28 patients (67%) improved their 6MWD during the second test with a mean change of 21±17 m, while 14 patients (33%) had a similar or a decreased 6MWD (mean change: −17±19 m). The improvement in 6MWD between the first test and the second was small but significant (8.4±25 m; p<0.05) and test–retest reliability for 6MWD showed excellent agreement (ICC 0.97, 95% CI 0.94–0.98; **figure 1**). Comparable results were found for various subgroups. For example, patients with IPF (n=14; 4.5±31 m), patients with other types of pulmonary fibrosis (n=28; 10.4±22 m), those with DLCO≥50% (n=16; 12.8±23 m) and those with DLCO<50% (n=26; 5.7±27 m). A total of 25 patients (60%) had an SpO_{2Low} of ≤88% during the first and second 6MWTs. Furthermore, no significant differences were found between the first and second 6MWT for SpO_{2Low} (85±8% versus 85±7%), HR_{peak} (127±20 versus 131±19 beats·min^{-1}), CR (49±20 versus 51±19), HRR_1 (14±17 versus 10±17 beats·min^{-1}), or Borg symptom scores (at end of 6MWT) for dyspnoea (4.5±2.1 versus 4.6±2.2 points) and fatigue (3.0±2.1 versus 3.3±2.3 points).

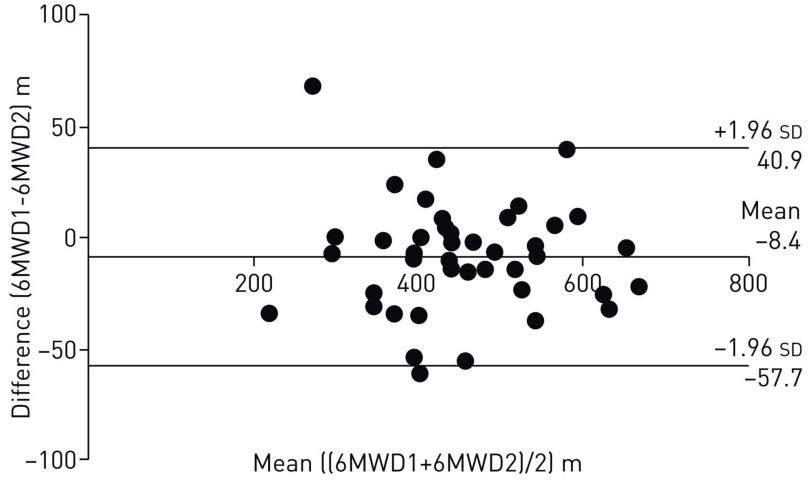

Figure 1: *Bland–Altman plot of the 6-min walk distance (6MWD). The mean difference and upper and lower limits of agreement (95% CI) are shown.*

The purpose of this study was to determine the test–retest reliability of the 6MWT when performed twice within the same day in patients with pulmonary fibrosis who visited a specialized outpatient ILD clinic. There are two main findings: 1) one in six pulmonary fibrosis patients was not able to walk the second 6MWT within the same day; 2) the 6MWT showed excellent test–retest reliability in the current sample of patients with pulmonary fibrosis. In the ERS/ATS technical standard[3], it is recommended to perform two 6MWTs in patients with chronic lung disease. However, this recommendation is mainly based on data from studies enrolling patients with COPD.[5] The current study shows a mean improvement of 8 m during the second 6MWT, which corroborates the data of KOZU et al.[6] While this difference is statistically significant, it clearly does not exceed the suggested minimal important difference for the 6MWD in patients with pulmonary fibrosis, which ranges between 21.6 and 30.5 m[5], and the current findings obviously need to be corroborated by others.

Interestingly, nine patients (18%) were not able to perform the second 6MWT. Patients stated that the ability to perform only one 6MWT was due to both physical limitations (exhaustion, n=1; knee pain, n=1) and non-physical limitations (insufficient time for the second 6MWT, n=7). Without a second 6MWT we cannot be sure that we have obtained the best result. Then again, one 6MWT seems adequate to identify those patients with pulmonary fibrosis who suffer from exercise-induced oxygen desaturation, a variable of clinical interest as patients with this trait have a poor prognosis.[2] Indeed, 60% of the patients had an SpO_{2Low} value of ≤88% during the first 6MWT and no "new" exercise-induced desaturators were identified in the second 6MWT. In conclusion, these data suggest that one 6MWT may not be sufficient to obtain the best 6MWD in patients with pulmonary fibrosis. However, one 6MWT seems sufficient to identify those patients with pulmonary fibrosis who suffer from exercise-induced oxygen desaturation.

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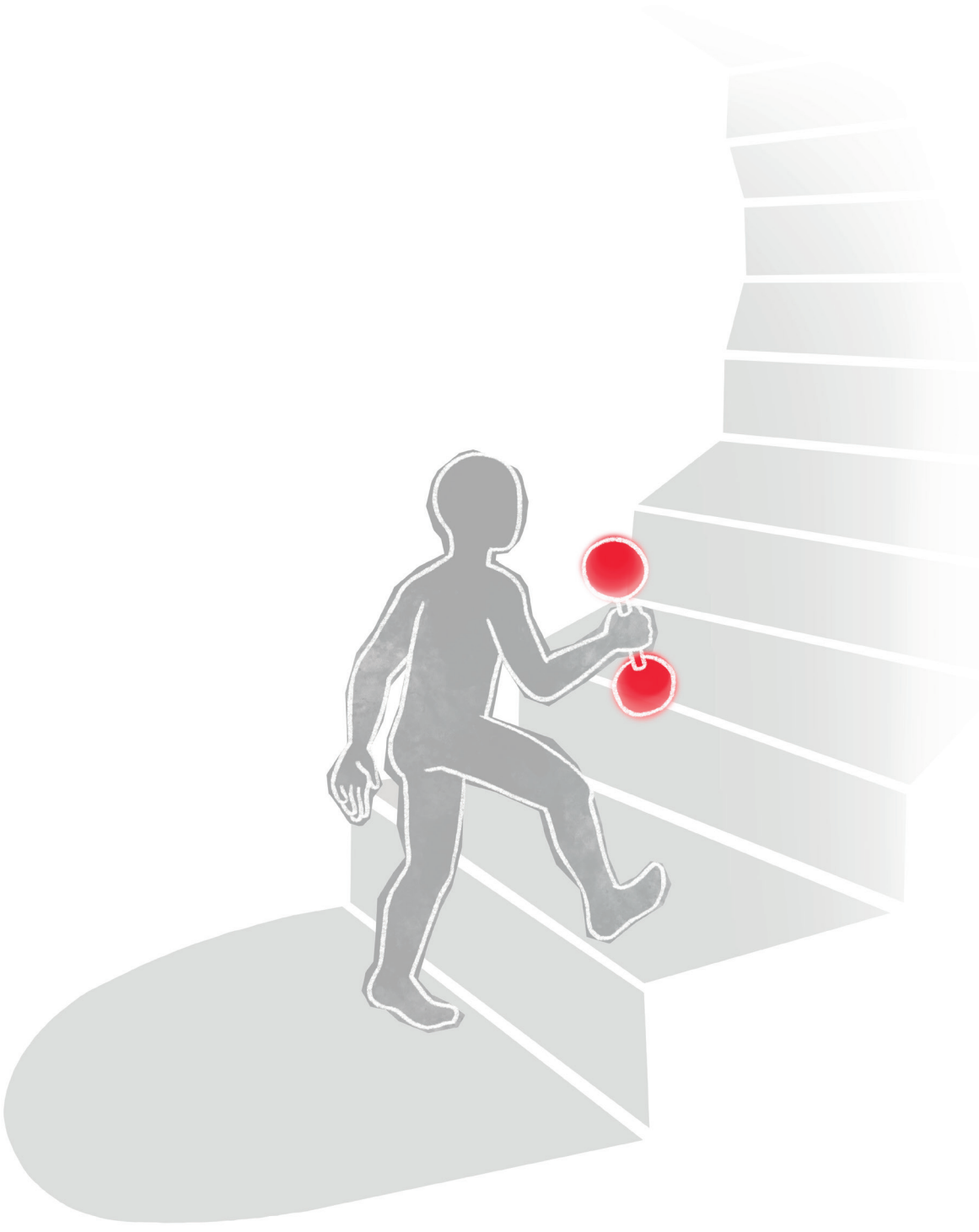

Chapter 7

Validation of 4-meter-gait-speed test and 5-repetitions-sit-to-stand in patients with pulmonary fibrosis: a clinimetric validation study

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Abstract

Background and objective: Patients with pulmonary fibrosis (PF) have a clear exercise intolerance. The 4-meter-gait-speed (4MGS) test and the 5-repetitions-sit-to-stand (5STS) test are easy, inexpensive and reliable measures of functional performance. Both tests have been validated in healthy adults and patients with chronic obstructive pulmonary disease. 4MGS test and 5STS test have not been studied in patients with PF.

Methods: In this cross-sectional clinimetric validation study 51 PF patients conducted in random order the 4MGS test, 5STS test and the 6-min walk test (6MWT) on a single day. Additionally, body weight, height, lean body mass, health-related quality of life, disease severity, handgrip strength, dyspnoea and leg fatigue were assessed. The setting was a tertiary referral center for Interstitial Lung Diseases

Results: Patients had a diagnosis of idiopathic pulmonary fibrosis (IPF, 37%), PF other than IPF (47%), or unclassified (16%). Patients walked 453±111m in six minutes. Moreover, it took the patients 2.0±0.5s to walk 4 m, and 12.0±3.8s for the 5STS test. The 4MGS test ($r = 0.77$; $p<0.01$) and the 5STS test ($r = -0.41$; $p<0.01$) correlated significantly with the distance walked in 6MWT. Indeed, 4MGS combined with handgrip strength and Medical Research Council dyspnoea grade could explain 75% of the variance in 6MWD.

Conclusions: 4-meter-gait-speed and 5-repetitions sit-to-stand are significantly and independently correlated with the 6-minute walk distance in patients with pulmonary fibrosis. Indeed, 4-meter-gait-speed test may serve as a simple initial field test to assess exercise performance in patients with pulmonary fibrosis.

Key words: exercise and pulmonary rehabilitation; pulmonary fibrosis; 6-minute walk test; gait

Introduction

Interstitial lung diseases (ILD) are a group of more than 150 different disorders characterized by inflammation of the lung parenchyma or interstitium often followed by the occurrence of pulmonary fibrosis (PF). Patients with PF complain about exertional dyspnoea, exercise intolerance and reduced quality of life.[1] As the disease progresses, patients become severely limited in their activity. Poor exercise tolerance is associated with reduced quality of life and poor survival.[2,3] Measures of exercise capacity or exercise-induced oxygen desaturation (EID) obtained from maximal and sub-maximal exercise tests are good predictors of survival in patients with PF.[4-6] Measuring the exercise capacity in patients with PF is a well-accepted and important element of clinical management.

The 6-Minute-Walk Test (6MWT) is one of the most widely used clinical tests in patients with PF, as it plays a key role in evaluating functional exercise capacity and assessing prognosis.[7,8] Nevertheless, there are some disadvantages with the 6MWT. First, the 6MWT is generally carried out in a hospital corridor and the length of the corridor can be an issue (i.e., ≥30m).[7] Secondly, it may also be time-consuming as repeat walks are needed due to the learning effect.[9] In regular clinical practice it is not a routine test every time patients with PF visit the medical outpatient consultation. Therefore, there is an increasing demand for reliable and easy to perform physical tests to provide clinicians with a first impression about the patients with PF functional exercise performance.[10-14]

In respiratory medicine, the 4-Meter-Gait-Speed test (4MGS) and 5-Repetitions-Sit-To-Stand test (5STS) are relatively new tests. Both tests require little space, time, equipment or training to measure, which makes them attractive measures of functional exercise performance for routine clinical use.[15] Clinimetric properties of the 4MGS and 5STS were reported to be adequate in patients with Chronic Obstructive Pulmonary Diseases (COPD).[10,13,15-17] However, clinimetric measurement properties of these tests in patients with PF are still unknown to our knowledge.

Therefore, the main research question was: What is the validity of the 4MGS and the 5STS, for assessing functional exercise performance in patients with PF?
The sub-question was: Can these performance tests, alone or with other office-available tests, contribute to explain the variances in the distance walked in 6MWT in patients with PF?

Method

This cross-sectional clinimetric validation study was undertaken on outdoor patients, visiting a tertiary referral center for ILD in the Netherlands, from June to December 2015. Participants were asked to perform three exercise performance tests, namely 4MGS, 5STS and 6MWT, on the one-day visit of the patient to the PF-specialized pulmonologist. This study was approved by the Medical research Ethics Committees United (MEC-U;NL51679.100.15/PT-PF)

Patients (age ≥18 year) with a confirmed PF diagnosis[1,18], visiting the Outpatient Pulmonary Clinic of the ILD Centre and who met the in- and exclusion criteria for 6MWT[7] were eligible to participate. Eligible patients were invited by an ILD-physician (MV) using an invitational letter. Subsequently the principle researcher (AB) contacted patients who responded (telephone, e-mail, return form). At the one-day visit two researchers executed the exercise tests.

All patients were instructed at start of the visit about the study procedure and give written informed consent before first test (**Figure 1**: flow chart overview of the study design).

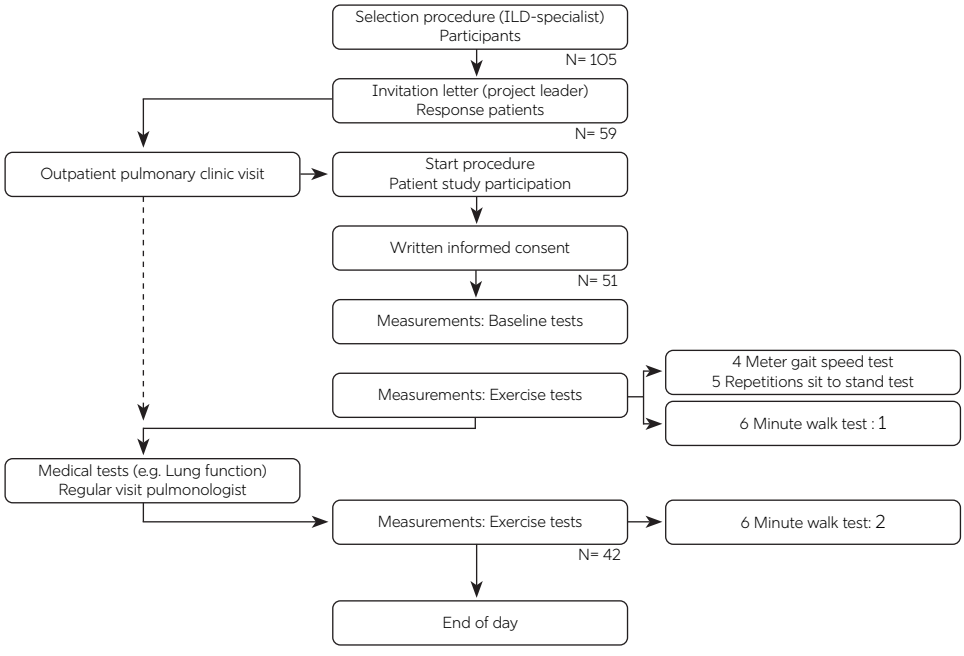

Figure 1: Flow chart overview of the study design with main procedures

The following patient data and lung function test values were extracted from the electronic patients files (dated for this specific one-day visit): age (year), gender (m/f), height (m), body weight (kg), forced vital capacity (L, %predicted), forced expiratory volume in 1 second (L, %predicted), diffusion capacity (mmol/min/kPa, %predicted), smoking status (packed-year) and medication.

Patients were asked to fill out the MOS 36-Item Short-Form Health Survey (SF-36) to assess generic health status[19-21], and the Medical Research Council (MRC) for situational perception of breathlessness.[21,22] Additionally, rest heart rate (HR_{rest}, beats-per-minute; Nellcor N-20), blood pressure (BP, mmHg), body mass index (BMI, weight/length^2), body fat percentage (fat%weight, Omron HBF 306)[23], transcutaneous oxygen saturation (SpO_2; %; Nellcor-N-20), and the ratings for perceived exertion for dyspnoea and leg fatigue for short-term intensity (0-10 modified Borg scale)[24] were obtained. Peak heart rate (HR_{peak}) was defined as 210-(0.63*Age). A low fat-free mass index (FFMI: FFM/height^2) was based on BMI-specific and gender-specific cut points as derived from the UK Biobank, classifying a FFMI below the fifth percentile as low.[25] The maximal isometric grip strength of the right hand (HGS, kg) was measured with a Jamar hand-grip dynamometer (protocol American Society of Hand Therapy[26,27]). Percentage of predicted was calculated using normative data of Spruit et al.[28]

Subsequently, the exercise tests were performed. Patients were randomly assigned to start the battery of functional exercise tests with either the two performance tests, 4MGS (first) and 5STS, followed by the 6MWT, or the other way around. Interval time for the second 6MWT was at least one hour.

Exercise tests were performed with continuous monitoring of SpO_2 and HR; each test started from resting values HR and SpO_2. For time measurements a stopwatch (Hi-TRAX-GO) and a simple timer (Eurochron Dual-Timer) were used. Tests were performed on a flat hard surface, a safety chair was placed near to test area. Before tests, exercise protocols were explained to the patient. The dyspnoea and leg fatigue scores were assessed before and directly after each test. Tests were supervised by one of two trained physiotherapists, who walked slightly behind the patient during the 6MWT to avoid setting the walking pace. Oxygen desaturation was defined as SpO_2 ≤88% and/or a decrease of >4%.[29,30] Patients were not stopped during exercise testing when SpO_2 was <80%, as this also occurs during daily activities.[29] If a patient was on long-term oxygen therapy, oxygen was given at their standard flow rate or as prescribed by a physician; the cylinder was carried by the assessor. Directly after finishing the test patients were asked to sit (chair) to recover. Three minutes recovery time was

measured for SpO_2 and HR (a failure of HR recovery to reduce by at least 13 bpm after 1 minute, HRR1, or 22 bpm after 2 minutes of recovery, HRR2).[31] All necessary safety procedures were be taken into account according to the ERS/ATS Technical Standard.[7] If a patient was unable to perform an exercise test according to test protocol, that test was excluded for statistical analysis.

4MGS is a performance measure of functional mobility and gait speed.[10,32] The patient was instructed to 'walk as quickly as possible' 4 meters (moving start); space to accelerate and to decelerate was 2 meter, before/after the set distance. The distances (0-2-6-8 meter) were marked with tape stripes on the floor. The test was performed three times (interval period 2 minutes). The fastest time to complete the 4-meter walk was used for analysis. Reference values are based on gender, age and height.[33]

5STS is a performance measure of functional mobility and lower limb muscle strength.[15,34] Patients sat with arms folded across chest, in upright position against the back (chair height 45 cm). Patients were asked to stand up and sit down 5 times, as quickly as they could without any form of assistance. The test was performed twice (interval period 2 minutes). The quickest time measured was used for further analysis. Normative values: the times for 5-repetitions can be considered worse for exceeding the following values: 11.4 s (60 to 69 years), 12.6 s (70 to 79 years), and 14.8 s (80 to 89 years).[11]

The 6MWT procedure was conform the Official ERS/ATS Technical Standard.[7] Briefly, 6MWT took place in a quiet 30-meter corridor and only standardized instructions and encouragement were given. Patients were instructed to walk as far as they could without running; they were permitted to slow down or stop to rest if needed. Reasons to stop the test were experienced chest pain, intolerable dyspnoea, diaphoresis, leg cramps and/or vertigo. The 6MWT was performed twice, with a minimal interval of one hour. The best 6MWD was used for further analysis.[30,35] If a patient was not able to complete a second 6MWT, the result of the first test was used for analysis. Walking distance will be compared with the mean distance %predicted compared to healthy elderly persons.[36] Data on the reproducibility of the 6MWT was published before.[9]

Outcome measures

The primary outcome measures were the main outcomes of the two performance tests, gait speed in 4MGS (m/s) and the time to raise from a chair five times in 5STS (s), and the distance covered in 6MWT (m).

Secondary outcomes included the patient characteristics (gender, age, disease classification, lung function and diffusion capacity, use of supplemental oxygen, BMI, FFMI, MRC, HR, SpO_2, BP, SF-36) and measurement outcomes from strength and exercise testing (HGS, HR_{peak}, CR, Lowest SpO_2, Borg scores of dyspnoea and leg fatigue, recovery time for HR and SpO_2)

Data analysis

SPSS software (version 23) was used for statistical analysis. Patients' characteristics are presented with appropriate measures of central tendency and dispersion. Numerical data were tested for normality by mean-median ratio, SD-mean ratio, and judging histogram.[37] Test-retest reliability was calculated by intraclass correlation coefficient (ICC) of single measures and absolute agreement with random effect (95%CI; p<0.05). The correlation between the 4MGS (m/s) and the 6MWD (m), and the correlation between the time to complete the 5STS (s) and the 6MWD (m), were calculated by Pearson's r or when the assumptions are violated by Spearman's rho. In case of missing values, cases were excluded pairwise. The range for what constitutes a low, moderate or high correlation was respectively $0.3 \leq r < 0.5$, $0.5 \leq r < 0.7$ and $0.7 \leq r < 1.0$.[38] A multivariable model was conducted to assess the associations between independent in univariate analysis significant variables and the dependent variable 6MWD. The level of significance was set on P<0.05.

Results

After invitation (n=105) 59 patients (56%) responded, whereby 8 Patients (13.6%) were excluded (excluded for 6MWT). The study sample consisted of 51 elderly patients with PF, of which 75% were men. The most common diagnosis was idiopathic PF (37%). Generally, patients were overweight, had to stop for breath after walking about 100 yards or after a few minutes on level ground, had an impaired spirometry and diffusion capacity, had a slightly impaired HGS (12% of the patients had a HGS <5 percentile) and a clearly impaired generic quality of life **(Table 1 and 2)**.

Table 1: Patient Characteristics (N = 51)

Variables	Values
Male (%)	37 (73)
Age, years* (IQR)	68 (63-74)
Pulmonary Fibrosis,	
Idiopathic Pulmonary Fibrosis (%)	19 (37)
Other than Idiopathic Pulmonary Fibrosis,	
Extrinsic Allergic Alveolitis (%)	9 (18)
Smoking related (%)	2 (4)
Connective Tissue related (%)	13 (26)
Unclassified (%)	8 (16)
Body mass index, kg/m²	27.4 ±4.6
Fat free mass index, kg/m²	18.5 ±2.2
Body fat percentage, % of weight	30.8 ±6.5
Number of patients with low FFMI (%)	10 (20)
Medical research council dyspnoea grade* (IQR)	3 (2 -3)
SpO_2 at rest, sat%	97 ±2
Supplemental oxygen, yes (%)	11 (22)
HRrest, bpm	76 ±12
Systolic blood pressure at rest, mmHg	131 ±16
Diastolic blood pressure at rest, mmHg	85 ±10
Walking aid, yes (%)	6 (12)
SF-36 PCS, points* (IQR)	32.6 (25.8-38.0)
SF-36 MCS, points* (IQR)	49.3 (43.0-56.5)
FVC, L	2.9 ±0.9
FVC, % predicted	79.7 ±21.5
FEV1, L	2.3 ±0.7
FEV1, % predicted	81.5 ±21.4
DLCOcSB, mmol/min/kPa	4.0 ±1.6
DLCOcS, % predicted	46.1 ±16.4
PF severity, Mild-Moderate/severe**, N (%)	29/22 (57/43)
Smoking code (n=50)	
Non smoker	14 (28%)
Stop smoking	35 (69%)
Active smoker	1 (2%)
Smoking pack-year*/*** (n=28, IQR)	10 (0-23)
Medication (n=50)	
Blood pressure decrease	20 (40%)
Heart frequency decrease	8 (16%)
Oral corticosteroids	24 (48%)

Data are presented as mean (SD) unless otherwise stated
** Median*
*** Mild-Moderate (FVC/FEV1 % pred (<80%) ≥50%, DLCOc (<80%) ≥40%), Severe (FVC/FEV1 % pred <50%, DLCOc <40%)); Classification Pulmonary Fibrosis According to National Institute For Health and Care Excellence (NICE)*
**** Pack-year = quantification of cigarette smoking, (number of cigarettes smoked per day/20) * number of years smoked. (1 pack has 20 cigarettes)*

Abbreviations: N=number, %=percentage, IQR=interquartile range, kg/m² = kilogram per square length in meters, FFMI=fat-free mass index, SpO_2=peripheral capillary oxygen saturation, HRrest=heart rate at rest, bpm=beats per minute, mmHg=millimeters of mercury, SF-36=short-form health survey 36 questions, PCS=physical component score, MCS=mental component score, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, L=litre, DLCOcSB=diffusion capacity to carbon monoxide corrected single breath, mmol/min/kPa=mmol CO per minute per kilopascal, PF=Pulmonary Fibrosis, SD=standard deviation

Table 2: Strength and exercise testing

Variables	Values
HGS Right hand highest value, Kg	35 ±13
HGS Right hand normative value <P5, N (%)[1]	6 (12)
6MWT	
Distance, m	453 ±117
Distance, % predicted[2]	70.7 ±15.8
Mean speed, m/s	1.26 ±0.33
Lowest SpO_2 , %	85 ±7
Distance saturation product, m·%	382 ±104
HRpeak, bpm	128 ±18
HRpeak, % predicted	77 ±11
Chronotropic response, bpm	53 ±32
Borg dyspnoea score end, points* (IQR)	4 (3/7)
Borg leg fatigue score end, points* (IQR)	3 (1/4)
4MGS test	
Time, s	2.0 ±0.5
Mean speed, m/s	2.1±0.5
Lowest SpO_2, %	96 ±2
HRpeak, bpm	92 ±11
HRpeak, % predicted	55 ±7
Borg dyspnoea score end, points* (IQR)	
1(0.5/2)	
Borg leg fatigue median score end, points* (IQR)	0.5 (0/2)
5STS test	
Time, s	12.0 ±3.8
Lowest value SpO_2, %	96 ±2
HRpeak, bpm	91 ±14
HRpeak, % predicted	54 ±8
Borg dyspnoea score end, points*** (IQR)	2 (0.5/3.8)
Borg leg fatigue score end, points*** (IQR)	1.5 (0/3)

Data are presented as mean (SD) unless otherwise stated
[1] 1=Low <P5 (percentile score)
[2] References Troosters et al, 1999
** Median*

Abbreviations: N=number, %=percentage, IQR=interquartile range, HGS=hand grip strength, Kg=kilograms, 6MWT=six minute walk test, m=meter, m/s=meter per second, SpO_2=peripheral capillary oxygen saturation, m·%=product of distance walked and lowest oxygen saturation, HRpeak=Heart Rate Peak, bpm=beats per minute, 4MGS=4 meter gait speed, s=second, 5STS=5 repetitions sit-to-stand, HRpeak=heart rate peak, SD=standard deviation

Research question 1

Mean walk time 4MGS (2.1±0.5 m/s) was comparable with healthy elderly subjects; 17 patients (33,3%) walked slower than reference value.[33] Mean time in 5STS was 12±4 s, thereby 47% of the patients scored worse than might be expected based on age.[11] Test-retest reliability (ICC) of 4MGS and 5STS were 0.95, 95% CI 0.92-0.97, p<0.01 and 0.87, 95% CI 0.63-0.94, p<0.01, respectively. Both tests, 4MGS and 5STS, showed an increase in HR (respectively 15±8 bpm and 13±10 bpm), which fully recovered after 2 minutes rest. In both tests no EID was observed.

On average, the 6MWD was moderately impaired with a mean distance %predicted of 71±16% (453 m; range 145-690 m; **Table 2**). During 6MWT, an increase in HR (50±18 bpm, p<0.01) and a decrease in SpO_2 (-12±7%, p<0.01) were observed. Direct after completing the 6MWT, 24 patients (47%) had a limited HR recovery (HRR1 -11±17bpm, HRR2 -21±17bpm; p<0.01). The lowest mean SpO_2 was 85±7%, 31 patients (61%) had an oxygen desaturation of ≤88%, 40 patients (78%) had a desaturation of >4%. After 3 minutes rest SpO_2 was fully recovered (SpO_2rest 97±2%, SpO_2-recovery-3min 96±3%, p>0.05), but not HR (HRrest 79±13 bpm, HR-recovery-3min 90±16 bpm, p<0.01). 6MWD was associated with 4MGS (r=0.77; p<0.05) and 5STS time (r=-0.41; p<0.05) **(Figure 2)**

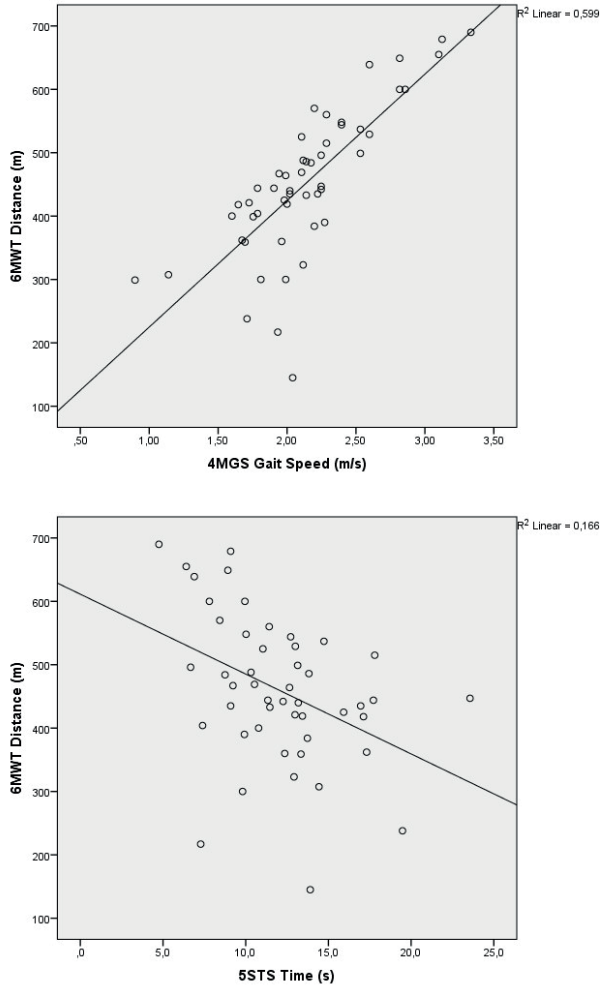

Figure 2

Table 3 summarizes the correlations between the exercise tests and other outcome parameters. In brief, 6MWD correlated best with HGS and the degree of dyspnoea (r=0.65, and r=-0.62, respectively; both p<0.01). The same was true for the 4MGS: r=0.57, and r=-0.40, respectively (both p<0.01).

Table 3: Relationship between the results of 4MGS, 5STS, 6MWT and other outcome parameters

Pearson and Spearman rank correlation coefficient			
Variables	4MGS	5STS	6MWT
	r	r	r
Age (yr)	-0,55**	0,22	-0,47**
Resting blood pressure diastolic (mmHg)	0,30*	-0,08	0,26
Resting blood pressure systolic (mmHg)	0,23	0,05	0,16
BMI (kg/m2)	-0.01	0,10	0,09
Body fat percentage (% weight)	-0,36*	0,31*	-0,42**
Fat free mass (kg)	0,24	0,01	0,42**
FVC (L)	0,10	0,02	0,38**
FEV1 (L)	0,17	-0,06	0,41**
Lung function: DLCOcSB (mmol/min/kPa)	0,23	-0,12	0,40**
PCS of SF-36	0,39**	-0,23	0,48**
MCS of SF-36	-0,05	-0,09	-0,02
MRC dyspnoe grade	-0,40**	0,18	-0,62**
HGS right hand highest value (kg)	0,57**	-0,24	0,65**
Baseline heart rate (bpm)	0,04	0,01	-0,25
Heart rate end (bpm)	0,14	0,07	0,22
Baseline SpO_2 (%)	0,17	-0,11	0,34*
SpO_2 end (%)	0,08	0.00	0,10
Baseline dyspnoea, Borg score	-0,33*	0,14	-0,43**
Dyspnoea end, Borg score	-0,32*	0,23	-0,09
Baseline leg fatigue, Borg score	-0.19	-0,02	-0,18
Leg fatigue end, Borg score	-0,32*	0,18	0,14

*r: Pearson's and Spearman rank correlation coefficient ; * 0,01<p≤0,05; ** p≤0,01*
Abbreviations: 4MGS=4 meter gait speed, 5STS=5 repetitions sit-to-stand, 6MWT=six minute walk test, yr=year, mmHg=millimeters of mercury, kg/m²=kilogram per square length in meters, %=percentage, kg=kilogram, BMI=Body Mass Index, FVC=forced vital capacity, L=liter, FEV1=forced expiratory volume in 1 second, DLCOcSB=diffusion capacity to carbon monoxide corrected single breath, mmol/min/kPa = mmol CO per minute per kilopascal, PCS=physical component score, SF-36=short-form health survey 36 questions, MRC=Medical Research Council, bpm=beats per minute

Research question 2

Multivariable linear regression models were fit for predicting 6MWD, including all variables which were statistically significant in univariate correlation **(Table 3)**. The final model, equation 6MWD=184.6+138.6*4MGS(m/s)+2.0*HGS(Kg, right hand)–35.2*MRC (R=0.87, R2=0.75; backward regression), showed that 4MGS (p<0.01), HGS (p<0.05), and MRC dyspnoea grade (p<0.01) were associated with 6MWD (collinearity: VIF<3) (**Table 4** Regression coefficients). These three variables could explain 75% of the variance in 6MWD in patients with PF.

Table 4: Regression Coefficients

Coefficients Dependent Variable: 6MWT Distance (m)							
Model	Unstandardized Coefficients		Standardized Coefficients			95,0% Confidence Interval for B	
	B	Standard Error	Beta	t-value	p-value	Lower Bound	Upper Bound
(Constant)	184,609	59,507		3,102	,003	64,756	304,463
4MGS Gait Speed (m/s)	138,603	23,772	,536	5,831	,000	90,724	186,482
HGS (Kg) Right Hand	2,028	,859	,220	2,361	,023	,298	3,757
MRC Dyspnoea Scale	-35,210	8,927	-,324	-3,944	,000	-53,189	-17,231

Abbreviations: 6MWT=six minute walk test, m=meter, 4MGS=4 meter gait speed, m/s=meter per second, HGS=hand grip strength, Kg=kilograms, 6MWT=six minute walk test, MRC=Medical Research Council

Discussion

The present study has two main findings: 1) 4MGS and 5STS time have good and moderate correlations with 6MWD, respectively; and 2) 75% of variance in the 6MWD can be explained by combining three office-available tests that can easily be performed during an outpatient consultation (i.e., 4MGS, HGS and MRC dyspnoea).

Our findings show a significant correlation between 6MWD with simple functional performance tests in a well-defined group of patients with PF. This is in line with previous results obtained in patients with chronic lung diseases, like COPD and ILD.[13,32,39,40] Besides, in patients with PF the 6MWD has been identified as an independent predictor of mortality.[18,41,42] So, measurements of functional exercise capacity are important in clinical management and the finding that 4MGS may serve as a simple surrogate for 6MWD is therefore probably of clinical importance.

Despite the significant correlations of the 4MGS and 5STS with the 6MWD, they are not a replacement of the 6MWT. Physical performance and physical activity are both part of the domain physical functioning. In the bigger concept of exercise capacity all three tests highlight different components. The 5STS is a very short test which especially requires muscle strength from the lower limbs. 4MGS and 6MWT are tests that require the same physical performance, namely walking. Only 4MGS represents a very short capacity test out of mainly the anaerobic energy system. Besides, the simple performance tests set a less limited stress on the cardiopulmonary system than the 6MWT.

First, the HRpeak and the lowest SpO2 in the performance tests were clearly different compared to the values obtained during the 6MWT. Indeed, the 6MWT is an endurance exercise capacity test, and given the fact that PF is a progressive fibrotic lung disease which affects diffusion capacity, probably patients may experience more limitations in their ability to perform an aerobic exercise test.[5,43,44]

Second, in the 6MWT both the distance walked as EID have been found to predict mortality. The composite of the product of distance and desaturation would predict mortality better than either measure alone.[45-47] During the 4MGS and 5STS tests, however, no EID was observed. So, when healthcare professionals are interested in EID in patients with PF, the simple performance tests are insufficient. Indeed, one 6MWT needs to be performed to accurately determine the presence/absence of EID.[9]

Limitations of the study

The current study sample was selective, as all patients were clinically stable outpatients with PF visiting a specialized ILD center for routine medical check-up. Indeed, during this one-day visit, patients were already asked to perform routine clinical tests, such as spirometry, chest-X-rays and blood drawing. Although patients started each exercise test from rest values (HR, SpO_2), it may to some extent have affected the exercise performance.

The 4MGS test was restricted to the fast speed protocol only (instruction: 'walk as fast as possible'). There is no evidence to indicate that measurement of usual-walking speed is more reliable than maximal speed.[10,33]

Another limitation is the sample size, which prevented generation of more robust prediction models.

To conclude, the 4MGS and 5STS scores correlate respectively good and moderate with the 6MWD in patients with PF. These results suggest that very simple performance tests may serve as an easy first step to provide healthcare professionals with valuable information of functional status of patients with PF. In fact, the 4MGS together with simple measurements of HGS and dyspnoea score (MRC) will guide healthcare professionals in their decision to request also for an additional 6MWT. Obviously, the 6MWT provides additional information on EID which cannot be adequately determined suing the 4MGS and 5STS

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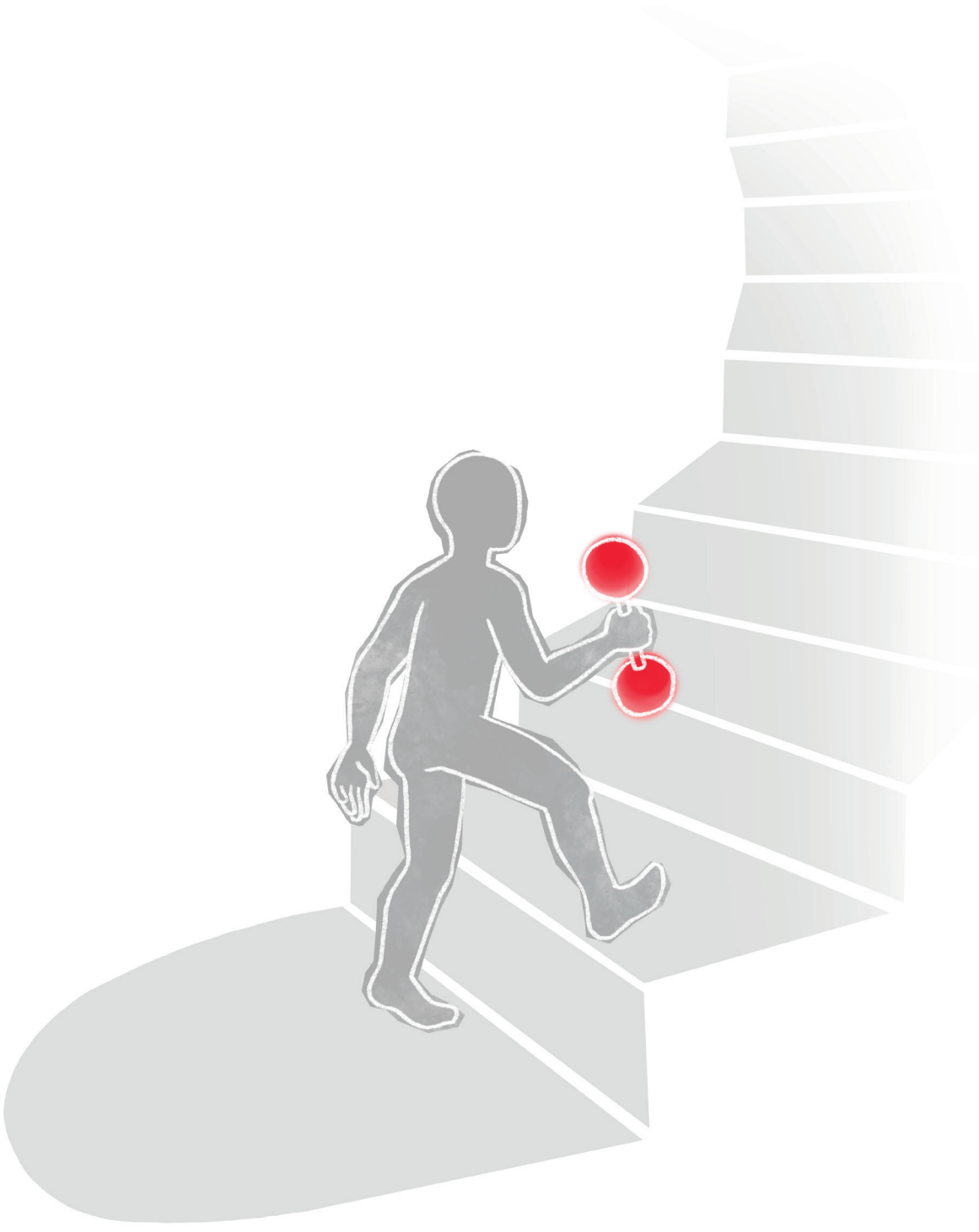

Chapter 8

Prognostic value of the 6-minute walk test derived attributes in patients with Idiopathic Pulmonary Fibrosis

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Abstract

Introduction: Idiopathic pulmonary fibrosis (IPF) is a fatal progressive fibrosing lung disease. A decreased 6-minute walk distance (6MWD) and exercise-induced oxygen desaturation measured during the 6-minute walk test (6MWT), are known predictors of mortality in patients with IPF. However, the use of antifibrotic drugs showed a survival benefit in IPF. Therefore, this study aimed to evaluate to what extend 6MWT-derived attributes are associated with two-year survival when antifibrotic drugs were introduced as part of standard IPF-care.

Methods: This real-world data-study included patients with IPF with a 6MWT between 2015-2020, and used composite outcome: mortality or lung transplantation within 2 years of follow-up. Data were collected systematically, including demographics, pulmonary function tests, comorbidities, medications and 6MWT-derived attributes. The prediction attributes of 6MWT were studied with a Cox Proportional-Hazards model and Kaplan-Meier survival curves. The best discriminating attribute to predict mortality was added to the prediction model Gender-Age-Physiology (GAP).

Results: In 216 patients, 2-year transplant-free survival cut-off points were identified for the 6MWD (≥413 m), 6MWD %predicted (≥83%), SpO_2-nadir (≥86%) and distance-saturation-product (≥374 m%), with the best discriminative value for SpO_2-nadir (area under the curve: 0.761). 2-Year survival percentage of patients with SpO_2-nadir below or above threshold (86%) was 37.1% and 80.0%, respectively. Exercise-induced oxygen desaturation added to the GAP model showed an improvement in its predictive power.

Conclusion: Patients with IPF who have an exercise-induced oxygen desaturation have worse prognosis. Addition of SpO_2-nadir to the GAP model seems promising for use in clinical care of IPF patients. .

Keywords: Idiopathic pulmonary fibrosis (IPF), 6-min walk test (6MWT), exercise capacity, prognostic,physiotherapy, GAP (Gender-Age-Physiology) model

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal lung disease with a median survival time of 3 to 5 years.[1,2] IPF is characterized by progressive scarring of the lungs with unknown aetiology resulting in lung function impairment, dyspnoea and exercise intolerance.[1,3,4] In 2014, the US Food and Drug Administration (FDA) approved two effective disease-modifying agents, Pirfenidone (Esbriet) and Nintedanib (Ofev) for the treatment of IPF.[5] These antifibrotic drugs have shown to slow the rate of lung function decline and improve survival in patients with IPF.[5,6,7,8] At present, antifibrotic treatment is seen as standard IPF care.[9,10]

A decreased 6-minute walk distance (6MWD) and exercise-induced oxygen desaturation measured during the 6-minute walk test (6MWT), are known predictors of mortality in patients with IPF.[11,12,13,14,15] However, most studies on the association between 6MWT-derived attributes and survival were performed in the era before antifibrotic therapy became the standard of IPF care.[5] Treatment with antifibrotics improves survival in patients with IPF.[3,5,7,8] In two studies after 2014 about the prognostic value of the 6MWT, patients were retrospectively included also before 2015 or the medication use was unknown.[15,16] Therefore, uncertainty remains regarding the extent to which 6MWT-derived features are independent predictors of survival in patients with IPF after antifibrotic treatment was available for standard IPF care. In 2012, the so-called GAP-model was introduced to predict mortality in patients with IPF[17], including gender (G), age (A), and two physiology (P) variables of the respiratory system (forced vital capacity (FVC) and diffusing capacity (DLCO)). Nowadays, the GAP-model is the most widely used prognostic tool in daily clinical practice, and has also been validated in patients with IPF treated with antifibrotic drugs.[18] Interestingly, no dimension of exercise capacity had been added to the original GAP-model, while, a low 6-min walk distance (6MWD) at the 6-min walk test (6MWT) has been identified as a predictor of mortality in patients with IPF.[11,12,16] Also the lowest transcutaneous-measured oxygen saturation during the 6MWT (SpO_2-nadir) and the distance-saturation product (DSP, 6MWD multiplied by SpO_2-nadir) have been identified as predictors of mortality in patients with IPF.[13] A recent study demonstrated a promising new scoring system for mortality in IPF by adding nadir SpO_2 during 6WMT to the GAP using retrospective data from the Korea IPF Cohort (KICO) registry.[19] However, insights in other attributes derived by the 6MWT, other than the exercise induced hypoxaemie, were not investigated. In 2023, the distance-oxygen-GAP index (DO-GAP), was introduced as a simple, point-based baseline-risk prediction model incorporating exercise capacity parameters (distance walked based on a 6MWD cut-off of <250m and exertional hypoxia) into the

GAP index. The DO-GAP improved mortality prediction in patients with IPF. However, this study included patients with IPF between January 2007 and March 2020, before AF medications became the standard of care.[20]

The aims of the current study were: 1) to assess the prognostic value of 6MWT-derived attributes on 2-years-transplant-free survival in a real-world cohort of well-defined patients with IPF; and 2) to investigate whether and to what extent 6MWT-derived attributes contribute to the predictive value of GAP-model in patients with IPF.

Materials and Methods

Patients

This was a retrospective cohort study at the ILD Center of Excellence of the St Antonius Hospital, a national referral center for patients with ILD in The Netherlands. The data search included the review of the medical records of patients with IPF (age ≥18 years), and the diagnosis was therefore confirmed based on a multidisciplinary discussion between healthcare professionals, based on the latest insights from clinical practice guidelines for the diagnosis and treatment of IPF by the American Thoracic Society and the European Respiratory Society.[1,5] Patients with IPF were included if they had performed a 6MWT in St Antonius Hospital between 01/01/2015 and 01/01/2020, and a pulmonary function test including diffusion capacity for carbon monoxide (DLCO) within ±3 months of the 6MWT date. Patients were excluded if they participated in medical trials and medication use was unknown or, after unblinding, it was found that study medication had been assigned. The primary outcome was two-year transplant-free survival defined as the period free of either death (all-cause) or lung transplantation.

The events deceased or lung transplantation were scored at least within two year of the 6MWT between 01/01/2015 and 01/01/2022. Patients who met any of the following criteria were excluded for the study: a not confirmed informed consent registration in the Biobank of St Antonius Hospital ILD Center of Excellence (approval number of the medical research ethics committee: r-05.08A) and/or participating in scientific intervention studies with possible conflict of interests.

Study protocol

The data search of the medical records of patients with IPF was performed by two researchers. Study data were collected and managed using REDCap electronic data capture tools[21,22] hosted at St Antonius Hospital. Patient data search included: age, sex, height and body weight, smoking status (never, ever), use of antifibrotic drugs (during 6MWT >90 days, yes/no). Comorbidities registered were gastroesophageal reflux disease (GERD), cardiac vascular disease and cardiac surgery (CVD), vascular neurologic disease, pulmonary hypertension (PH), hypertension, lung cancer, chronic obstructive pulmonary disease (COPD) and hyperglycaemia/ diabetes mellitus (DM). Dilatation of the main pulmonary artery can indicate the presence of PH.[23,24] To avoid underdiagnosis of PH, the diameter of the main pulmonary artery (pulmonary trunk) based on High-resolution computed tomography (HRCT) (+/- 6 months of date 6MWT) was included as a marker for possible PH (cut-off >30 mm, yes/no).[25,26] Pulmonary function tests (PFTs) were performed according to the current guidelines[27,28] and included were: forced vital capacity % predicted (FVC %pred) and diffusing capacity to carbon monoxide corrected for haemoglobin % predicted (DLCOc %pred)

Exercise capacity

The 6MWTs were all performed according ERS/ATS guidelines.[29] Enright's reference equations were used, taking into account age, height and weight.[30] In short: Patients were asked to walk as far as possible in 6-minutes on a flat surface, self-paced, at a parcourse of 30 metre, with standardised instructions and encouragement during the test. Patients were not stopped during the test when SpO_2 was below 80%, as this also occurs during daily activities.

Statistical analyses

Continuous and categorical variables were presented with appropriate measures of central tendency and dispersion. Numerical data were tested for normality by Shapiro-Wilkinson test, a mean-median ratio, SD-mean ratio, and judging the histogram. Differences between groups for continuous data were analysed by an unpaired t-test (2 groups) or the non-parametric pendant (Mann–Whitney U test) where appropriate, and the One-Way ANOVA analysis (more than 2 groups). Categorical data were be analysed with the Chi-square or Fisher Exact test. A p-value of ≤0.05 will be

considered as statistically significant.[31] Receiver operating characteristic (ROC) curves were used to evaluate ability of the predictive power of various factors of the 6MWT to predict 2-year transplant-free survival. Receiver operating characteristic (ROC) curves were constructed and area under the curves (AUC) were calculated to investigate the diagnostic accuracy of 6MWT variates in discriminating for deceased or transplant patients and patients who survived 2-year.[32] Optimal cut-off points were determined and the best trade-off between sensitivity (true positives) and specificity (true negatives) were calculated for 6MWD, 6MWD %predicted, SpO_2-nadir and DSP. Survival analyses (transplant-free survival) were performed using Kaplan-Meier method with log-rank test. Survival curves were constructed based on the achieved cut-off points for comparisons with 6MWD, SpO_2-nadir or DSP above their specific thresholds to those falling below these cut-off points. The variable of 6MWT with best predictive value according to the AUC from ROC will be added to the GAP model[17] based on the new cut-off threshold (weight +2 points below threshold, zero points above threshold: GAPI-6MWT attribute 0-3 points, GAPII-6MWT attribute 4-6 points, GAPIII-6MWT attribute 7-10 points). The C-statistic was used as a measure of goodness of fit for binary outcomes in the logistic regression model; The independent Hazard Ratio (HR) of this variable with the best fit was determined in a multivariable analysis with the original GAP and checked for its significant contribution compared to the model. Statistical analyses were carried out using IBM SPSS Statistics version 27 (IBM Corp, Armonk, NY, USA).

Results

Patients

The original electronic patient record search consisted of 1032 patients with IPF, of whom 233 patients met the inclusion criteria. Subsequently, 17 patients were excluded due to participation in drug trials that may have been biased by use of trial-medication disclosed after unblinding.

Baseline characteristics of the study sample of 216 patients with IPF are summarised in **table 1**. In general, most patients were men (80%) with a mean age of 68 years at time of 6MWT, slightly overweighted (BMI >25 kg/m2, 61%), and a history of smoking (82%). 57% of patients were on AF medications >90 days at the time of the 6MWT, and overall (including the 2 years of follow-up) 87% used AF medications >90 days.

The baseline GAP index was calculated on date 6MWT; median time from diagnosis to 6MWT was 0.70 year (0.13-1.63 IQR). CVD was the most prevalent comorbidity (32.9%), next to hyperglycaemia or DM (21.4%) and hypertension (20.9%). Although the prevalence of PH was relatively low (3.7%), a truncus dilatation was observed in almost a third of the patients (31.5%).

6-minute walk test

The mean distance walked was 420.0 ± 121.7 meter (80.0 ± 22.3% predicted), and the SpO_2-nadir was 83.4 ± 8.0%. 18 Patients (8.4%) had to rest at least once during the test. Attributes derived from 6MWT are shown in **table 2**. The mean difference between baseline and maximum heart rate was 41.4 ± 17.2 bpm, between baseline oxygen saturation and SpO_2-nadir -12.9 ± 7.2 %, and the mean differences between experienced baseline and end of tests for shortness of breath or level of fatigue were 2.6 ± 1.7 points and 1.6 ±1.8 points, respectively.

Survival

Within two years after the 6MWT, 74 patients (34.3%) died and 20 patients (9.3%) underwent a lung transplantation **(Table 1)**. At baseline, patients who died within 2-years from 6MWT had a significantly lower BMI, FVC %pred, DLCO %pred and a higher GAP stage, but no differences in the comorbidities were seen **(Table 3)**. Moreover, patients who did not achieve 2-year transplant-free survival on 6MWT had a significantly higher baseline heart rate, a lower baseline SpO_2, had a lower distance walked with a lower predicted 6MWD%, had a higher perceived post-exercise dyspnoea score, and had lower exercise-induced oxygen saturation, resulting in lower DSP **(Table 3)**.

The ROC analysis showed good diagnostic accuracy for 6MWD (AUC 0.675), 6MWD %pred (AUC 0.706), SpO_2-nadir (AUC 0.761) and DSP (AUC 0.739) in predicting 2-year transplant-free survival **(Figure 1)**. Optimal cut-off points were set for 6MWD of 413 m (sensitivity = 0.80, specificity = 0.53), for 6MWD %pred of 83% (sensitivity = 0.72, specificity = 0.64), for SpO_2-nadir of 86% (sensitivity = 0.77, specificity = 0.67) and for DSP of 374 m% (sensitivity = 0.75, specificity = 0.64). Transplant-free survival curves and life tables of the total patient group and of the subgroups based on established thresholds for 6MWD, 6MWD % pred, SpO_2-nadir or DSP are presented in **figure 2**.

Table 1. Baseline characteristics of patients with Idiopathic Pulmonary Fibrosis (IPF)

Variables	Total n=216
Demographic variables	
Sex, male	173 (80.1)
Age (at diagnosis), years	67.0 ±9.7
Age (at 6MWT), years	68.0 ±9.4
Age ≤60 years *	44 (20.4)
Age 61-65 years *	37 (17.1)
Age >65 years *	135 (62.5)
BMI (kg/m^2)	26.2 ±4.0
Overweight (BMI >25 kg/m^2)	132 (61.1)
Smoking, ever a	176 (81.5)
Pack-years**, smoking ever [d]	20.0 [9.5-30.0]
Pulmonary function tests	
FVC %predicted [b]	79.3 ±19.7
FVC %predicted >75% *	127 (59.3)
FVC %predicted 50-75% *	72 (33.6)
FVC %predicted <50% *	15 (7.0)
DLCO (% predicted)	40.6 ±13.6
DLCO % predicted >55% *	24 (11.1)
DLCO % predicted 36-55% *	98 (45.4)
DLCO % predicted ≤35% *	85 (39.4)
DLCO % predicted 'unable to perform' *	9 (4.2)
GAP [b]	
Stage I	68 (31.8)
Stage II	113 (52.8)
Stage III	33 (15.4)
Comorbidity	
GERD	10 (4.6)
Cardiovascular disease	71 (32.9)
Vascular neurologic disease	17 (7.9)
Pulmonary hypertension	8 (3.7)
Truncus pulmonalis dilatation*** [c]	58 (31.5)
Hypertension [a]	45 (20.9)
Lung cancer	6 (2.8)
COPD	29 (13.4)
Hyperglycaemia/DM [a]	46 (21.4)
Medication treatment prescribed	
Antifibrotic drugs at time 6MWT (>90 days)	124 (57.4)
Antifibrotic drugs (>90 days), use (days) [e]	351.5 [175.8-602.8]
Antifibrotics drugs in total (>90 days)	187 (86.6)
Proton Pump Inhibitors	141 (65.3)
Corticosteroids	14 (6.5)
Disease-Modifying Anti Rheumatic Drugs	5 (2.3)

Continues on next page

Table 1. Baseline characteristics of patients with Idiopathic Pulmonary Fibrosis (IPF) *(Continued)*

Biologicals	1 (0.5)
Anticoagulants	78 (36.1)
Antihypertensive drugs	81 (37.5)
Lipid lowering therapy	79 (36.6)
Bèta2-sympathicomimetica	51 (23.6)
Anti-diabetic drugs	40 (18.5)
Survival	
Deceased ≤2 year after 6MWT	74 (34.3)
Variables	**Total n=216**
Deceased ≤2 year after 6MWT	74 (34.3)
Lung transplantation, ≤2 year after 6MWT	20 (9.3)

*Data are presented as mean ±SD, median [IQR] or n (%). Numeric or alphabetic characters in superscript indicate a sample size deviant, in the order: [a] n=215; [b] n=214; [c] n=184; [d] n=149; [e] n=124. Abbreviations: AF-medication. Antifibrotic-Medication; BMI, Body Mass Index (kg/m2); bpm, beats per minute; COPD, Chronic Obstructive Pulmonary Disease; DLCO, diffusing capacity to carbon monoxide corrected for haemoglobin (measured in ml/min/kPa); FVC, Forced Vital Capacity; GAP, Gender-Age-Physiology (FVC %predicted, DLCO %predicted); GERD, Gastroesophageal Reflux Disease; IPF, Idiopathic Pulmonary Fibrosis; L/min, Litres per minute; m, metre; na, not applicable; p, points; SpO_2-nadir, lowest SpO_2 during 6MWT. * Strata according to GAP index; ** Pack-year, number of years smoking x average number of cigarettes smoked per day/20; *** Truncus pulmonalis dilatation, Cut-off >30mm, based on High-resolution computed tomography (HRCT) +/- 6 months 6MW*

Table 2. 6MWT attributes in patients with IPF

6MWT (n=216)	
Baseline measurements	
Baseline heart rate (bpm)	81.6 ±14.4
Baseline oxygen saturation (%, SpO_2)	96.4 ±2.6
Baseline BORG (shortness of breath) (0-10 p) [d]	1.4 ±1.4
Baseline BORG (level of fatigue) (0-10 p) [d]	0.9 ±1.4
Oxygen supply, yes	35 (16.2)
Oxygen supply if yes L/min [e]	2.5 ±1.0
Walking aid, yes	7 (3.2)
End of test measurements	
Distance walked (m)	420.0 ±121.7
Distance walked % predicted [30]	80.0 ±22.3
End heart rate (bpm)	111.3 ±21.8
End oxygen saturation [c] (%, SpO_2)	86.1 ±8.0
End BORG (shortness of breath) [b]	4.1 ±1.8
End BORG (level of fatigue) [b]	2.6 ±2.0
Heart rate max. (bpm) [c]	121.8 ±19.1
SpO_2-nadir, %	83.4 ±8.0
Distance saturation product*	352.9 ±112.4
Rests, yes [a]	18 (8.4)
Rest, yes 1x	6 (33.3)
Rest, yes 2x	8 (44.4)
Rest, yes 3x	4 (22.2)

*Data are presented as mean ±SD or n (%). Numeric or alphabetic characters in superscript indicate a sample size deviant, in the order: [a] n=215; [b] n=214; [c] n=190; [d] n=189; [e] n=35. Abbreviations: 6MWT, 6 minute walk test; bpm, beats per minute; IPF, Idiopathic Pulmonary Fibrosis; m, metre; n, number; SpO_2, peripheral capillary oxygen saturation; SpO_2-nadir, lowest point of SpO_2. * Distance saturation product, (6MWT distance walked)*(SpO_2-nadir)/100)*

Table 3. Characteristics of patients with IPF for 2-year transplant-free survival after 6MWT

	2-year after 6MWT		
	Alive n=122 0(56.5)	**Deceased or LoTX** n=94 (43.5)	**p**
Variables			
Sex, male	98 (80.3)	75 (79.8)	ns[α]
Age (at 6MWT)	68.6 ±9.7	67.3 ±9.1	ns
BMI (kg/m^2)	27.3 ±3.6	26.1 ±4.3	0.02
Smoking, ever [a]	101 (82.8)	75 (79.8)	ns[α]
Pack-years *[g]	22.6 ±18.3	22.3 ±19.6	ns
Pulmonary function tests			
FVC % predicted [b]	86.0 ±17.3	70.4 ±19.3	<0.001
DLCO % predicted [c]	46.0 ±14.0	33.3 ±8.7	<0.001[β]
GAP [b]			<0.001[α]
Stage I	50 (41.0)	18 (19.1)	
Stage II	64 (52.4)	49 (52.1)	
Stage III	8 (6.6)	25 (26.5)	
Comorbidity			
GERD	5 (4.1)	5 (5.3)	ns[α]
Cardiovascular disease	42 (34.4)	29 (30.9)	ns[α]
Vascular neurologic	7 (5.7)	10 (10.6)	ns[α]
Pulmonary Hypertension	2 (1.6)	6 (6.4)	ns[α]
Truncus Pulmonalis dilatation [f]	25 (26.0)	33 (35.1)	ns[α]
Hypertension [a]	27 (22.1)	18 (19.4)	ns[α]
Lung cancer	3 (2.5)	3 (3.2)	ns[α]
COPD	13 (10.7)	16 (17.0)	ns[α]
Hyperglycaemia/DM [a]	25 (20.5)	21 (22.6)	ns[α]
Antifibrotic medication			
AF-medication use during 6MWT	72 (59.0)	75 (79.8)	0.001[α]
AF-medication after 6MWT (>90 days)	99 (81.1)	70 (74.5)	ns[α]
6MWT_Baseline measurements			
Baseline heart rate (bpm)	79.9 ±14.0	83.8 ±14.6	0.048
Baseline oxygen saturation (SpO_2)	97.0 ±1.7	95.5 ±3.2	<0.001[β]
Baseline BORG (shortness of breath) (0-10 p) [e]	1.3 ±1.4	1.6 ±1.5	ns
Baseline BORG (level of fatigue) (0-10 p) [e]	0.7 ±1.4	1.1 ±1.3	ns
6MWT_End of test measurements			
Distance walked (m)	457.6 ±101.3	371.1 ±129.0	<0.001 [β]
Distance walked % predicted	88.2 ±18.7	69.3 ±22.1	<0.001
End BORG (shortness of breath) [b]	3.9 ±1.8	4.5 ±1.9	0.01
End BORG (level of fatigue) [b]	2.3 ±2.1	2.8 ±1.9	ns
Heart rate max [d]	120.7 ±18.1	123.4 ±20.4	ns
SpO2-nadir	86.6 ±6.4	79.3 ±8.2	<0.001 [β]
Distance saturation product	397.2 ±95.4	295.5 ±107.2	<0.001

*Data are presented as mean ±SD or n (%). Numeric or alphabetic characters in superscript indicate a sample size deviant, in the order: [a] n=215, [b] n =214, [c] n=207, [d] n=190, [e] n=189, [f] n=184, [g] n=149. Abbreviations: AF-medication. Antifibrotic Medication; BMI, Body Mass Index (kg/m2); bpm, beats per minute; COPD, Chronic Obstructive Pulmonary Disease; DLCO, diffusing capacity to carbon monoxide corrected for haemoglobin (measured in ml/min/kPa); FVC, Forced Vital Capacity; GAP, Gender-Age-Physiology (FVC %predicted, DLCO %predicted); GERD, Gastroesophageal Reflux Disease; IPF, Idiopathic Pulmonary Fibrosis; L/min, Litres per minute; LoTX, Lung Transplantation; m, metre; na, not applicable; p, points; SpO_2-nadir. * Pack-year, number of years smoking x average number of cigarettes smoked per day/20. [α] Chi-Square Test, [β] Levene's test for Equality of variances (p<0.05)*

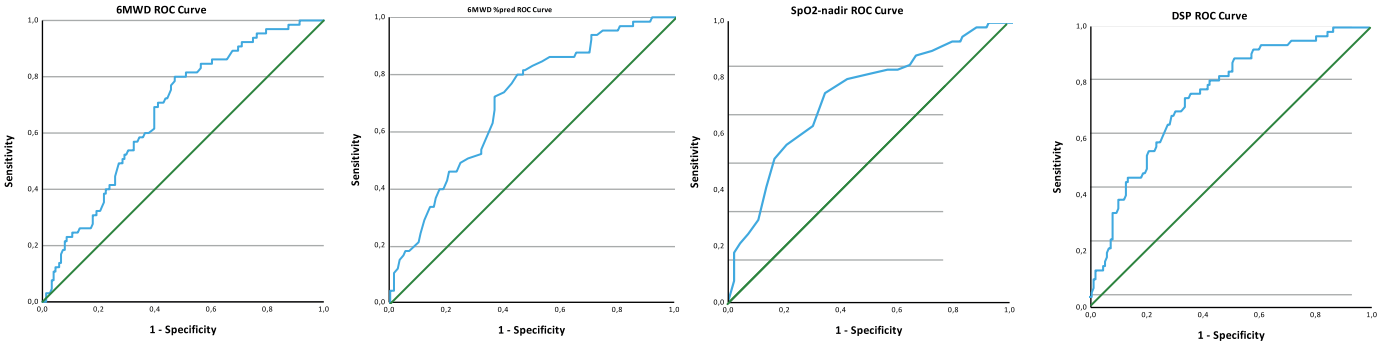
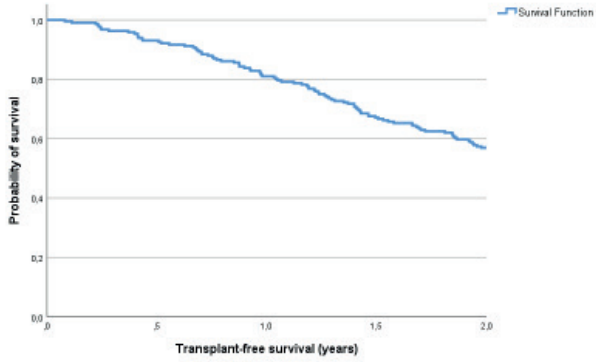


Figure 1. *Six-minute walk test: Receiver operating characteristic (ROC) curves and area under the curve (AUC) A. 6MWD AUC 0.675, Sens 0.800, Spec 0.530, Cut-off 413 m; B. 6MWD %pred AUC 0.706, Sens 0.723, Spec 0.636, Cut-off 83%; C. SpO_2-nadir AUC 0.761, Sens 0.769, Spec. 0.669, Cut-off 86%; D. DSP AUC 0.739, Sens 0.754, Spec 0.642, Cut-off 374 m%*

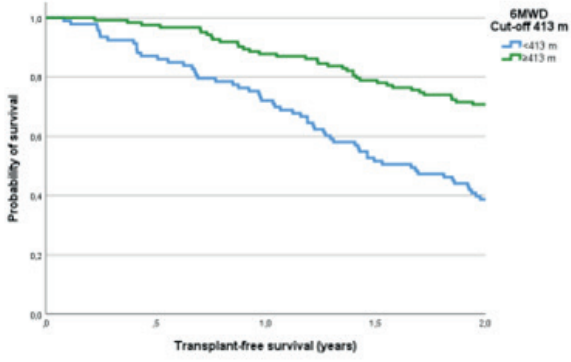
Abbreviations: 6MWD, 6 minute walk distance; 6MWT, 6 minute walk test; AUC, area under the curve; DSP, distance-saturation-product; Sens, sensitivity; Spec, specificity; SpO_2-nadir, lowest point of peripheral capillary oxygen saturation.



	0 yr	1 yr	2 yr
Patients, n	216	175	122

Transplant-free survival, median not applicable

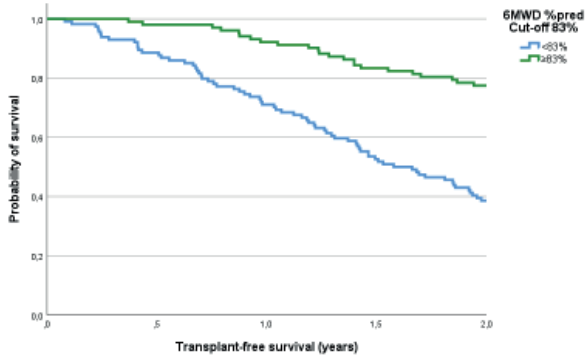
A. Total group



6MWD	0 yr	1 yr	2 yr
<413 m, n	93	67	36
≥413 m, n	123	108	87

6MWD <413 m, median 1.7 [95% CI: 1.3-2.0]
6MWD ≥413 m, median not applicable
p<0.001

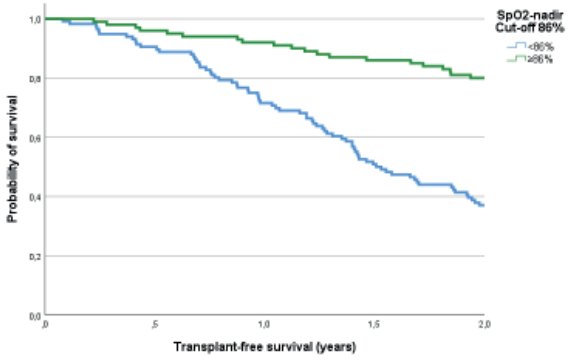
B. 6MWD



6MWD %pred	O yr	1 yr	2 yr
<83%, n	114	81	44
≥83%, n	102	94	79

6MWD %pred <83%, median 1.6 [95% CI: 1.2-1.9]
6MWD %pred ≥83%, median not applicable
p<0.001

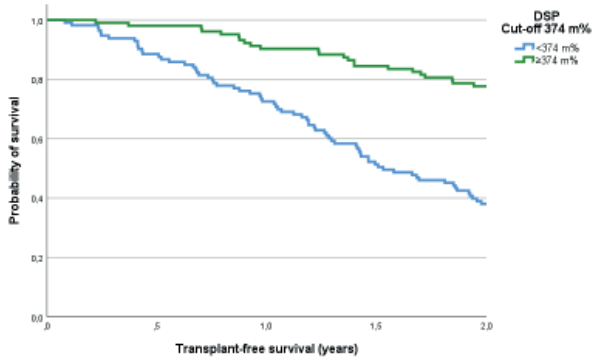
C. 6MWD %pred



SpO_2-nadir	O yr	1 yr	2 yr
<86%, n	116	83	43
≥86%, n	100	92	80

6MWT-SpO2-nadir <86%, median 1.5 [95% CI: 1.3-1.8]
6MWT-SpO_2-nadir ≥86%, median not applicable
p<0.001

D. SpO_2-nadir



DSP	0 yr	1 yr	2 yr
<374 m%, n	113	82	43
≥374 m%, n	103	93	80

6MWT-DSP <374 m%, median 1.5 [95% CI: 1.2-1.9]
6MWT-DSP ≥374 m%, median not applicable
p<0.001

E. DSP

Figure 2. *Transplant-free survival of patients with idiopathic pulmonary fibrosis, Kaplan-Meier curve and life-table*

Abbreviations: 6MWD, 6 minute walk distance; 6MWT, 6 minute walk test; DSP, distance-saturation-product; SpO_2-nadir, lowest point of peripheral capillary oxygen saturation.

Survival according to predictive models

Application of the original GAP-model on our cohort revealed 68 patients with GAP stage I (32%), 113 patients with GAP stage II (53%), and 33 patients with GAP stage III (15%) (figure 3.A). Mean SpO_2-nadir was significant ($p<0.001$) different between the GAP stages: GAP-I 87.6% ± 6.5, GAP-II 82.3% ±8.2, GAP-III 79.2% ± 6.9 **(Figure 3.A)**.

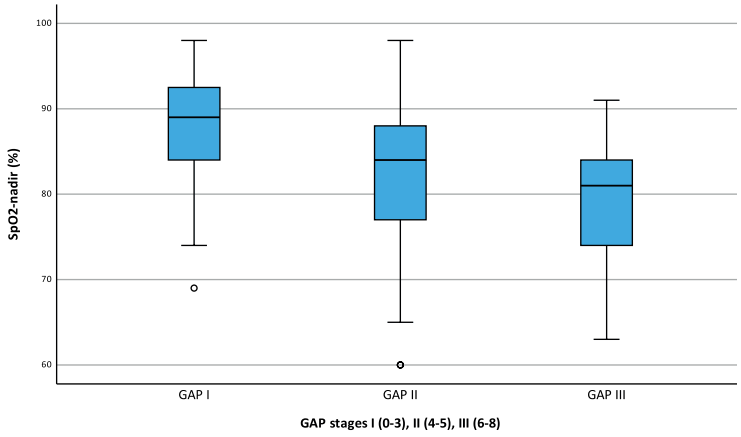


Figure 3.A Mean of SpO_2-nadir in patients with IPF classified by GAP stages

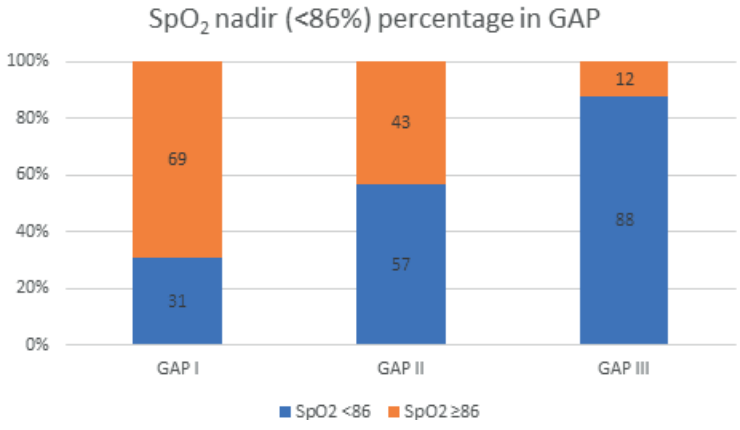


Figure 3.B SpO_2-nadir percentage (threshold <86%) in patients with IPF classified by GAP stages

Figure 3. *SpO_2-nadir of 6MWT in patients with IPF classified by GAP stages: mean of SpO_2-nadir (Fig. 3.A) or SpO_2-nadir percentage (threshold <86%, Fig. 3.B)*
GAP I, n=68 (31.8%); GAP II, n=113 (52.8%); GAP III, n=33 (15.4%); p<0.0001

Abbreviations: 6MWT, six Minute Walk Test; GAP, Gender-Age-Physiology; IPF, Idiopathic Pulmonary Fibrosis; SpO_2-nadir, lowest point of peripheral capillary oxygen saturation during 6 minute walk test

The number of IPF patients and survival per GAP stage are presented in **figure 4**. Survival differed significantly by stage, however, the median survival of GAP stages I and II was beyond the range of two-year follow-up time. The median survival of GAP stage III was: 1.0 (95% CI: 0.7-1.3) years, p<0.001 **(figure 4A)**. The predicted two-year mortality of the GAP stages were: GAP I 10.9%, GAP II 29.9%, GAP III 62.1%.19 The observed two-year mortality for GAP stage I, II and III was 26%, 43% and 76% respectively. In the modified GAP-SpO_2-nadir (SpO_2-nadir ≥86% score 0, <86% score +2) two-year mortality was 14% in GAP-SpO_2-nadir-I, 39% in GAP-SpO_2-nadir-II and 73% in GAP-SpO_2-nadir-III, also significantly different between stages **(Figure 4.B)**. The C-statistic index value showed an improvement over the original GAP stage model (0.62, 95%CI 0.58-0.67) at GAP-SpO_2-nadir stage (0.66, 95%CI 0.62-0.70) **(Table 4, 5).** To confirm the statistically significant contribution of the SpO_2-nadir compared to the model with the original GAP, the Cox proportional-hazards model, regression model for transplant-free survival, was performed with two variables, the GAP-model (stages) and the SpO_2-nadir (threshold 86%) **(Table 5)**. A SpO_2-nadir below 86% increases the likelihood of dying or being lung transplanted (HR 2.6; 95%CI 1.76-3.71, p<0.001) within 2 years after the 6MWT date.

Table 4. Two-year mortality equation with the variables GAP and SpO_2-nadir

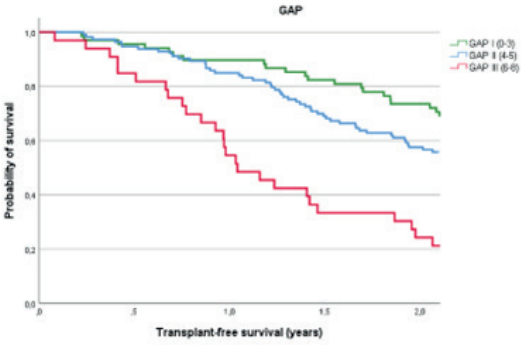
	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
GAP stage						
GAP I (0-3)	ref			ref		
GAP II (4-5)	1.774	1.186-2,654	0.005	1.372	0.905-2.082	0.136
GAP III (6-8)	4.680	2.872-7.626	<0.001	2.753	1.630-4.650	<0.001
SpO_2-nadir	3.239	2.292-4.577	<0.001	2.556	1.759-3.715	<0.001

Abbreviations: CI, Confidence Interval; GAP, Gender-Age-Physiology (FVC %predicted, DLCO %predicted); HR, Hazard Ratio; SpO_2-nadir, lowest point of peripheral capillary oxygen saturation during 6 minute walk test
Concordance statistics = 0.62 (95% CI [0.58-0.67])

Table 5. Hazard ratio and mortality rate per GAP-SpO2-nadir stage

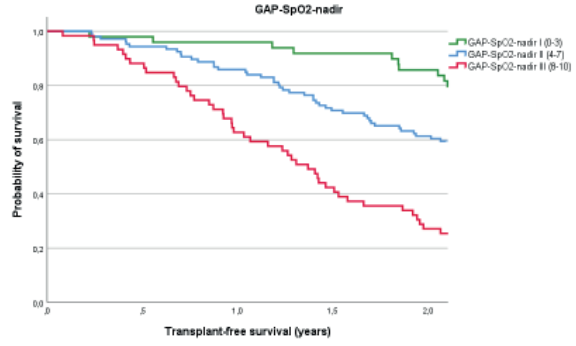
						Mortality rate (%)	
	n	HR	95% CI	p-value	C-stat (95% CI)	1-y	2-y
GAP-SpO_2-nadir stage	214				0.66 (0.62-0.70)		
GAP-SpO_2-nadir I (0-3)	49	ref				4.1	14.3
GAP-SpO_2-nadir II (4-6)	106	2.559	1.544-4.243	<0.001		14.2	38.7
GAP-SpO_2-nadir III (7-10)	59	5.270	3.105-8.944	<0.001		37.3	72.9

Abbreviations: CI, Confidence Interval; C-stat, Concordance statistics; GAP, Gender-Age-Physiology (FVC %predicted, DLCO %predicted); HR, Hazard Ratio; n, number; SpO_2-nadir, lowest point of peripheral capillary oxygen saturation during 6 minute walk test



GAP	0 yr	1 yr	2 yr	
Stage I, n	68	61	50	*Stage I, median > 2 year not applicable, 2 year survival 73.5%*
Stage II, n	113	96	65	*Stage II, median >2 year [95% CI: 1.9- >2.0], 2 year survival 57.5%*
Stage III, n	33	18	8	*Stage III, median 1.0 [95% CI: 0.7-1.3], 2 year survival 24.2%*
				p<0.001

Figure 4.A GAP stages



GAP-SpO_2-nadir	0 yr	1 yr	2 yr	
Stage I, n	49	47	42	*Stage I, median > 2 year not applicable, 2 year survival 85.7%*
Stage II, n	106	91	65	*Stage II, median >2 year not applicable, 2 year survival 61.3%*
Stage III, n	59	37	16	*Stage III, median 1.4 [95% CI: 1.2-1.6], 2 year survival 27.1%*
				p<0.001

Figure 4.B GAP-SpO_2-nadir stages

Figure 4. Kaplan-Meier curves and survival per GAP stage **(4.A)** or GAP-SpO_2-nadir stage **(4.B)**

Abbreviations: GAP, Gender-Age-Physiology SpO_2-nadir, lowest point of peripheral capillary oxygen saturation during 6 minute walk test

Discussion

This is the first retrospective real-world study to investigate the prognostic value of the 6MWT on two years transplant-free survival in patients with IPF after the introduction of antifibrotic agents in 2015 in the Netherlands. We identified novel cut-off points for different attributes of the 6MWT such as 6MWD, SpO_2-nadir and DSP, regarding their optimal prognostic value. The prognostic accuracy of the mortality prediction GAP model in patients with IPF improves by implementing the SpO_2-nadir.

In daily clinical practice, it is important to provide patients with evidence-based information about the prognosis of the disease course and the patients' functioning. This supports shared decisions about treatment strategies, including antifibrotics, oxygen delivery, screening for lung transplantation, pulmonary rehabilitation and/or palliative care. The current study shows that attributes of the 6MWT, such as the distance walked in 6 minutes, SpO_2-nadir or DSP, can make an important contribution as prognostic indicators of two-year transplant-free survival. Moreover, prediction of mortality is important in patients with IPF when considering referral to a transplant center. The consensus statement of the International Society for Heart and Lung Transplantation recommends that lung transplantation should be considered for adults with chronic lung disease who have a high risk (>50%) of death from lung disease within 2 years if lung transplantation is not performed.33 From a clinical decision-making perspective, the 2-year mortality is therefore important for referral for lung transplantation. Also because the age limit for lung transplantation in Europe has shifted from 65 to 70 years. The Lung Allocation Score (LAS) was introduced in The Netherlands in 2014.[34] The LAS is based on the estimated medical urgency for lung transplantation combined with the probability of success after transplantation.[35] It also includes the distance walked in 6 minutes. Whether its predictive power improves by adding SpO_2-nadir remains to be determined.

New thresholds for 6MWD (≥413 m), 6MWD %pred (≥83%), SpO_2-nadir (≥86%) and DSP (≥374 m%) to predict transplant-free survival at 2 years were established. Previously, before the changed policies of patient management with antifbrotic medication in 2015, Du Bois et al presented in 2014 a twofold increase in 1-year mortality by a 6-min walking distance of less than 250 m.[12] It remains unclear how this threshold was established. Also, the source population of this study was from a trial study36, resulting in a more restricted IPF cohort by the inclusion criteria of this study then in our real-world study. Using the receiver operating characteristic curve, Caminati et al

identified 212 m as the optimal threshold to predict 1-year mortality in a small study sample of 44 patients.[11] Lederer and colleagues reported a similar threshold (207 m) to predict 6-month mortality in IPF patients on the waiting list for lung transplantation using similar methodology.[37] But, then again, all these aforementioned studies were before the era of antifibrotic medication.

The newly presented threshold value for the 6MWD of 413 m is close to 432 m used in a Swedish registry-based cohort study in 2020.[16] In contrast to us, the Swedish colleagues used the mean baseline 6MWD to determine their threshold, instead of calculating the optimal threshold using ROC curves. However, the 6MWD remained a significant predictor of 2-year transplant-free survival after adjustment for total lung capacity, quality of life and GAP stage.[16]

The second aim of this study was to assess whether and to what extent SpO_2-nadir contribute to the predictive value of the multidimensional GAP model. The multivariable Cox regression model with GAP stage and SpO_2-nadir showed that the SpO_2-nadir is an independent significant predictor of 2 year survival **(Table 4)**. To date, 6MWD and exercise-induced hypoxemia are not incorporated. Although several studies already showed that the GAP model should be extended with the 6MWD, the SpO_2-nadir or the DSP[16,19,20], these studies used patient data from before the introduction of antifibrotic medication in 2015, or only the endpoint death from all causes was analysed and not the transplant-free survival. The DO-GAP is a new predictive model with the distance walked based on a 6MWD cut-off of <250m and exertional hypoxia.[20] The used cut-off point of 250m was not elucidated and exertional hypoxia was defined by either an active prescription for supplemental oxygen or if desaturation (SpO_2 <88%) was observed during the 6MWT performed on room air. Current study used the new established cut-off score of SpO_2-nadir for adding in the GAP model by weighting a score below threshold with +2 points. Both features, distance and exertional hypoxia, were weighted with a score of +5 in the DO-GAP, resulting in a more divergent stage classification on the original GAP, with a new assessment score between 0 and 18. Our study is in congruence with the study by Lee et al in 2023[19], who demonstrated that SpO_2-nadir is an important predictor of mortality and adding SpO_2-nadir to the GAP model seems very reasonable. Baseline characteristics between the aforementioned cohort versus the current cohort showed more patients over the age of 60 years in the Korean study with a lower FVC %pred and less severe limited diffusion capacity, resulting in a GAP-I stage of 52.5% in the Korean cohort versus 32.9% in the current Dutch cohort. A possible reason that this study showed better GAP values may be the

exclusion of patients for whom no DLCO was known (n=336, almost 1/3 of the final cohort n=966). Notably, no patient had a score of +3 on the DLCO (impossible to perform), which may have had an impact on the GAP distribution. Then, the GAP6 model was run based on 3 levels of SpO_2-nadir, ≥90% (zero point), ≤80-90% (+1 point) and <80% (+2 points). It remains unknown how these cut-offs were determined. Compared to the Korean study, the current study provides more insight into the IPF study population (including comorbidities and medication use), the measurement of the 6MWT was transparent and therefore several more reliable exercise outcome measures were available. To the best of our knowledge, the current study is the first to extend the GAP with SpO_2-nadir based on the newly established SpO_2-nadir threshold in IPF patients from the era of mortality-reducing AF medication.

Hence, this study was focused on prognostic factors of the 6MWT (distance walked, SpO_2-nadir and DSP). The cut-off points were based on findings of the best trade-off between sensitivity (slightly above 0.70 for all variables) and specificity (below 0.70 for all variables). Although these were not perfect results, it seemed a reasonable test to determine who was and who was not at increased risk of death. Further research is needed to externally validate the current cut-off points in other IPF cohorts. A validation sample was lacking in the current study. Obviously the current findings need to be confirmed by others. In clinical trials, there will always be friction with external validity due to restrictive inclusion criteria. The current retrospective study was conducted with patient real-world data from pulmonary clinic, which will better support external validity compared to analyses from clinical trials.

The study has some more limitations common for (retrospective) studies in electronic clinic data. First, this was a monocenter study involving a cohort of patients in an ILD center of excellence and this might call into question the generalisation of our findings to other cohorts. However, baseline and clinical characteristics, were rather similar to those of other recent cohort studies.[16,19] Subsequently, only data from patients with a broad informed consent for research purposes (81% of patients with IPF) were used for analyses, which could introduce selection bias.

Second, there might be an inclusion bias since in our clinic the 6MWT was used in usual care for prognostic insight and/or to identify the need for supplemental oxygen. 6MWT was part of the standard of care screening/follow-up for lung transplants and was often used for non-pharmacological therapies such as pulmonary rehabilitation. But unfortunately, standardised exercise capacity measurements are still not integrat-

ed in standard care in early disease. Possibly partly as a result of this, only a quarter of the IPF patients known to the medical clinic (n=246 of 1032 patients) had a 6MWT. Due to the absence of the 6MWT at the diagnosis stage, the GAP model (intended to predict mortality in patients with IPF at the time of diagnosis) was applied at the date of the first 6MWT after diagnosis. Further studies on addition of the 6MWT to the IPF GAP model at the time of diagnosis are needed. In addition, insight into basic characteristics of patients with a 6MWT compared to patients without a walk test is lacking. Bias on missing data from the 6MWT is a concern not only seen in retrospective studies, but also in several longitudinal prospective IPF registry studies.[16,38] However, the same standardised methodology and location was used for all 6MWT in this mono-center study and were recorded in the electronic medical record. As a result, there were minimal missing data of the various variables of the 6MWT. Also, it is worth noting that the number of patients participating in pharmacological trials suitable for an ILD center of excellence has increased sharply in recent years, which is also a possible reason for a lower inclusion percentage of this retrospective study (7.3% of patients was excluded by use of medication in a trial study). Referral bias, a form of selection bias of the patients with IPF, can play a role in an ILD center of excellence. However, since IPF is a rare disease and in the Netherlands the medical diagnostic process is mainly reserved for the ILD centers of excellence, it is to be expected that most patients with IPF living in the Netherlands are known to one of the three IPF centers of expertise.

Conclusions

In summary, these data reflect the day-to-day reality of the clinic and the data accurately reflect the predictive value of the 6MWT. Patients with IPF who have an exercise-induced oxygen desaturation have worse prognosis. We recommend the 6MWT as part of standard care for prognostic purposes. Addition of SpO_2-nadir to the GAP model seems promising for use in clinical care of IPF patients. Further investigation into the prognostic value of exercise capacity and SpO_2-nadir at the time of diagnosis is recommended.

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Chapter 9

General discussion

General discussion

Scope of the thesis

The diagnostic trajectory and management of ILDs are complex, as ILDs encompasses a wide heterogeneity of diseases with different causes, that require personalized management and lead to variable outcomes.[1,2] The clinical presentation of ILDs is non-specific with the most common symptoms being dyspnoea, cough, and fatigue.[3] This thesis is limited to the two most well-known interstitial lung diseases: pulmonary fibrosis and sarcoidosis. Pulmonary fibrosis is a chronic, progressive lethal interstitial lung disorder characterized by scarring (fibrosis) in the lungs that limits oxygen uptake.[4] Sarcoidosis is a disease in which abnormal collections of inflammatory cells, granulomas, develop spontaneously in various organs and tissues of the body.[5] Most people recover from sarcoidosis, but in a subgroup of patients pulmonary fibrosis also develops. Both ILDs have an important impact on the quality of life of the patients. Managing symptoms and maintaining exercise tolerance is important for maintaining quality of life in patients with pulmonary fibrosis, but is extremely challenging given the lack of evidence-based therapies.[6,7] The 2011 ATS/ERS/JRS/ALAT guidelines[8] recommend pulmonary rehabilitation as part of the management of IPF, given its potential to improve exercise capacity, dyspnoea, and quality of life.[9]

Symptom management is part of a broader holistic approach of optimizing patient's functioning and health. Models of functioning and health are the basis for clinical practice, teaching and research.[10,11] The current ICF-ILD health perspective attempts to describe the spectrum of impairment type (symptomatic and anatomical) and to quantify the burden of disability of a population, as well as capturing "environmental factors" that either improve function and mitigate disability, or worsen impairment.[12] This thesis addresses symptom burden and functional exercise capacity in ILD focuses primarily on the ICF classification domain, "body function", which includes the physiological functions (such as functional exercise capacity) and the burden of perceived symptoms (such as fatigue, dyspnoea and cough). This thesis links certain contextual factors such aspersonal factors (such as anxiety, depression and activation to self-management).

This thesis includes newly obtained data from original patient research to better map the symptom burden and the functional exercise capacity of patients with pulmonary fibrosis or pulmonary sarcoidosis. The first part was focused on research into patient

reported outcomes (PROs), that what matters to the patient, in patients with IPF or pulmonary sarcoidosis at Zuyderland MC (Heerlen, The Netherlands). To investigate these PROs, patients with IPF or pulmonary sarcoidosis were asked to complete a sequence of predetermined paper-and-pencil questionnaires. Clinicians' understanding of the effect of disease and treatment on patients' daily lives is important for their broader uptake to improve quality of care.

The second part focuses on testing the functional exercise capacity in patients with pulmonary fibrosis at St. Antonius Hospital, a national referral center for ILD (Nieuwegein, The Netherlands), and is therefore more directly related to the physical condition of the patient. Testing the exercise capacity of patients with pulmonary fibrosis provides insights into possible physical limitations and symptom burden during exercise, has a value in predicting survival (it is part of the Lung Allocation Score, LAS, which is used in patients listed for lung transplantation) and may provide information for more personalized individual physical training programs.[13,14] In brief: patients with pulmonary fibrosis were invited to participate in a cross-sectional one-day study into the validity of performance tests on exercise capacity with the 6MWT as the reference test. This study also included a reliability study of the 6MWT on the test-retest reliability on one day of the 6MWT. The latest retrospective study, based on patients' medical records, investigated the prognostic values of the attributes derived from 6MWT in IPF. In this final chapter, the main findings of the studies are summarized followed by a more in-depth general discussion of selected themes, a view on future directions in clinical practice and research, and a reflection on the scientific and social impact of the present findings

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Summary of main findings:

Severe fatigue is common in patients with IPF (48%) and in patients with sarcoidosis (69%). Patients with severe fatigue experienced more dyspnoea, sleepiness, anxiety, depression, fatigue-related catastrophizing, functional activity impairments, and lower quality of life. **(Chapter 2)**

The description of fatigue by patients with severe fatigue with IPF or sarcoidosis included significantly more adjectives and also adjectives with a more negative connotation compared to non-severely fatigued patients. Just as severely fatigued patients with IPF describe their fatigue as less 'pleasant', patients with sarcoidosis and severe fatigue describe their fatigue perceptions as 'frustrating', 'exhausting', 'frightening' significantly more often than patients without severe fatigue. **(Chapter 3)**

Patients with IPF or sarcoidosis have a significantly higher respiratory and non-respiratory symptom burden compared to a control group without reduced spirometry (FEV1 and FVC), after a gender and age matching procedure. Patients with IPF reported the greatest differences compared to controls in symptoms such as shortness of breath, coughing, fatigue, muscle weakness and insomnia. Patients with sarcoidosis also experienced increased pain, itching, thirst and micturition problems compared to controls. **(Chapter 4)**

Self-management is seen as the key to increasing patients' ability to cope with the consequences of their disease and thus maintain a satisfactory quality of life. However, 56% of patients with IPF and 46% of patients with sarcoidosis showed low patient activation levels for self-management. These results suggest that for a substantial proportion of patients, their role in managing health, and the knowledge, the skills and/or confidence to do so, may be insufficient for optimal health self-management behavior. Interestingly, levels of patient activation were not associated with the degree of lung function impairment in patients with IPF or sarcoidosis. In contrast, lower levels of patient activation for self-management were associated with more dyspnoea, more anxiety, more depression, and worse health status. **(Chapter 5)**

In the current guideline on 6MWT it is recommended that the 6MWT is performed twice due to a learning effect on repetition. Performing the 6MWT twice on one day in patients with pulmonary fibrosis showed an excellent test-retest reliability of the 6MWT and the improvement in second test was small but significant, with a mean difference of 8.4 m (± 25 m). However, one in six patients with pulmonary fibrosis were unable to complete the second 6MWT within the same day, and of patients who completed two tests, 33% did not improve on the second test. Also, no differences were seen in the test on repetition in other attributes derived from 6MWT, such as SpO_2-nadir or heart rate recovery. As a result, one 6MWT appears sufficient to identify patients with pulmonary fibrosis suffering from exercise-induced oxygen desaturation. **(Chapter 6)**

The 4 meter gait speed (4MGS) test and 5 repetitions of sit-to-stand (5STS) test are relatively easy to perform across all clinical settings, and are significantly and independently correlated with the distance covered in 6MWT (functional capacity test) in patients with pulmonary fibrosis. Indeed, the 4MGS test may serve as a simple initial field test to assess exercise performance in patients with pulmonary fibrosis. 4MGS in combination with handgrip strength and Medical Research Council dyspnoea grade

could explain 75% of the variance in the distance walked in 6MWT. Clearly, the 6MWT provided additional information regarding exercise-induced oxygen desaturation (SpO_2-nadir), which could not be adequately determined using the 4MGS and 5STS. **(Chapter 7)**

Attributes of the 6MWT, such as the distance walked in 6 minutes, SpO_2-nadir or distance saturation product (DSP) are known for their important contribution as prognostic indicators of two-year transplant-free survival. The prognostic value of the 6MWT on two years transplant-free survival in patients with IPF after the introduction of antifibrotic agents in 2015 in the Netherlands gained renewed insights: novel cut-off points were identified for different attributes of the 6MWT such as 6MWD, SpO_2-nadir and DSP, regarding their optimal prognostic value. Also, the prognostic accuracy of the mortality prediction GAP model in patients with IPF improved by implementing the SpO_2-nadir. **(Chapter 8)**

Interpretation and discussion

In the following section, three topics related to the main findings of the thesis will be discussed:

1. Severe fatigue in patients with IPF or sarcoidosis;
2. Patient activation for self-management in patients with IPF or sarcoidosis;
3. Exercise capacity in patients with pulmonary fibrosis.

Severe fatigue in patients with IPF or sarcoidosis: its prevalence and experience

Severe fatigue was prevalent in 48% of patients with IPF and 69% of patients with pulmonary sarcoidosis, determined by the CIS-fatigue. Fatigue was significantly associated with both respiratory (dyspnoea, cough) and non-respiratory symptoms (depression), fatigue-related catastrophizing (meaning the psychological process characterized by the presence of catastrophizing thoughts of fatigue), activity impairments and with quality of life **(Chapter 2)**.

Fatigue is also a common symptom in the general population.[15] To determine the differences in burdensome fatigue in patients with IPF or sarcoidosis, the prevalence rates were compared with individuals without impaired spirometric values (controls). The study of the respiratory and non-respiratory symptom burden **(Chapter 4)** showed that both patient groups had significantly higher fatigue levels in comparison to the

control groups after they were matched by age and gender. This means that severe fatigue is an important symptom in patients with IPF or sarcoidosis. However, fatigue severity does not reflect a person's perception and appraisal of the fatigue. Therefore, the quantitative way of assessing fatigue fails to capture the nuances and differences in the experience of fatigue.[16] The Fatigue Quality List (FQL) is an assessment method for determining the quality of fatigue in a patient using adjectives.[16] To better understand what fatigue means for the individual patient with IPF or sarcoidosis, the FQL was used to identify different perceptions of severe fatigue **(Chapter 2)**. If patients with IPF experienced severe fatigue they used more negative connotations such as upsetting, incessant, wearisome and persistent than the non-fatigued patients to express this fatigue. Not one patient stated fatigue as normal. Severely fatigued patients with sarcoidosis used a higher number of adjectives to describe their experience of fatigue than the non-severe fatigued patients: 5 versus 2 adjectives, respectively. Also, the severely fatigued patients more often reported the following adjectives of fatigue: discouraging, temporary, exhausting, incessant, wearisome, annoying, extreme, persistent, frustrating, inexplicable and normal.

It has been recognized that fatigue itself is a multidimensional construct that includes a physical and mental component.[17,18] Physical fatigue is characterized by difficulties in performing physical activities, while mental/cognitive fatigue is described as difficulties concentrating and performing cognitive tasks. One way to distinguish the fatigue construct concerns peripheral and central fatigue.[19] Peripheral fatigue represents 'the inability to maintain a specific force exertion or work rate during exercise', and central fatigue represents 'the failure to initiate and/or sustain attentional tasks and physical activities requiring self-motivation'. Central fatigue is a complex symptom that involves several dimensions and concepts. It can be divided into physiological fatigue, a natural signal to rest and avoid injury, and pathological fatigue, when adaptive function is lost. Central fatigue also consists of several dimensions, namely physical fatigue, mental fatigue and lack of motivation. Each of these dimensions can be assessed in a subjective or objective manner and possibly treated.[17] However, to measure the prevalence of perceived fatigue, in daily practice a questionnaire is usually used that questions the fatigue experienced at a certain time or over a certain period, with or without a defined context. As a result, a recent systematic review of 23 studies of patients with COPD showed a wide range of prevalence rates of fatigue in COPD varying between 17% and 95%.[20] This heterogeneity in the rates may be explained by the different fatigue measurement methods with different cut-off scores to differentiate between normal and severe fatigue. Indeed, fatigue can be assessed with many questionnaires such as

the Fatigue Severity Scale[21], MOS Short form-36 (SF-36) subscale Vitality[22], Checklist Individual Strength subscale fatigue[23], Fatigue Assessment Scale[24] or Visual Analog Scale.[25,26] To measure fatigue, a good content validity and a brief scale is needed with the ability to detect change. There is a growing interest in evaluating this dimension of treatment response.[27,28] In our search for a reliable and validated instrument for the assessment of fatigue, we decided to use the CIS-fatigue. Due to the good psychometric properties of this questionnaire in various chronic conditions and in working adults, and its well-validated cut-off scores for normal/mild/severe fatigue, it has been used in many clinical practices and research.[15,23,29] Moreover, the CIS-fatigue is generally easy to use and provide a first impression of the perceived fatigue over the past two weeks.[23]

In addition to COPD, severe fatigue is also observed in other chronic conditions such as asthma, cancer survivors, long COVID or coronary artery disease.[30-35] Interestingly, the review in COPD studies pointed out significant related factors in either physical, psychological, disease-severity and sociodemographic domains.[20] More specific, the results suggested that the degree of airflow limitation was not a major, let alone the primary, underlying cause of fatigue in patients with COPD. This meant that the causes of fatigue also had to be sought in other physical, psychological and behavioral factors. Respiratory and non-respiratory factors were also significantly associated with fatigue in IPF (sex; coffee use; immunosuppressant medication; dyspnoea; depression; fatigue-related catastrophizing; functional impairment; quality of life, health status) and in sarcoidosis (education level; smoking intensity; psychologic support; dyspnoea; excessive sleepiness; anxiety; depression; fatigue-related catastrophizing; functional Impairment; quality of life, health status). In patients with IPF there was a significant but weak correlation of fatigue with DLCO but not with FEV1 or FVC and in patients with sarcoidosis none of the lung function parameters was associated with severe fatigue **(Chapter 2)**. Our findings also support the need to take a broader view of the possible factors that contribute to fatigue in IPF or sarcoidosis. As mentioned previously, fatigue appears to be a problem that affects all chronic diseases and is unlikely to be disease or domain specific. Fatigue is best explained by an interplay between biological, psychological, and social factors, and these factors are likely transdiagnostic.[36-38]

Our study focused on severe fatigue, but unfortunately was methodologically limited due to the lack of objectively measured exertion values (physical capacity and activity). We were unable to make the direct link between respiratory and non-respiratory symptoms and the relationship with exercise capacity and physical activity. However, it

seems reasonable to assume that patients who experience more shortness of breath and/or are more fatigued, also show poorer exercise capacity and/or activity. This had been seen before in patients with respiratory diseases such as asthma and COPD.[31,32] Indeed, measured with the self-report questionnaire QoL-RIQ/activity, it was seen that patients with IPF or sarcoidosis with severe fatigue felt more limited in their activities compared to normal/mildly fatigued patients **(Chapter 2)**. This might indicate that there is also a relation in daily activity and perceived symptoms in patients with IPF or sarcoidosis.

The patient is often asked to perform physical activity via self-report questionnaires and/or self-report activity diaries. More objective and reliable methods that can be used in research or in daily practice are devices such as accelerometers, pedometers or heart rate monitors.[39] In today's era, with the increasing public-friendly use of modern technologies in smartwatches or simple pedometers, this would provide a practical manageable solution for collecting data on daily exercise activity.

It is still largely unknown which factors, or combinations of factors, play a role in the fatigue experienced during exercise in patients with pulmonary fibrosis or sarcoidosis. This once again underlines the importance of a broad intake and personalized, tailor-made care and, secondly, that further research into this is recommended.

Patient activation for self-management in IPF or sarcoidosis: An underestimated aspect in disease management?

Patients with pulmonary fibrosis described a sense of personal responsibility for maintaining their health and indicated that self-management is crucial.[40,41] Patients expressed a strong desire for information regarding self-management and how to stay well with pulmonary fibrosis.[40,42] And while patients understood that they had a poor prognosis, many wanted their providers to offer a more positive outlook and more options for self-management. Having treatment options (e.g., choosing rehabilitation, recognizing and managing exacerbations, and getting vaccinations) gave patients hope and a greater sense of control.[41,43] Self-management is therefore very important for the individual patient with pulmonary fibrosis. However, for a patient to manage health issues on their own, patients must have the knowledge, skills, confidence, and essentials to do so. Our study found that 56% of outpatients with IPF and approximately half of outpatients with sarcoidosis showed low levels of activation for self-management. The patients with low levels of patient activation also generally reported more dyspnoea, anxiety, depression and lower health status **(chapter 5)**.

Interventions for self-management have previously been described as structured interventions for individuals, aimed at improving self-health behavior, developing self-management skills and increasing the patient's responsibility for healthcare decisions.[44-46] Low levels of patient activation occurs in the general adult population (25 to 40%) but is higher in frail elderly people (up to 70%) and in several other chronic diseases[47-49], suggesting again a trans-diagnostic issue. The effects of self-management interventions in people with chronic respiratory diseases, such as COPD and asthma, shows improvements in health related QoL, while reducing unplanned hospital admissions.[50-53] Activated people are also more likely to make use of online health information.[54]

The results of different studies on the effect of self-management interventions in patients with ILD, reviewed in[55], are disappointing.[55] Meta-analysis showed no difference in health related QoL and no evidence for the effects of self-management interventions on functional capacity, exacerbations, and survival was found in patients with ILD. A recent randomized controlled trial into e-health in IPF in the Netherlands showed that a comprehensive home monitoring program did not improve overall health related QoL, but tended to improve psychological wellbeing.[56] Although the researchers question the outcome measure 'overall health' and instead 'psychological wellbeing' would have been a more appropriate outcome measure, it appears to be challenging to capture QoL and the concept of self-management in research and treatment. Pulmonary function measurements appear to correlate moderately to poorly with QoL. To improve the patient's perceived quality of life, a broader approach is needed, taking into account the patient's activation for self-management. This is an approach that should be embraced by both the patient and the healthcare provider. The study of Lee et al, 2022, explored the perspectives of people with pulmonary fibrosis and HCPs regarding self-management for pulmonary fibrosis.[57] Both groups agreed that self-management involved personal responsibility of the individual with pulmonary fibrosis, that effective self-management required supports and reliable information, and must be individualized.[57] Menichetti and colleagues investigated the contents of patient engagement interventions for older adults.[58] When the 3 components of patient activation, cognition, behavior and emotion, are not addressed, this could result in failure to obtain positive outcomes for the patient. However, the contents of the interventions that focused on patient engagement of older adults tend to focus more on behavioral and educational dimensions than the affective dimension.[58,59] The effects of a lower affective experience are chronic feelings of depression, anxiety, frustration and anger.[58] To activate patients better for self-management, there is a need for a

more comprehensive ILD self-management intervention that focuses on all aspects of the patient's activation. Interventions should therefore encompass all the aspects of patient engagement and activation, including the behavioral, the cognitive and the emotional perspective. Examples of current effective strategies to engage patients to more self-management in the educational, behavioral and affective components are listed below.[58]

- Educational components: multimedia educational programs (written information, verbal education sessions, audiovisual materials), provision of assessment of physical or mental symptoms to improve patients' awareness and information regarding their physical and mental health status.
- Behavioral components: goal setting exercises, action planning, health empowerment interventions, question-asking encouragement, interactive learning/skills training, personal self-management workbook.
- Affective components: positive thinking exercises, motivational interviewing techniques, personal/contextual resource mapping exercises, relaxation exercises, and support of familiars/friends and to come into contact with other fellow sufferers going through similar experiences.

The patient activation measurement (PAM) can be used to assess the self-management abilities of patients with pulmonary fibrosis or sarcoidosis. The PAM tool has been shown to be useful as an outcome measure, as a screening instrument to tailor education, and as a quality indicator for healthcare provision.[60,61] Also in the context of expected healthcare costs, better patient self-management ability measured by the PAM showed a correlation with lower healthcare use in both primary and secondary care.[62] Further research should investigate the nature and impact of outcomes of self-management strategies on patients with ILD. Research should consider the basic activation for self-management and including interventions that encompass the three components necessary for patient engagement and activation: educational, behavioral and affective.

Exercise capacity in pulmonary fibrosis: The true importance remains undervalued

The clinical presentation of pulmonary fibrosis is non-specific with the most common symptoms being dyspnoea on exertion, dry cough and fatigue.[2,3,63] Patients with IPF from the European IPF registry in 2018 were classified according to the New York Heart Association (NYHA) classification based on the severity of shortness of breath and limitation of physical activity.[63] More than 87% of patients were classified as mini-

mal mild (≥NYHA class II), meaning patients can complete physical activities of moderate intensity that require up to 5 MET (metabolic equivalent of task, a measure of how much energy is expended in a given action compared to a resting situation). Patients were able to walk 7 km/h on a level surface or climb stairs at a normal pace, but were unable to perform this physical activity without symptoms such as fatigue or shortness of breath. One third of these patients were classified as moderate, meaning that they were still comfortable at rest, but less than usual physical activity (stair climbing or walking speed >4 km/h) caused symptoms of discomfort. Nearly 9% of patients were classified as severe and were unable to perform any physical activity without discomfort and had possible symptoms of discomfort even at rest. In summary, most patients with pulmonary fibrosis were already limited in their physical activities in daily live at the time of enrollment in the registry system. However, objective measures of physical activity or exercise capacity were lacking because the NYHA classification was based on a patient questionnaire. Objective measures of physical activity and exercise capacity are known to be predictive of survival in people with IPF because individuals often exhibit various pathophysiological mechanisms that limit their ability to perform exercise, such as gas exchange and pulmonary circulation disorders, respiratory restriction and muscle dysfunction.[64] Most studies on the prognostic value of exercise capacity used data before antifibrotic drugs became standard of care in treatment of patients with IPF, i.e. before 2015.[65-67] Therefore, in our study on the functional exercise capacity test, the 6MWT **(Chapter 8)**, we were especially interested in the prognostic value of these attributes derived from 6MWT in the era of antifibrotic drugs (after 2015). We have been able to re-establish cut-off points for 2-year transplant-free survival for the 6MWD (≥413 m), 6MWD %predicted (≥83%), SpO_2-nadir (≥86%) and distance-saturation-product (≥374 m%), with the best discriminative value for SpO_2-nadir (area under the curve: 0.761). Also, adding SpO_2-nadir to the GAP model seems promising for use in clinical care of IPF patients for better a better determination of prognosis.

Testing exercise capacity via the 6MWT is the most commonly used clinical approach, but certain conditions must be met when performing the test. The 6MWT requires sufficient space (i.e. ≥30 m), skilled personnel, and it takes time to conduct the test because repetitive walks are needed due to the learning effect.[68,69] The advantage of simple performance tests is that they require less time and are easy to perform in the clinical setting, possibly even in a healthcare practice close to the patient's home. The study into the performance tests, the 4MGS and the 5STST **(Chapter 7)**, showed that the 4MGS and 5STS scores correlate respectively good and low with the distance walked in 6MWT in patients with pulmonary fibrosis. However, exercise-induced de-

saturation cannot be adequately assessed using the 4MGS and 5STS in patients with of pulmonary fibrosis.

Our findings regarding the prognostic value of exercise capacity in IPF support the conclusion from a recently published systematic review and meta-analysis: 'Exercise capacity measure was associated with mortality risk in people with ILD and 6MWT shows potential to be used as a predictor of mortality in clinical practice'.[70] Interventions to improve physical activity and exercise capacity may have the potential to delay premature mortality in people.[70] Pulmonary rehabilitation involves a multidisciplinary approach to improve exercise capacity and activity.[71] Pulmonary rehabilitation has been proven to be safe and effective in people with fibrotic or chronic interstitial lung diseases and improves dyspnoea, exercise capacity and quality of life, especially if started when people are not yet severely impaired.[64,72-74] Pulmonary rehabilitation will be discussed as a separate section 'future directions'.

Future directions

Fatigue management

Both patients with IPF and sarcoidosis suffer from fatigue and patients often report fatigue as one of the most burdensome symptoms **(Chapter 2)**. Fatigue may have an negative impact on different aspects of the lives of patients.[75] Notably, the fatigue experienced by the two groups, IPF and sarcoidosis, appears to be somewhat different in character. Patients with sarcoidosis report a greater frequency of mental fatigue, while IPF patients appear to suffer from exhaustion, possibly related to shortness of breath.[76] As mentioned before, nowadays it is well established that fatigue is best explained by an interplay between biological, psychological and social factors, and these factors are at least partly to be transdiagnostic.[36] Fatigue is therefore not simply seen as a consequence of reduced lung function in patients with chronic respiratory diseases and many factors appear to play a role in causing or maintaining the perceived fatigue.[36,77] Even in patients with sarcoidosis in clinical remission, fatigue is often reported as a symptom and experienced as a serious and long-lasting problem. In addition to psychological problems and reduced health status associated with fatigue, reduced physical activity and muscle weakness were also observed.[78] It is presently known that inflammation and cytokine release play a central role in the pathogenesis of this sarcoidosis-associated fatigue.[79,80] There are various fatigue management strategies prescribed for physical and/or mental fatigued patients with chronic respiratory diseases,

including medication, exercise therapy, cognitive behavioral therapy, or sleep advice.[81] In 2016, the Netherlands Respiratory Society started the National Program for Respiratory Research ('Lungs that last a lifetime'), setting reduction of fatigue in patients with lung diseases as one of the six main goals.[82] The goal was to reduce the burden of disease (patient) and increase social participation (society). Interestingly, 6 year later, a 2022 study found that less than 25% of fatigued individuals with non-communicable chronic diseases reported having been treated for fatigue.[81]

In daily practice, a measurement of fatigue often consists of a questionnaire administered to the patient, such as the CIS-Fatigue used in our study. Besides the fact that the CIS-questionnaire is a snapshot in time, it relies on retrospective self-report and is therefore subject to recall bias. Also, fatigue is not a 'stable' symptom and more fundamentally, there is an increasing awareness that experiences of fatigue are dynamic, situated, and highly context driven.[83] There is therefore a reason to investigate fatigue in the context in which fatigue occurs. An alternative to retrospective self-report is to study outcomes in real-time (momentary) in real-life environments (ecological).[84,85] A promising method to measure day-to-day/diurnal variations of fatigue is thus the ecological momentary assessment (EMA), a real-time capture of self-reported participant behaviors and perceptual experiences.[86] The EMA method consists of monitoring the experience of symptoms over time with a questionnaire that participants must complete at various random times during the day, in addition to questions in the morning, upon waking and in the evening at bedtime.[85,87] EMA can provide unique insight into context for perceived fatigue, not only during rest, but also during physical and/or daily activity. Unfortunately, we were not able to study fatigue in the construct of EMA. The opportunity to elicit measures of fatigue regularly as part of a health monitoring system could contribute to better care for people with ILD and additional research is recommended. In the future, it will be interesting to study the fatigue experienced by EMA in relation to physical, psychological, disease severity and socio-demographic factors. The resulting insights into possible causal or perpetuating aspects of severe fatigue may provide further treatment insights and better tailored therapy options for the patient.

Most studies on fatigue management in ILDs have been conducted in patients with sarcoidosis.[88,89] The diagnosis sarcoidosis-associated fatigue (SAF) can only be diagnosed if other causes of fatigue (as example diabetes mellitus, heart failure, obstructive sleep apnoea or mental disorders as depression) have been ruled out according to the European Respiratory Society (ERS) guidelines for the treatment of sarcoidosis.[5]

The first recommendation was that patients with sarcoidosis who have troublesome fatigue should be given the option to follow a pulmonary rehabilitation program for 6-12 weeks to improve fatigue (conditional recommendation, low quality of evidence). Recently, a randomized controlled trial in the Netherlands showed the benefit of mindfulness-based cognitive therapy in the treatment of fatigue with improvements in fatigue, anxiety, depression and health status.[90] What is known in patients with IPF is that patients already experienced significant fatigue before medical treatment, that fatigue worsened over time, and that increasing fatigue was associated with younger age, antifibrotic treament (nintedanib) treatment, and low levels of fatigue at baseline.[91]

Although the burden of fatigue in patients with IPF or sarcoidosis is well-recognized, studies that have investigated treatment options are limited. It is known that fatigue in ILD is often a multifactorial and multidimensional problem.[92] As a result, therapeutic interventions should ideally be focused on different domains (physical, mental and motivational). In 2020, Kahlmann introduced a decision-making flowchart on how to handle fatigue in ILD.[93] After a comprehensive patient history, the first step is to optimize treatment of the underlying disease, manage comorbidities and rule out fatigue as a possible side effect of prescribed medications. At the same time, optimal relief of physical symptoms should be sought through both pharmacological and non-pharmacological interventions, such as physiotherapy and/or pulmonary rehabilitation. Attention must also be paid to psychological complaints and/or social factors that contribute to fatigue.

In conclusion, in addition to optimizing medical treatment of the underlying disease, causes of fatigue will need to be identified and treated. In clinical practice, a comprehensive, multidisciplinary and individually tailored approach seems most suitable to optimize the treatment of fatigue in patients with ILD.[93]

Pulmonary rehabilitation

In 2013 the ATS/ERS defined pulmonary rehabilitation as follows: "Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors".[71] Pulmonary rehabilitation is

implemented by a dedicated, interdisciplinary team, including physicians, physiotherapists and other healthcare professionals. A Cochrane systematic review in 2021 concluded that pulmonary rehabilitation in patients with ILDs resulted in clinically meaningful improvement in symptoms as dyspnoea, functional exercise capacity, and quality of life.[64] Improvements in functional exercise capacity, dyspnoea and quality of life were sustained longer term, i.e. 6 to 12 months. Positive findings for improvement in 6-min walk distance, dyspnoea and health related QoL were similar when only people with IPF were included, meaning that PR is one of the few treatments that improves patient-centered outcomes in this group. There are no studies reporting exercise-related side effects, which supports the conclusions of reviews into pulmonary rehabilitation in ILD that exercise is safe for individuals suffering from ILD.[94,95] Although there may be concerns that some patients may not feel well enough to reap benefits from PR, no study has identified a threshold below which patients are unlikely to improve with rehabilitation.[96,97] Patients with IPF showed a similar effectiveness of pulmonary rehabilitation compared with the current "golden standard" group of patients with COPD, in exercise capacity, dyspnoea, and health related quality of life. The improvements and completion rates in patients with IPF were of similar magnitude to those observed in patients with COPD, with both groups matched on baseline exercise tolerance and breathing disability.[95] In IPF, noncompletion of and nonresponse to pulmonary rehabilitation were associated with increased all-cause mortality at 1 year.[95]

To date, gaps remain in the existing knowledge of pulmonary rehabilitation for people with ILD, particularly regarding the duration of benefits, the mechanisms underlying these changes, the optimal program components, and when to offer it during the disease course.[96,97] Moreover, further work is needed to determine whether there may be differential responses to pulmonary rehabilitation among patients with different types of ILD or those with different stages of disease.[96] The positive results of exercise training in the longer term were maintained, with some retention of improvements in leg strength and quality of life, but they appear to be reduced, especially in people with a progressive course of the disease.[98,99] In 2023, a study found that 6-minute walking distance did not improve in the longer term (52 weeks) after pulmonary rehabilitation in patients with IPF taking antifibrotic medications. However, there was a greater improvement in endurance time measured using cycle ergometry, in patients receiving pulmonary rehabilitation compared to patients receiving usual care with the addition of antifibrotics.[99] The UK-based NICE guidelines concluded that because of its positive impact on health status, pulmonary rehabilitation is cost effective in IPF and the pulmonary rehabilitation assessment should be offered at every 6-12 month intervals.[100]

This also provides the opportunity to make informed decisions with the patients with pulmonary fibrosis about their care. Moreover, initiating pulmonary rehabilitation as early as possible after diagnosis is advisable, especially for individuals with IPF, to ensure the best opportunity to participate and reap the benefits of rehabilitation.[94,101,102]

In addition to the aforementioned gaps in existing knowledge regarding pulmonary rehabilitation, there are also considerations to be made regarding the degree of respiratory mechanical strain during exercise. The pathophysiology of lung fibrosis leads to speculation on whether the forces acting on the lung during spontaneous breathing (i.e., vigorous inspiratory effort) may determine a local excessive stretch, thus favoring a feed-forward loop of fibrosis.[103] The course of damage to the fibrotic lung as a result of mechanical ventilation was already known, but whether and to what extent intensive spontaneous breathing during exercise training may also cause lung damage remains unknown. In current science, it is known so far that no amount of physical training and/or increasing physical activity will certainly lead to an accelerated decline in physical, emotional and social functioning.[64]

For normal or deep breathing a sufficient diaphragm function is needed. Santana and colleagues were able to evaluate diaphragm function with ultrasound imaging.[104] Patients with ILD presented decreased diaphragmatic mobility during deep breathing and a lower thickening fraction (TF, proportional diaphragm thickening from FRC to TLC), in comparison with healthy control subjects (matched for age, gender, body mass index, and smoking status). Patients with lower FVC had lower diaphragmatic mobility during deep breathing. Although ultrasound imaging is not a measurement of diaphragm force, diaphragm dysfunction is correlated with the extent of the parenchymal involvement, as quantified by FVC.[104]

Science does not yet have an answer to the aforementioned hypothesis about lung damage due to intensive breathing patterns. Albert and colleagues[105] stated the following: “the physiological and psychological benefits of regular exercise, together with the fact that the possible progressive damage of lung fibrosis by intensive spontaneous breathing is currently an untested hypothesis that lacks even a single study demonstrating proof of concept, lead us to conclude that making any recommendation regarding limiting the frequency or intensity of exercise is premature”.[105]

Target points for respiratory physiotherapy, depending on the diagnosed limitations, are: the respiratory system, the physical exercise capacity (what the patient is capable

of) and the physical activity (the actual daily activity level). Physical activity is behavior that encompasses all forms of activity, including walking and cycling, work-related activity, gardening, etc.. Physical activity appears to be only partially related with the physical capacity, it is also determined by environmental factors and psychosocial factors.[106] Physical inactivity is related to poor health outcomes and associated with mortality risk in people with ILD.[70] In patients with pulmonary fibrosis a reduced physical activity in daily life has been found compared to healthy, age- and sex-matched control subjects.[107] Patients showed a 65% decrease in steps per day and a 45% decrease in energy expenditure >2.5 METs per day compared to the sedentary healthy control population. In addition, fatigue and exercise capacity appear to be strong and independent predictors of physical activity in patients with IPF.[107] Interventions to improve physical activity and exercise capacity may have potential to delay premature mortality in people with ILD.[70] Physical activity can be measured quite easily using accelerometers stored in wearable devices. A recent published randomized controlled study in 2024 used a telecoaching program with wearable-driven devices (step counter and smartphone application) as an intervention to improve physical activity in ILDs.[108] However, twelve weeks of telecoaching did not improve physical activity, physical fitness or quality of life in patients with ILD as compared to usual care. Also subgroups analyses could not identify responders and non-responders on exercise tolerance and disease type. To improve physical activity the researchers suggested a supervised pulmonary rehabilitation program to increase patient's self-efficacy regarding physical activity. Inducing and sustaining behavioral change in physical activity requires a multi-level approach, a broad package based on intrapersonal level, interpersonal level and social, cultural and environmental conditions.[106]

Unfortunately, pulmonary rehabilitation is still not standard care in patients with IPF living in Europe.[109] When listening to the unmet needs and gaps of care for patients with pulmonary fibrosis, pulmonary rehabilitation as a vital part of holistic care really matters to the patients.[109,110] Surprisingly, only 42% of patients stated that they had access to outpatient pulmonary rehabilitation and 11% of patients also had access to inpatient pulmonary rehabilitation. Regardless of the possible underlying reasons given for these outcomes (unawareness of pulmonary rehabilitation, not fully reimbursed, or accessibility, etc.), it can be concluded that much work remains to be done to improve knowledge about pulmonary rehabilitation in patients with pulmonary fibrosis and their practitioners. More attention should be paid to the potential benefits of pulmonary rehabilitation, and then to ensure that patients with pulmonary fibrosis are provided with appropriate exercise care.[109,111]

Impact

ILDs have a great impact on the patient's daily functioning and life. Patients with IPF reported at a 2014 U.S. Food and Drug Administration (FDA) public meeting that they were becoming increasingly weaker, while losing much of their physical function, ability to care for themselves, and ability to engage in activities.[112] Obtaining appropriate and optimal non-pharmaceutical and holistic care appears to be a largely unmet need for patients with ILD across Europe. Patient advocacy groups from nine countries reported that pulmonary rehabilitation was not always available or easily accessible to patients, the reimbursement for treatment was limited and multidisciplinary care teams consisting of pulmonologists, specialist nurses and physiotherapists were lacking.[113] Pulmonary rehabilitation classes were experienced as a tremendous source of emotional support by patients with IPF. Pulmonary rehabilitation was also of great importance for the mental and physical health of the patients and had a positive effect on their coping skills and relationships with their peers. An educational intervention embedded in pulmonary rehabilitation seems to be a promising way to provide structured education and support.[40] An important role is reserved for a multidisciplinary team approach. However, physiotherapy was often not even contemplated as part of the process of disease management.[113] The European IPF Patient Charter recommends standardizing IPF management with a holistic approach, involving all aspects of support from early diagnosis to treatment and rehabilitation, including appropriate referral, access to multidisciplinary teams, lung transplantation, emotional support, outpatient and home services.[113] This includes comprehensive and high-quality information about IPF, including treatment, transplant information and emotional care for both patients and families.[40,114]

However, in the Netherlands, the Pulmonary Fibrosis Patient Association showed in 2019 that many patients experienced problems in obtaining the right exercise care, or they were unfamiliar with physiotherapy specialized in lung diseases. In that year, a small group of experts came together, namely an ILD pulmonologist, a professor of rehabilitation, a pulmonary physiotherapist/lecturer and a pulmonary nurse, with the aim of achieving optimal specialist exercise care for patients with pulmonary fibrosis in the Netherlands. This was the start of a longer-term and broader process with the aim of developing an exercise care program for patients with pulmonary fibrosis. In addition, the process was carried out together with an advisory group of various experts in the field of ILD. This focus group consisted of patients with pulmonary fibrosis, ILD pulmonologists, pulmonary physiotherapists, occupational therapists, pulmonary

nurses, rehabilitation experts and project supervisors from Boehringer Ingelheim. The developed exercise care process consists of a flow chart and an explanation section, starting with the intake of exercise care by the ILD nurse until the final evaluation of the exercise care received. The flowchart is shown in **Figure 1** (unpublished, version May 2024). When this thesis is published, the development phase will have been completed and work will be underway on the final phase with the aim of rolling out the proposed referral policy nationally. The care pathway explicitly takes into account the value of the 6MWT as a functional capacity test and will be considered at an early stage after diagnosis as an indication for referral for exercise care. During the exercise care process, the 6MWT will be part of monitoring exercise capacity and symptom burden during exercise.

It is worth noting that more attention has been paid in recent years to the further training of pulmonary physiotherapists in the field of interstitial lung diseases. Symposia and/or webinars have been organized by the Dutch ILD pulmonologists, the ILD expertise centers and the Cardiovascular-Pulmonary Association (VHVL) of the Association for Physiotherapy (KNGF). The master's program in cardiovascular respiratory physiotherapy (CRF) has currently been developed at Utrecht University of Applied Sciences and the first specialized CRF physiotherapists have been graduated in the autumn of 2024. In the program, attention is paid to lung diseases in addition to cardiovascular diseases. The complexity of ILD treatment is discussed, both from a pathophysiological and a biomedical perspective, taking into account multi-morbidities and associated drug interactions. From a physical therapy perspective, attention is paid to exercise-related aspects and training, and various contextual aspects such as self-management, low health literacy, transdisciplinary working and palliative care. Developing the exercise care process for patients with pulmonary fibrosis, based on current science and expert opinions, gives substance to the concept of 'The right care at the right place', which was embraced by Dutch government policy in 2018 ('De juiste zorg op de juiste plek').[115,116] The essence is: Preventing (more expensive) care, moving care (closer to people's homes) and replacing care (with other care such as e-health). From a good triage perspective, early detection of an exercise care problem is important in order to provide optimal care at the right time.

Nonpharmacologic treatment strategies such as exercise care and pulmonary rehabilitation help patients with pulmonary fibrosis live healthier, more normal lives, and the importance of these approaches cannot be overemphasized.[117]

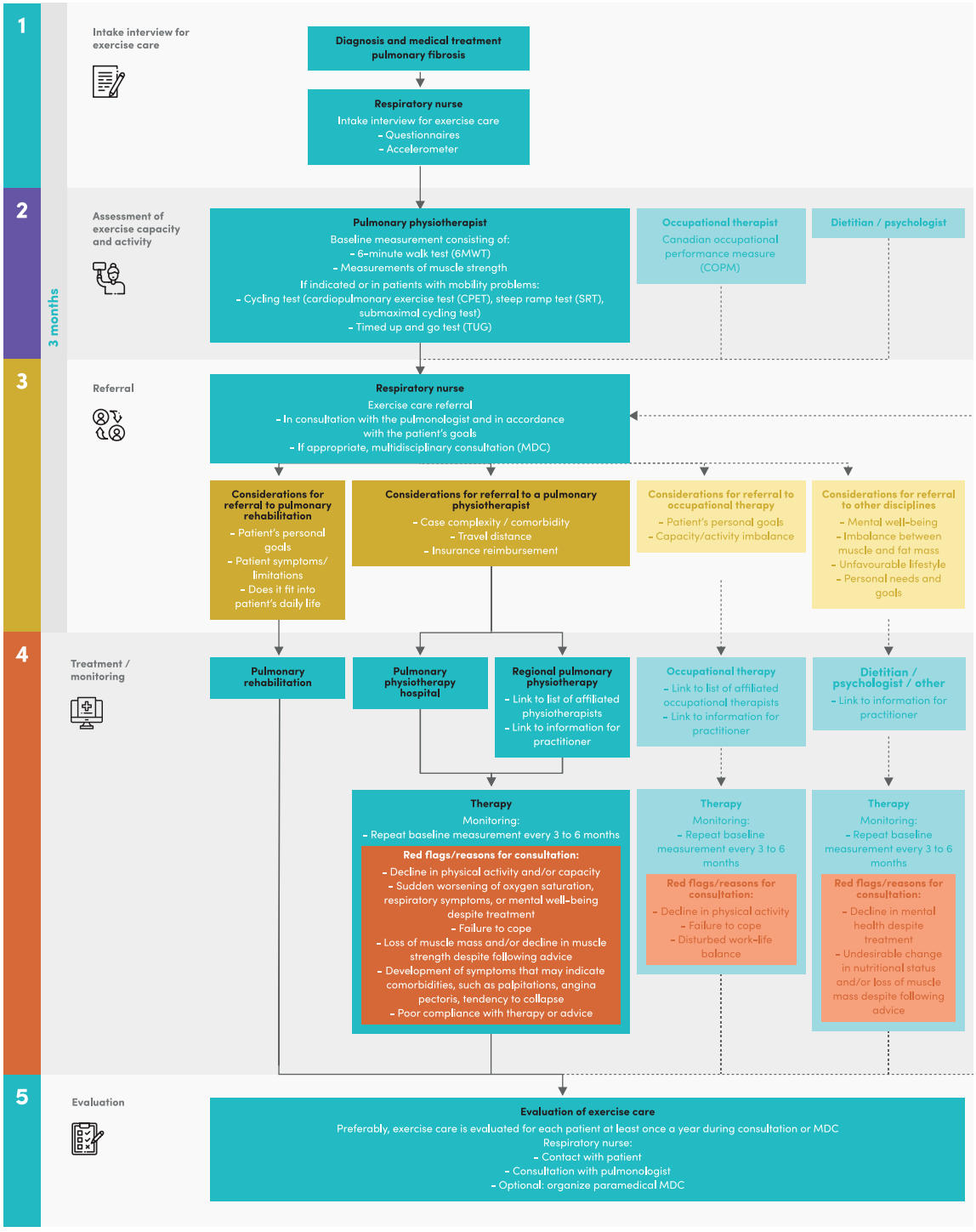
1
Intake interview for exercise care
Diagnosis and medical treatment pulmonary fibrosis
Respiratory nurse
Intake interview for exercise care
- Questionnaires
- Accelerometer
2
3 months
Assessment of exercise capacity and activity
Pulmonary physiotherapist
Baseline measurement consisting of:
- 6-minute walk test (6MWT)
- Measurements of muscle strength
If indicated or in patients with mobility problems:
- Cycling test (cardiopulmonary exercise test (CPET), steep ramp test (SRT), submaximal cycling test)
- Timed up and go test (TUG)
Occupational therapist
Canadian occupational performance measure (COPM)
Dietitian / psychologist
3
Referral
Respiratory nurse
Exercise care referral
- In consultation with the pulmonologist and in accordance with the patient's goals
- If appropriate, multidisciplinary consultation (MDC)
Considerations for referral to pulmonary rehabilitation
- Patient's personal goals
- Patient symptoms/ limitations
- Does it fit into patient's daily life
Considerations for referral to a pulmonary physiotherapist
- Case complexity / comorbidity
- Travel distance
- Insurance reimbursement
Considerations for referral to occupational therapy
- Patient's personal goals
- Capacity/activity imbalance
Considerations for referral to other disciplines
- Mental well-being
- Imbalance between muscle and fat mass
- Unfavourable lifestyle
- Personal needs and goals
4
Treatment / monitoring
Pulmonary rehabilitation
Pulmonary physiotherapy hospital
Regional pulmonary physiotherapy
- Link to list of affiliated physiotherapists
- Link to information for practitioner
Occupational therapy
- Link to list of affiliated occupational therapists
- Link to information for practitioner
Dietitian / psychologist / other
- Link to information for practitioner
Therapy
Monitoring:
- Repeat baseline measurement every 3 to 6 months
Red flags/reasons for consultation:
- Decline in physical activity and/or capacity
- Sudden worsening of oxygen saturation, respiratory symptoms, or mental well-being despite treatment
- Failure to cope
- Loss of muscle mass and/or decline in muscle strength despite following advice
- Development of symptoms that may indicate comorbidities, such as palpitations, angina pectoris, tendency to collapse
- Poor compliance with therapy or advice
Therapy
Monitoring:
- Repeat baseline measurement every 3 to 6 months
Red flags/reasons for consultation:
- Decline in physical activity
- Failure to cope
- Disturbed work-life balance
Therapy
Monitoring:
- Repeat baseline measurement every 3 to 6 months
Red flags/reasons for consultation:
- Decline in mental health despite treatment
- Undesirable change in nutritional status and/or loss of muscle mass despite following advice
5
Evaluation
Evaluation of exercise care
Preferably, exercise care is evaluated for each patient at least once a year during consultation or MDC
Respiratory nurse:
- Contact with patient
- Consultation with pulmonologist
- Optional: organize paramedical MDC

Figure 1

In conclusion, IPF and pulmonary sarcoidosis are complex and heterogeneous interstitial lung diseases. Patients of both diseases experience respiratory and non-respiratory symptoms and these perceived symptoms are more severe than in healthy controls. Severe fatigue is a common in patients with IPF or sarcoidosis (69%) and patients mentioned this severe fatigue with more negative connotations. In clinical practice, this implicates that fatigue in patients with IPF or sarcoidosis should be routinely assessed and a personalized treatment approach should be considered. Although self-management is the cornerstone of current patient care, a substantial group of patients with IPF or sarcoidosis lack the knowledge, the skills and/or the confidence to do so. Assessing patients' activation for self-management provides insight into where the patient can be supported towards optimal self-management behavior in the field of health

.

The 6MWT is used in clinical practice to measure functional exercise capacity. The 4MGS test can serve as a simple initial field test to assess exercise performance in patients with pulmonary fibrosis. But the 6MWT provides more additional information about exercise capacity such as exercise-induced oxygen desaturation (SpO_2-nadir). Performing a 2nd 6MWT on the same day provides no additional value to the achieved SpO_2-nadir and a limited improvement in the distance walked. This has led to the clinical consequence of only one 6MWT being administered to patients for a one-day hospital visit. The distance walked, the SpO_2-nadir and the distance-saturation product show a predictive value for 2-year survival, with the SpO_2-nadir proving to be the best discriminating value. It is therefore advisable to gain insight into the exercise capacity of the patient with pulmonary fibrosis immediately after the diagnosis. In the future, early screening, referral and treatment with pulmonary physiotherapy guidance and/or pulmonary rehabilitation should prove beneficial for experienced exercise care and quality of life for patients with pulmonary fibrosis.

To summarize, the topics addressed in this thesis visualized in **figure 2**

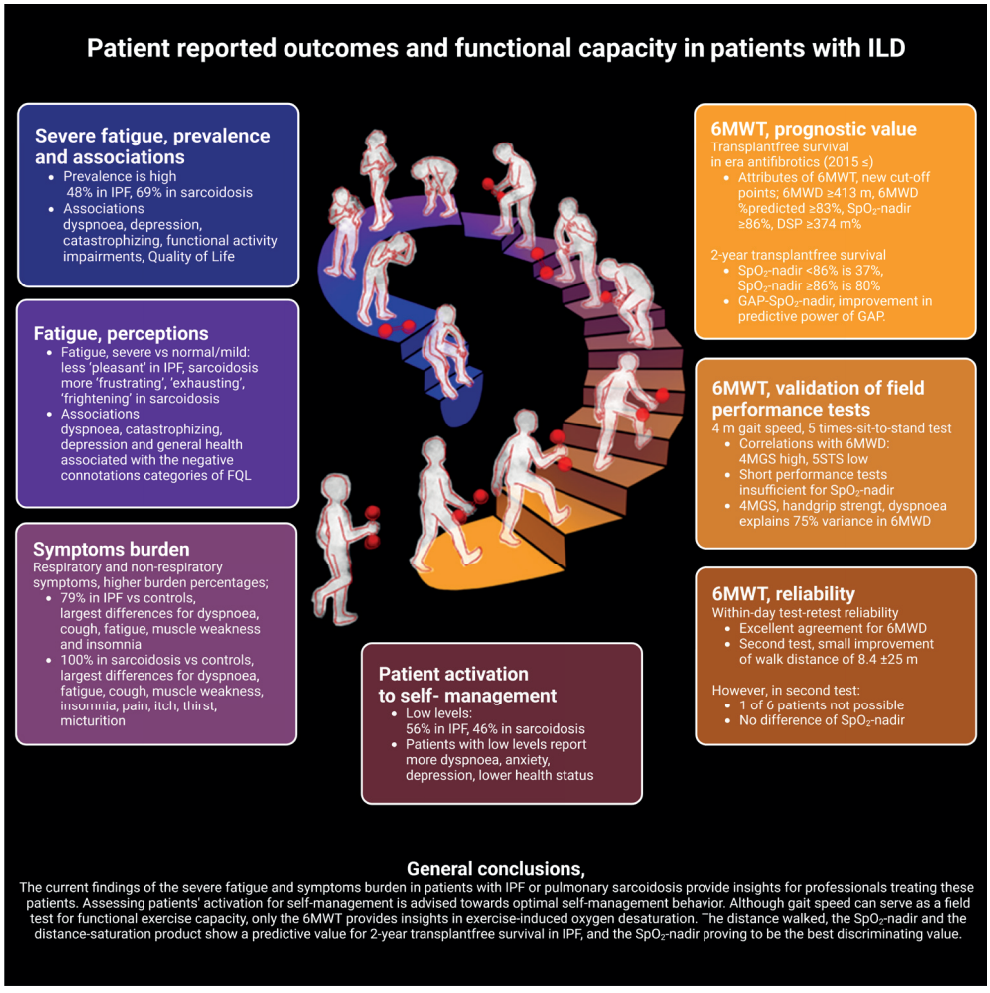
Patient reported outcomes and functional capacity in patients with ILD
Severe fatigue, prevalence and associations
Prevalence is high 48% in IPF, 69% in sarcoidosis
Associations dyspnoea, depression, catastrophizing, functional activity impairments, Quality of Life
Fatigue, perceptions
Fatigue, severe vs normal/mild: less 'pleasant' in IPF, sarcoidosis more 'frustrating', 'exhausting', 'frightening' in sarcoidosis
Associations dyspnoea, catastrophizing, depression and general health associated with the negative connotations categories of FQL
Symptoms burden
Respiratory and non-respiratory symptoms, higher burden percentages;
79% in IPF vs controls, largest differences for dyspnoea, cough, fatigue, muscle weakness and insomnia
100% in sarcoidosis vs controls, largest differences for dyspnoea, fatigue, cough, muscle weakness, insomnia, pain, itch, thirst, micturition
Patient activation to self- management
Low levels: 56% in IPF, 46% in sarcoidosis
Patients with low levels report more dyspnoea, anxiety, depression, lower health status
6MWT, prognostic value
Transplantfree survival in era antifibrotics (2015 ≤)
Attributes of 6MWT, new cut-off points; 6MWD ≥413 m, 6MWD %predicted ≥83%, SpO2-nadir ≥86%, DSP ≥374 m%
2-year transplantfree survival
SpO2-nadir <86% is 37%, SpO2-nadir ≥86% is 80%
GAP-SpO2-nadir, improvement in predictive power of GAP.
6MWT, validation of field performance tests
4 m gait speed, 5 times-sit-to-stand test
Correlations with 6MWD: 4MGS high, 5STS low
Short performance tests insufficient for SpO2-nadir
4MGS, handgrip strengt, dyspnoea explains 75% variance in 6MWD
6MWT, reliability
Within-day test-retest reliability
Excellent agreement for 6MWD
Second test, small improvement of walk distance of 8.4 ±25 m
However, in second test:
1 of 6 patients not possible
No difference of SpO2-nadir
General conclusions,
The current findings of the severe fatigue and symptoms burden in patients with IPF or pulmonary sarcoidosis provide insights for professionals treating these patients. Assessing patients' activation for self-management is advised towards optimal self-management behavior. Although gait speed can serve as a field test for functional exercise capacity, only the 6MWT provides insights in exercise-induced oxygen desaturation. The distance walked, the SpO2-nadir and the distance-saturation product show a predictive value for 2-year transplantfree survival in IPF, and the SpO2-nadir proving to be the best discriminating value.

Figure 2

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Appendices

Summary

The term Interstitial lung disease (ILD) is an umbrella term that encompasses various but mostly rare lung diseases, most of which primarily affect the pulmonary interstitium (the space between the alveoli and blood vessels). This large, heterogeneous group of interstitial lung diseases is characterized by affecting the lung parenchyma via inflammation and/or fibrosis with a considerable heterogeneity in life expectancy. Progressive scarring of lung tissue eventually affects the ability to breathe and exercise-induced hypoxemia affects the ability to perform physical activity. ILDs exhibit a distinctive pathophysiology compared to the more commonly known obstructive pulmonary diseases such as chronic obstructive pulmonary disease (COPD) or asthma. However, the clinical presentation of ILDs is non-specific, with the most common symptoms being shortness of breath (on exertion), cough and fatigue. Managing symptoms and stabilization exercise tolerance is important for maintaining quality of life in patients with ILD. However, this is extremely challenging given the lack of evidence-based therapies.

This thesis is mainly limited to the two most common types of ILDs: pulmonary fibrosis and sarcoidosis. Pulmonary fibrosis is characterized by scarring (fibrosis) of the lungs, which ultimately limits the oxygen uptake capacity in the lung. Unlike most ILDs where the cause is known, the most common pulmonary fibrosis disease has an unknown cause, idiopathic pulmonary fibrosis (IPF). IPF is characterized by chronic irreversible progressive fibrosis of the lung with a fatal outcome. It is more common in men, with an median age of 68 years and an average life expectancy of 3-5 years from the time of diagnosis. There is currently no curative treatment for IPF other than lung transplantation. However, since 2015, medications have become available that can slow the progression of fibrosis. These antifibrotic medications do not cure the disease but slow down the rate of decline in lung function and show an increase in median survival in patients with IPF.

Sarcoidosis is an inflammatory systemic disease, characterized by a very different pathophysiology than IPF. It is a disorder of the immune system, characterized by the formation of non-necrotizing granulomas (accumulations of white blood cells). These inflammations can occur almost anywhere in the body, with the lungs and lymph nodes being involved in the disease process in 90-95% of cases. The cause of this disease is also unknown, but a genetic predisposition may play a role in this disease. Sarcoidosis can affect people of all ages, men and women, but usually develops

before the age of 50 in young and middle-aged adults. The course and symptoms of sarcoidosis vary from person to person and largely depend on which organs are involved. Most patients recover spontaneously within a few years, although a subgroup may retain a severe disease burden. Most patients recover spontaneously from the disease within a few years, although a subgroup may retain a severe disease burden. One of the most common complaints, even when there is no longer evidence of disease activity, is fatigue. The main purpose of the first part of this thesis is to gain more insight into the experienced symptom burden, both respiratory and non-respiratory related, in patients with IPF or sarcoidosis. The study consisted of research using paper and pen questionnaires on patient-reported outcome measures among patients with IPF or sarcoidosis who attended the lung disease outpatient clinic of a specialized ILD pulmonologist.

The second part of this thesis focuses on testing functional exercise capacity in patients with pulmonary fibrosis. Testing the exercise capacity of patients with pulmonary fibrosis provides insight into possible physical limitations and the symptom burden experienced as a result of this effort. Exercise capacity is an important parameter for possible pulmonary rehabilitation. It provides information for more personalized treatments to maintain or improve physical exercise capacity. In addition, exercise capacity has a prognostic value for survival and is part of the Lung Allocation Score (LAS) used in patients on the waiting list for a lung transplant.

First, in the study described in **Chapter 2**, we examined the prevalence of fatigue in patients with IPF or sarcoidosis. The presence of severe fatigue was assessed using the validated fatigue subscale of the Individual Strength Checklist (CIS). The results of this study show that severe fatigue occurs in 48% of patients with IPF and in 69% of patients with sarcoidosis. Experiencing severe fatigue is associated with more dyspnoea, more depressed feelings, a higher degree of fatigue-related catastrophizing thoughts, more functional activity limitations and a poorer quality of life. However, the research also shows that the degree of lung function limitation has little to no correlation with experiencing severe fatigue compared to no/mild fatigue.

Chapter 3 presents research into how patients with IPF or sarcoidosis describe their perceived severe fatigue using a list of diverse adjectives ranging from 'pleasant' to 'exhausting'. Patients with severe fatigue describe the experienced fatigue significantly with more adjectives and also adjectives with a more negative connotation than patients who are not severely fatigued. Severely fatigued patients with IPF describe their

fatigue as less 'pleasant', and patients with sarcoidosis and severe fatigue describe their fatigue perceptions as 'frustrating', 'exhausting', 'frightening' significantly more often than patients without severe fatigue.

Chapter 4 studies the perceived symptom burden of various symptoms (n=14) known in patients with lung diseases, both respiratory and non-respiratory related. This chapter shows the differences in the perceived symptom burden of patients with IPF (n=44) or patients with sarcoidosis (n=45) compared to healthy controls. Individuals were considered healthy if confirmed by general practitioners, and in any case all controls had no impaired spirometry values (FVC and FEV1). All patients are matched on age and gender with someone from the control group. Patients with IPF scored higher on 11 symptoms compared to controls ($p<0.05$), with the largest differences for dyspnoea, cough, fatigue, muscle weakness and insomnia. Patients with sarcoidosis scored higher on all 14 symptoms ($p<0.05$), with the largest differences for dyspnoea, fatigue, cough, muscle weakness, insomnia, pain, itch, thirst, micturition (night, day). This study shows that the symptom burden is perceived to be higher in patients with ILD compared to matched healthy controls, both for respiratory and non-respiratory symptoms.

In today's healthcare system, self-management is seen as the key to increasing patients' ability to cope with the consequences of their disease and thus maintain a satisfactory quality of life. In chapter 5 the level of patient activation for self-management is examined using the Patient Activation Measure (PAM) in patients with IPF or sarcoidosis. It appears that 56% of patients with IPF and 46% of patients with sarcoidosis had low scores on the PAM (≤55.1 score, level 1-2). This suggests that for these patients, their role in managing health, the knowledge, skills and confidence to do so, may be insufficient for optimal health self-management behaviour. The degree of patient activation for self-management does not appear to be related to the degree of lung function impairment in either patient group, but lower levels of patient activation are associated with more dyspnoea, more anxiety, more depressive feelings and a poorer health status.

Part 2 of this thesis presents the results of three studies on functional exercise capacity in patients with pulmonary fibrosis. Patients with pulmonary fibrosis have several routine clinical examinations (such as spirometry, blood sampling and chest X-ray examination) during their one-day visit to the interstitial lung disease expertise center. To determine functional exercise capacity, the 6-minute walk test (6MWT) is performed.

The 6MWT should actually be performed twice because of the learning effect on repetition. To achieve this in one day may be too burdensome or too time-consuming for the patient. **Chapter 6** investigates whether performing two 6MWTs in one day is possible in patients with pulmonary fibrosis (in terms of physical load and logistics) and whether the 2nd test provides additional information about functional exercise capacity based on the learning effect. Performing the 6MWT twice in one day in patients with pulmonary fibrosis showed excellent test-retest reliability of the 6MWT. The improvement in the second test was significantly different with a small mean difference of 8.4 m (± 25 m). However, one in six patients with pulmonary fibrosis could not complete the second 6MWT on the same day. Also, no differences were seen in the 2nd test compared to the 1st test in other attributes derived from 6MWT, such as the exercise-induced desaturation (SpO_2-nadir), the maximum heart rate or the recovery in heart rate after exercise. In addition, the subjective measured values such as dyspnoea and fatigue experienced by the patient during the test also indicated no significant differences. As a result, one 6MWT appears sufficient to identify those patients with pulmonary fibrosis suffering from exercise-induced oxygen desaturation.

Chapter 7 examines the relationship between simple performance tests, the 4-meter gait speed (4MGS) and the 5-repeated sit-to-stand test (5STS) and the 6MWT in patients with pulmonary fibrosis. The 4MGS showed a high correlation and the 5STS a low correlation, both significant ($p<0.05$), with the distance walked in the 6MWT (6MWD). However, exercise-induced desaturation or reduced heart rate recovery after exercise as seen with the 6MWT were less present and also not correlated with the measurements obtained from the 6MWT. This implies that the 4MGS can serve in daily clinical practice as a possible simple first field test to measure functional exercise capacity, but only to indicate the distance walked in the 6MWT. To determine SpO_2-nadir based on physical exertion, neither the 4MGS nor the 5STS were suitable practice field tests.

In chapter 8, the focus is on the prognostic value of the 6MWT on 2-year transplant-free survival, reaffirmed in the era in which antifibrotic medication is part of regular care (2015-2020). Through a retrospective study at an ILD Center of Excellence, using the patient medical records, various attributes obtained from the 6MWT, the walking distance (6MWD), the lowest desaturation during exercise (SpO_2-nadir) and the distance saturation product (DSP) are examined. In a cohort of 216 patients with IPF, 2-year transplant-free survival cut-off points were identified for the 6MWD (≥413 m), 6MWD %predicted (≥83%), SpO_2-nadir (≥86%) and distance-saturation-product

(≥374 m%), with the best discriminative value for SpO_2-nadir (area under the curve: 0.761). 2-Year survival percentage of patients with SpO_2-nadir below or above threshold (86%) was 37.1% and 80.0%, respectively. By adding exercise-induced oxygen desaturation to the GAP model, the new model GAP-SpO_2-nadir showed an improvement in its predictive power.

Finally, in **Chapter 9** the main findings of this thesis, as well as the clinical implications, methodological considerations and directions for future research, are discussed. In the first part of this thesis we concluded that severe fatigue is a common symptom in individuals with IPF and sarcoidosis. Patients with severe fatigue use more adjectives and adjectives with a more negative connotation than patients who are not/moderately fatigued. Within our research into perceived fatigue, we have chosen to use the questionnaire the Individual Strength Checklist (CIS) domain fatigue. The CIS is easy to use, has a well-validated cut-off value for severe fatigue and has been used in various studies of fatigue in different chronic diseases. Nowadays it is well known that the degree of fatigue is not related to the degree of lung function abnormalities, but is rather seen as an interaction between biological, psychological and social factors. Our findings in studies of fatigue in pulmonary fibrosis and sarcoidosis support this view that severe fatigue is not so much related to disease-specific factors. By objectifying the experience of fatigue through the CIS, the fatigue of the last 2 weeks is questioned. However, it is not placed in the context of the patient in which fatigue occurs (such as with activity and in emotional or social circumstances). In the future, the objectification of fatigue during different activities of daily life, during exercise and at different times of the day should be investigated. A promising method to measure day-to-day/diurnal variations of fatigue is therefore ecological momentary assessment (EMA).

Patients with pulmonary fibrosis or sarcoidosis will need to be activated for self-management in order to properly manage their health and disease, and the associated symptoms. Our research shows that a substantial proportion of patients with IPF (56%) or sarcoidosis (46%) are not sufficiently capable of activation for self-management. This insight means that when guiding patients to good self-management behaviour, attention must be paid to the knowledge, skills and confidence with regard to self-management aspects. Effective strategies to involve patients in more self-management behaviour, as appropriate in pulmonary rehabilitation, should include at least the following components necessary for patient involvement and activation: educational, behavioural and affective components.

Patients with pulmonary fibrosis often report symptoms such as shortness of breath on exertion, increasing dyspnoea, dry cough and fatigue. The European IPF registration system showed that when newly diagnosed patients were registered for this registry, they were already limited in their physical activities in activities of daily living. Research shows that objectively measuring exercise capacity with the 6MWT at an early stage after diagnosis has a predictive value for 2-year transplant-free survival. In addition, knowing at an early stage after diagnosis the exercise capacity, the physical activity and the experienced symptoms can also provide better guidance for exercise care in patients with pulmonary fibrosis. Because most patients with pulmonary fibrosis will continue to experience symptom burden despite optimal medical treatment. Pulmonary rehabilitation has been proven to be safe and there are positive findings in reducing perceived shortness of breath, fatigue, improving exercise capacity and quality of life in patients with pulmonary fibrosis. This underlines the importance of pulmonary rehabilitation, which is based on a multidimensional approach in which the patient is supported to cope with the consequences of this chronic lung disease under different and challenging changing circumstances.

Samenvatting (Summary in Dutch)

De aanduiding Interstitiële longziekte (ILD, Engelse afkorting voor 'Interstitial Lung Disease') is een verzamelnaam voor diverse meestal zeldzame longziekten, waarvan de meesten primair het longinterstitium (de ruimte tussen de longblaasjes en de bloedvaten) aantasten. Deze grote, heterogene groep interstitiële longaandoeningen, wordt gekenmerkt door het aantasten van het longparenchym via ontstekingen en /of littekenvorming met een aanzienlijke heterogeniteit in de levensverwachting. Progressieve fibrosering in het longweefsel beïnvloedt uiteindelijk het vermogen om te ademen, en door inspanning geïnduceerde hypoxemie beïnvloedt het vermogen om fysieke activiteit uit te voeren. ILDs vertonen een onderscheidende pathofysiologie vergeleken met de meer algemeen bekende obstructieve longziekten zoals chronische obstructieve longziekte (COPD) of astma. De klinische presentatie van ILDs is echter niet-specifiek, waarbij de meest voorkomende symptomen kortademigheid (bij inspanning), hoesten en vermoeidheid zijn. Het omgaan met de symptomen en het handhaven van inspanningstolerantie is belangrijk voor het behoud van de kwaliteit van leven bij patiënten met ILD. Dit is echter uiterst uitdagend gezien het gebrek aan evidence-based therapieën.

Deze thesis beperkt zich met name tot de twee meest bekende interstitiële longaandoeningen: longfibrose en sarcoïdose. Longfibrose wordt gekenmerkt door littekenvorming in de longen waardoor uiteindelijk de zuurstofopnamecapaciteit in de long beperkt wordt. In tegenstelling tot de meeste ILDs waarbij de oorzaak te achterhalen is, is van de meest voorkomende ziekte van longfibrose de oorzaak onbekend (idiopathisch), de idiopathische pulmonale fibrosis (IPF). IPF kenmerkt zich door chronische progressieve onomkeerbare fibrosevorming in de long met een ongunstig beloop. Het komt vaker voor bij mannen, met een mediane leeftijd van 68 jaar en met een mediane levensverwachting van 3-5 jaar vanaf het moment van de diagnose stellen. Er bestaat momenteel nog geen curatieve behandeling voor IPF, anders dan longtransplantatie. Sinds 2015 zijn er echter wel medicijnen beschikbaar die de voortgang van de fibrose kunnen remmen. Deze antifibrotische medicatie geneest de ziekte echter niet maar vertraagt de achteruitgang van de longfunctie en laat een toename zien in de mediane overleving bij patiënten met IPF.

Sarcoïdose is een inflammatoire systemische aandoening, gekenmerkt door een hele andere pathofysiologie dan IPF. Het is een aandoening van het immuunsysteem, gekenmerkt door de vorming van niet-necrotiserende granulomen (ophopin-

gen van witte bloedcellen). Deze ontstekingen kunnen vrijwel overal in het lichaam voorkomen, waarbij de longen en de lymfeklieren in 90-95% van de gevallen bij het ziekteproces betrokken zijn. Ook de oorzaak van deze ziekte is niet bekend, mogelijk speelt een genetische aanleg een rol bij deze ziekte. Sarcoïdose kan mensen van alle leeftijden treffen, mannen en vrouwen, maar ontwikkelt zich meestal vóór de leeftijd van 50 jaar bij jonge volwassenen van middelbare leeftijd. Het beloop en klachten van sarcoïdose is per individu verschillend en afhankelijk grotendeels van door welke organen betrokken zijn. De meeste patiënten genezen binnen enkele jaren spontaan, alhoewel een subgroep ernstige ziektelast kan behouden. Eén van de meest voorkomende klachten, zelfs als er geen bewijs voor ziekteactiviteit is, is vermoeidheid.

Het belangrijkste doel van het eerste deel van dit proefschrift is om meer inzicht te verkrijgen in de ervaren symptoomlast, zowel long- als niet-longgerelateerd in patiënten met IPF of sarcoïdose. Het onderzoek bestond uit een vragenlijstonderzoek naar patiëntgerapporteerde uitkomstmaten onder patiënten met IPF of sarcoïdose die de polikliniek longziekten bezochten bij een gespecialiseerde ILD-longarts.

Het tweede deel van dit proefschrift richt zich op het testen van het functionele inspanningscapaciteit bij patiënten met longfibrose. Het testen van de inspanningscapaciteit van patiënten met longfibrose geeft inzicht in mogelijke fysieke beperkingen en de ervaren symptoomlast als gevolg van deze inspanning. Inspanningscapaciteit is een belangrijke parameter voor de in te zetten mogelijke pulmonale revalidatie. Het levert informatie op voor meer gepersonaliseerde behandelingen voor behoud dan/wel verbeteren van de fysieke inspanningscapaciteit. Daarnaast heeft de inspanningscapaciteit een prognostische waarde op overleving en maakt het onderdeel uit van de Lung Allocation Score (LAS) die gebruikt wordt bij patiënten op de wachtlijst voor longtransplantatie.

Als eerste hebben wij gekeken naar de prevalentie van vermoeidheid bij patiënten met IPF of sarcoïdose, zoals in de studie beschreven in **hoofdstuk 2**. De aanwezigheid van ernstige vermoeidheid is bepaald met de gevalideerde subschaal vermoeidheid van de Checklist Individual Strength (CIS). De resultaten van dit onderzoek laten zien dat ernstige vermoeidheid bij 48% van de patiënten met IPF voorkomt en bij 69% van de patiënten met sarcoïdose. Het ervaren van ernstige vermoeidheid hangt samen met meer kortademigheid, meer depressieve gevoelens, een hogere mate van vermoeidheidgerelateerde catastroferende gedachten, meer functionele activiteitenbeperkingen en een mindere kwaliteit van leven. De studie laat echter ook zien dat de

mate van longfunctiebeperking niet tot nauwelijks samenhangt met het ervaren van ernstige vermoeidheid ten opzichte van geen/milde vermoeidheid.

In **hoofdstuk 3** wordt het onderzoek gepresenteerd met welke bewoordingen patiënten met IPF of sarcoïdose de ernstige vermoeidheid omschrijven aan de hand van een lijst met een diversiteit aan adjectieven, variërend van 'prettig' tot 'uitputtend'. Patiënten met ernstige vermoeidheid beschrijven de ervaren vermoeidheid significant met meer adjectieven en ook adjectieven met een negatievere connotatie dan niet ernstig vermoeide patiënten. Ernstig vermoeide patiënten met IPF omschrijven hun vermoeidheid als minder 'aangenaam', en patiënten met sarcoïdose en ernstige vermoeidheid omschrijven daarbij hun vermoeidheidspercepties significant vaker als 'frustrerend', 'uitputtend', 'beangstigend' dan patiënten zonder ernstige vermoeidheid.

Hoofdstuk 4 bestudeert de ervaren symptoomlast van meerdere symptomen (n=14) bekend bij patiënten met longziekten, zowel long als niet-longgerelateerde symptomen. Dit hoofdstuk laat de verschillen zien in ervaren symptoomlast van patiënten met IPF (n=44) of patiënten met sarcoïdose (n=45) in vergelijking met gezonde controles. Personen werden als gezond beschouwd indien dit vastgesteld was door een huisarts en er geen beperkingen op de spirometriewaarden aanwezig waren (FEV1 en FVC). Alle patiënten zijn gematcht op leeftijd en geslacht met iemand uit de controlegroep. Patiënten met IPF scoorden hoger op 11 vd 14 symptomen vergeleken met controles ($p<0.05$), met de grootste verschillen voor dyspnoe, hoesten, vermoeidheid, spierzwakte en slapeloosheid. Patiënten met sarcoïdose scoorden hoger op alle 14 symptomen ($p<0.05$), met de grootste verschillen voor dyspnoe, vermoeidheid, hoesten, spierzwakte, slapeloosheid, pijn, jeuk, dorst en mictie (nacht, dag). Dit onderzoek laat zien dat zowel op ervaren respiratoire als niet-respiratoire klachten de symptoomlast hoger wordt ervaren in patiënten met ILD ten opzichte van gematchte gezonde controles.

In de huidige gezondheidszorg wordt zelfmanagement gezien als de sleutel tot het vergroten van het vermogen van patiënten om met de gevolgen van hun ziekte om te gaan en zo een bevredigende kwaliteit van leven te behouden. In **hoofdstuk 5** is de patiëntactivatie tot zelfmanagement onderzocht middels de Patient Activatie Meetinstrument (PAM) in patiënten met IPF of sarcoïdose. Het blijkt dat in 56% van de patiënten met IPF en 46% van de patiënten met sarcoïdose lage scores op de PAM werden vastgesteld (≤55.1 score, level 1-2). Dit suggereert dat voor deze patiënten hun rol in het managen van de gezondheid, de kennis en het vertrouwen om dit te doen,

mogelijk onvoldoende zijn voor optimaal zelfmanagementgedrag op het gebied van de gezondheid. Het niveau van patiëntactivatie voor zelfmanagement blijkt niet geassocieerd met de mate van longfunctiestoornis bij beide patiëntengroepen te zijn, maar lagere levels van patiëntactivatie zijn wel geassocieerd met meer dyspnoe, meer angst, meer depressieve gevoelens en een slechtere gezondheidsstatus.

Deel 2 van dit proefschrift presenteert de resultaten van drie onderzoeken met betrekking op de functionele inspanningscapaciteit bij patiënten met longfibrose. Patiënten met longfibrose hebben tijdens hun ééndaags poliklinisch bezoek bij het expertisecentrum voor interstitiële longziekten verschillende routinematige klinische testen (zoals spirometrie, bloedafname en thorax röntgenonderzoek). Om de functionele inspanningscapaciteit te bepalen wordt de 6 minuten wandeltest (6MWT) uitgevoerd. De 6MWT moet eigenlijk tweemaal uitgevoerd worden vanwege het leereffect bij herhaling. Dit realiseren op één dag kan mogelijk te belastend zijn voor de patiënt dan/wel te veel tijd vragen. **Hoofdstuk 6** onderzoekt of het uitvoeren van twee 6MWT-en op één dag mogelijk is bij patiënten met longfibrose (qua fysieke belasting en logistiek) en of de 2e test vanuit het leereffect aanvullende informatie oplevert over de functionele inspanningscapaciteit. Het tweemaal op één dag uitvoeren van de 6MWT bij patiënten met longfibrose liet een uitstekende test-hertest betrouwbaarheid van de 6MWT zien. De verbetering in de tweede test was significant verschillend met een klein gemiddeld verschil van 8,4 m (± 25 m). Eén op de zes patiënten met longfibrose was echter niet in staat om de tweede 6MWT op dezelfde dag te lopen. Ook werden er in de 2e test geen verschillen gezien op de 1e test in andere kenmerken afgeleid van 6MWT, zoals de door inspanning geïnduceerde desaturatie (SpO_2-nadir), de maximale behaalde hartslag of op het herstel in hartslag frequentie na de inspanning. Daarnaast gaven de subjectieve bemeten waardes zoals dyspnoe en vermoeidheid ervaren tijdens de test door de patiënt ook geen significante verschillen aan. Als gevolg hiervan lijkt één 6MWT voldoende om die patiënten met longfibrose te identificeren die inspanninggeïnduceerde desaturatie van zuurstof laten zien.

Hoofdstuk 7 onderzoekt de samenhang tussen simpele performancetesten, de 4-meter gait speed (4MGS) en de 5-herhaalde sit-to-stand test (5STS) en de 6MWT in patiënten met longfibrose. De 4MGS liet een hoge correlatie en de 5STS een lage correlatie, beide significant ($p<0.05$) met de gelopen afstand in de 6MWT (6MWD) zien. Echter door inspanning geïnduceerde desaturatie of een verminderde hartslagherstel na de inspanning zoals gezien bij de 6MWT waren minder aanwezig en ook niet gecorreleerd aan de metingen verkregen uit de 6MWT. Dit betekent dat in de

dagelijkse klinische praktijk de 4MGS kan dienen als een mogelijke simpele eerste veldtest om functionele inspanningscapaciteit te bemeten, maar alleen om duiding te geven aan de gelopen afstand bij de 6MWT. Om de SpO_2-nadir te bepalen vanuit lichamelijke inspanning bleken zowel de 4MGS als de 5STS niet geschikte inspanningsveldtesten.

In **hoofdstuk 8** ligt de focus op de prognostische waarde van de 6MWT op 2-jaars transplantatievrije overleving, herbevestigd in het tijdperk dat antifibrotische medicatie tot de reguliere zorg behoort (2015-2020). Middels een retrospectieve studie bij een ILD expertise centrum, gebruik makend van het medisch elektronische patiëntendossier, wordt gekeken naar verschillende waardes te verkrijgen vanuit de 6MWT, de loopafstand (6MWD), de laagste desaturatie bij inspanning (SpO_2-nadir) en de distance-saturation product (DSP). In het cohort van 216 patiënten met IPF werden afkappunten voor de 2-jaars transplantatievrije overleving geïdentificeerd voor de 6MWD (≥413 m), 6MWD% voorspeld (≥83%), SpO_2-nadir (≥86%) en DSP (≥374 m%), met de beste onderscheidende waarde voor SpO_2-nadir (oppervlakte onder de curve, AUC: 0,761). Het tweejaar overlevingspercentage van patiënten met SpO_2-nadir onder of boven de drempelwaarde (86%) was respectievelijk 37,1% en 80,0%. Door de inspanninggeïnduceerde zuurstofdesaturatie toe te voegen aan het GAP-model, liet het nieuwe model GAP-SpO_2-nadir een verbetering op de voorspellende waarde zien.

Tot slot, in **hoofdstuk 9** zijn de belangrijkste bevindingen van dit proefschrift, evenals de klinische implicaties, methodologische overwegingen en mogelijkheden voor toekomstig onderzoek besproken. In het eerste deel van dit proefschrift hebben we geconcludeerd dat ernstige vermoeidheid een veelvuldig voorkomend symptoom is bij personen met IPF en sarcoïdose. Patiënten met ernstige vermoeidheid gebruiken méér bijvoeglijk naamwoorden en deze hebben vaker een meer negatieve lading dan patiënten die niet dan wel matig vermoeid zijn. Binnen ons onderzoek naar ervaren vermoeidheid hebben wij ervoor gekozen om gebruik te maken van de vragenlijst Individual Strength Checklist (CIS) domein vermoeidheid. De CIS is gebruiksvriendelijk, kent een goed gevalideerde afkappunt voor ernstige vermoeidheid en is gebruikt in diverse onderzoeken naar vermoeidheid bij verschillende chronische ziekten. Tegenwoordig is het algemeen bekend dat de mate van vermoeidheid eigenlijk niet samenhangt met de mate van longfunctieafwijkingen, maar veel meer wordt gezien als interactie tussen biologische, psychologische en sociale factoren. Onze bevindingen in onderzoek naar vermoeidheid in pulmonale fibrose en sarcoïdose ondersteunen deze zienswijze over ernstige vermoeidheid en dat deze ernstige vermoeidheid niet zozeer

resultaat is van ziekte-specifieke factoren. Met het objectiveren van het gevoel van vermoeidheid middels de CIS wordt de ervaren vermoeidheid van de laatste 2 weken bevraagd, echter het wordt niet in de context van de patiënt geplaatst waarbinnen die vermoeidheid optreedt (zoals bijv. in activiteit en bij emotionele of sociale omstandigheden). In de toekomst zal het objectiveren van vermoeidheid in de verschillende activiteiten van het dagelijks leven, bij inspanning en op verschillende momenten van de dag onderzocht moeten worden. Een veelbelovende methode om dagelijkse/dagelijkse variaties in vermoeidheid te meten is daarom de ecologische momentane beoordeling (EMA).

Patiënten met longfibrosis of sarcoïdose zullen, om goed om te gaan met hun gezondheid en ziekte, en de daarbij komende symptomen, geactiveerd moeten zijn voor zelfmanagement. Uit ons onderzoek blijkt dat een substantieel deel van de patiënten met IPF (56%) of sarcoïdose (46%) niet voldoende in staat is tot activatie voor zelfmanagement. Dit inzicht heeft tot gevolg dat in de begeleiding van patiënten tot goed zelfmanagementgedrag, er aandacht zal gegeven moeten worden aan de kennis, de kunde en het vertrouwen in eigen handelen ten aanzien van zelfmanagementaspecten. In interventies om tot effectieve strategieën te komen om de patiënt te betrekken tot zelfmanagement, zoals ook passend bij pulmonale revalidatie, horen educatieve, gedragsmatige en affectieve componenten een plek te hebben.

Patiënten met longfibrose geven vaak symptomen aan zoals kortademig bij inspanning, toenemende benauwdheid, droge hoest en vermoeidheid. Uit het Europese IPF registratie systeem bleek op het moment van aanmelding voor dit register dat de nieuw gediagnosticeerd patiënten al beperkt waren in hun fysieke activiteiten bij algemene dagelijkse levensverrichtingen. Uit onderzoek blijkt dat het objectief meten van de inspanningscapaciteit met de 6MWT in een vroeg stadium na de diagnose een voorspellende waarde heeft op de 2-jaars transplantatievrije overleving. En inderdaad, op het moment dat in een vroeg stadium na diagnose de inspanningscapaciteit en de fysieke activiteit bekend zijn en de ervaren symptoomlast in kaart gebracht is, kan dit gezamenlijk ook een gerichtere leidraad bieden aan de beweegzorg bij patiënten met longfibrose. Want de meeste patiënten met longfibrose zullen ondanks optimale medische behandeling symptoomlast blijven ervaren. Pulmonale revalidatie is bewezen veilig en laat positieve bevindingen zien op het verminderen van ervaren kortademigheid, vermoeidheid, een verbetering op inspanningscapaciteit en de kwaliteit van leven bij patiënten met longfibrose. Dit onderstreept het belang van pulmonale revalidatie die uitgaat van een multidimensionale benadering waarbij de patiënt ondersteund wordt in het omgaan, onder verschillende en uitdagende veranderende omstandigheden, met de gevolgen van deze chronische longziekte.

Impact section

This thesis has provided a deeper insight into the prevalence of symptoms, especially fatigue, and patient activation for self-management in patients with IPF or sarcoidosis. It has also provided better insights into functional exercise capacity tests in patients with pulmonary fibrosis. The purpose of this impact and valorisation section is to reflect on the thesis and its potential contribution to applied science and society, and the relevance of the social impact on target groups that has already been or is expected to be achieved.

Main objectives, findings and conclusions

This thesis aims to shed light on the functioning of patients with ILD, in particular how they cope with various symptoms and perceived limitations in physical exercise capacity that influence their quality of life. Within this context, this thesis addresses two important themes regarding patients with ILD. First, the prevalence and symptom burden are studied in patients with IPF or sarcoidosis, with a specific focus on burdensome fatigue and the patients ability to self-manage. Secondly, several aspects of the 6MWT in patients with pulmonary fibrosis are studied, such as reliability and prognostic value and the correlation with simple field exercise performance tests as 4MGS and 5STS.

Patients with pulmonary fibrosis or sarcoidosis experiences a wide ranges of symptoms. Next to dyspnoea and cough, fatigue is one of the most prominent and disabling symptom affecting the patients quality of life. The main objectives of the first part of this thesis in IPF and sarcoidosis was to investigate the symptom burden, with a special attention to fatigue, and in which degree patients were activated for self-management strategies. Patients with severe fatigue experienced more dyspnoea, sleepiness, anxiety, depression, fatigue-related catastrophizing, functional activity impairments, and they reported a lower quality of life. To express the experienced fatigue, severe fatigued patients with IPF or sarcoidosis used not only significantly more connotations but also more negative connotation compared to non-severely fatigued patients. Patients with interstitial lung disease often report multiple clinical symptoms. Fourteen of these symptoms were asked in patients with IPF or sarcoidosis in a questionnaire using the VAS scales. The results could be compared to those of subjects without lung disease, who were matched to the patients based on gender and age. In IPF, 78% of symptom burden was higher compared to their matched controls, and in sarcoidosis

this was the case for all symptoms. Low levels of activation for self-management in patients were found in 56% of patients with IPF and approximately half of the patients with sarcoidosis. The patients with low levels of patient activation also generally reported more dyspnoea, anxiety, depression and lower health status.

Overall, our main conclusion is that severe fatigue is common in patients with IPF or sarcoidosis, and that these patients generally experience multiple symptoms with a more severe symptom burden than healthy controls. In addition, a substantial number of patients with IPF or sarcoidosis do not have the knowledge, skills and confidence to meet the challenges associated with their health problem.

The second part of the thesis shows the following aspects of testing functional exercise capacities in patients with pulmonary fibrosis. Firstly, one 6MWT in a day is sufficient to determine exercise-related desaturation (reliability test-hertest 6MWT). Second, the 4 meter gait speed test may serve as a practical indicator of distance traveled on the 6MWT, but is not sufficient to confirm SpO_2-nadir (the validity of performance tests compared with 6MWT for testing functional capacity). Finally, both attributes derived from 6MWT, the walking distance and the SpO_2-nadir, have a predictive value for two-year survival, with the best predictive value of SpO_2-nadir (prognostic value of the 6MWT). With these findings, the value of the 6MWT has been reconfirmed and new cutoffs for prognosis have been established. This data includes the era when antifibrotics became the standard of care in the treatment of patients with IPF, namely from 2015 onwards.

Potential contribution to (applied) science

This thesis highlights the relevance of screening for symptoms in general and for severe fatigue in particular. Regularly measuring the symptom burden from diagnosis onwards gives the patient the feeling of being heard and gives the healthcare professional more information to provide a more in-depth, targeted care. The research into perceived fatigue shows that patients describe their severe fatigue with more negative connotations and that this is related to the perceived quality of life (Chapter 2 and 3). The current research also shows that, for example, the cohort of patients with IPF (median age 68 year, almost 80% male) experiences significantly more serious complaints than persons of the same gender and age. Feeling heard by healthcare professionals when speaking about this increased symptom burden can support patients and will lead to better symptom management of the disease. The fact that not

everyone is capable of good patient activation for self-management is confirmed in Chapter 5. Discussing patient activation by patients and healthcare professionals and looking for solutions together is part of a strong approach to self-management. These findings mean that healthcare providers must be aware of which strategies in the field of self-management (e.g. knowledge, skills and/or confidence) the patient can or cannot apply and how they can tackle the problems experienced together with the patient (and relatives).

Furthermore, the findings of this thesis also encompasses different tests of functional exercise capacity. This provides physical therapists, clinicians and scientists with a more in-depth understanding of functional exercise capacity in pulmonary fibrosis. Simple practical tests can be a solution to the problems with exercise measurement in the treatment of rare diseases in general practice, if the SpO_2-nadir is not the intended outcome measure. Furthermore, the findings of the value of the 6MWT will provide several starting points for future research into the influence of functional exercise capacity on quality of life through more personalized specific training modalities.

Target groups

In a nutshell, this thesis provides a broader insight into the symptom burden experienced by patients with ILD, patient activation for self-management and renewed insights into the value of functional capacity measurements. As a result, several groups will benefit from the results of this thesis, especially patients, healthcare providers and researchers.

Patients with pulmonary fibrosis or sarcoidosis will benefit from this study into the symptom burden and into functional exercise capacity. Patients will ultimately benefit from recognition of that symptom burden and benefit from good insights into their exercise capacity, because this provides tools for an individualized pulmonary rehabilitation plan. Moreover, they can be better guided in self-management strategies during pulmonary rehabilitation if the reasons for the limitations of patient activation are known. Patient care, both in terms of exercise capacity control and good physical exercise care, can be provided closer to the patient than only reserved for the ILD expertise centers, as has largely been customary until now. In addition, it is important for patients with a rare disease such as most ILDs are, to know that their perceived limitations deserve a deeper scientific approach to arrive at a more optimal treatment strategy.

Physiotherapists working in the cardiovascular respiratory field are becoming increasingly aware of their responsibility in guiding patients with pulmonary fibrosis in their perceived symptom burden, the functional exercise impairments and the patient's capacity for self-management activities. Their professional actions with patients with ILD will be based on a more focused evidence-based practice and informed practice. Ultimately, collaboration within and outside the lung expertise profession will lead to better and more optimal treatment of patients.

Pulmonologists, but possibly also other physicians such as general practitioners, benefit from the perspective that functional exercise testing makes it possible to better determine prognosis. In addition, starting an pulmonary rehabilitation program early after the diagnosis of pulmonary fibrosis (and regularly being reoffered to the patient) will lead to more optimal individualized and multidisciplinary guidance for the patient in dealing with the consequences of the disease and may lead to a better perceived quality of life. Based on the collaboration between the various disciplines for the benefit of good exercise-based care for the patient, the insights from this dissertation on symptom burden and activation for self-management can also be important for ILD nurses, occupational therapists, dietitians and psychologists/social therapists.

Finally, the results are also important for other researchers. Research into pulmonary rehabilitation in pulmonary fibrosis is still an area in which many unexplored areas remain. Conducting research in a patient group whose prevalence is relatively low requires addressing different challenges and more complex problems than with a better-known condition such as COPD. This applies to formulating the right research questions, and finding both financial support and the right research environment to shape the research. However, it is extremely important for patients with ILD and can make a significant difference in quality of life.

Activities

Several activities have been undertaken to promote the dissemination of the results of this thesis among patients, physiotherapists, clinicians, and researchers.
The research procedures included close collaboration of the principal investigator with the ILD Center of Excellence of the St. Antonius Hospital, Nieuwegein, with the research group of Research and Development, CIRO, Horn, with the ILD center Zuyderland MC, Heerlen, and the Institute of Movement Studies of the University of Applied Sciences Utrecht, all in the Netherlands.

All research results have been published in an international, peer-reviewed journal. The results have been presented and discussed at congresses national (Dutch Lung Congress) and international (European Respiratory Society), symposia and meetings. Educational activities have taken place for the cardiovascular respiratory expertise group of the physiotherapy association in the Netherlands (VHVL/KNGF) and for the ILD nurses. Awareness about physiotherapeutic care for pulmonary fibrosis is provided through guest presentations at symposia of the Dutch Association for Pulmonology and Tuberculosis (NVALT) and the physiotherapy department of pulmonary diseases of the St Antonius Hospital Nieuwegein, intended for both patients and their relatives and pulmonary physiotherapists, nurses or occupational therapists.

The core section of cardiovascular respiratory lecturers at Utrecht University of Applied Sciences has developed and rolled out a master's program in the specialized cardiovascular respiratory domain in which ILD has received the necessary recognition.
In addition, a close collaboration between various healthcare professionals and the Dutch pulmonary fibrosis patient association, at the initiative of Boehringer Ingelheim, has led to the exercise care path pulmonary fibrosis (see also general discussion, paragraph 'impact'). In order to safeguard this Dutch process of referral to the right care in the right place, this exercise care process will need to be rolled out step by step. Before the plan can be rolled out nationally, a pilot feasibility study will first be carried out at the ILD expertise center St Antonius Hospital in Nieuwegein. Close collaboration with the Dutch Pulmonary Fibrosis Patient Association is seen as an important condition for the success of this ambitious plan.

All these activities together have contributed to increasing awareness of exercise care in ILD, in particular IPF and sarcoidosis, and will help patients with pulmonary fibrosis in the future to receive the best possible exercise care, tailored to their experienced symptoms and wishes regarding to quality of life.

List of abbreviations

Abbreviations	Definition
4MGS	4-Meter-Gait-Speed
5STS	5-repetitions-Sit-To-Stand
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AF-medication	Antifibrotic Medication
ANOVA	Analysis of Variance
ATS	American Thoracic Society
AUC	Area Under the Curve
BMI	Body Mass Index
CAL	Causal Attribution List
CBT	Cognitive Behavioral Therapy
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CIS-Fatigue	Checklist Individual Strength, Domain-Fatigue
CR	Chronotropic Response
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Testing
CVA	Cerebrovascular Accident
CVD	Cardiac Vascular Disease
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DM	Diabetes Mellitus
DSP	Distance-Saturation Product
EBP	Evidence Based Practice
EDS	Excessive Daytime Sleepiness
EID	Exercise-induced Oxygen Desaturation
EMA	European Medicines Agency
EMA	Ecological Momentary Assessment
EQ-5D-5L	EuroQol Five-Dimensional Five-Level Descriptive System
EQ-VAS	EuroQol Five-Dimensional Five-Level subscale Visual Analog Scale
ERS	European Respiratory Society
ESS	Epworth Sleepiness Scale
FCS	Fatigue Catastrophizing Scale
FEV1	Forced Expiratory Volume in one Second
FFMI	Fat-Free Mass Index

FQL	Fatigue Quality List
FQL-Adjectives	Fatigue Quality List Adjectives
FQL-Categories	Fatigue Quality List Categories
FVC	Forced Vital Capacity
GAP	Gender-Age-Physiology
GERD	Gastroesophageal Reflux Disease
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale subscale Anxiety
HADS-D	Hospital Anxiety and Depression Scale subscale Depression
HGS	Hand Grip Strength
HR	Heart Rate
HRCT	High-Resolution Computed Tomography
HRQL	Health-Related Quality of Life
HRR	Heart Rate Recovery
IBM SPSS	International Business Machines Corporation Statistical Product and Service Solutions
ICC	Intraclass Correlation Coefficient
ICD-10	International Classification of Diseases and Related Health Problems
ICF	International Classification of Functioning, Disability and Health
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IQR	Interquartile Range
Kg	Kilogram
m	meter
METC	Medical Research Ethics Committee of the Institution
mMRC	modified-Medical Research Council
MRC	Medical Research Council
n	number
NAC	N-acetylcysteine
p	points
PAM	Patient Activation Measure
PCS	Pain Catastrophizing Scale
PF	Pulmonary Fibrosis
PFT	Pulmonary Function Test
PH	Pulmonary Hypertension
PRO	Patient-Reported Outcome

QoL	Quality of Life
QoL-RIQ-Activity	Quality-of-Life Respiratory Illness Functional Activity Impairment
ROC	Receiver Operating Characteristic
RV	Residual Volume
s	second
SD	Standard Deviation
SEE	Standard Error of the Estimate
SF-36	Short-form Health Survey 36 Questions
(SF-36) PCS	Physical Component Score
(SF-36) MCS	Mental Component Score
SFN	Small Fiber Neuropathy
SpO_2	Peripheral Capillary Oxygen Saturation (Transcutaneous)
SpO_2-nadir	Indication of the Minimum Pulse Oximetry SpO2 Value during the 6MWT
TIA	Transient Ischemic Attack
TLC	Total Lung Capacity
TLCO	Transfer Factor of the Lung for Carbon Monoxide
US FDA	United States Food and Drug Administration
VAS	Visual Analogue Scale
VIF	Variance Inflation Factor
WHO	World Health Organization

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Vanaf mijn zeventiende wist ik dat ik wilde gaan studeren, maar wel in contact met mensen en er moest actie inzitten. Fysiotherapie trok me aan, zeker omdat het aansloot bij mijn sport volleybal. Na de opleiding kon ik starten in het ziekenhuis bij de vakgroep longaandoeningen waar ik eerder stage had gelopen. De 23 jaar die ik werkzaam was als klinisch longfysiotherapeute heb ik ervaren als een mooie intensieve, leerzame en rijke periode. In 2012 zette ik mijn eerste schreden in het hoger onderwijs met als doel het opleiden en coachen van nieuwe zorgprofessionals. Deze stap zette gelijk de deur open naar het toegepaste praktijkonderzoek; ik kon een brug gaan slaan tussen de praktijk, het onderwijs en het onderzoek in longaandoeningen. In 2013 startte ik daarvoor met mijn masteropleiding Evidence Based Practice (EBP), dat uiteindelijk het fundament bleek te zijn voor mijn promotietraject. Praktijkonderzoek bij patiënten met een vrij zeldzame en minder algemeen bekend zijnde interstitiële longaandoening (ILD) in zowel het St Antonius Ziekenhuis als het Zuyderland Medisch Centrum, zorgde voor de input van de verschillende wetenschappelijke artikelen. Dit proefschrift was nooit tot stand gekomen zonder hulp en onvoorwaardelijke steun van mijn promotoren, copromotoren, andere begeleiders, collega's, familie en vrienden. Ik zou graag iedereen die ik heb mogen ontmoeten in mijn loopbaan, in de praktijk, het onderwijs en het onderzoek willen bedanken. Maar ook zij die mij een luisterend oor dan/wel een brede schouder boden, of zij die voor de heerlijke ontspanning hebben gezorgd, ook hen wil ik allemaal bedanken.

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List of scientific publications

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Conference contributions

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About the author

Aadje (Ada Elisabeth Maria) Bloem was born on May 31, 1968 in Nijmegen, the Netherlands. She was the youngest child in a family of seven children. After finishing secondary school at the Dominicus College in Nijmegen in 1986, she studied Physiotherapy at the 'Hogeschool Midden Nederland', nowadays called the Institute of Human Movement Studies University of Applied Science Utrecht, The Netherlands.

After completing her internship and graduating her bachelor's degree Cum Laude, she started working at the St. Antonius Hospital in Nieuwegein, The Netherlands. As a member of team 'blue', she developed into a senior clinical physiotherapist with expertise in the field of respiratory disorders through practical clinical experience and through various training courses in this respiratory field.

During her 23-year working period in the hospital, she has built up extensive work experience in various areas of hospital healthcare (such as cardiovascular, internal, and neurological diseases and worked in weekend shifts in intensive care unit). She completed additional studies post-bachelor in physiotherapy and sports and in physiotherapy and oncology. She also worked as an internal auditor for a number of years within the various departments of the hospital. From 1991 to 1996, in addition to her work as a clinical pulmonary physiotherapist, she worked as a sports physiotherapist as a member of the technical staff of the Dutch women's youth volleyball team (NeVoBo).

Since 2012 Aadje worked as a lecturer cardiovascular respiratory physiotherapy (CRF) at the institute for movement studies at the University of Applied Science Utrecht (IBS/HU). She continued her academic education with the Master of Science, Evidence Based Practice (EBP) at the University of Amsterdam from 2013-2016. In collaboration with the ILD Center of Excellence of the St Antonius Hospital she conducted a study in exercise capacity tests in patients with pulmonary fibrosis as part of her master thesis (St. Antonius Hospital, Nieuwegein, The Netherlands). This study with new original patient data resulted in her first two publications in international peer-reviewed journals. She continued her research ambitions in patient care for ILDs at the Zuyderland Medical Center (Heerlen, Netherlands) with research into

patient-reported outcomes in patients with IPF or sarcoidosis. In the meantime, she remained attached as an additional researcher to the ILD research group of the ILD Center of Excellence St. Antonius Hospital Nieuwegein. Within this research center, she subsequently conducted a study focused on the prognostic value of the 6-minute walk test using electronic patient file data from the ILD expertise center. During her entire professional development as a clinical researcher, she was supervised by Prof. dr. Martijn Spruit. This collaboration has led to her being officially registered as an external PhD candidate at Maastricht University in 2021. The results of her research have been published in international, peer-reviewed journals and presented at national and international conferences and meetings.

As a senior lecturer at the HU, Aadje currently educates physiotherapy bachelor's students in the domain of CRF, she assesses bachelor's theses and is a core team member of the module 'Intramural Care' that she co-developed. She is chair of the CRF expertise group of lecturers. Within the master's programs, she is part of the core team and lecturer of the newly developed CRF master's degree. This CRF master is the first and so far the only one in this recognized specialized CRF domain in physiotherapy in the Netherlands.

Through intensive collaboration with the Pulmonary Fibrosis Patient Association and with a group of experts within various healthcare disciplines surrounding exercise care for pulmonary fibrosis, she is committed to increasing public awareness about patients with ILD and exercise care for patients with pulmonary fibrosis in the Netherlands in particular.

In her private life, Aadje Bloem lives with Winfried Witsenboer and they have three children: Jelmer, Tibbe and Kallie.