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Early View

Original research article

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Please cite this article as: Tremblay Labrecque PF, Didier Saey GD. Functional clinical impairments and frailty in interstitial lung diseases patients. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00144-2022).

ORIGINAL RESEARCH

Short running header:

1. Functional Clinical Impairments and Frailty in Interstitial Lung Diseases Patients

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Key words: interstial lung diseases; frailty; functional capacity; muscle function; Health-related quality of life

Word count: 2 999

ABSTRACT

Background: Patients with interstitial lung diseases (ILD) often present with persistent dyspnea and reduced exercise capacity and quality of life, but their functional limitation in relation to their frailty status remain unclear. We thus aimed to compare the exercise tolerance, functional mobility and muscle function and composition between ILD participants and healthy subjects and according to their frailty status.

Method: A total of 36 ILD participants and 15 heathy subjects performed a six-minute walking test (6MWT), a 1-minute Sit-to-Stand test (1STS), a Short Physical Performance Battery (SPPB) test, a hand grip test and a complete quadriceps function testing. Patient-related impacts were assessed via questionnaires. Muscle composition was obtained using non-contrast computed tomography scans. The frailty status of patients with ILD was determined using the Fried Frailty Phenotype Assessment.

Results: In comparison to control subjects, ILD participants exhibited a significantly lower performance in every exercise and functional capacity tests, a higher dyspnea and depression scores and a worse quality of life. In ILD participants, the same observations was noted for frail subgroup in comparison to the robust subgroup. No difference in muscle function and composition was observed between the ILD and control group but mid-thigh muscle cross-sectional area and skeletal muscle index were significantly reduced in frail ILD participants.

Conclusion: ILD patients present a reduced exercise tolerance and functional capacity, and have a decreased health-related quality of life when compared to a healthy subjects. Physical frailty seems associated with worse clinical status, exercise tolerance, muscle and functional impairment and decreased quality of life. 1STS may be a good discriminatory test for frailty status in ILD patients.

INTRODUCTION

Interstitial lung diseases (ILD) constitute more than 200 diseases that cause progressive fibrosing of the pulmonary interstitium. The excessive deposition of fibrosing tissue results in a reduction of the elastic properties of the lung, a reduction of lung volumes, a thickening of the alveolar-capillary membrane and gas exchange abnormalities.[1,2] Consequently, patients with ILD present a progressive dyspnea, diminished exercise tolerance[3] and physical activity levels[4, 5] that reduce significantly their health-related quality of life (HRQoL).[6]

Although evidence on causal relationship is still missing, several well-established muscle dysfunction promoting factors such as chronic hypoxemia, inflammatory and oxidative stress, corticosteroid use, physical inactivity and malnutrition are also frequently reported in ILD patients and some evidence showed that lower limb muscle atrophy and dysfunction are present in patients with ILD. [7]

Multiple tests were designed to characterize the exercise tolerance and functional capacity of the ILD patients. The 6MWT is currently the gold-standard for the evaluation of the exercise tolerance due to its mortality prediction [3] but other tests such as the 1STS and Short Physical Performance Battery (SPPB) have been studied with increasing interest in recent years. [8 9 10]

Frailty is described as the vulnerability to adverse outcomes resulting from the cumulative declines across multiples systems. [11] The accumulation of functional and perceptual limitations reported in patients with ILD are main factors in the development of frailty in this population. Frailty predicts mortality in multiple chronic diseases [12,13] and is associated with an augmentation of healthcare utilization in chronic obstructive pulmonary diseases (COPD) [14]. In patients with ILD, frailty have been associated with worse HRQoL and increased hospitalization and mortality [15]. The prevalence of frailty of 50% recently observed by Milne et al. [16] suggest that frailty is

common in ILD patients but little information is available to quantify the nature and severity of the functional and exercice limitations, muscle function and composition alterations, perceptual limitations and quality of life of the patients in regard of their frailty status. From a rehabilitation perspective, it is clinically relevant to obtain a holistic portray of the ILD patient's functional status. It allows to intervene early in implementing home resources and referring to pulmonary rehabilitation programs that are adapted to the patients needs. [17]

The main objective of the present study was to compare the exercise capacity, the functional mobility, the muscular function and composition and the HRQoL of a group of ILD participants to a group of healthy subjects matched for comparable age and sex. Using the same variables, the secondary objective was to determine if significant differences exist between the subgroups of ILD patients when separated according to their frailty status.

METHOD

Study design and participants

A total of 36 consecutive patients with a diagnosis of fibrosing ILD were prospectively and randomly recruited from the outpatient ILD referral center at the *Institut universitaire de cardiologie et de pneumologie de Québec*, Université Laval (Québec, Canada) from May 2018 to March 2021. The ILD participants were classified according to frailty status and matched with 15 healthy controls of similar age and sex recruited via our research center data bank consisting of healthy participants who accepted to be contacted for future studies. Participants of both groups were excluded if they had a history of syncope, significant cardiac disease or incapacitating musculoskeletal, neurological, or rheumatological conditions. ILD participants with any other significant respiratory disease (i.e. chronic obstructive pulmonary diseases (COPD)), a diagnosis

of sarcoidosis, a hospitalization for acute exacerbation of ILD within the last 3 months, and having participated in a pulmonary rehabilitation program in the past 6 months were also excluded. The study was approved by the local ethic committee board (N 2018-3010, 21595) and all participants signed a consent form before the initiation of study procedures.

Procedures

The protocol consisted of two visits. At the first visit, age, sex, ILD diagnosis (according to the ATS/ERS classification), age at diagnosis, medication and oxygen supplementation were collected from the medical records. Anthropometric data was then collected using a stadiometer for the height weight from which the BMI was calculated. Pulmonary function tests, including spirometric testing, plethysmography and measurement of the diffusing capacity for carbon monoxide (DL_{CO}) was conducted in accordance to the ATS/ERS guidelines [18] for the ILD subjects and a spirometry was conducted for the participants of the control group. After a familiarization to the procedures, participants performed a 1STS test according to the protocol described by Ozalevli et al.[19] and a Short Physical Performance Battery (SPPB) test according to the National Institute on Aging protocol. [20] The SPPB test consist of the sum of three separate functional components. 1. Fastest time to complete 5 times sit-to-stand (5TSTS), 2. 10-sec static standing balance test and 3. 4-meter walk test. [21] Each component is scored on 4 for a total of 12 points ranging from 0 (functional impairment) to 12 (maximal functional mobility).[22] Functional limitation was defined at a cutoff of ≤ 9 such as described in a previous study. [23]

On the second visit, participants completed the remaining tests: a 6MWT (2 trials) according to the official ATS/ERS technical standard field walking tests in chronic respiratory diseases.[24], a hand grip test using The Jamar® hydraulic hand dynamometer (J. A. Preston Corporation,Clifton,

NJ) protocol [25] and a a battery of quadriceps muscle function tests with a computerised dynamometer (Biodex System 4 Biodex Medical Systems, Shirley, New York, NY, USA) using test procedures that have been described in detail elsewhere [26]. A rest period of a minimum of 15 minutes was provided between each test to allow for both the cardiorespiratory parameters and dyspnea perception to return to baseline values. A mid-thigh computed tomodensitometry (CT scan) of the thigh was performed at the beginning of the second visit.

Three questionnaires (The St-George's Respiratory Questionnaire (SGRQ), The University of California San Diego Shortness of Breath questionnaire (UCSD) and the Center for Epidemiologic Studies Depression Scale (CES-D) scale) [27] were administered randomly throughout the course of the two sessions. The CES-D scale questionnaire was completed in its entire form both as part of the HRQoL assessment and the frailty status determination process described below.

Physical frailty was defined using the Fried phenotype model, [11] [28] including five criteria: unintentional weight loss, exhaustion, low level of physical activity, slow walking speed and weakness. [11] Participants who fulfilled none of the criteria were considered robust, participants who fulfilled 1 or 2 criteria were classified as pre-frail, and participants who fulfilled ≥3 criteria were classified as frail.

A detailed description of all these procedures is available in the *Supplementary appendix*.

Statistical analysis and sample size determination

Based on the study of Corrêa et al. [29] who described the differences in multiple functional exercise tests between chronic obstructive pulmonary disease and a control group, we calculated that 15 participants in the control and the pooled ILD group with a power of 80% with an alpha

of $\alpha < 0.05$ would be sufficient.

Continuous variables were analyzed using one-way ANOVA. A mixed statistical model following the means procedure permitted to compare both the ILD vs. control groups and the frailty divided subgroups using the same model.

Variables were expressed as mean ± standard deviation and results were considered significant at $p < 0.05$. Statistical analyses were performed using the SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of ILD participants, controls and the three ILD subgroups in relation to their frailty status are provided in **table 1** alongside the diagnosis distribution of the different ILD. Among participants with ILD, 22% were robust, 53% pre-frail and 25% frail. Control and ILD groups were similar in age, sex distribution and BMI. No significant difference was observed for the diffusing capacity for carbon monoxide (DLCO) and the forced vital capacity (FVC) throughout the frailty phenotypes although the sample size remain modest for any further interpretation of these parameters. Weekly energy expenditure was significantly lower for frail participants, in comparision to robust and pre-frail groups. Distribution of the Fried frailty phenotype criteria for each group/subgroup is shown in **figure 1**. Amongst the frail criteria, reduced physical activity (89%) and unintentional weight loss (78%), were the most common marker of frailty followed by, exhaustion (CES-D) (56%), handgrip weakness (56%) and slow gait-speed (33%).

Exercise tolerance and functional mobility

The comparison for exercise tolerance and functional mobility between the different subgroups are presented in **table 2**. The control group performed significantly better than the ILD group for each of the 6MWT, 1STS and the SPPB (including both the 5TSTS and walking speed categories as part of separate analysis) tests. The 6MWT elicited a slightly more profound desaturation compared to the 1STS (6MWT: 85 ± 4% vs 1STS: 89 ± 2%; p= 0.0003) in the pooled group of ILD participants. In comparison to robust participants, frail ILD participants walked lower distance on 6MWT, had a lower number of repetitions on 1STS, walked slower on 4 meters and took more time to perform 5 rising from a chair. The 1STS was the only test for which a significant difference was observed between each subgroups of ILD participants according to their frailty status.

Muscles function and composition

The muscle function and composition data (**table 3)** showed no difference in the hand grip strength measurements both between the control and ILD groups but also within the three frailty subgroups of ILD participants. No difference was observed in the quadriceps measurements when the pooled ILD group is compared to the control group but all quadriceps functions (power, strength and endurance) were significantly lower in the frail subgroup when compared to both the pre-frail and robust subgroups .

Whilst, presenting similar subcutaneous adipose tissue and total muscle cross-sectional area (CSA), ILD participants exhibited a significantly reduced muscle attenuation and higher deep adipose tissue of the mid-thigh cross-sectional area when compared to the control group.

Dyspnea, depression and HRQoL questionnaires

The results of the UCSD, CES-D and SGRQ questionnaires for ILD and control groups are presented in **table 4**. The three questionnaires exhibited respectively significantly higher reported dyspnea, higher score of depression and higher score on SGRQ representing worse health-related quality of life for the ILD group. The same observations were seen for fail participants, in comparison to the robust ones.

DISCUSSION

This study shows that ILD patients present significantly reduced exercise tolerance and functional capacity, higher dyspnea and reduced health-related quality of life in comparison to control subjects. Although ILD participants present some muscle composition alterations (low attenuation), the muscle function seems preserved. When the cohort of ILD participants is subdivided into their respective frailty status phenotypes, the exercise and functional tests performance as well symptoms of dyspnea, depression and quality of life significantly worsens as the frailty status progresses, which may emphasize the cumulative declines across multiples systems.

Exercise tolerance and functional moblity

Interstitial lung diseases participants included in the study had a lower weekly physical activity and present a worse performance to all of the exercise tolerance and functional tests, in comparison to the control group. Although our ILD participants presented a preserved 6MWD (476 +/- 94 m), this performance was significantly worse in comparison to control healthy subjects (615 +/- 83 m). The walking distance for our ILD participants is coherent with the upper limit of previously published data ranging from 377-487m. [30,31] [32,33] and is also similar to mean walk distance in major therapeutic studies in IPF (397-420 m). The mean number of one minute

sit to stand repetitions (21 +/- 4) for our ILD group was significantly lower than the control healthy subjects (30 +/- 7) and was similar to other studies in ILD participants (21-22 repetitions). [9,34] The slightly more profound desaturation at the end of the 6MWT when compared to the 1STS is also consistent with previously reported results in ILD population. [34] This confirm the poor exercise tolerance and functional capacity of the ILD participants, in comparison to healthy subjects.

When the ILD participants were classified according to their frailty status, the performance of the 6MWT, the 1STS test and the 5TSTS was significantly lower between the frail subgroup and the robust group in ILD participants but no difference was observed between subgroup of patient for the total score of the SPPB, for which performance ceiling is probably too low to adequately assess the ILD population. The 1STS test results allowed the best differentiation between the frail subgroups since each of frailty-separated subgroups was significantly different from each other. Nonetheless, even if the 6MWT didn't allowed this differentiation, it effectively detected the frail participants from the robust ones. No significant difference was observed for the FVC, DLCO and the level of end-test saturation on functional and exercice tests between the frailty-separated ILD subgroups. Although these tests might be good indicators of the presence and progression of ILD diseases, [35,36] these clinical markers may be poor follow-up indicators for the detection of frailty in the ILD population.

Muscles function and composition

Results concerning hand grip (HG) tests remains conflicting in the literature. Even if some previous studies [37] [38] did not find significant weakness in HG testing (95-97% of predicted value) in patients with ILD in accordance to our results, at least two other studies presented reduced

muscle function in ILD patients. [39] [40]. Although the HG being part of the frailty assessment, the mild differences between the results of the frailty subgroups did not reach a significant statistical point. This suggest that the HG might not be an effective tool to discriminate frailty phenotypes in ILD patients. Additionnal data will be necessary before to conclude about this subject.

Lower limb function seems preserved in robust and prefrail patients and only appears to be affected in frail ILD patients. Some ILD, such as IPF, progress rapidly and had a worse prognosis. Since physical inactivity and secondary muscle composition alterations usually develop over time, this may contribute to explain the absence of significant differences in muscle function between the ILD and control groups.

Contrary to the extensive study of Maddocks et al. who reported lesser muscle CSA in COPD subjects while density and intramuscular fat showed insignificant differences, [41] our ILD participants exhibit similar macroscopic muscle CSA in comparison to the control group, but increased intramuscular fat infiltration (as portrayed by the lower attenuation which reflects the lower muscle fiber quality). This correlates with Guler et al study which show a higher fat mass in ILD individuals with more impaired pulmonary function. [48] These muscular composition alterations are particularly interesting considering there is a considerable overlap between frailty and muscle alterations [42] that our data seem to confirm in ILD frail patients. The loss of muscle function and mass as well as alteration of muscle composition occur with ageing[43] and in other respiratory chronic disease, such as COPD. [44] Mechanisms underlying alterations of lower limb muscle function and composition are complex and interrelated as addressed in a recent joint ERS/ATS statement in patients with chronic respiratory diseases. [44] Despite the fragmentary data from a very heterogeneous groups of patients and respectful to the fact that this study was not designed to address this question, muscular alterations in some patients could be consequence of

systemic disease such as connective tissue or inflammatory disease. [45] In addition, muscle alterations in frail ILD patients may result from the consequences of disease such as age, chronic hypoxaemia, inflammatory and oxidative stress, corticosteroid use, physical inactivity and malnutrition who may exert a synergistic, deleterious effect on muscle function. [7]

It is also interesting to observe that impairment of several markers of functional capacity (6MWT, percentage of predicted distance; 1STS, repetitions and 5TSTS, time) and patient-related impacts are present in pre-frail ILD patients. Although larger and adequately designed studies are needed to confirm this hypothesis our data suggest that the alteration of functional physical performance precede muscular alterations.

Dyspnea, depression and HRQoL questionnaires

As expected, ILD participants had a significantly higher level of dyspnea. Our results also showed a significantly higher prevalence of depression symptoms in ILD participants than the control group. If the cut-off of 16 points or greater was used to identify individuals at risk of clinical depression on CES-D questionnaire, 28 % of the ILD participants were identify at risk of clinical depression[37]. This is much higher than reported depression prevalence in the general population (3.8% to 12.6%) which highlights the multidisciplinary needs in evaluating ILD diseases. [46]

Finally, ILD participants had higher score on SGRQ in comparison to control healthy subjects. This result confirm that health-related quality of life is profoundly impaired in patients with ILD. Scores on SGRQ were comparable to previous studies in IPF and a comparable population. [47]

Methodological considerations and study limitation

This study raise some methodological considerations and limitations. The first concerns the sample size which was determined in order to compare ILD patients to healthy subjects. Interpretation between the subgroups of ILD patients according to their frailty status must be taken cautiously due to the limited number of patients in each group and should be validated by a larger and adequately powered study.

Regarding the recruitment of participants, the consecutive and randomly-selected patient recruitment strategy and classification according to their fraithy status used in the study ensures to have a reprensentative group of ILD's patients. It is thus reassuring that the group of patient is similar to previously published data both for their clinical and respiratory status and for their frailty status distribution. [48]

In addition, since the control participants were recruited via our research center data bank, we are aware of a possible social participation bias explaining the high performance of our control group for respiratory function and functional exercice capacity. However, in regard with the huge magnitude of the between-groups (ILD vs. healthy subjects) values, the authors are confident that the observed differences were only slightly altered by this potential bias and that the impairments described in the present study are well present in ILD patients when compared to healthy subjects of comparable age, sex and BMI.

Clinical Implications

Aside from a significant muscle dysfunction, the ILD population are less active and present a decreased exercise tolerance and functional status, a higher level of dyspnea, fatigue, anxiety and depressive symptoms, and a lower quality of life compared to control population, especially in patients with frail status. This is clinically relevant because all of these concern may be

addressed by pulmonary rehabilitation (PR) which includes exercise training and behavior change interventions. [49] The most recent review on the PR outcomes [50] puts emphasis on the potential benefits in improving the functional performance and quality of life (moderate certainty) and maximum exercise capacity, dyspnoea and long-term survival (low certainty) in ILD patients. In COPD patients, frail patients respond favorably to PR [17] and similar effect could be expected in population with ILD, although data are still missing for this population. [51] Because of the high reported prevalence of frailty in patients with ILD [51] [48], it is thus crucial to identify and understand the multidimensional concerns of these patients in order to individualise the intervention to suit their needs and priorities. [52]

Finally, from the novel perspective brought by our findings, the 1STS appear to be a good discrimination test to assess the frailty status in the ILD population. Regarding that last aspect, the number of repetitions cut-off to which the 1STS is predictive of a frail status would be an interesting topic for further studies.

CONCLUSION

Despite the relatively preserved muscle function and structure, ILD patients are less active, present a reduced exercise tolerance and functional capacity, higher level of dyspnea, fatigue, anxiety and depressive symptoms, and have a decreased health-related quality of life when compared to healthy subjects of comparable age and sex distribution. In patients with ILD, physical frailty seems associated with worse clinical status, exercise tolerance, muscle and functional impairment and decreased quality of life and leisure time physical activity. 1STS may be a good discriminatory test for frailty status in ILD patients.

Acknowledgements

Pierre-François Tremblay Labrecque was supported by l'Ordre professionnel de la physiothérapie du Québec (OPPQ) -Subvention de maitrise de recherche. The study was supported by Le Fonds sur les maladies respiratoires J.-D.-Bégin – P.-H.-Lavoie, Université Laval. The authors are thankful for the help of Mickaël Martin for his contribution to the Ct-scans analysis, Jany Harvey for her help in collecting the data, Marie-Ève Pouliot and the staff of the *Clinique des maladies interstitielles* of the *l'Institut universitaire de cardiologie et de pneumologie de Québec* for their clinical support and Serge Simard for his assistance with the statistical analysis.

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Tables and figures

Table 1 Characteristics of participants

	Controls (n=15)	ILD (n=36)	*P value*	ILD subgroups		
				Robusts (n=8)	Pre-frail (n=19)	Frails (n=9)
Mean age	69 ± 7	70 ± 7	0,69	67 ± 7 [a]	69 ± 8 [a]	74 ± 4 [a]
Males (%)	67	78	0,77	88	74	78
BMI	26 ± 4	28 ± 5	0,09	30 ± 5 [a]	29 ± 5 [a]	27 ± 7 [a]
Smoking history, pack-years	13 ± 15	24 ± 24	0,04	11 ± 10 [a]	25 ± 28 [ab]	35 ± 20 [b]
Pulmonary function						
FVC (L)	3,9 ± 0,5	2,5 ± 0,5	<0,0001	2,8 ± 0,6 [a]	2,5 ± 0,4 [a]	2,3 ± 0,3 [a]
FVC (%)	119 ± 17	70 ± 14	<0,0001	77 ± 15 [a]	67 ± 10 [a]	71 ± 18 [a]
D_{LCO} (%)	-	51 ± 20	-	61 ± 11 [a]	48 ± 18 [a]	49 ± 29 [a]
LTPA-Q (kcal/week)	1988 ± 849	877 ± 1044	0,002	1651 ± 1481[a]	877 ± 838[a]	188 ± 192[b]
Diagnosis distribution						
IIP						
IPF		17 (47)		3	10	4
NSIP		2 (6)		-	2	-
Unclassifiable		8 (22)		2	3	3
CTD-ILD		7 (19)		3	3	1
HP		1 (3)		-	1	-
Occupational exposure		1 (3)		-	-	1
Time after diagnosis, months		49 ± 38		60 ± 50 [a]	41 ± 28 [a]	53 ± 46 [a]
Medication						
Steroids		6		1	4	1
Anti-fibrotic agents		13		1	7	5
Immunosuppressants		7		1	5	1
Oxygen supplementation		1		0	0	1

Abbreviations : BMI: body mass index; FVC: forced vital capacity; CTD: connective-tissue disease; DLCO: Diffusing capacity for carbon monoxide; HP: hypersensitivity pneumonia; LTPA-Q: leisure time physical activity questionnaire; ILD: interstitial lung diseases; IIP: interstitial idiopathic pneumonias; IPF: idiopathic pulmonary fibrosis; NSIP: non-specific interstitial pneumonia;
CTD-ILD included: occupational exposure to Asbestos (n=1); rheumatoid arthritis (n=1); sclerodermia (n=2); undifferentiated (n=3)
Different superscript letters (a, b, c) indicate a statistically significant difference (p <0,05) in between subgroups of patients with ILD such as groups with the letter [a] are statistically similar but different from groups with the letter [b]
Percentages are indicated between parenthesis

Table 2 Exercise tolerance and functional capacity

	Controls (n=15)	ILD (n=36)	*P value*	ILD subgroups		
				Robusts (n=8)	Pre-frail (n=19)	Frails (n=9)
6MWT						
Distance (m)	615 ± 83	476 ± 94	<0,0001	570 ± 89[a]	477 ± 73[a]	389 ± 50[b]
Distance (% of predicted value)	124 ± 15	101 ± 18	<0,0001	118 ± 11[a]	100 ± 15[b]	87 ± 16[b]
End-test saturation (%)	95 ± 4	85 ± 6	<0,0001	86 ± 6[a]	85 ± 6[a]	85 ± 9[a]
1STS						
Repetitions	30 ± 7	21 ± 4	<0,0001	26 ± 2[a]	21 ± 3[b]	17 ± 3[c]
End-test saturation (%)	96 ± 2	89 ± 5	<0,0001	89 ± 5[a]	90 ± 5[a]	88 ± 4[a]
5TSTS time	9,9 ± 2,4	12,9 ± 3,3	0,0019	10,3 ± 1,6[a]	13,0 ± 2,6[b]	15,0 ± 4,3[b]
SPPB Total score	11,6 ± 0,7	10,5 ± 1,2	0,0007	11,4 ± 0,7[a]	10,5 ± 0,9[a]	9,7 ± 1,6[a]

Abbreviations : 6MWT: 6-minute walk test; 1STS: 1-minute sit-to-stand; SPPB: Short Physical Performance Battery; 5TSTS: 5 times sit-to-stand
Different superscript letters (a, b, c) indicate a statistically significant difference ($p < 0,05$) in between subgroups of patients with ILD such as groups with the letter [a] are statistically similar but different from groups with the letter [b]

Table 3 Muscle function and composition

	Controls (n=15)	ILD (n=36)	*P value*	ILD subgroups		
				Robusts (n=8)	Pre-frail (n=19)	Frails (n=9)
Hand grip (kg)	37 ± 12	34 ± 8	0,37	38 ± 7[a]	34 ± 9[a]	31 ± 8[a]
Quadriceps						
Peak torque (Nm)	107 ± 26	95 ± 27	0,10	111 ± 26[a]	100 ± 22[a]	70 ± 24[b]
MVC (Nm)	148 ± 45	141 ± 38	0,57	170 ± 37[a]	144 ± 32[a]	106 ± 21[b]
Endurance (J)	2424 ± 743	2212 ± 620	0,27	2631 ± 603[a]	2290 ± 502[a]	1620 ± 469[b]
Ct-Scan						
Mid-thigh Muscle CSA (cm^2)	245 ± 42	231 ± 50	0,33	271 ± 43[a]	232 ± 46[ab]	194 ± 35[b]
Skeletal Muscle Index	85 ± 12	79 ± 23	0,37	96 ± 15[a]	77 ± 26[ab]	70 ± 15[b]
Attenuation (mean HU)	44 ± 4	41 ± 5	0,01	42 ± 5[a]	42 ± 5[a]	39 ± 5[a]

Abbreviations : MVC: maximal voluntary contraction, CSA: cross-sectional area
Different superscript letters (a, b, c) indicate a statistically significant difference ($p < 0,05$) in between subgroups of patients with ILD such as groups with the letter [a] are statistically similar but different from groups with the letter [b] or [c]

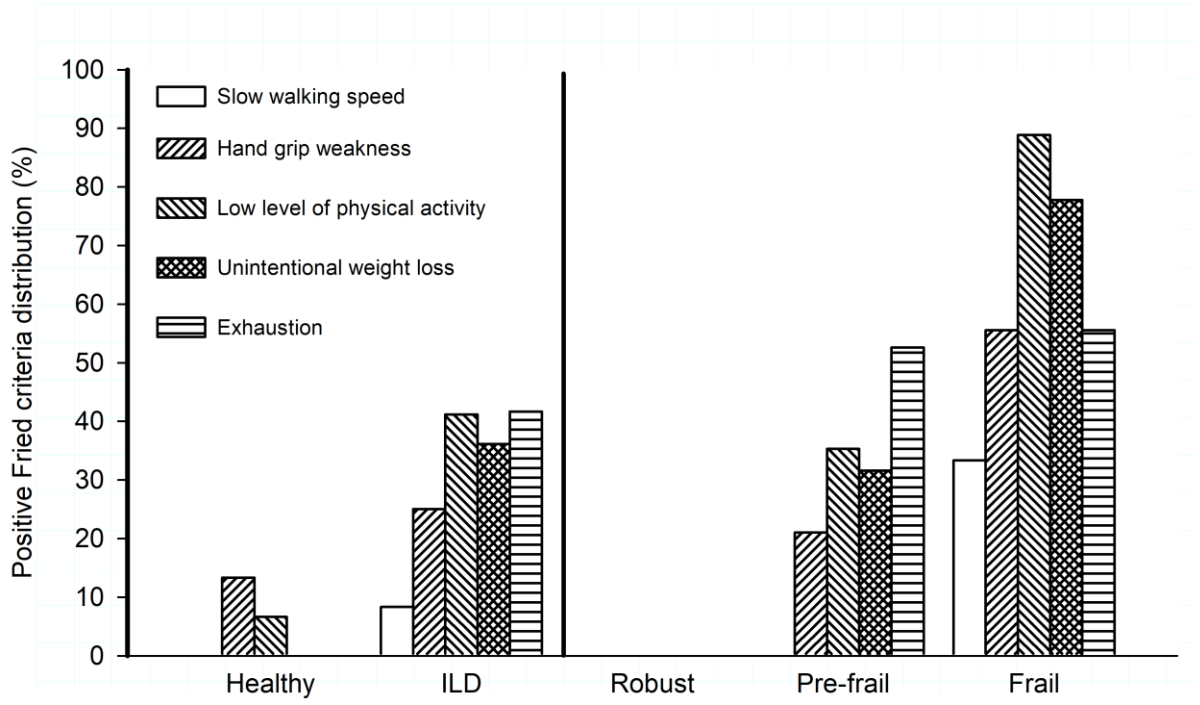
Table 4 Dyspnea, depression and health-related quality of life questionnaires

	Controls (n=15)	ILD (n=36)	*P value*	ILD subgroups		
				Robusts (n=8)	Pre-frails (n=19)	Frails (n=9)
UCSD	8 ± 8	42 ± 24	<0,0001	16 ± 7 [a]	46 ± 23 [b]	56 ± 17 [b]
CES-D	3 ± 5	10 ± 9	0,003	4 ± 5 [a]	12 ± 10 [b]	12 ± 7 [ab]
SGRQ						
Total	4 ± 7	46 ± 18	<0,0001	32 ± 14 [a]	47 ± 18 [a]	57 ± 14 [b]
Symptoms	12 ± 20	56 ± 24	<0,0001	47 ± 16 [a]	54 ± 27 [a]	69 ± 21 [a]
Activities	7 ± 10	75 ± 22	<0,0001	49 ± 19 [a]	80 ± 17 [b]	88 ± 14 [b]
Impact	2 ± 6	48 ± 26	<0,0001	32 ± 19 [a]	47 ± 27 [ab]	62 ± 21 [b]

Abbreviations : USCD: The University of California San Diego Shortness of Breath Questionnaire; CES-D: The Center for Epidemiological Studies-Depression; SGRQ: St. George's Respiratory Questionnaire

Different superscript letters (a, b, c) indicate a statistically significant difference (p <0,05) in between subgroups of patients with ILD such as groups with the letter [a] are statistically similar but different from groups with the letter [b]

Figure 1


Positive Fried criteria distribution (%)
100
90
80
70
60
50
40
30
20
10
0
Slow walking speed
Hand grip weakness
Low level of physical activity
Unintentional weight loss
Exhaustion
Healthy
ILD
Robust
Pre-frail
Frail

Functional Clinical Impairments and Frailty in Interstitial Lung Diseases Patients

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ONLINE SUPPLEMENTARY MATERIAL 1

DETAILED PROCEDURES

Study design and participants

36 consecutive patients with a diagnosis of fibrosing ILD were recruited from an outpatient ILD referral center at the *Institut universitaire de cardiologie et de pneumologie de Québec*, Université Laval (Québec, Canada) from May 2018 to March 2021. Participants of the ILD group were recruited according to their frailty status, to represent the frailty distribution of the clinic (data awaiting publication). The ILD participants were matched with 15 healthy controls of similar age and sex. Participants of both groups were excluded if they had a history of syncope, significant cardiac disease or incapacitating musculoskeletal, neurological, or rheumatological conditions. ILD participants with any other significant respiratory disease (i.e. chronic obstructive pulmonary diseases (COPD)), a diagnosis of sarcoidosis, a hospitalization for acute exacerbation of ILD within the last 3 months, and having participated in a pulmonary rehabilitation program in the past 6 months were also excluded. The study was approved by the

local ethic committee board (N 2018-3010, 21595) and all participants signed a consent form before the initiation of study procedures.

Procedures

The protocol consisted of two visits. At the first visit, age, sex, ILD diagnosis (according to the ATS/ERS classification) and age at diagnosis were collected from the medical records. Anthropometric data was then collected using a stadiometer for the height weight from which the BMI was calculated. Pulmonary function tests were also performed and after a familiarization to the procedures, participants executed the Short Physical Performance Battery (SPPB) and the 1STS. On the second visit, participants completed the remaining tests: 6MWT (2 trials), the hand grip and quadriceps muscle function tests. A rest period of a minimum of 15 minutes was provided between each test to allow for both the cardiorespiratory parameters and dyspnea perception to return to baseline values. Questionnaires were administered randomly throughout the course of the two sessions and a mid-thigh computed tomodensitometry (CT scan) of the thigh was performed at the beginning of the second visit.

Pulmonary function

Pulmonary function including spirometric testing, plethysmography and measurement of the diffusing capacity for carbon monoxide (DL_{CO}) was conducted in accordance with the ATS/ERS guidelines [1] for the ILD subjects. Data were reported as % of predicted values using ERS Global Lung Function Initiative reference equations. [2] For participants who had realized those tests as part of their required medical follow-up in the last 3 months, the pulmonary function tests were not repeated and the result of their recent exam were used instead. Participants of the control group performed only the spirometry to rule-out any abnormalities suggestive of lung disease.

Physical Frailty

Physical frailty was defined using the Fried phenotype model, [3] [4] including five criteria: unintentional weight loss, exhaustion, low level of physical activity, slow walking speed and weakness. The unintentional body mass loss history ≥4.5 kg was assessed by answering "yes" to the question: "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" Self-reported exhaustion was assessed by asking to participants two questions of the Center for Epidemiologic Studies Depression Scale (CES-D) [39] : In the las week: (a) I felt that everything I did was an effort; (b) I could not get going. Criteria for exhaustion was met if the participant answer that he felt one of this way for 3 or more days in the last week. Low physical activity criteria was reached if the reported physical activity level was <383 Kcals for men or <270 Kcals for women base on the short version of the Minnesota Leisure-Time Physical Activity Questionnaire (LTPA-Q). The LTPA-Q consisted of a list of 26 activities to which the patient recalled its participation during the past year. Each activity was associated with an intensity score. The total score (Kcal/week of expenditure) was used to determine the frailty positive criteria score related to physical activity. [3] Slow walking speed and weakness were assessed by the 4-meter gait speed test (4MGS; slow walk) and handgrip dynamometry (weakness), respectively and positive criteria were determined via previously published cutoffs stratified by gender and height. [3] Participants who fulfilled none of the criteria were considered robust, participants who fulfilled 1 or 2 criteria were classified as pre-frail, and participants who fulfilled ≥3 criteria were classified as frail.

Exercise tolerance

Exercise tolerance was assessed with the 6MWT and the 1STS tests.

6-minute walk test (6MWT). The 6MWT was performed according to the official ATS/ERS technical standard field walking tests in chronic respiratory diseases.[5] The prediction values were used from the equations of Enright et al. [6] The test was performed indoor, along a flat, straight, 30-meter long corridor with two cones placed 0.5 meters from the extremities to mark the turning points in the course. Participants were systematically instructed to walk the longest distance possible back and forth, around the cones in 6 minutes. The best result of two separate trials was kept for analysis.

1-minute sit-to-stand. The 1STS tests were completed according to the protocol described by Ozalevli et al.[7] and supervised by trained research staff. A standardized 48 cm chair without armrest was used and positioned against a wall. The participant was positioned with their knees at a 90° angle, both feet on the floor and arms crossed around the chest and was instructed to stand-up completely and to sit back down as many times possible within one minute, without using their hands. The pace of the test was determined by the participant. It was not mandatory to fully sit back on the chair, but the back had to reach vertical. Participants were informed of the time when 15 seconds were left but no encouragement was provided during the test. The number of fully completed repetitions within the minute was used for analysis.

Functional mobility

Short performance physical battery test (SPPB). Functional mobility was assessed with the SPPB performed according to the National Institute on Aging protocol. [8] The SPPB test consist of the sum of three separate functional components. 1. Fastest time to complete 5 times sit-to-

stand (5TSTS): rising from a chair with their arms across their chest for 5 repetitions. The test environment is the same as the one previously described in the 1STS section. 2. 10-sec static standing balance tests requiring participants to maintain each of three stances for 10 seconds with feet in three positions (feet placed side-by-side, semi-tandem, and in tandem). 3. 4-meter walk test performed at usual speed. [9] Each component is scored on 4 for a total of 12 points ranging from 0 (functional impairment) to 12 (maximal functional mobility).[10] Functional limitation was defined at a cutoff of ≤ 9 such as described in a previous study. [11]

Muscle composition and function

Muscle function was tested for both the upper and lower limbs via the hand grip strength and quadriceps muscle testing, respectively. The muscle composition was obtained using the computed tomography scans.

Hand grip strength. Hand grip strength was tested using The Jamar® hydraulic hand dynamometer (J. A. Preston Corporation,Clifton, NJ) protocol [12] which requires the participant to be seated, elbow flexed at 90º, wrist between 0º and 30º and between 0º and 15º of ulnar deviation. The participant was then instructed and verbally reinforced to squeeze the dynamometer at his maximal strength. 3 trials separated of 15 seconds were performed for each hand. The best of two reproducible trials was used for analysis.

Quadriceps muscle function. Quadriceps strength, power and endurance were measured with a computerised dynamometer (Biodex System 4 Biodex Medical Systems, Shirley, New York, NY, USA) using test procedures that have been described in detail elsewhere [13].

Quadriceps strength was measured during a maximal voluntary contraction (MVC) using an isometric (static) protocol at a 90° knee angle [13], performed in line with international

recommendations [14]and reported in Newton-meters (Nm).

Quadriceps power, and endurance were obtained during a 30 maximal isokinetic contractions protocol of 30 maximal knee extensions throughout the full range of movement at 90° per second, with passive knee flexion in which the total work (J) and peak torque (Nm) were considered such as endurance and power respectively.

Muscle composition.

The mid-thigh muscle surface and attenuation data was obtained using non-contrast computed tomography scans (CT scan) at the mid femur level. The scan parameters were a voltage of 140 kilovolts (kV) measured according to the weight of the subject, an acquisition load (number of X-rays) fixed to 200 milliampere-seconds (mAs) and a five millimeters slice thickness (mm). All images were assessed using specialized image analysis software (Slice-O-Matic, Tomovision, Montréal, Québec, Canada) and according to standardized techniques. [15] Muscle tissue areas (cm2) were computed using an attenuation range of -29 to 150 HU, such as recommended. [16] Since skeletal muscle with relatively lower attenuation contain proportionally more adipose tissue [17], muscle tissue corresponding to attenuation range of -29 to 34 HU was considerate as low attenuation muscle and muscle tissue between 35 and 150 HU as normal attenuation muscle. Skeletal muscle index (SMI) was obtained after CSA indexation for height (CSA/height^2). [18]

Questionnaires

Three self-administered questionnaires were used to assess the patient-reported impacts associated with ILD. The St-George's Respiratory Questionnaire (SGRQ) contains 76 items separated in three sections: Symptoms (SGRQ-S), Activities (SGRQ-A) and Impacts (SGRQ-I)

which are summarized into a total score. [19] Even though the SGRQ was originally developed for COPD [20], its psychometric properties were also addressed in several IPF studies which concluded to its adequacy in measuring health-related quality of life. [21] [22] The University of California San Diego Shortness of Breath questionnaire (UCSD) contain 21 various activities which the participant rates his dyspnea from 0 ("Not at all") to 5 ("Maximally or unable to do because of breathlessness") and 3 items regarding the perceived impact of the breathlessness. [23] Similar studies concluded to its validity to adequately assess dyspnea in both IPF [23] and heterogeneous groups of fibrotic ILD patients [24]. The CES-D scale is a 20-item questionnaire which aims to screen depression symptomatology. [25] This last questionnaire was completed in its entire form both as part of the HRQoL assessment and the frailty status determination process described below.

Statistical analysis and sample size determination

Based on the study of Corrêa et al. [26] who described the differences in multiple functional exercise tests between chronic obstructive pulmonary disease and a control group, we calculated that 15 participants in the control and the pooled ILD group with a power of 80% with an alpha of $\alpha < 0.05$ would be sufficient.

Continuous variables were analyzed using one-way ANOVA. Differences between ILD and control groups and frailty divided subgroups analysis. A mixed statistical model following the means procedure permitted to compare both the ILD vs. control groups and the frailty divided subgroups using the same model. The Satterthwaite's degree of freedom statement was added for variables analyzed using unequal variance structures. Posteriori comparisons were performed using the Tukey's technique.

Receiver operating characteristics (ROC) curves were created to analyze the sensitivity,

specificity, area under the curve (AUC) and the positive and negative likelihood ratio (LR) of SPPB cutoff points to detect physical frailty. The odds ratios of various cutoff points of these tests to predict physical frailty were also calculated along with their respective confidence intervals.

Variables were expressed as mean ± standard deviation and results were considered significant at $p < 0.05$. Statistical analyses were performed using the SAS version 9.4 (SAS Institute Inc, Cary, NC).

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