Original Paper

Chronic Respiratory Disease

Chronic Respiratory Disease
Volume 21: 1–11

DOI: 10.1177/14799731241240786
journals.sagepub.com/home/crd

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Clinical implications of frailty assessed in hospitalized patients with acute-exacerbation of interstitial lung disease

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Abstract

Background: Approximately 50% of patients with interstitial lung disease (ILD) experience frailty, which remains unexplored in acute exacerbations of ILD (AE-ILD). A better understanding may help with prognostication and resource planning. We evaluated the association of frailty with clinical characteristics, physical function, hospital outcomes, and post-AE-ILD recovery.

Methods: Retrospective cohort study of AE-ILD patients (01/2015–10/2019) with frailty (proportion ≥0.25) on a 30-item cumulative-deficits index. Frail and non-frail patients were compared for pre- and post-hospitalization clinical characteristics, adjusted for age, sex, and ILD diagnosis. One-year mortality, considering transplantation as a competing risk, was analysed adjusting for age, frailty, and Charlson Comorbidity Index (CCI).

Results: 89 AE-ILD patients were admitted (median: 67 years, 63% idiopathic pulmonary fibrosis). 31 were frail, which was associated with older age, greater CCI, lower 6-min walk distance, and decreased independence pre-hospitalization. Frail patients had more major complications (32% vs 10%, p = .01) and required more multidisciplinary support during hospitalization. Frailty was not associated with 1-year mortality (HR: 0.97, 95%CI: [0.45–2.10]) factoring transplantation as a competing risk.

Conclusions: Frailty was associated with reduced exercise capacity, increased comorbidities and hospital complications. Identifying frailty may highlight those requiring additional multidisciplinary support, but further study is needed to explore whether frailty is modifiable with AE-ILD.

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Keywords
Interstitial lung diseases, frailty, hospitalization, prevalence, symptom of acute exacerbations

Date received: 14 November 2023; revised: 8 February 2024; accepted: 14 February 2024

Introduction

Interstitial lung diseases (ILD) are a group of heterogeneous disorders with progressive fibrosis and associated functional decline.[1] Acute exacerbations of ILD (AE-ILD) occur annually in 3%–14% of ILD patients and are associated with high morbidity and mortality, with in-hospital mortality ranging between 20 and 50% dependent on the ILD diagnosis.[2–4] Identifying contributing risk factors for AE-ILD is crucial for prognostication, facilitating resource utilization, transplant candidacy evaluation, and optimizing functional recovery.[5]

Frailty, a syndrome marked by reduced physiological reserve and heightened vulnerability to stressors,[6] may serve as a prognostic marker in AE-ILD.[7] Frailty is associated with greater risks in chronic lung diseases, specifically hospitalization and mortality.[8,9] Frailty is common in ILD patients[10] with over 50% of those with fibrotic ILD affected.[11,12] It is independently associated with several respiratory disease-related risk factors including older age, increased co-morbidities and hypoxemia.[13,14] Moreover, frailty has been associated with increased dyspnea,[11,12] hospitalizations and mortality rates, and diminished quality of life and transplant-free survival in patients with chronic respiratory diseases.[10,15] Frail patients with ILD also tend to experience more respiratory exacerbations.[16]

The extent of frailty and its clinical effects in patients with AE-ILD have not been well characterized. Hypoxia, inactivity, and use of high dose corticosteroids during AE-ILD may induce or worsen frailty.[17,18] Establishment of frailty on admission to the hospital may facilitate resource allocation of multidisciplinary support services and help guide discussions among the healthcare team, patients, and caregivers related to prognosis.[10]

Given the critical importance of prognostication and discharge planning post AE-ILD, this study aimed to diagnose frailty on admission to:

(1) Compare pre-admission characteristics of frail and non-frail AE-ILD patients including type of ILD, physical function, and comorbidities.
(2) Characterize the hospital course among frail and non-frail patients admitted with an AE-ILD.
(3) Evaluate the association of frailty with post-discharge clinical outcomes.

We hypothesized: (1) frailty will be associated with lower pre-admission exercise capacity, more comorbidities, and higher ILD-GAP (gender-age-physiology index) and (2) frail AE-ILD patients will have a longer hospital stay, greater readmission risk, and lower 1-year survival than non-frail AE-ILD patients.

Methods

Study design

This retrospective, single-center cohort study included consecutive adult ILD patients admitted to Toronto General Hospital between January 1, 2015, and August 20, 2019, with an AE-ILD. The criteria for an AE-ILD were based on the established criteria for acute exacerbations of idiopathic pulmonary fibrosis (IPF) outlined by the International Working Group Consensus and extrapolated to encompass patients with non-IPF diagnosis.[2] The follow-up period for the cohort was until October 15, 2019. Patients admitted specifically for lung transplant assessment or those transferred from another facility were excluded. The study was approved by the University Health Network Research Ethics Board (REB # 19-5146). This ILD cohort, utilized in a prior study, informed on feasibility of the standardized management protocol of AE-ILD at our center, explored the transplant-free survival in IPF and non-IPF patients and identified patient characteristics related to radiological improvements post AE-ILD treatment, with limited characterization of the hospital course.[19]

Frailty definition

Frailty was evaluated on hospital admission via a 30-point cumulative deficits index. Frailty was characterized by a score of ≥0.25 (*proportion of positive deficits/total deficits*).[20] Our index was comprised of 30 items, including 19 comorbidity parameters, four laboratory and seven functional assessments, as described in supplemental Table S1.[14,21] Established procedures were used to develop the frailty index for the AE-ILD cohort. Specifically, we included health related deficits in diverse physiologic systems (i.e., cardiac, metabolic, hematologic, etc.) and a data saturation of 80% for each deficit was required in order to be incorporated into the frailty index.[22]

Data collection

Demographic data, comorbidities, and ILD diagnosis specifications were collected from chart review. Complete

medication histories pre-admission, including antifibrotics (pirfenidone or nintedanib), corticosteroids and other immunosuppressive medications were abstracted. Pulmonary function, Medical Research Council (MRC) dyspnea scale scores, six-minute walk distance (6MWD), and resting oxygen requirements within 1-year prior to AE-ILD hospitalization were ascertained. ILD severity was characterized using the ILD gender-age-physiology (ILD-GAP) index[23] and comorbidities assessed using the Charlson Comorbidity Index (CCI).[24] The timing of lung transplant assessment, listing, and transplantation were abstracted from charts.

Hospital outcomes included length of stay, medical complications, consultations with healthcare services, discharge disposition (i.e., home, inpatient rehabilitation, or palliative care unit), and hospital mortality. Medications (i.e., corticosteroids, antibiotics, opioids) prescribed during hospitalization, oxygen requirements on admission and discharge were recorded. Medical complications were categorized into major events with significant impact on morbidity (e.g., respiratory, and cardiovascular events, delirium, intensive care unit admission, acute kidney injury), and minor events associated with a lower morbidity burden (e.g., electrolyte imbalance, hyperglycemia, decubitus ulcers).[25–27]

Post-hospital discharge, 6MWD and pulmonary function tests (forced vital capacity, diffusion capacity) were recorded closest to date of hospital discharge and performed in a pulmonary function lab. as per American Thoracic Society Standards.[28,29] Re-exacerbations captured at our facility, days between discharge and hospital readmissions, and 1-year all-cause mortality were ascertained. Lung transplant status (assessment, listing and transplant date) were recorded.

Statistical analysis

Data distribution was verified using the Shapiro-Wilk test. Continuous data is presented as median with interquartile range and categorical data as proportions with percentages. Comparisons between frail and non-frail patients were performed with Mann-Whitney-U test for continuous data and Chi-square test for categorical data. The association between frailty and hospital outcomes was evaluated using logistic regression models adjusting for age, sex, and diagnosis (IPF vs non-IPF).[30] The effect of frailty on 1-year survival post AE-ILD was assessed with Kaplan-Meier survival analysis. Multivariable Cox regression models evaluated the association of frailty with 1-year mortality, adjusted for a priori-identified confounders: age,[23,31] sex,[23] ILD type (IPF vs non-IPF),[23] CCI,[32] forced vital capacity[33] and lung transplant listing prior to hospitalization. Regression model diagnostics tested for assumptions of independence (variation inflation factor >3 for collinearity), normality and constant error variation. We conducted a competing risk regression analysis (Fine-Gray model) to estimate standardized hazard ratios for mortality, considering lung transplantation as a competing risk, using significant factors ($p < .05$) from the Cox regression models. Analyses were performed with R-software (version 4.2.2) with statistical significance defined as $p < .05$ (See supplemental table S2 for the details on the used R-packages).

Results

Patient characteristics

89 patients were hospitalized with AE-ILD with a median age of 67 years (IQR: 62; 71), 61% male and median BMI of 27.1 kg/m^2 (IQR: 23.6; 30.4). 31 (35%) patients were deemed frail (Supplemental Figure S1). Frail AE-ILD patients, compared to non-frail, were older, more likely to have a non-IPF diagnosis, higher CCI, had more often corticosteroids or immunosuppression prescribed, shorter 6-MWD and greater dependence on activities of daily living prior to hospitalization, as shown in Table 1. No difference was observed in oxygen supplementation prior to hospitalization, on admission or discharge (Figure 1).

There was a higher proportion of frail ILD patients with connective tissue disease (CTD) compared to those deemed non-frail (26% compared to 10%, $p = .06$). With comparison of CTD-ILD and non-CTD-ILD patients, the frailty scores were similar ($p = .47$) with a trend towards increased frail patients compared to non-frail in the CTD-ILD group (57% compared to 31%, $p = .06$, Supplemental table S3).

Hospital related clinical outcomes

Hospital length of stay was not different between frail (10 days IQR [8; 13]) and non-frail patients (8 days [7; 11], $p = .14$, Table 2). Frail patients had a greater number of major medical complications (OR: 5.73 [1.56 – 24.45], $p = .01$) and hospital length of stay was longer in patients experiencing major complications (13 days [8; 19]) compared to patients experiencing minor complications (9 days [6; 11], $p = .048$) or no complications (8 days [7; 12], $p = .005$).

Occupational therapy and palliative care were more commonly consulted for frail AE-ILD patients (Table 2), with increased prescription of opioids for management of cough or dyspnea. Of all AE-ILD patients, 74% were discharged home, 4% to a rehabilitation center or palliative care unit, and 22% died in hospital. Most patients died from

Table 1. Characteristics of patients admitted to hospital with acute exacerbations of interstitial lung disease.

	Total (n = 89)	Frail (n = 31)	Non-frail (n = 58)	p-value
Age, y	67 (62; 71)	71 (66; 76)	65 (60; 69)	**<0.01**
Sex, males, n (%)	54 (61)	17 (55)	37 (64)	0.41
Body mass index, kg/m^2 (n = 30; 57)	27.1 (23.6; 30.4)	27.6 (25.2; 31.1)	26.7 (21.6; 28.7)	**0.02**
Interstitial lung disease diagnosis, n (%)				**0.01**
Idiopathic pulmonary fibrosis	56 (63)	14 (45)	42 (72)	
Non- idiopathic pulmonary fibrosis	33 (37)	17 (55)	16 (28)	
Hypersensitivity pneumonitis	8 (9)	3 (10)	5 (9)	
Connective tissue disease	14 (16)	8 (26)	6 (10)	
Drug-induced	3 (3)	3 (10)	0 (0)	
Non-specific interstitial pneumonia	6 (7)	2 (6)	4 (7)	
Other	2 (2)	1 (3)	1 (2)	
Comorbidities, CCI	3 (2; 5)	5 (4; 6)	3 (2; 4)	**<0.01**
ILD-GAP (n = 28; 50)	5 (3; 6)	4 (3; 5)	5 (3; 6)	0.45
MRC dyspnea, n (%)				0.53
1	7 (8)	2 (7)	5 (9)	
2	13 (15)	6 (19)	7 (12)	
3	29 (33)	9 (29)	20 (34)	
4	13 (15)	6 (19)	7 (12)	
5	8 (9)	4 (13)	4 (7)	
Not reported	19 (21)	4 (13)	15 (26)	
Prior to hospitalization				
Medication history, n (%)				
Anti-fibrotic	26 (29)	7 (23)	19 (33)	0.31
Corticosteroids or other immunosuppression medications	36 (40)	18 (58)	18 (31)	**0.01**
Pulmonary function, % pred.				
Forced vital capacity (n = 28; 51)	51 (42; 66)	56 (45; 66)	50 (41; 65)	0.33
Diffusion capacity (n = 19; 38)	47 (41; 55)	49 (41; 55)	46 (41; 55)	0.66
Days between PFT and admission	83 (53; 124)	92 (56; 122)	78 (52; 126)	0.74
Oxygen supplementation, n (%)	57 (64)	17 (55)	40 (69)	0.19
6-min walk distance, m (n = 23; 33)	360 (278; 478)	291 (212; 375)	396 (335; 492)	**<0.01**
6-min walk distance, % pred. (n = 23; 33)	79.7 (59.4; 97.4)	61 (51; 87)	86 (74; 101)	**0.04**
Days between 6-min walk distance and admission	119 (72; 196)	121 (83; 196)	117 (65; 192)	0.60
Independent for ADL, n (%)	43 (48)	8 (26)	35 (60)	**0.01**
Homecare prior to admission, n (%)	8 (9)	4 (13)	4 (7)	0.35

Data are expressed as median (IQR) or frequency (percentage). In case data was missing for some patients, the sample size for each specific parameter is provided next to each variable as (n = Frail; Non-frail). Statistical signifcant p-values ($p < 0.05$) are marked in bold.
Abbreviations: ADL: Activities of Daily Living, CCI: Charlson Comorbidity Index, ILD-GAP: Gender-Age-Physiology Index, MRC Medical research council, PFT: pulmonary function testing.

hypoxic respiratory failure, except for one who experienced hemorrhagic shock due to hematuria of unclear etiology. Hospital mortality was 26% for frail and 19% for non-frail patients with no difference after adjusting for age, sex, and ILD diagnosis (OR: 2.07 [0.62 – 7.04], p = .23).

Post-discharge clinical outcomes

Table 3 provides the clinical outcomes post-hospital discharge after AE-ILD. Re-exacerbations were similar between frail (22%) and non-frail (28%, p = .60) patients over 1-year. Fewer frail patients (26%) were transplanted 1-year following hospital discharge compared to non-frail patients (55%, p = .02). Similar proportions of frail and non-frail patients were listed for transplantation before and during hospitalization (23% vs 31%, p = .40, Supplemental Figure S2). Patients with IPF were more frequently transplanted (n = 23, 41%) compared to patients with non-IPF (n = 6, 18%, p = .03).

One-year crude all-cause mortality post AE-ILD was higher for frail patients (46%) compared to non-frail patients (33%, p = .03, Table 3 and Figure 2(A)). Frailty was associated with increased 1-year mortality in both univariate and multivariate models (Table 4). When

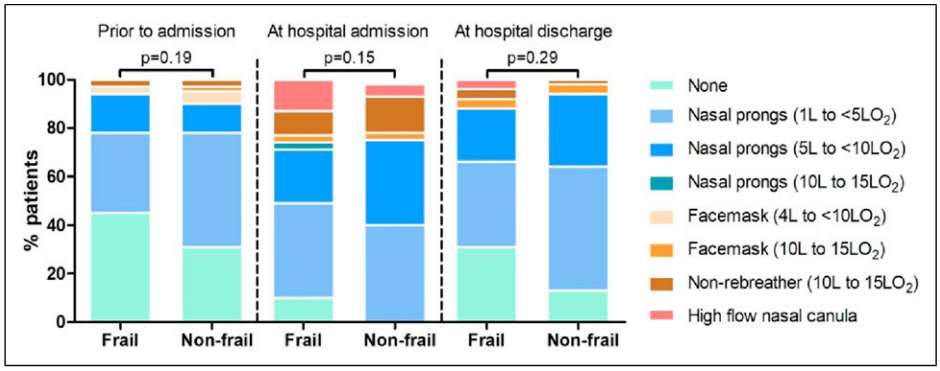

Figure 1. Oxygen supplementation at rest: Oxygen supplementation was ascertained prior to admission with a median of 83 days (IQR: 53; 124) before admission. Oxygen supplementation not reported for one patient in non-frail group as required mechanical ventilation shortly after hospital admission.

Table 2. Clinical outcomes during hospitalization.

	Frail (n = 31)	Non-frail (n = 58)	p-value	Adjusted OR[a] Frail vs non-frail (95%CI)	p-value
Medical complications[b], n (%)	18 (58)	16 (28)	0.01	3.30 (1.21 – 9.36)	**0.02**
Major complications	10 (32)	6 (10)	0.01	5.73 (1.56 – 24.45)	**0.01**
Minor complications	8 (26)	10 (17)	0.34	1.18 (0.36 – 3.72)	0.78
Multi-disciplinary consultations					
Physiotherapy consultation	18 (58)	33 (57)	0.92	1.03 (0.39 – 2.77)	0.95
Occupational therapy consultation	12 (39)	10 (17)	0.03	2.85 (0.96 – 8.80)	0.06
Palliative care	16 (52)	17 (29)	0.04	3.23 (1.16 – 9.63)	**0.03**
Medical consultations[c], n (%)	12 (39)	14 (24)	0.15	2.42 (0.84 – 7.22)	0.11
New medications prescribed:					
Opioids	16 (52)	16 (28)	0.02	3.48 (1.25 – 10.45)	**0.02**
Corticosteroids	30 (97)	58 (100)	0.17	NA[d]	
Antibiotics	24 (77)	48 (83)	0.54	0.66 (0.30 – 2.22)	0.50
Hospital length of stay, days	10 (8; 13)	8 (7; 11)	0.14	Median regression: 0.01 (−0.001 to 0.04)[e]	0.15
Disposition, n (%)					
Home	20 (65)	46 (79)			
Rehabilitation center	1 (3)	1 (2)			
Palliative care unit	2 (6)	0 (0)			
Died during hospital stay	8 (26)	11 (19)	0.56[f]	2.07 (0.62 – 7.04)[f]	0.23[f]

Data are expressed as median (IQR), frequency (percentage total group), odds ratios (OR) or median regression with 95% confidence interval (95%CI). Statistical signifcant p-values ($p < 0.05$) are marked in bold.
Minor complications: Electrolyte imbalance, hyperglycemia, decubitus ulcer or bacteremia were considered minor complications.
Abbreviations: OR: odds ratio.
[a]Odds ratio for frailty adjusted for age, sex, and diagnosis (idiopathic pulmonary fibrosis vs non-idiopathic pulmonary fibrosis).
[b]Major complications were delirium, respiratory complications, cardiovascular events, ICU transfer or kidney failure.
[c]Medical consultations include cardiology, rheumatology, infectious diseases, psychiatry, urology, neurology, gastrointestinal, intensive care, nephrology, pain clinic, plastic surgery, and dermatology.
[d]Calculating an odds ratio is not feasible when one of the two groups exhibits either a complete absence of events (0%) or a sole incidence of events (100%).
[e]Data represents median regression analyses adjusted for age, sex, and diagnosis (idiopathic pulmonary fibrosis vs non-idiopathic pulmonary fibrosis) with coefficient and 95%CI.
[f]p-value and odds ratio represent discharged patients versus those that died during hospital stay.

lung transplantation within 1-year of AE-ILD was evaluated as an outcome (Figure 2(B)), frailty, age, CCI, and pre-hospitalization transplant listing were important co-variates, whereas transplant listing was the only significant covariate in the multivariate model (Table 4). As a competing risk model of transplantation on all-cause mortality, frailty was not associated with 1-year mortality (HR: 0.97, 95%CI [0.45 – 2.10]), whereas CCI (HR: 1.32, 95%CI [1.05 – 1.65]) was the only independent measure of increased 1-year mortality risk (supplemental Table S4).

Table 3. Post-hospital discharge.

	Frail (n = 23)	Non-frail (n = 47)	p-value
Pulmonary function[a], %pred.			
Forced vital capacity (n = 15; 35)	51 (43; 67)	54 (38; 58)	0.27
Diffusion capacity (n = 8; 12)	46 (41; 56)	46 (43; 52)	0.91
Days between discharge and PFT	77 (40; 102)	36 (18; 87)	0.13
Change in pulmonary function[a], %			
Δ forced vital capacity (n = 15; 30)	−7 (−16; 4)	−3 (−7; 4)	0.48
Lung transplantation[a], n (%)	6 (26)	26 (55)	**0.02**
Days between discharge and LTx	50 (30; 263)	82 (32; 130)	0.85
Re-exacerbation[a], n (%)	5 (22)	13 (28)	0.60
Days between discharge and re-exacerbation	70 (48; 253)	61 (30; 210)	0.38
One-year mortality post hospital discharge, n (%)[b]	9 (43)	8 (19)	**0.04**

Data are expressed as median (IQR), frequency (percentage total group) or odds ratios (OR) with 95% confidence interval (95%CI). Patients who died during hospitalization (frail: n = 8, non-frail: n = 11) were excluded. In case data was missing, the sample size for each specific variable was provided next to each variable as (n = Frail; Non-frail). Statistical signifcant p-values ($p < 0.05$) are marked in bold.

Abbreviations: LTx: Lung transplantation, PFT: pulmonary function test.

[a]Data were collected within the year following discharge from hospital. In patients receiving a lung transplantation post-discharge, pulmonary function parameters were collected prior to transplantation. Change in pulmonary function was calculated as: pulmonary function within 1-year post discharge – pulmonary function prior to AE-ILD hospitalization. One patient was censored for lung transplantation 1-year following discharge.

[b]2 patients in each group were censored for 1-year mortality.

Discussion

Main findings

Frailty, as assessed by our 30-item frailty index, was observed in one-third of patients admitted with an AE-ILD. Frailty was more common in those with a diagnosis of non-IPF, patients with more comorbidities, daily corticosteroid or immunosuppression use, and lower exercise capacity. Frail AE-ILD patients were more likely to experience major complications and higher utilization of healthcare services during hospitalization. Frailty was not associated with 1-year mortality when factoring lung transplantation as a competing risk.

Frailty in AE-ILD patients

The frailty prevalence of 35% in our cohort was lower than in previous studies where 50 to 55% was observed in patients with fibrotic and connective tissue disease associated ILD.[11,12,15] The lower prevalence may be due to the high proportion (about one-third) being listed for lung transplantation upon hospital admission, which may have accounted for fewer comorbidities in our ILD study population.[34] Moreover, admission and follow-up at a lung-transplant center, along with younger age and higher socioeconomic status have been shown to be associated with lung transplantation in IPF.[35] Given that our cohort was admitted to a transplant center, it is conceivable that patient characteristics, including frailty, may differ from those with AE-ILD admitted to non-transplant centers. In addition, although the study encompassed ILD patients with connective tissue disease, which contributes to the 30-item frailty score, this subgroup's inclusion did not significantly alter the overall frailty score or patients' classification as frail. While the previous studies utilized a 42-item index, we used 30 items which incorporated lab. parameters such as hemoglobin and electrolyte abnormalities.[11,12,15] Integrating lab-derived parameters in the index enhances the patient's overall health assessment and clinical utility in the inpatient setting.[36] Our approach aligned with another study that applied a 32-item cumulative frailty index and had a frailty prevalence of 37% pre-transplant.[37] Thus, frailty is prevalent in ILD patients and will vary depending on patient setting, disease severity, and total number and type of deficits incorporated into the frailty index.

Hospital care and resources

Frail AE-ILD patients were more likely to have major complications during hospitalization, irrespective of age, sex and type of ILD. Consistent with findings in frail populations, such as critically-ill patients,[38] hospitalized geriatric populations[39] and patients with pneumonia,[40] our study reinforces the pattern of increased healthcare use and extended hospitalization in the frail population.[41] Specifically, frail AE-ILD patients were more likely to require occupational therapy and palliative care consultations with a threefold likelihood to be referred for palliative care independent of age, sex and diagnosis. This heightened support during hospitalization can be attributed to lower pre-hospitalization functional independence, increased comorbidities, and reduced exercise capacity in frail patients,

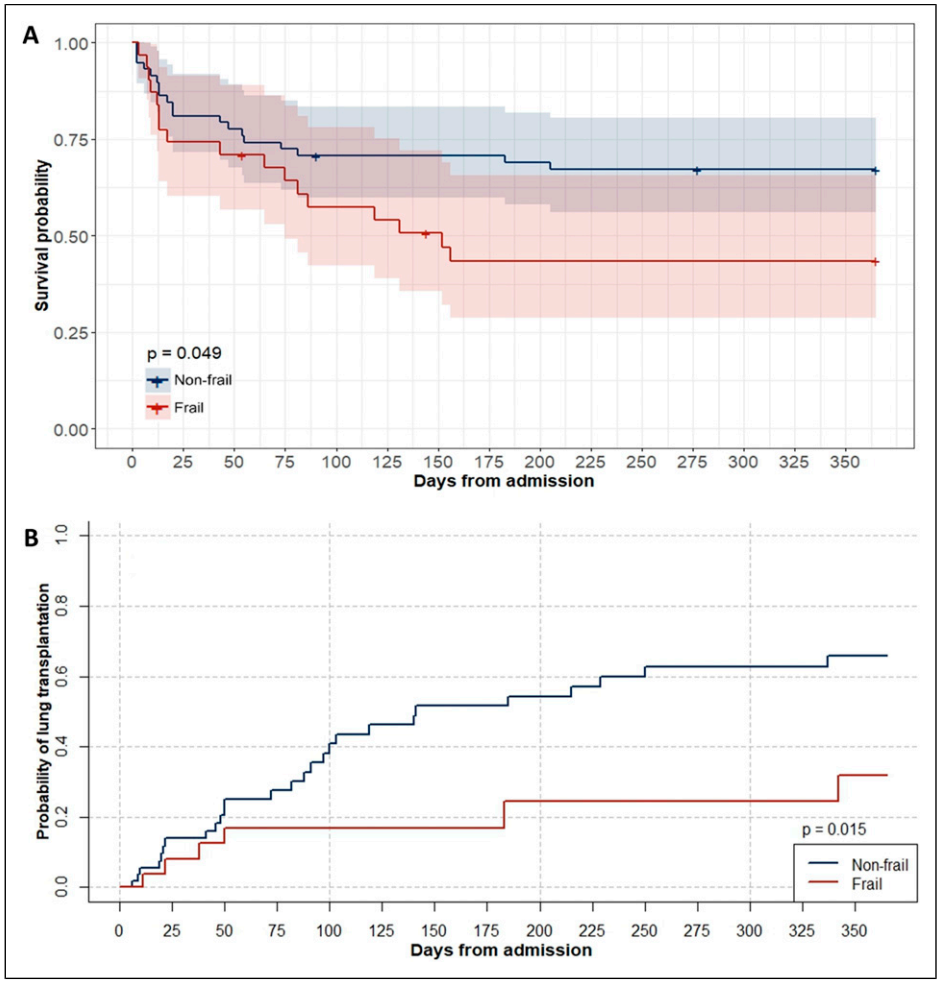

Figure 2. One-year Survival and incidence of lung transplantation Post-Acute Interstitial Lung Disease Exacerbation: Panel A depicts a Kaplan-Meier plot for 1-year survival post exacerbation according to presence of frailty on hospital admission, including those transplanted. Four patients were censored for death given end of follow-up period. Panel B represents the cumulative incidence of lung transplantation post exacerbation according to presence of frailty on hospital admission, one patient was censored for lung transplantation.

as previously described.[38] Pre-hospital corticosteroid or immunosuppression use was also more frequent among frail patients, likely as a consequence of non-IPF patients requiring immunosuppression for connective tissue disease associated ILD management, which increases risks of steroid-induced myopathy and impairments in physical function.[42,43] These data highlight the vulnerability of frail AE-ILD patients, with numerous comorbidities and reduced physiological reserve which is aggravated by stressors associated with AE-ILD hospitalizations, including systemic inflammation, higher corticosteroid use, hypoxia, and immobility.

Frailty and post-discharge hospital outcomes

Frail AE-ILD patients were less likely to be transplanted compared to non-frail patients over the 1-year follow-up period, in the univariate model, but only transplant listing status was an independent predictor of transplantation. Transplantation guidelines highlight that older age and increased comorbidities should be considered relative contraindications to transplantation, but do not recommend excluding patients based on frailty.[34,44] However, a study of 100 ILD lung transplant candidates highlights that frail ILD patients often face barriers to transplantation, and their post-transplant 1-year survival tends to be lower compared to non-frail recipients (58% in frail vs 86% in non-frail).[45] Lung transplant programs may perceive frail ILD patients as having higher post-transplant risk because of older age, greater comorbidities, functional limitations, and diminished physiological reserve.[13] Further, frail patients may be perceived as having a lower rehabilitation potential pre-transplant in preparation for transplantation.[44] However, several studies have demonstrated improvement in physical frailty with in-person and virtual exercise programs in

Table 4. Factors associated with one-year mortality post-acute exacerbation of interstitial lung disease.

	Death				Transplantation			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Parameters	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Frailty	1.91 (0.99 – 3.68)	0.054	2.27 (1.01 – 5.13)	**0.04**	0.31 (0.12 – 0.80)	**0.02**	0.51 (0.18 – 1.49)	0.22
Age, per year	1.02 (0.98 – 1.06)	0.26	1.04 (0.96 – 1.11)	0.36	0.93 (0.90 – 0.97)	**<0.01**	0.95 (0.87 – 1.03)	0.22
Sex, male	1.32 (0.67 – 2.60)	0.43	1.18 (0.48 – 2.86)	0.72	0.77 (0.38 – 1.56)	0.46	1.50 (0.53 – 4.19)	0.44
ILD type, non-IPF	0.67 (0.33 – 1.36)	0.27	0.75 (0.32 – 1.77)	0.51	0.64 (0.29 – 1.39)	0.26	0.72 (0.27 – 1.93)	0.51
CCI, per point	1.06 (0.94 – 1.24)	0.49	0.91 (0.63 – 1.32)	0.62	0.64 (0.50 – 0.81)	**<0.01**	0.82 (0.49 – 1.35)	0.43
FVC, 0.1 L	1.00 (0.99 – 1.04)	0.83	1.02 (0.59 – 1.74)	0.95	0.95 (0.90 – 1.00)	0.06	0.60 (0.31 – 1.18)	0.14
LTx listing, yes	1.40 (0.70 – 2.80)	0.34	1.52 (0.64 – 3.60)	0.34	3.05 (1.49 – 6.21)	**<0.01**	2.23 (1.01 – 4.92)	**0.04**
Concordance (C-statistic)			0.64				0.76	

Data are presented as models to determine the association of several variables with 1-year mortality or lung transplantation within 1-year. The association of each variable separately is provided in the univariate analysis and in the multivariate Cox regression model in which we added a priori-identified confounders. Regression model diagnostics were tested for assumption of independence.
Two frail and two non-frail patients were censored for 1-year mortality and one non-frail patient for 1-year transplantation.
Abbreviations: CCI: Charlson comorbidity index, ILD: Interstitial lung disease, IPF: idiopathic pulmonary fibrosis, FVC: forced vital capacity, LTx: Lung transplantation.

advanced lung disease,[46–48] and benefits of transplantation on frailty in lung transplant candidates.[49,50] Further study is needed to evaluate the degree that the cumulative frailty index is reversible with transplantation, especially in ILD.

Patients with IPF were observed to have a lower transplant-free survival compared to those with non-IPF from a prior study at our center.[19] Our current study further shows that increased comorbidities were independently associated with 1-year mortality. However, transplantation mitigated the risk of frailty on mortality in the competing risk model, which may have been related to a higher proportion of non-IPF patients in the frail group who are known to have a more favorable prognosis.[51,52] This underscores the complex interplay between frailty, ILD diagnosis, comorbidities, transplantation, and mortality.

Clinical implications

The cumulative frailty index utilizes readily accessible parameters from patients' medical records, ensuring its clinical relevance and validity for identifying frailty and its application can be tailored to data available at individual centers.[14,20] Recognizing frail patients upon admission for AE-ILD enables identification of a vulnerable subset of ILD patients who could benefit from in-hospital multidisciplinary support, close monitoring and interventions aimed at increasing physical activity and exercise training post AE-ILD.[38] Identifying patients with frailty and comorbidities may help facilitate timely allocation of resource supports, multidisciplinary care during and post hospitalization, and promote dialogue among the healthcare team, patients, and caregivers on their post-exacerbation prognosis.[10] Furthermore, interventions targeting physical activity and function are key for addressing frailty-related physical impairments in elderly and chronic lung disease populations.[43,47,53] Programs aimed at enhancing muscle strength, power, balance, flexibility, and exercise capacity can help improve various aspects of physical function and frailty.[43,53] Furthermore, mitigating frailty in AE-ILD patients could potentially reduce morbidity, and improve quality of life.[11,12,38]

Strengths and limitations

To our knowledge, this is the first study investigating frailty in hospitalized AE-ILD patients. Despite the retrospective single-center study design, data were complete with more than 90% data saturation. Furthermore, the study was underpowered to evaluate survival outcomes, however, its strength lies in the characterization of frailty and in-hospital outcomes. Our approach to developing the frailty index followed established principles and yielded comparable prevalence of frailty to other ILD studies.[14,20] Despite limitations inherent to our retrospective study design and inpatient setting which precluded the availability of certain physical functional assessments (i.e., strength testing, physical performance batteries) and pulmonary rehabilitation program history, the strength of the study lies in its well-characterized post-discharge outcomes such as transplantation and survival. To validate our 30-item frailty index, a comparison with established frailty measures such as the Fried frailty score would have been helpful.[54] However, due to the absence of prospective frailty assessment tools during routine clinical practice at our center, this

comparison was not feasible. Lastly, due to the reliance on pre-AE-ILD pulmonary function testing up to 1-year, our ability to correlate frailty with the ILD-GAP index may have been reduced.

Conclusions

In summary, frailty was prevalent in AE-ILD patients and associated with increased CCI, non-IPF, and reduced exercise capacity prior to hospitalization. Frail patients experienced more medical complications in hospital and required greater multidisciplinary support during hospitalization, underscoring their diminished physiological reserves that is further exacerbated by stressors associated with AE-ILD. Assessment of frailty may help identify patients requiring greater multidisciplinary support, tailored rehabilitation strategies and risk stratification for lung transplantation. Future research is needed to evaluate if frailty is modifiable prior to or during hospitalization with AE-ILD and if offering rehabilitation strategies during or after hospitalization can improve hospital and post-discharge outcomes.

Author contributions

KC, CA, JHF, SS, LF, ECG, TM, LW, SM, LGS, WDR, DR contributed to conceptualization, Data curation performed by KC and MVH, Formal analyses, visualization and writing - original draft was performed by MVH and KC, Funding acquisition was obtained by DR and WDR, the project was supervised by DR, writing – review & editing were performed by MVH, KC, CA, JHF, SS, LF, ECG, TM, LW, SM, LGS, WDR and DR.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Lee Fidler has received a grant from the Canadian Pulmonary Fibrosis Foundation and honoraria for speaking/lecturing from Boehringer Ingelheim, AstraZeneca, and Pfizer. Jolene Fisher acknowledges grants from Boehringer Ingelheim (for the Canadian Registry for Pulmonary Fibrosis) and payments made to the University of British Columbia, with subsequent support for the University of Toronto. She has received consulting fees and honoraria from AstraZeneca and Boehringer Ingelheim, as well as honoraria from Boehringer Ingelheim for a presentation. She serves as an unpaid Medical Advisory Board Member for the Canadian Pulmonary Fibrosis Foundation. W. Darlene Reid and Dmitry Rozenberg received a grant from the Canadian Institutes of Health Research for their project "Translating the interplay of cognition and physical performance to daily activities in COPD and ILD: Identifying Needs and Advancing Research Priorities. "Shane Shapera acknowledges a grant from Boehringer Ingelheim Canada and honoraria for speaking at CME events from AstraZeneca, Boehringer Ingelheim, and Hoffman La-Roche. All other authors have no conflicts of interest to declare.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Canadian Pulmonary Fibrosis Foundation. Marine Van Hollebeke was funded by CIHR project grant (PJM 179846). Dmitry Rozenberg receives support from the Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine and Temerty Faculty of Medicine, University of Toronto.

Ethical statement

Ethical approval

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by University Health Network Research Ethics Board - approval: REB # 19-5146.

Patient consent

The ethics committee confirmed that no informed patient consent was needed due to retrospective study design.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical reasons.

Supplemental Material

Supplemental material for this article is available online.

References

1. Plantier L, Cazes A, Dinh-Xuan AT, et al. Physiology of the lung in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2018; 27(147): 170062.
2. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194(3): 265–275.
3. Miyashita K, Kono M, Saito G, et al. Prognosis after acute exacerbation in patients with interstitial lung disease other than idiopathic pulmonary fibrosis. *Clin Res J* 2021; 15(3): 336–344.
4. Xie M, Zhu C and Ye Y. Incidence, risk factors, and prognosis of acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. *BMC Pulm Med* 2023; 23(1): 255.

5. Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27(150): 180071.
6. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011; 27(1): 1–15.
7. Farooqi MAM, O'Hoski S, Goodwin S, et al. Prevalence and prognostic impact of physical frailty in interstitial lung disease: a prospective cohort study. *Respirology* 2021; 26(7): 683–689.
8. Marengoni A, Vetrano DL, Manes-Gravina E, et al. The relationship between COPD and frailty: a systematic review and meta-analysis of observational studies. *Chest* 2018; 154(1): 21–40.
9. Bone AE, Hepgul N, Kon S, et al. Sarcopenia and frailty in chronic respiratory disease. *Chron Respir Dis* 2017; 14(1): 85–99.
10. Symvoulakis EK, Kamekis A, Drakonaki E, et al. Frailty and chronic respiratory disease: the need for a multidisciplinary care model. *Sarcoidosis Vasc Diffuse Lung Dis* 2021; 38(3): e2021031.
11. Guler SA, Kwan JM, Winstone TA, et al. Severity and features of frailty in systemic sclerosis-associated interstitial lung disease. *Respir Med* 2017; 129: 1–7.
12. Milne KM, Kwan JM, Guler S, et al. Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease. *Respirology* 2017; 22(4): 728–734.
13. Singer JP, Diamond JM, Anderson MR, et al. Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. *Am J Transplant* 2018; 18(8): 1995–2004.
14. Varughese RA, Theou O, Li Y, et al. Cumulative deficits frailty index predicts outcomes for solid organ transplant candidates. *Transplant Direct* 2021; 7(3): e677.
15. Guler SA, Kwan JM, Leung JM, et al. Functional ageing in fibrotic interstitial lung disease: the impact of frailty on adverse health outcomes. *Eur Respir J* 2020; 55(1): 1900647.
16. Guler SA and Ryerson CJ. Frailty in patients with interstitial lung disease. *Curr Opin Pulm Med* 2020; 26(5): 449–456.
17. Suzuki A, Kondoh Y, Brown KK, et al. Acute exacerbations of fibrotic interstitial lung diseases. *Respirology* 2020; 25(5): 525–534.
18. Mendes P, Wickerson L, Helm D, et al. Skeletal muscle atrophy in advanced interstitial lung disease. *Respirology* 2015; 20(6): 953–959.
19. Adams CJ, Chohan K, Rozenberg D, et al. Feasibility and outcomes of a standardized management protocol for acute exacerbation of interstitial lung disease. *Lung* 2021; 199(4): 379–387.
20. Rockwood K, Andrew M and Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007; 62(7): 738–743.
21. Koutsokera A, Sykes J, Theou O, et al. Frailty predicts outcomes in cystic fibrosis patients listed for lung transplantation. *J Heart Lung Transplant* 2022; 41(11): 1617–1627.
22. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; 8: 24.
23. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest* 2014; 145(4): 723–728.
24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; 40(5): 373–383.
25. Wu X, Li Z, Cao J, et al. The association between major complications of immobility during hospitalization and quality of life among bedridden patients: a 3 month prospective multi-center study. *PLoS One* 2018; 13(10): e0205729.
26. Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 2010; 303(13): 1259–1265.
27. Lawthers AG, McCarthy EP, Davis RB, et al. Identification of in-hospital complications from claims data. Is it valid? *Med Care* 2000; 38(8): 785–795.
28. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med* 2019; 200(8): e70–e88.
29. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166(1): 111–117.
30. Fox J and Weisberg S. *An {R} companion to applied regression*. 3rd ed. Newcastle upon Tyne: Sage, 2019.
31. Ebeling M, Rau R, Malmström H, et al. The rate by which mortality increase with age is the same for those who experienced chronic disease as for the general population. *Age Ageing* 2021; 50(5): 1633–1640.
32. Murohashi K, Hara Y, Saigusa Y, et al. Clinical significance of Charlson comorbidity index as a prognostic parameter for patients with acute or subacute idiopathic interstitial pneumonias and acute exacerbation of collagen vascular diseases-related interstitial pneumonia. *J Thorac Dis* 2019; 11(6): 2448–2457.
33. Lassenius MI, Toppila I, Pöntynen N, et al. Forced Vital Capacity (FVC) decline, mortality and healthcare resource utilization in idiopathic pulmonary fibrosis. *Eur Clin Respir J* 2020; 7(1): 1702618.
34. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; 40(11): 1349–1379.
35. Swaminathan AC, Hellkamp AS, Neely ML, Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry investigators, et al. Disparities in lung transplant among patients with idiopathic pulmonary fibrosis: an analysis of the IPF-pro registry. *Ann Am Thorac Soc* 2022; 19(6): 981–990.

36. Nan J, Duan Y, Wu S, et al. Perspectives of older adults, caregivers, healthcare providers on frailty screening in primary care: a systematic review and qualitative meta-synthesis. *BMC Geriatr* 2022; 22(1): 482.
37. Wilson ME, Vakil AP, Kandel P, et al. Pretransplant frailty is associated with decreased survival after lung transplantation. *J Heart Lung Transplant* 2016; 35(2): 173–178.
38. Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ (Can Med Assoc J): Canadian Medical Association Journal = Journal de l'Association medicale canadienne* 2014; 186(2): E95–102.
39. Evans SJ, Sayers M, Mitnitski A, et al. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. *Age Ageing* 2014; 43(1): 127–132.
40. Huang S, Wang Y, Chen L, et al. Use of a frailty index based upon routine laboratory data to predict complication and mortality in older community-acquired pneumonia patients. *Arch Gerontol Geriatr* 2022; 101: 104692.
41. Stone K, Zwiggelaar R, Jones P, et al. A systematic review of the prediction of hospital length of stay: towards a unified framework. *PLOS Digit Health* 2022; 1(4): e0000017.
42. Surmachevska N and Tiwari V. Corticosteroid induced myopathy. *StatPearls*. Treasure Island, FL: StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC, 2023.
43. Angulo J, El Assar M, Álvarez-Bustos A, et al. Physical activity and exercise: strategies to manage frailty. *Redox Biol* 2020; 35: 101513.
44. Schaenman JM, Diamond JM, Greenland JR, et al. Frailty and aging-associated syndromes in lung transplant candidates and recipients. *Am J Transplant* 2021; 21(6): 2018–2024.
45. Montgomery E, Macdonald PS, Newton PJ, et al. Frailty as a predictor of mortality in patients with interstitial lung disease referred for lung transplantation. *Transplantation* 2020; 104(4): 864–872.
46. Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax* 2016; 71(11): 988–995.
47. Maddocks M, Brighton LJ, Alison JA, et al. Rehabilitation for people with respiratory disease and frailty: an official American thoracic society workshop report. *Ann Am Thorac Soc* 2023; 20(6): 767–780.
48. Singer JP, Soong A, Bruun A, et al. A mobile health technology enabled home-based intervention to treat frailty in adult lung transplant candidates: a pilot study. *Clin Transplant* 2018; 32(6): e13274.
49. Venado A, McCulloch C, Greenland JR, et al. Frailty trajectories in adult lung transplantation: a cohort study. *J Heart Lung Transplant* 2019; 38(7): 699–707.
50. Rozenberg D, Mathur S, Wickerson L, et al. Frailty and clinical benefits with lung transplantation. *J Heart Lung Transplant* 2018; 37(10): 1245–1253.
51. Antoniou K, Markopoulou K, Tzouvelekis A, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. *ERJ Open Res* 2020; 6(1): 00172–02019.
52. Ole H, Anna-Maria H-V, Vanessa S, et al. Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. *ERJ open research* 2022; 8(1): 00597–02021.
53. Amasene M, Medrano M, Echeverria I, et al. Malnutrition and poor physical function are associated with higher comorbidity index in hospitalized older adults. *Front Nutr* 2022; 9: 920485.
54. Fried LP, Tangen CM, Walston J, Cardiovascular Health Study Collaborative Research Group, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M146–M156.

Appendix

Abbreviations

6MWD:	6-min walk distance
ADL:	Activities of daily living
AE-ILD:	Acute exacerbations of interstitial lung diseases
BMI:	Body mass index
CCI:	Charlson Comorbidity Index
CI:	Confidence interval,
FVC:	Forced vital capacity
HR:	Hazard ratio
ILD:	Interstitial lung diseases
ILD-GAP:	Interstitial lung disease gender-age-physiology
IPF:	Idiopathic pulmonary fibrosis
IQR:	Interquartile range
LTx:	Lung transplantation
MRC:	Medical Research Council
OR:	Odds ratio
PFT:	Pulmonary function test