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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.

Introduction

The two most common types of interstitial lung diseases (ILDs) are idiopathic pulmonary fibrosis (IPF)[1–3] 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[5–7], 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

Abbreviation: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebrovascular accident; DM, Diabetes Mellitus; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; ILD, Interstitial Lung Disease; IPF, Idiopathic Pulmonary Fibrosis; OSAS, Obstructive Sleep Apnea Syndrome; RV, Residual Volume; TIA, Transient Ischemic Attack; TLC, Total Lung Capacity; TLCO, Transfer Factor of the Lung for Carbon Monoxide; VAS, Visual Analogue Scale

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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 (FEV_1)) (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, online supplement)

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 Sarcoidosis (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/m^2)	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
FEV_1 (liter)	2.4 ±0.6	3.2 ±0.8	<0.001	2.8 ±0.8	3.1 ±0.6	0.032
FEV_1 (% 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
Myocardial infarction, Cardiac failure	6 (13.6)	5 (11.4) [α]	ns	0 (0.0)	1 (2.2) [α]	ns
TIA, CVA or Hemiplegia	3 (6.8)	4 (9.1) [α]	ns	2 (4.4)	4(8.9) [α]	ns
Peripheral vascular disease	4 (9.1)	2 (4.5) [α]	ns	1 (2.2)	0 (0.0) [α]	ns
COPD, Asthma	0 (0.0)	0 (0.0) [α]	ns	6 (13.3)	0 (0.0) [α]	p=0.011
Diabetes mellitus	6 (13.7)	4 (9.1) [α]	ns	4 (8.9)	1 (2.2) [α]	ns
Medication use (≥1)						
Pulmonary[a], *n* (%)	3 (6.8)	8 (18.2)	0.125	24 (54.5)	2 (4.4)	<0.001
Cardiovascular[a], *n* (%)	21 (47.7)	22 (50.0)	1.000	11 (25.0)	14 (31.1)	0.521
Immunosuppressive[a], *n* (%)	3 (6.8)	2 (4.5)	0.607	17 (38.6)	0 (0.0)	<0.001
Antidepressant[a], *n* (%)	4 (9.1)	3 (6.8)	0.646	1 (2.3)	2 (4.4)	0.570
Other[a], *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/m^2); 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
[α]Charlson Comorbidity Index (CCI)

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 (Fig. 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%. (Fig. 2; all p<0.05) The proportion of patients reporting ≥3 symptoms was significantly higher compared to the controls (70.4 *vs* 13.6%) (Fig. 3.A). Fig. 4A 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, online supplement)

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) (Fig. 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

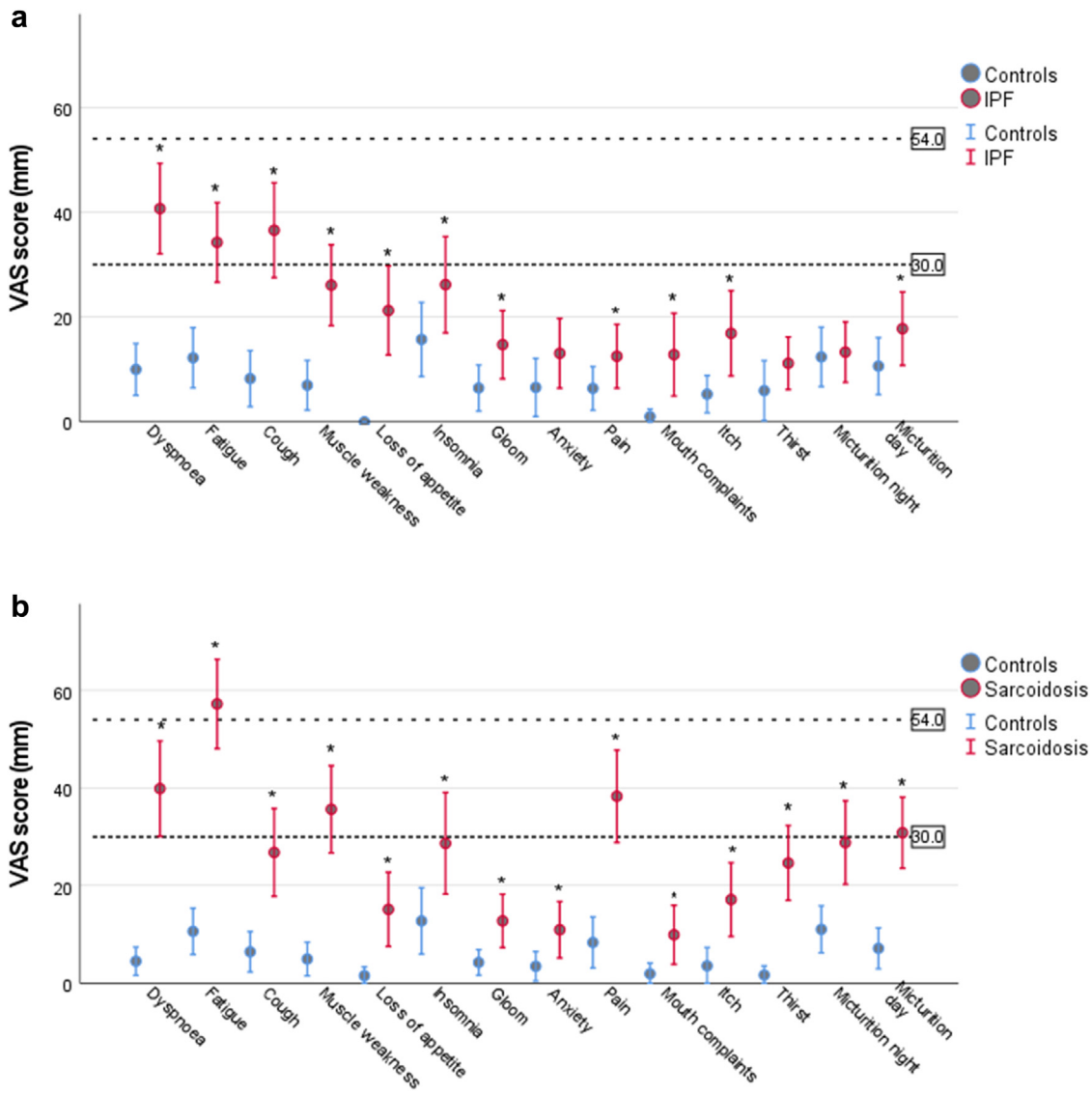


Fig. 1. A Mean (standard deviation [SD]) visual analogue scale (VAS score) of symptoms in patients with idiopathic pulmonary disease (IPF) or controls without pulmonary disease. Mean VAS scores >30 mm (dotted line) represent moderate severity; Mean VAS scores >54 mm (dotted line) represent severe symptom 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

35.6% vs 0%, micturition night 37.8% vs 11.1% and micturition day 46.7% vs 9.1% (Fig. 2). More patients (73.7%) than controls (11.6%) reported 3 or more symptoms (Fig. 3.B). Fig. 4B shows that respiratory and non-respiratory symptoms also co-occur frequently in patients with sarcoidosis. For example, all patients suffering gloom also reported fatigue.

Discussion, methodological considerations and conclusion

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

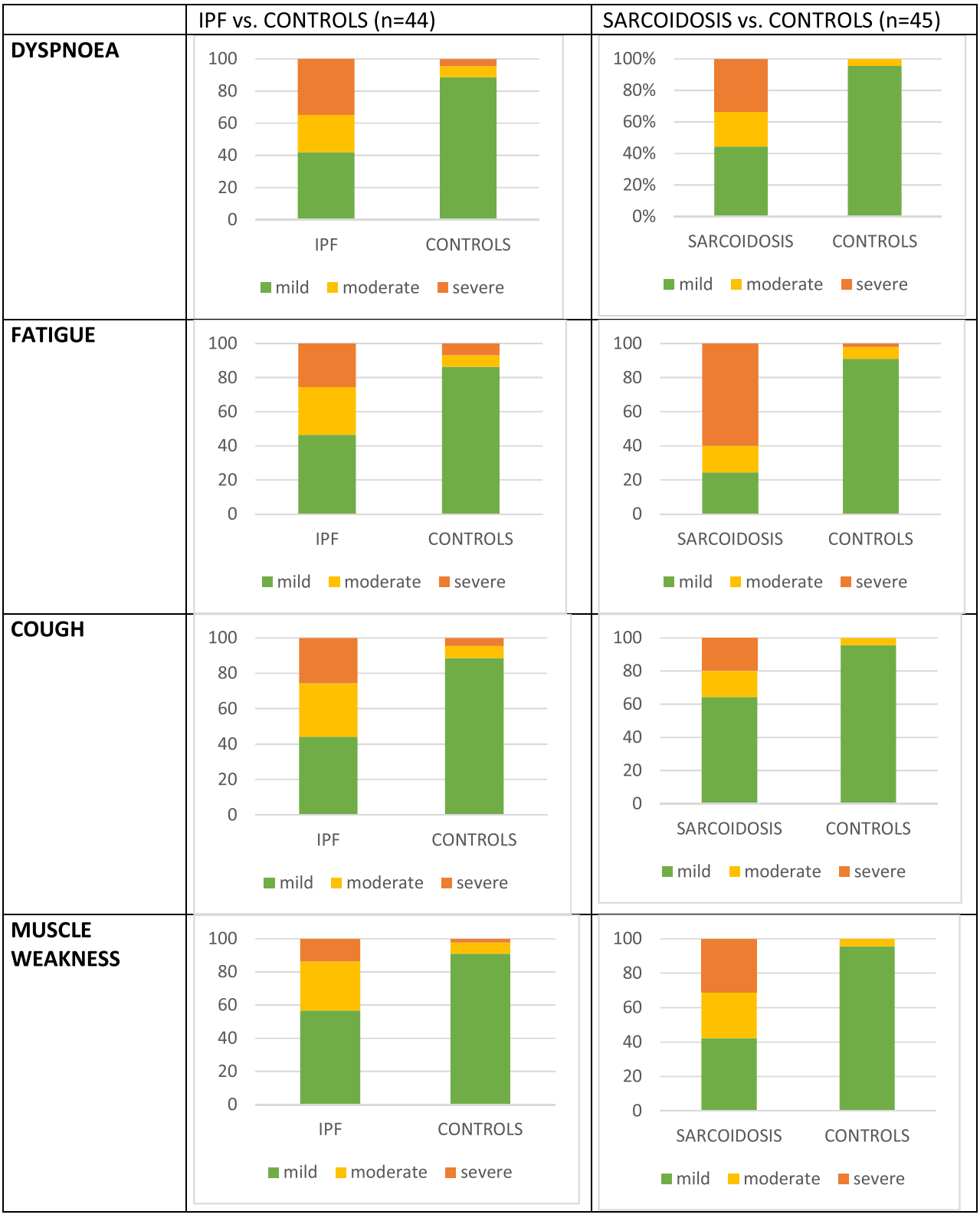
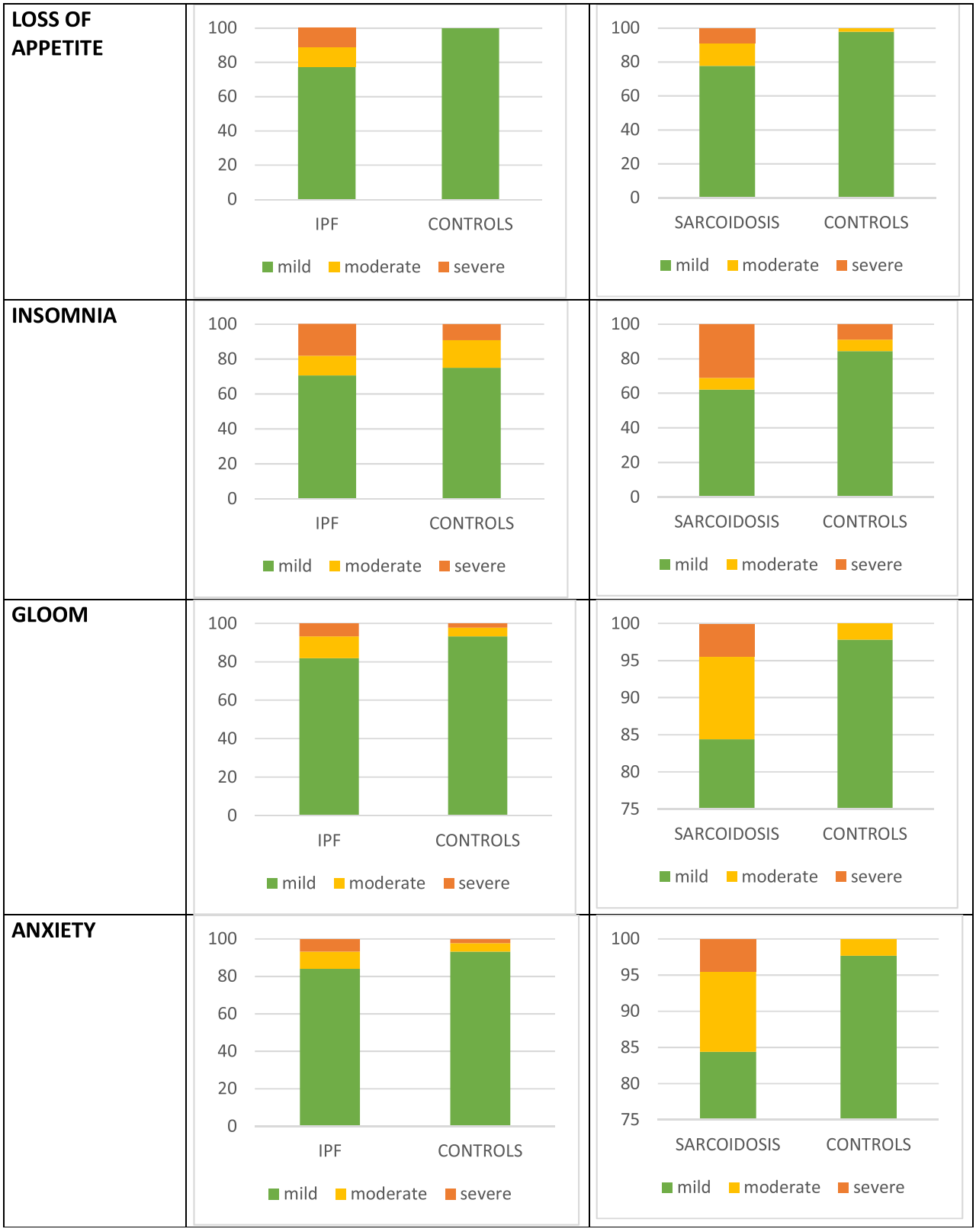


Fig. 2. Symptoms severity mild-moderate-severe on visual analogue scale (VAS score) in patients with idiopathic pulmonary disease (IPF) or sarcoidosis versus individuals without respiratory disease (controls). VAS score, symptom burden mild, moderate or severe: mild ≤ 30 mm, >30 mm moderate ≤54 mm, severe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



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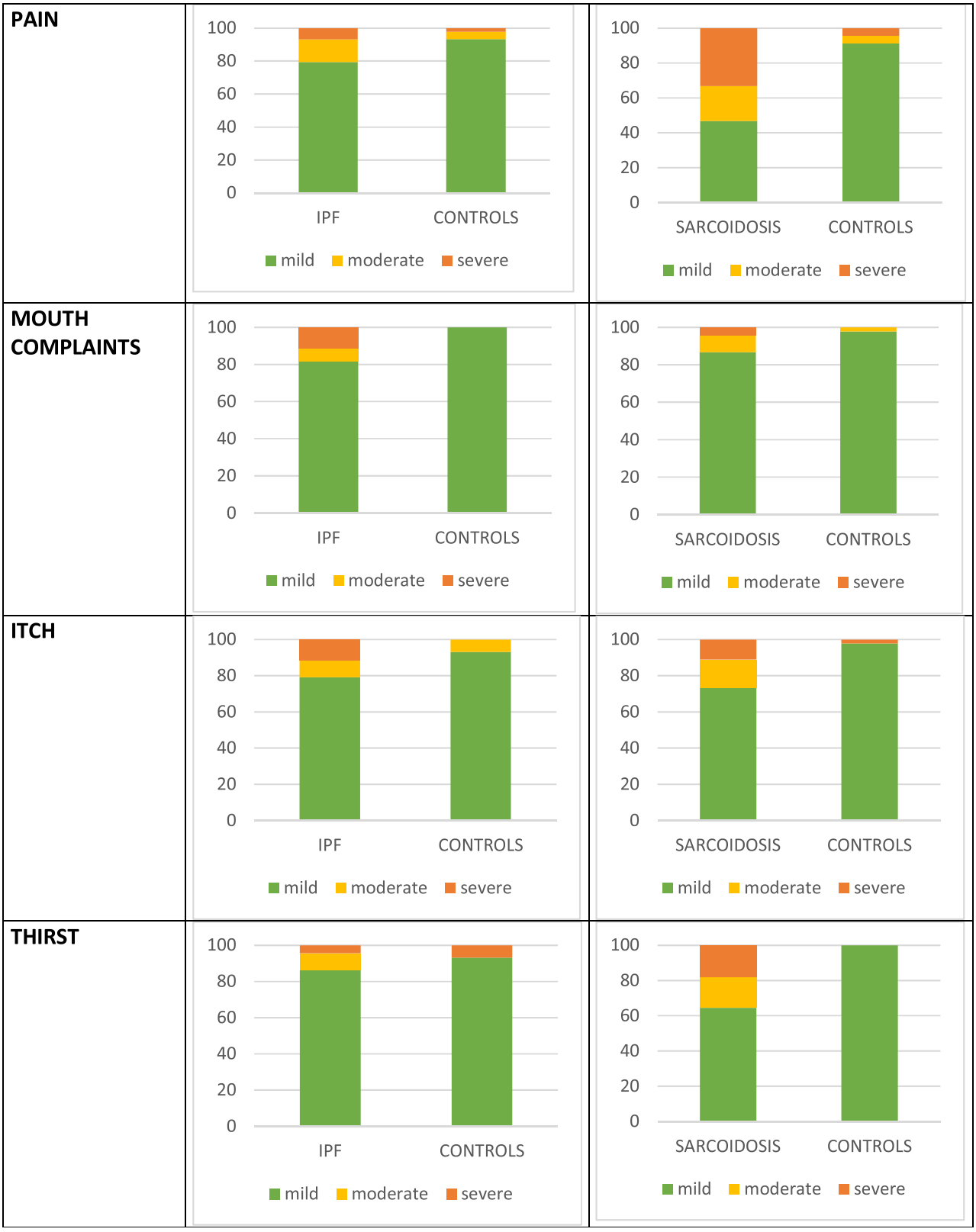

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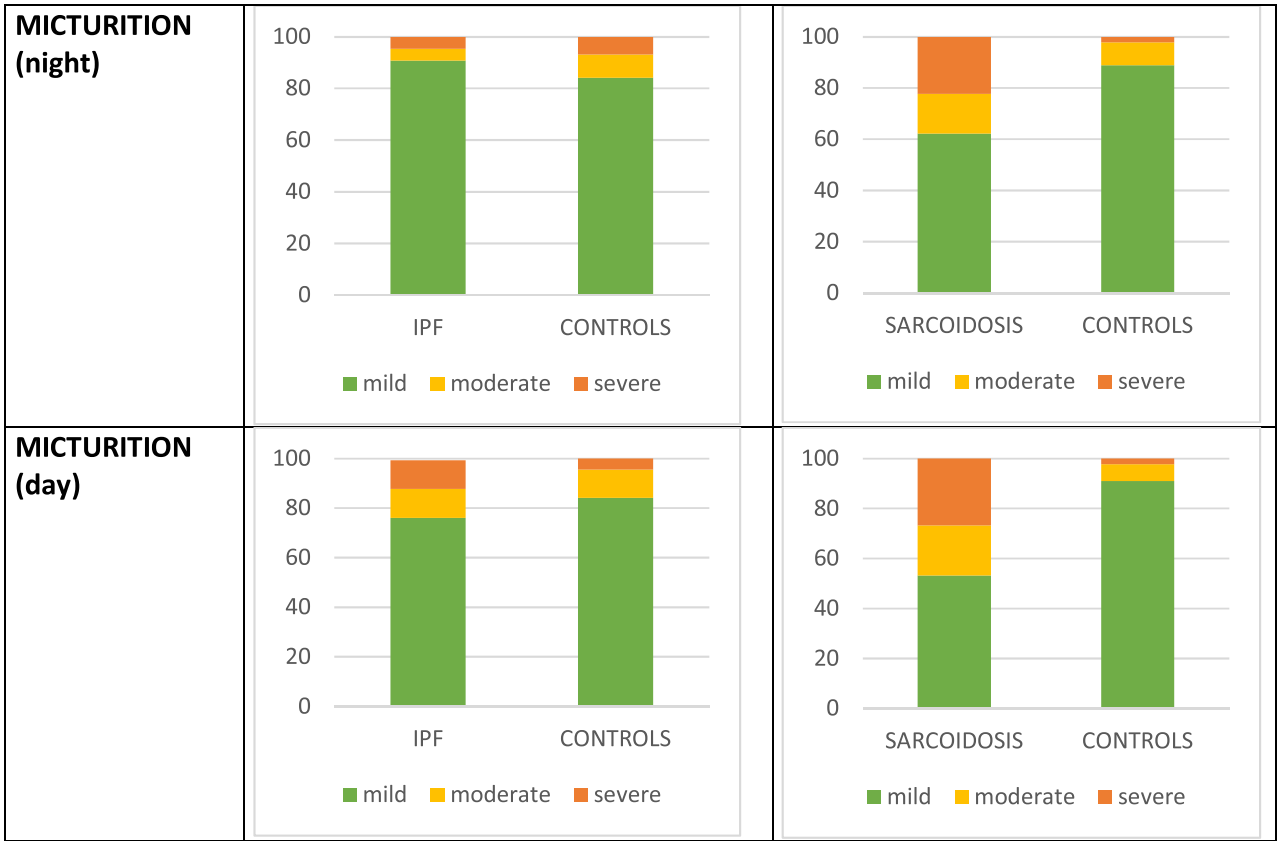

Fig. 2. Continued.

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 dyspnea 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.[9,37-39] 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

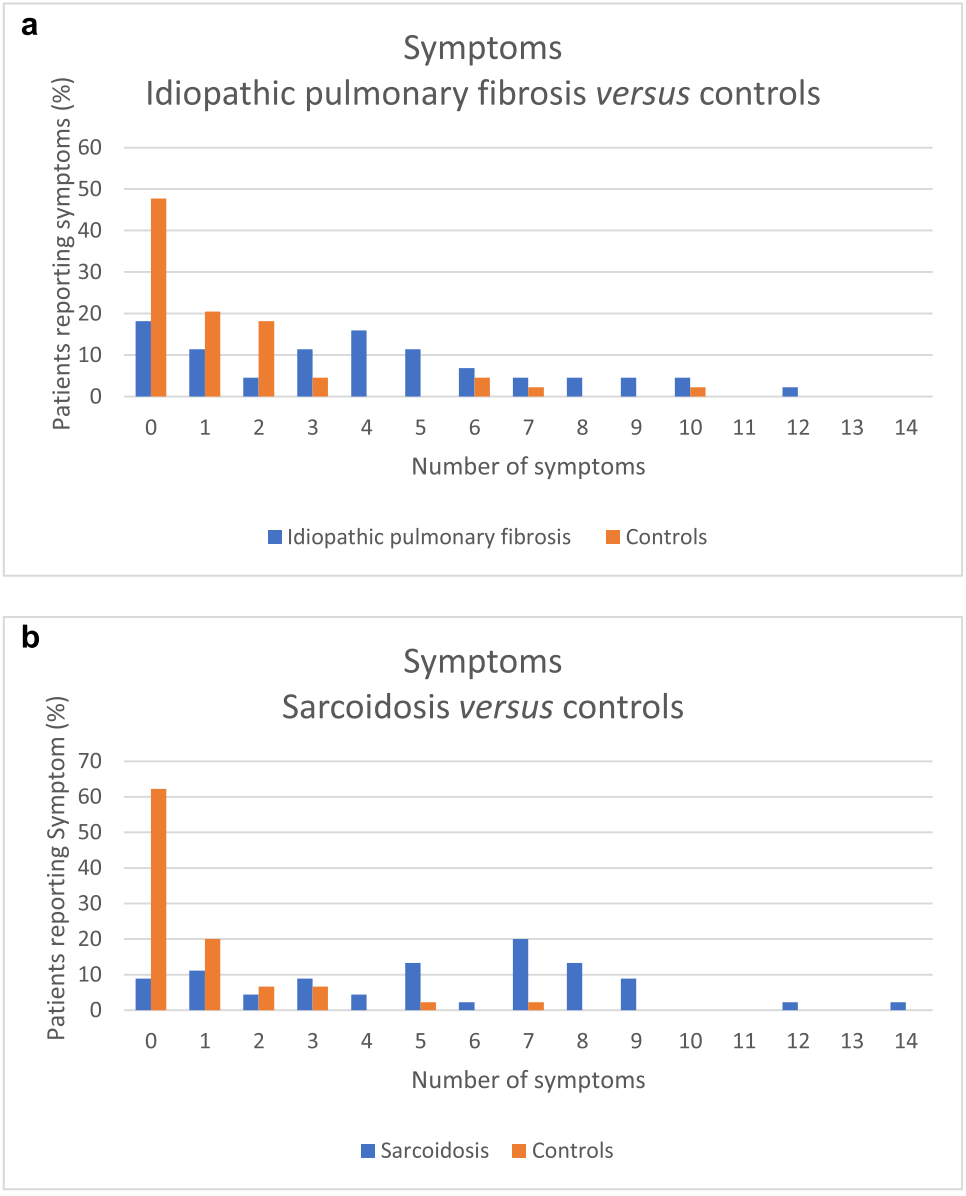

Fig. 3. A. Percentage of symptoms, with a symptom severity score >30 mm on Visual Analogue Scale (VAS), in patients with idiopathic pulmonary fibrosis (IPF) or individuals without respiratory disease (controls)

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)

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. Therefor 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.

a

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

b

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

Fig. 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.

4.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.

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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Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2023.05.013.

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