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The clinical frailty scale for risk stratification in patients with fibrotic interstitial lung disease

Key word list

Aging

Disease Progression

Frailty

Idiopathic Pulmonary Fibrosis

Interstitial Lung Disease

Survival

Abbreviation list

BMI, body mass index

CI, confidence interval

CFS, clinical frailty scale

CTD, connective tissue disease

DLCO, diffusing capacity of the lung for carbon monoxide

FVC, forced vital capacity

GAP, gender age physiology

GERD, gastroesophageal reflux disease

HP, hypersensitivity pneumonitis

HR, hazard ratio

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

IQR, interquartile range

MDD, multidisciplinary discussion

OR, odds ratio

PH, proportional hazard

SE, standard error

SLB, surgical lung biopsy

6MWD, 6-minute walk distance

ABSTRACT

Background: Previous studies have shown the importance of frailty in patients with fibrotic interstitial lung disease (ILD).

Research question: Is the Clinical Frailty Scale (CFS) a valid tool to improve risk stratification in patients with fibrotic ILD?

Study design and Methods: Patients with fibrotic ILD were included from the prospective multicenter Canadian Registry for Pulmonary Fibrosis. The CFS was assessed using available information from initial ILD clinic visits. Patients were stratified into fit (CFS 1-3), vulnerable (CFS 4), and frail (CFS 5-9) subgroups. Cox proportional hazards and logistic regression models with mixed effects were used to estimate time to death or lung transplantation. A derivation and validation cohort were used to establish prognostic performance. Trajectories of functional tests were compared using joint models.

Results: Of the 1587 patients with fibrotic ILD, 858 (54%) were fit, 400 (25%) vulnerable and 329 (21%) frail. Frailty was a risk factor for early mortality (HR 5.58, 95%CI 3.64-5.76, p<0.001) in the entire cohort, in individual ILD diagnoses, and after adjustment for potential confounders. Adding frailty to established risk prediction parameters improved the prognostic performance in derivation and validation cohorts. Frail patients had larger annual declines in forced vital capacity (FVC) %-predicted compared to fit patients (-2.32 (95%CI -3.39 to -1.17) vs. -1.55 (95%CI -2.04 to -1.15); p=0.02, respectively).

Interpretation: The simple and practical CFS is associated with pulmonary and physical function decline in patients with fibrotic ILD and provides additional prognostic accuracy in clinical practice.

Fibrotic interstitial lung diseases (ILDs) are severe, chronic, and frequently progressive disorders that damage the lung parenchyma.(1, 2) People suffering from fibrotic ILD have a decreased life expectancy and frequently poor quality of life due to a high symptom burden, including dyspnea, cough, fatigue, and reduced physical performance and function in daily life. In addition to its impact on patients and their caregivers, fibrotic ILD also results in significant economic burden and impact on the healthcare system and society.(3, 4)

Biological hallmarks of aging such as cellular senescence and accelerated telomere shortening have been described in fibrotic ILD, supporting the concept of these as age-associated diseases.(5, 6) Furthermore, age-associated comorbidities are frequent in patients with fibrotic ILD and can further worsen long-term outcomes.(7) The combination of accelerated biopsychosocial aging, comorbidities, symptoms, and potentially medication side effects can contribute to an accumulation of age-associated health deficits which reduce physiological reserves and lead to a state of increased vulnerability that has been termed frailty.(8, 9) Patients with fibrotic ILD have multiple risk factors for frailty,(10) and frailty is very common in this population.(11) Previous studies show that frailty is associated with worse survival and more frequent hospitalisations in patients with fibrotic ILD.(12, 13) Overall, frailty seems to be of prognostic importance in ILD; however, previous studies have used research-oriented tools that are not well suited for implementation in clinical decision making and risk stratification in clinical practice.

The Clinical Frailty Scale (CFS) is a simple tool designed to summarize overall fitness and frailty in a person. Originally the CFS was developed using the Canadian Study of Health and Aging including adults aged 65 years and older.(8) Since then multiple studies have also validated the CFS in younger patients,(14, 15) in a variety of acute and chronic diseases, and

different health care settings.(16, 17) The goal of this study was to establish if the simple and practical CFS might be a valid tool to improve risk stratification in patients with fibrotic ILD. Specifically, we aimed to determine the relationship between frailty assessed by the CFS and transplant-free survival in the most common fibrotic ILDs, to determine the incremental contribution of the CFS to mortality risk prediction, and to explore ILD progression by frailty status.

METHODS

Study design and patient population

This study includes patients with fibrotic ILD who consented to participate in the Canadian Registry for Pulmonary Fibrosis (CARE-PF), a multi-center prospective cohort study.(18, 19) The diagnosis of fibrotic ILD was verified by multidisciplinary discussion (MDD) in all patients. Each of the specialized ILD centres obtained Research Ethics Board approval (coordinating centre University of British Columbia: H20-02619). For the purposes of the study, patients from the Western Canadian centres in Vancouver (British Columbia), Calgary (Alberta), and Saskatoon (Saskatchewan) were included in the derivation cohort and patients from the Eastern Canadian centres in Hamilton (Ontario), Toronto (Ontario), and Montreal (Quebec) were included in the validation cohort. There were no exclusion criteria for this study.

The Clinical Frailty Scale

The CFS ranges from very fit (1), to well (2), managing well (3), vulnerable (4), mildly frail (5), moderately frail (6), severely frail (7), very severely frail (8), and terminally ill (9).(8, 17) The CFS can be assessed by any health care professional in direct interaction with the patient or by review of medical records.(20-22) For example, people with CFS 3 typically have medical

problems that are well controlled, but are not active beyond walking. Vulnerable patients (CFS 4) typically don't need daily help from others but have symptoms that limit their daily activities, while people with CFS 6 need help with all outside activities or housekeeping (e-Table 1). For this study, the CFS was determined using the available information from the first ILD clinic visit. Based on previous validation studies patients were stratified into fit (CFS 1-3), vulnerable (CFS 4), and frail (CFS 5-9) subgroups.(14, 22, 23)

Other measurements and outcomes

Patient demographics and other baseline characteristics were collected from the clinical record. Antifibrotic treatment included nintedanib and pirfenidone; immunosuppressive treatment included azathioprine, mycophenolate mofetil, cyclophosphamide, tacrolimus, cyclosporine, rituximab, and prednisone ≥10mg per day for ≥1 month. Pulmonary function tests including measurement of forced vital capacity (FVC), carbon monoxide diffusing capacity (DLCO), and 6-minute walk tests were performed using established protocols.(24-26) Time to death, lung transplantation, or censoring was calculated from the date of the first ILD clinic visit.

Statistical analysis

Patient characteristics are reported as number (percentage) or median (interquartile range [IQR]). Kaplan-Meier survival function with log-rank tests and Cox proportional hazards (PH) models with random effects for clustering by centre and fixed effects for pre-specified confounders with conceptual importance were used to estimate time to death or lung transplantation up to 5 years from assessment. The PH assumption was verified using log-log plots of survival. The estimated hazard ratios (HR) and its 95% confidence intervals (95%CI)

for the association between frailty and mortality were adjusted for age, sex, body mass index, ever smoking, idiopathic pulmonary fibrosis (IPF) diagnosis, baseline FVC %-predicted, baseline DLCO %-predicted, oxygen therapy and ILD drug treatment. Similarly, mixed effects logistic regression models were adjusted for the same confounders to estimate odds ratios (ORs) and corresponding 95%CI for 1-, 2-, and 5-year mortality. The discriminative performance of Cox PH models was compared using the Harrell's C-statistic. To investigate the incremental contribution of frailty to mortality risk prediction, C-indices with respective standard errors (SE) were estimated by adding frailty to different models of established risk prediction parameters in the derivation and the validation cohort.

Joint models were used to compare trajectories of pulmonary function tests in fit, vulnerable, and frail patients. Joint models consist of a longitudinal mixed effect submodel to account for repeated measurements per patient (random intercepts and slopes) and a Cox proportional hazards submodel for time to death or lung transplant outcome. This approach accounts for potential informative dropout given the likely differences in FVC, DLCO, and 6-minute walk distance (6MWD) trajectories of patients who survived until censoring and those who died or received a lung transplantation. The models were fitted using maximum likelihood estimation and adjusted for potential confounders included as fixed effects (age, sex, body mass index, ever smoking, ILD drug treatment).(27, 28) A two-sided significance level of $p<0.05$ was considered statistically significant. Data were analysed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 1587 patients with fibrotic ILD were included in the study, 1084 were from Western Canadian centres and allocated to the derivation cohort and 503 were from Eastern Canadian centres and allocated to the validation cohort (**e-Table 2**). The median (IQR) CFS in the overall population was 3 (3-4), with 858 patients (54%) classified as fit, 400 (25%) as vulnerable and 329 (21%) as frail (**Table 1**). Frail patients were older (mean age 67.7 versus 64.3 years), less frequently male (43% versus 53%), more frequently ever smokers (68% versus 59%) and had a higher mean body mass index (BMI) (28.5 versus 26.2) compared to fit patients. Pulmonary and physical function was more severely impaired in frail compared to fit patients: Mean FVC was 64 and 78 %-predicted, DLCO 43 and 57%, and 6MWD 67 and 82%-predicted, in frail and fit patients respectively. Frail fibrotic ILD patients were less likely to have a multidisciplinary diagnosis of IPF (20% versus 29%), and more likely to have a diagnosis of hypersensitivity pneumonitis (HP) (18% versus 11%) and unclassifiable ILD (12% versus 9%). The proportion of patients with connective tissue disease (CTD)-ILD was similarly distributed in frail and fit patients (41% and 44%). Oxygen therapy at rest and at exercise was more frequently prescribed in frail compared to fit patients (26% versus 10%). Few patients were already on antifibrotics at the time of their first ILD clinic visit (2% of the total cohort), with a higher proportion of frail patients treated with immunosuppressives (39% versus 24%).

Transplant-free survival by frailty status

By the end of the 5-year observation period, 441 patients died, and 83 patients underwent lung transplantation. Transplant-free survival at 1-/2-/5-years was 99%/95%/78% in fit, 93%/83%/55% in vulnerable and 84%/68%/38% in frail patients ($p<0.001$, **Figure 1**).

Vulnerability and frailty were significant risk factors for early mortality. Frail patients had more than 5-times higher hazard rate for mortality compared to fit patients (HR 5.58, 95%CI 3.64-5.76, p<0.001), which remained statistically significant after adjustment for potential confounders (HR 2.79, 95%CI 2.03-3.86, p<0.001). Similarly, vulnerability and frailty were associated with a higher odds of 1-, 2-, and 5-year mortality, in the entire cohort (**Table 2**) and in the derivation and validation cohorts (**e-Table 3, e-Figure 1**).

When patients were stratified according to diagnosis, frailty was associated with mortality in patients with IPF, CTD-ILD, fibrotic HP, and unclassifiable ILD (all p<0.001, **Figure 2**). Across diagnoses, frailty was most strongly associated with mortality in patients with unclassifiable ILD (HR 6.20, 95%CI 4.71-8.15, p<0.001), followed by CTD-ILD (HR 5.57, 95%CI 3.57-8.68, p<0.001), IPF (HR 4.53, 95%CI 3.06-6.71, p<0.001), and fibrotic HP (HR 2.68, 95%CI 2.14-3.37, p<0.001). These estimates remained significant with adjustment for age, sex, BMI, ever smoking, FVC and DLCO %-predicted, oxygen therapy and ILD drug treatment (**Table 3**).

Mortality or lung transplantation risk prediction

Prognostic performance increased substantially when frailty was added to established risk prediction parameters. For example, in the derivation cohort when frailty was added to age, sex, BMI and ever smoking, the C-index increased from 69.1 to 74.4%, and when frailty was added to the Gender Age Physiology (GAP)-ILD index the C-index increased from 72.9 to 76.2%. The findings from the validation cohort were replicated in the derivation cohort (**Figure 3**).

Progression of pulmonary and physical function by frailty status

Over the median (IQR) follow-up time of 1.3 (0.4-2.6) years, 8597 FVC measurements from 1452 patients were available. In the joint models accounting for informative dropout due to death or lung transplantation, fit, vulnerable and frail patients had a decline in mean annual FVC %-predicted of -1.55 (95%CI -2.04 to -1.15), -1.92 (95%CI -3.10 to -0.94) and -2.32 (95%CI -3.39 to -1.17), respectively. Slopes differed significantly between fit and frail patients (p=0.02), and estimates were robust to adjustment for confounders.

Similarly, 6914 DLCO measurements from 1359 patients were available. In corresponding models, fit, vulnerable and frail patients had a decline in mean annual DLCO %-predicted of -1.96 (95%CI -2.44 to -1.57), -2.20 (95%CI -3.61 to -1.11) and -2.56 (95%CI -4.02 to -1.24), respectively. Slopes did not differ significantly between fit, vulnerable, and frail patients, with similar estimates in models that were adjusted for the above confounders.

Lastly, 2991 6-minute walking tests from 898 patients were available. Fit, vulnerable, and frail patients had a decline in mean annual 6MWD %-predicted of -2.23 (95%CI -2.89 to -1.60), -4.23 (95%CI -6.63 to -2.46) and -3.40 (95%CI -5.47 to -1.48), respectively. Slopes differed significantly between fit and vulnerable (p=0.006), but not between fit and frail patients (p=0.12), and estimates were robust to adjustment for the above confounders (**Table 4**).

Patient and measurement sample sizes allowed for explorations in the subgroups of patients with IPF and CTD-ILD. In IPF mean annual FVC %-predicted decline was significantly larger in frail (-4.67, 95%CI -7.19 to -2.67) compared to fit patients (-2.62, 95%CI -3.57 to -2.14), p=0.006, which was robust to adjustment for confounding by age, sex, BMI, ever smoking

and ILD drug treatment. Similarly, mean annual DLCO %-predicted decline was larger in frail (-5.78, 95%CI -8.40 to -3.61) compared to fit patients (-3.74, 95%CI -4.42 to -3.17), p=0.02, and 6MWD %-predicted trajectories differed between fit (-4.47, 95%CI -6.07 to -3.29) and vulnerable patients (-7.30, 95%CI -11.9 to -3.93), p=0.03 (**e-Table 4**). In CTD-ILD, FVC and DLCO %-predicted trajectories were not significantly different between fit, vulnerable, and frail patients. Mean annual 6MWD %-predicted trajectories were -0.58 (95%CI -1.49 to 0.37), -2.66 (95%CI -5.67 to 0.01) and -2.40 (95%CI -5.32 to 0.21) in fit, vulnerable, and frail patients with significant slope differences between fit and vulnerable patients (p<0.001, **e-Table 5**).

DISCUSSION

This multicentre cohort study establishes the simple and practical CFS as a valuable contributor to risk stratification in patients with fibrotic ILD. We demonstrate that frail ILD patients have a more than 5-fold higher hazard of death over 5 years and confirm frailty as a risk factor for mortality in the most common fibrotic ILDs beyond confounding effects of age, sex, disease severity based on pulmonary function, and ILD treatment. The CFS' prognostic performance on top of established predictors of mortality was also confirmed in a separate validation cohort. Furthermore, we demonstrate for the first time that frail and vulnerable patients have greater ILD progression compared to fit individuals. The association between frailty status and pulmonary function decline (FVC %-predicted) was particularly evident in patients with IPF, while the association between frailty and decline in physical function (6MWD %-predicted) was highly significant in patients with CTD-ILD.

Mortality risk prediction in fibrotic ILD is challenging, with demographics and pulmonary function being the most frequently used variables in prognostic models. The ILD-GAP model has been validated in various ILD populations,(29, 30) and its prognostic performance can be improved by adding additional parameters.(31) Given the importance of comorbidities for patients with fibrotic ILD,(7) and previous findings showing prognostic validity of frailty in this population,(12) it seems logical to integrate factors beyond pulmonary impairment into ILD risk stratification. In oncology, functional status has been a key factor for therapeutic decision making for many years and has been integrated in mortality risk prediction tools,(32, 33) which further supports the incorporation of functionality and frailty in ILD clinical care.

Beyond the relationship between the CFS and mortality, we found that frail ILD patients have a higher risk for disease progression. There are several potential reasons for this observation. Accelerated biological aging (indicated by telomere shortening) is a risk factor for ILD progression,(6, 34) and given the interaction between biological and functional aging (frailty), accelerated aging might be responsible for the faster pulmonary function decline in frail patients. Furthermore, the effectiveness of specific ILD medications might be lower in frail versus fit patients with potentially reduced tolerability and adherence. Frail ILD patients might also experience difficulties in accessing non-pharmacological treatment such as patient education and rehabilitation, and the management of comorbidities might be less optimal in this population. Lastly, social disadvantages and socioeconomic status are risk factors for frailty and have been shown to be associated with ILD progression.(35, 36) Trajectories of DLCO %-predicted were only significantly different in patients with IPF but not in the overall fibrotic ILD population. We suspect that this is due to the imprecision and relatively small effect size of DLCO decline in patients with non-IPF ILD. The larger decline in

6MWD %-predicted in vulnerable compared to frail patients seems counterintuitive but may be explained by the higher baseline 6MWD in the vulnerable patients and a floor effect in the frail subgroup (i.e., frail patients have a lower 6MWD to begin with and have less room to decline further).

There are some limitations of our study inherent to observational cohort studies, such as missing data. In this cohort 8.5% of patients had no FVC, 14% no DLCO, and 6-minute walking tests were only available in 57% of patients. We did not impute any of these missing data and only performed subgroups analyses if sample sizes allowed for stable models. Findings from this Canadian study might not apply unconditionally to other countries and clinical settings; however, the multicentre design and the confirmation of the prognostic performance of the CFS in a separate validation cohort makes our findings robust and generalizable to a wide range of patients with fibrotic ILD. We chose the CFS for its simplicity and great potential for implementation in daily clinical practice. However, more elaborate frailty assessment tools such as the Fried Frailty Phenotype,(37) the Short Physical Performance Battery, the cumulative Frailty Index,(38) or the comprehensive geriatric assessment might provide more granularity and insight on the causes of frailty in the individual patient. Previous studies have demonstrated that frailty, assessed by these more laborious tools, is associated with mortality in patients with ILD,(12, 37) and with this current study we confirm the prognostic importance of frailty also if assessed by the practical CFS. Similarly, in other contexts the CFS has been validated against more complex frailty assessment tools,(15) and has been established as a valuable tool to triage patients for advanced health interventions.(39) Unfortunately, there is a lack of consensus on how to assess frailty in the general population and in patients with chronic lung diseases, and additional research on frailty in this patient population has been called for.(40)

A task force of the European Respiratory Society recently emphasized the importance of frailty in patients with chronic lung diseases and the need for a stronger focus on frailty in clinical trials and guidelines to address patients and caregiver needs in a holistic way.(40) The CFS offers a means to quantify the clinician's overall "gestalt" of a patient and can serve as a valuable instrument to communicate risks associated with decreasing physiological reserves. Frailty is a preventable and potentially reversible state, and preliminary findings suggest that frailty can improve in lung transplant candidates after pulmonary rehabilitation.(41) Prevention of frailty progression is likely equally important in ILD and screening ILD patients for frailty might have the potential to improve the effectiveness of pharmacological and non-pharmacological treatment approaches. For example, frailty could be used to identify individuals who need additional supports to manage medication side effects resulting in improved medication tolerability or guide modifications in nutrition or pulmonary rehabilitation programs. Integrating the CFS in ILD clinical practice may also support treatment decisions and foster discussions on care goals and timing of referral to palliative care.(42) The high prevalence of frailty, along with its prognostic and therapeutic implications, supports the rationale for screening frailty in ILD patients, particularly using simple assessment tools like the CFS.

INTERPRETATION

In summary, we established the potential role of the CFS for risk stratification in patients with fibrotic ILD. The CFS might support communication among ILD specialists, patients, and caregivers, and serve as a tool for individual allocation of disease-modifying and supportive treatments.

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Take-Home Points

Study question: Is the Clinical Frailty Scale a valid tool to improve risk stratification in patients with fibrotic interstitial lung disease (ILD)?

Results: Frailty is a significant risk factor for mortality (HR 5.58, 95%CI 3.64-5.76, p<0.001), improves prognostication in derivation and validation cohorts, and is associated with a larger decline in forced vital capacity in patients with fibrotic ILD.

Interpretation: The simple Clinical Frailty Scale contributes to risk stratification beyond established risk prediction parameters and is associated with pulmonary and functional disease progression in patients with fibrotic ILD.

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FIGURES

Figure 1. Survival by frailty in all patients with fibrotic ILD.

Abbreviations: CFS, clincial frailty scale; ILD interstitial lung disease

Figure 2. Survival by frailty in patients with IPF (A), CTD-ILD (B), fibrotic HP (C), and unclassifiable ILD (D).

Abbreviations: CFS, clincial frailty scale; CTD, connective tissue disease; HP, hypersensitivity pneumonitis; ILD interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Figure 3. Prognostic performance of survival models with and without the addition of frailty in the derivation (A) and the validation (B) cohort.

Every row indicates a separate Cox Proportional Hazard model for mortality hazard up to 5 years from baseline. The change in prognostic performance is quantified by the C-Index of the same models without (yellow) and with frailty (green). The models include established risk prediction parameters; the simplest model only age and sex, with additional parameters up to the most complex model which includes age, sex, BMI, ever smoking, FVC %-predicted, DLCO %-predicted, IPF diagnosis, ILD drug treatment and oxygen therapy.

Abbreviations: BMI, body mass index; C-Index, Harrel's concordance index (%), DLCO%, diffusing capacity of the lung for carbon monoxide percent predicted; medication; any ILD specific drug treatment (antifibrotic and immunosuppressive); FVC%, forced vital capacity percent predicted; GAP-ILD, Gender Age Physiology ILD index; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; O_2, oxygen therapy; smoking, having ever smoked

TABLES

Table 1. Characteristics of fit, vulnerable, and frail patients with fibrotic ILD.

	Fit (CFS ≤3) n=858	**Vulnerable (CFS=4) n=400**	**Frail (CFS ≥5) n=329**
	mean ± standard deviation or number (percent)		
Age, years	64.3±12	67.7±11	67.7±12
Sex, male	457 (53%)	198 (50%)	142 (43%)
BMI, kg/m²	26.2±4.7	27.1±5.6	28.5±7.5
Ever smoker	502 (59%)	266 (67%)	222 (68%)
Pack years	13.9±19	17.9±22	19.1±23
FUNCTIONAL TESTS			
FVC, %-predicted	78.3±20	70.6±20	63.8±21
DLCO, %-predicted	56.5±20	47.0±19	42.6±17
6MWD, meters	416±126	324±118	282±102
6MWD, %-predicted	82.2±24	66.5±23	57.8±21
DIAGNOSIS			
IPF (n=444)	251 (29%)	126 (32%)	67 (20%)
CTD-ILD (n=679)	373 (44%)	170 (43%)	136 (41%)
Fibrotic HP (n=198)	91 (11%)	47 (12%)	60 (18%)
Unclassifiable ILD (n=156)	80 (9%)	37 (9%)	39 (12%)
TREATMENT			
Antifibrotic	20 (2%)	8 (2%)	7 (2%)
Immunosuppressive	207 (24%)	112 (28%)	128 (39%)
Any ILD treatment	224 (26%)	119 (30%)	133 (40%)
Oxygen therapy			
- **at rest**	87 (10%)	72 (18%)	86 (26%)
- **at exercise**	86 (10%)	76 (19%)	86 (26%)
COMORBIDITIES			
Obstructive lung disease	71 (8%)	47 (12%)	49 (15%)
Lung cancer	9 (1%)	3 (1%)	4 (1%)
GERD	441 (51%)	237 (59%)	176 (54%)
Obstructive sleep apnea	79 (9%)	41 (10%)	44 (13%)
Cardiovascular disease	97 (11%)	71 (18%)	65 (20%)
Pulmonary hypertension	17 (2%)	17 (4%)	43 (13%)
Pulmonary embolism	13 (2%)	9 (2%)	9 (3%)
Arthritis	90 (11%)	38 (10%)	28 (9%)
OUTCOMES			

Died	154 (18%)	132 (33%)	155 (47%)
Lung transplant	34 (4%)	27 (7%)	22 (7%)

Abbreviations: BMI, body mass index; CFS, clinical frailty scale; CTD, connective tissue disease; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; 6MWD, 6-minute walk distance

Table 2. Mortality risk in vulnerable and frail versus fit patients with fibrotic ILD.

	Unadjusted models†		**Adjusted models¥**	
n=1587	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Time to death or lung transplant			
Vulnerable	2.49 (1.96-3.16)	<0.001	1.61 (1.17-2.20)	0.001
Frail	5.58 (3.64-5.76)	<0.001	2.79 (2.03-3.86)	<0.001
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
	1-year mortality			
Vulnerable	5.31 (2.67-10.5)	<0.001	2.21 (0.92-5.33)	0.08
Frail	12.9 (6.80-24.6)	<0.001	6.61 (2.90-15.1)	<0.001
	2-year mortality			
Vulnerable	3.68 (2.42-5.59)	<0.001	2.24 (1.29-3.89)	0.004
Frail	8.43 (5.67-12.5)	<0.001	5.27 (3.02-9.20)	<0.001
	5-year mortality			
Vulnerable	2.57 (1.94-3.40)	<0.001	1.73 (1.17-2.55)	0.006
Frail	5.19 (3.88-6.93)	<0.001	2.83 (1.84-4.37)	<0.001

Hazard of early death or lung transplantation (hazard radio, HR) or the odds for death or lung transplantation at 1-,2- and 5-years after baseline (odds ratio, OR) compared to fit patients (reference group). CFS, Clinical Frailty Scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5

†accounting for clustering by center

¥additionally adjusted for age, sex, body mass index, ever smoking, IPF diagnosis, FVC %-predicted, DLCO %-predicted, oxygen therapy and ILD drug treatment (fixed effects).

Table 3. Mortality risk in vulnerable and frail versus fit patients in fibrotic ILD subpopulations.

	Unadjusted models[†]		**Adjusted models[¥]**	
	HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*
	Idiopathic Pulmonary Fibrosis (n=444)			
Vulnerable	2.58 (1.82-3.67)	<0.001	1.81 (1.13-2.87)	0.01
Frail	4.53 (3.06-6.71)	<0.001	3.70 (2.17-6.30)	<0.001
	Connective Tissue Disease associated ILD (n=679)			
Vulnerable	3.26 (2.06-5.15)	<0.001	2.05 (1.15-3.65)	0.02
Frail	5.57 (3.57-8.68)	<0.001	2.76 (1.48-5.13)	0.001
	Unclassifiable ILD (n=156)			
Vulnerable	1.26 (0.90-1.77)	0.17	1.29 (0.83-2.01)	0.26
Frail	6.20 (4.71-8.15)	<0.001	6.16 (4.10-9.23)	<0.001
	Hypersensitivity Pneumonitis (n=198)			
Vulnerable	1.10 (0.82-1.46)	0.53	1.19 (0.79-1.80)	0.42
Frail	2.68 (2.14-3.37)	<0.001	1.60 (1.03-2.49)	0.037

Hazard of early death or lung transplantation (hazard radio, HR) compared to fit patients (reference group). CFS, Clinical Frailty Scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5

[†]accounting for clustering by center

[¥]additionally adjusted for age, sex, body mass index, ever smoking, FVC %-predicted, DLCO %-predicted, oxygen therapy and ILD drug treatment (fixed effects).

Table 4. Pulmonary and physical function trajectories in fit, vulnerable, and frail patients with fibrotic ILD from joint models.

	Crude Model†		**Adjusted model¥**	
	Mean annual change (95% CI)	*p-value for interaction*	*Mean annual change (95% CI)*	*p-value for interaction*
n=1452	**Change in FVC %-predicted**			
Fit	-1.55 (-2.04 to -1.15)	-	-1.56 (-1.97 to -1.37)	-
Vulnerable	-1.92 (-3.10 to -0.94)	0.25	-1.93 (-2.99 to -1.08)	0.22
Frail	-2.32 (-3.39 to -1.17)	0.02	-2.34 (-3.57 to -1.08)	0.037
n=1345	**Change in DLCO %-predicted**			
Fit	-1.96 (-2.44 to -1.57)	-	-1.94 (-2.24 to -1.58)	
Vulnerable	-2.20 (-3.61 to -1.11)	0.58	-2.19 (-3.30 to -1.01)	0.57
Frail	-2.56 (-4.02 to -1.24)	0.21	-2.51 (-4.19 to -1.19)	0.26
n=989	**Change in 6MWD %-predicted**			
Fit	-2.23 (-2.89 to -1.60)	-	-2.28 (-3.16 to -1.69)	
Vulnerable	-4.23 (-6.63 to -2.46)	0.006	-4.26 (-6.74 to -2.48)	0.007
Frail	-3.40 (-5.47 to -1.48)	0.12	-3.43 (-6.42 to -1.66)	0.17

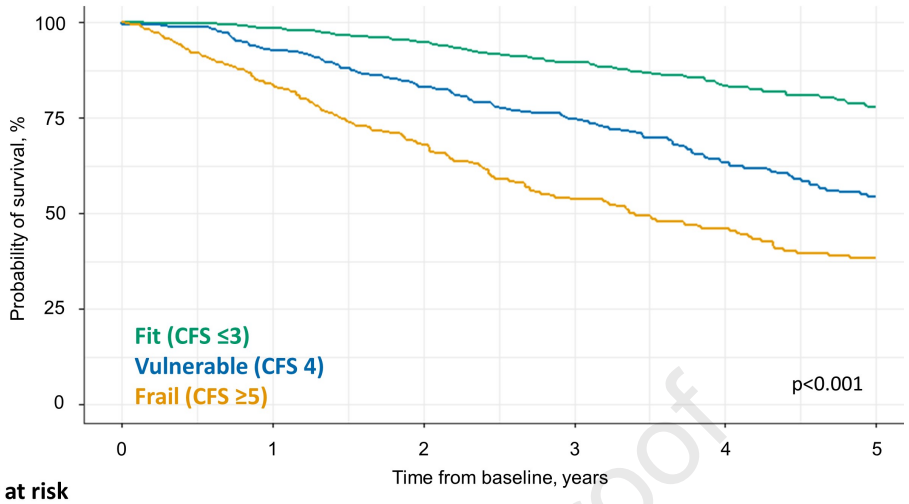
Mean annual changes are significantly different from zero if 95% confidence intervals (CI) do not cross zero. Negative estimates signify a decline. P-values for interaction refer to differences in slopes between vulnerable or frail and fit (reference) patients.

†accounting for informal drop out due to death or lung transplantation

¥adjusted for age, sex, body mass index, ever smoking, and ILD drug treatment (fixed effects).

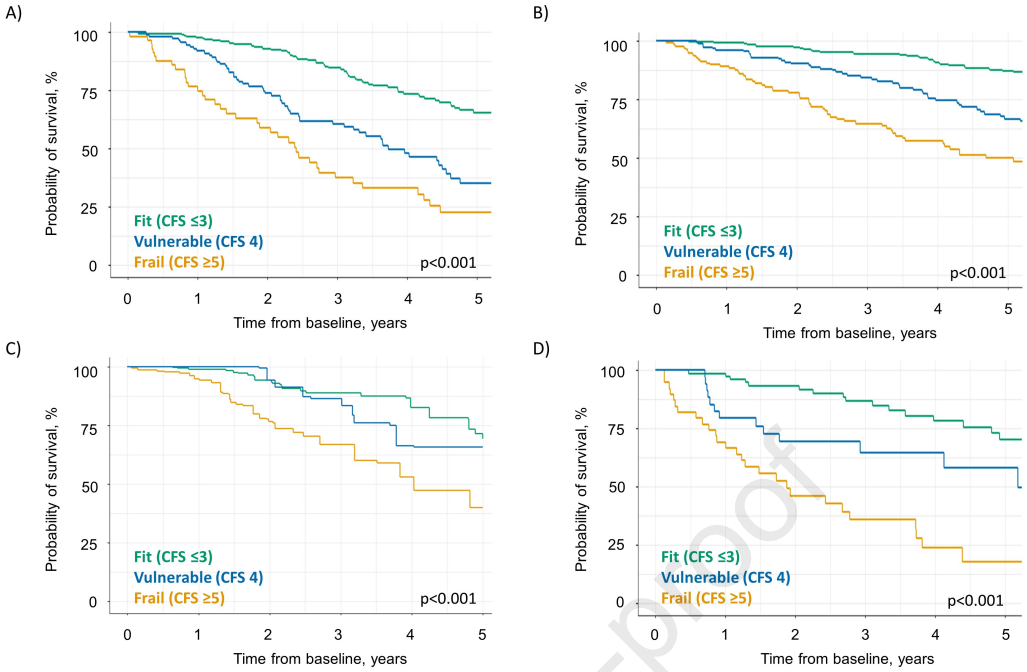
Abbreviations: CFS, clinical frailty scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5

DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; 6MWD, 6-minute walk distance

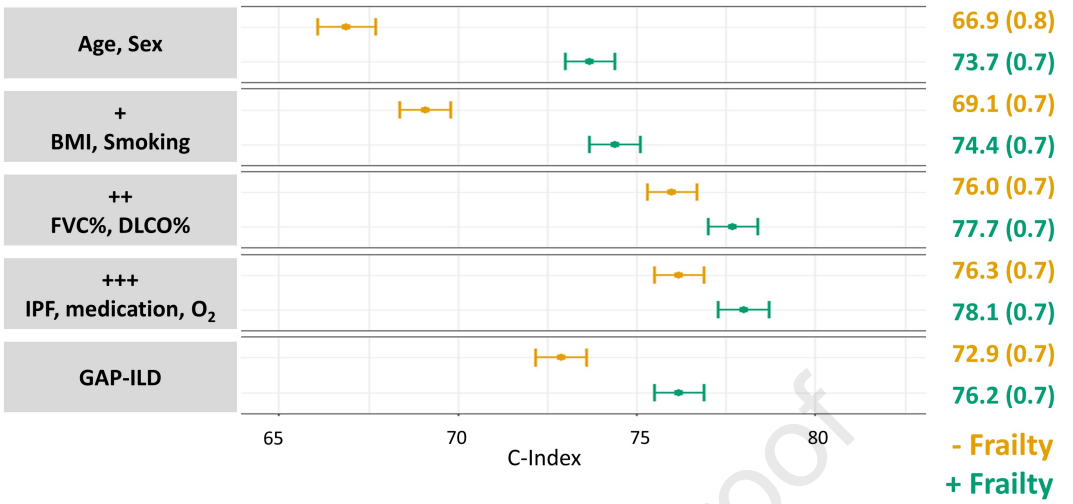


Number at risk

Fit	858	812	699	558	429	332
Vulnerable	400	340	273	201	141	103
Frail	329	252	178	118	88	54



A)



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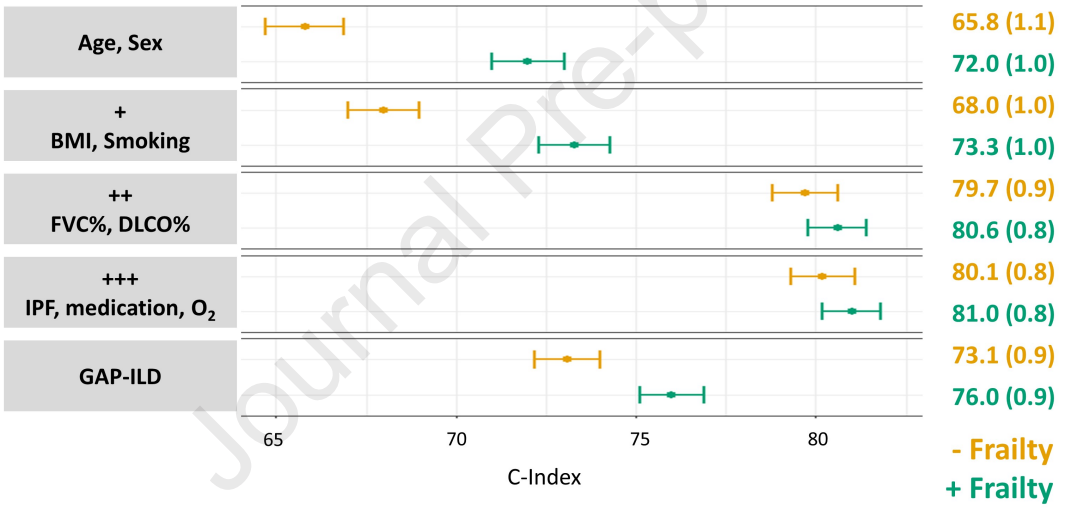


SUPPLEMENTAL MATERIAL

The clinical frailty scale for risk stratification in patients with fibrotic interstitial lung disease

e-Table 1. Description of the Clinical Frailty Scale

Clinical Frailty Scale (1, 2)		Description
1	Very Fit	People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.
2	Well	People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.
3	Managing well	People whose medical problems are well controlled but are not regularly active beyond routine walking.
4	Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “slowed up”, and/or being tired during the day.
5	Mildly frail	These people often have more evident slowing, and need help in high order instrumental activities of daily living (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
6	Moderately frail	People need help with all outside activities and with keeping house. Inside they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing
7	Severely frail	Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
8	Very Severely frail	Completely dependent, approaching the end of life. Typically, they could not recover from a minor illness.
9	Terminally ill	Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

e-Table 2. Patient characteristics in the derivation and validation cohort

	Derivation cohort n=1084	Validation cohort n=503
	mean ± standard deviation or number (percent)	
Age, years	65.7±12.1	66.2±11.5
Sex, male	578 (53%)	291 (58%)
BMI, kg/m²	26.8±5.8	26.7±5.3
Ever smoker	662 (61%)	328 (65%)
Pack years	14.7±20	18.6±22
FUNCTIONAL TESTS		
FVC, %-predicted	74.7±21	70.4±21
DLCO, %-predicted	50.6±19	53.5±22
6MWD, meters	373±131	351±125
6MWD, %-predicted	74.6±26	70.9±24
DIAGNOSIS		
IPF	259 (24%)	185 (37%)
CTD-ILD	498 (46%)	184 (36%)
Fibrotic HP	145 (13%)	53 (10%)
Unclassifiable ILD	120 (11%)	36 (7%)
TREATMENT		
Antifibrotic	25 (2%)	10 (2%)
Immunosuppressive	340 (31%)	107 (21%)
Any ILD treatment	359 (33%)	117 (23%)
OUTCOMES		
Died	305 (28%)	136 (27%)
Lung transplant	49 (5%)	34 (7%)
FRAILTY		
Frailty (CFS continuous)	3.61±1.2	3.48±1.0
Fit (CFS ≤3)	570 (53%)	288 (57%)
Vulnerable (CFS 4)	257 (24%)	143 (28%)
Frail (CFS ≥5)	257 (24%)	72 (14%)

Abbreviations: BMI, body mass index; CFS, clinical frailty scale; CTD, connective tissue disease; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; 6MWD, 6-minute walk distance

e-Table 3. Mortality risk in vulnerable and frail versus fit patients in the derivation and the validation cohort.

	Crude models		**Adjusted models**	
	DERIVATION COHORT			
n=1084	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Time to death or lung transplant			
Vulnerable	2.42 (1.79-3.27)	<0.001	1.69 (1.15-2.49)	0.008
Frail	5.03 (3.83-6.60)	<0.001	2.73 (1.83-4.07)	<0.001
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
	1-year mortality			
Vulnerable	4.98 (2.11-11.7)	<0.001	3.32 (1.81-6.12)	<0.001
Frail	14.1 (6.53-30.5)	<0.001	7.18 (3.93-13.1)	<0.001
	2-year mortality			
Vulnerable	3.32 (2.01- 5.46)	<0.001	2.65 (1.37-5.12)	0.004
Frail	8.14 (5.17-12.8)	<0.001	5.11 (2.55-10.2)	<0.001
	5-year mortality			
Vulnerable	2.60 (1.83-3.69)	<0.001	1.89 (1.59-2.26)	<0.001
Frail	5.70 (4.06-8.01)	<0.001	2.91 (2.37-3.57)	<0.001
	VALIDATION COHORT			
n=503	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Time to death or lung transplant			
Vulnerable	2.53 (1.69-3.77)	<0.001	1.50 (0.87-2.58)	0.14
Frail	3.46 (2.21-5.42)	<0.001	2.70 (1.48-4.91)	0.001
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
	1-year mortality			
Vulnerable	5.99 (1.87-19.1)	0.003	2.21 (0.52-9.42)	0.28
Frail	8.78 (2.56-30.1)	<0.001	4.65 (0.91-23.9)	0.07
	2-year mortality			
Vulnerable	4.85 (2.22- 10.6)	<0.001	2.61 (0.93-7.33)	0.07
Frail	7.86 (3.39-18.2)	<0.001	6.24 (1.99-19.5)	0.002
	5-year mortality			
Vulnerable	2.68 (1.68-4.25)	<0.001	1.48 (0.73-3.00)	0.28
Frail	3.85 (2.21-6.73)	<0.001	2.97 (1.27-6.96)	0.01

Hazard of early death or lung transplantation (hazard radio, HR) or the odds for death or lung transplantation at 1-,2- and 5-years after baseline (odds ratio, OR) compared to fit patients (reference group). CFS, Clinical Frailty Scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5

[†]accounting for clustering by center

¥additionally adjusted for age, sex, body mass index, ever smoking, IPF diagnosis, FVC %-predicted, DLCO %-predicted, oxygen therapy and ILD drug treatment (fixed effects).

e-Table 4. Pulmonary and physical function trajectories in fit, vulnerable, and frail patients with IPF.

IPF	Crude Model†		Adjusted model¥	
	Mean annual change (95% CI)	*p-value for interaction*	*Mean annual change (95% CI)*	*p-value for interaction*
n=408	**Change in FVC %-predicted**			
Fit	-2.62 (-3.57 to -2.14)	-	-2.60 (-3.51 to -1.91)	-
Vulnerable	-3.48 (-5.86 to -1.93)	0.17	-3.48 (-5.37 to -1.35)	0.19
Frail	-4.67 (-7.19 to -2.67)	0.006	-4.67 (-6.86 to -2.54)	0.006
n=383	**Change in DLCO %-predicted**			
Fit	-3.74 (-4.42 to -3.17)	-	-3.73 (-4.63 to -3.10)	-
Vulnerable	-4.88 (-7.48 to -2.93)	0.12	-4.86 (-8.37 to -2.81)	0.09
Frail	-5.78 (-8.40 to -3.61)	0.02	-5.77 (-9.75 to -3.45)	0.06
n=245	**Change in 6MWD %-predicted**			
Fit	-4.47 (-6.07 to -3.29)	-	-4.48 (-6.17 to -3.14)	-
Vulnerable	-7.30 (-11.9 to -3.93)	0.03	-7.34 (-13.3 to -3.69)	0.046
Frail	-4.98 (-11.8 to -0.14)	0.82	-4.80 (-13.8 to 1.46)	0.91

Mean annual changes are significantly different from zero, if 95% confidence intervals (CI) do not cross zero. Negative estimates signify a decline. P-values for interaction refer to differences in slopes between vulnerable or frail and fit (reference) patients.
†accounting for informal drop out due to death or lung transplantation
¥adjusted for age, sex, body mass index, ever smoking, and ILD drug treatment (fixed effects).

Abbreviations: CFS, clinical frailty scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5
DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; 6MWD, 6-minute walk distance

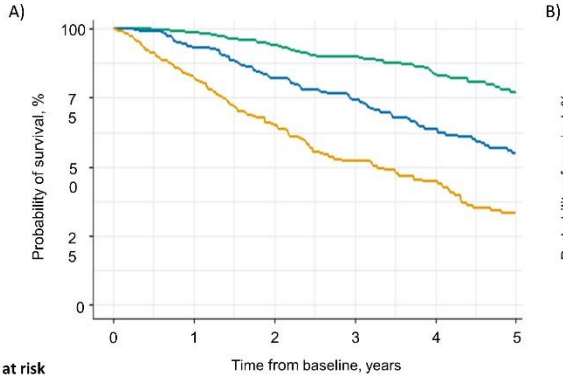
e-Table 5. Pulmonary and physical function trajectories in fit, vulnerable, and frail patients with CTD-ILD.

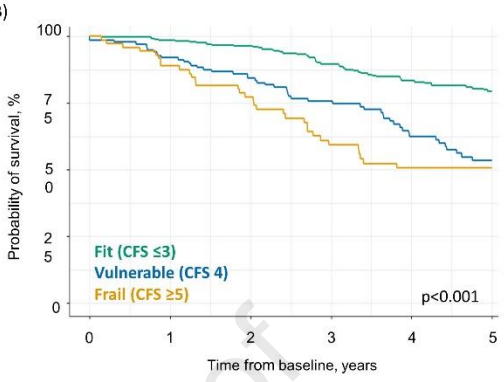
CTD-ILD	Crude Model†		Adjusted model¥	
	Mean annual change (95% CI)	*p-value for interaction*	*Mean annual change (95% CI)*	*p-value for interaction*
n=628	**Change in FVC %-predicted**			
Fit	-0.63 (-0.98 to -0.17)	-	-0.63 (-1.19 to -0.28)	-
Vulnerable	-0.79 (-2.56 to 0.40)	0.74	-0.80 (-2.16 to 0.15)	0.70
Frail	-0.65 (-2.27 to 1.15)	0.96	-0.66 (-2.16 to 1.07)	0.96
n=598	**Change in DLCO %-predicted**			
Fit	-0.70 (-1.22 to -0.20)	-	-0.69 (-1.22 to -0.22)	
Vulnerable	-0.93 (-3.02 to 0.60)	0.71	-0.88 (-2.54 to 0.79)	0.76
Frail	-1.25 (-3.01 to 0.50)	0.38	-1.06 (-2.75 to 0.67)	0.58
n=441	**Change in 6MWD %-predicted**			
Fit	-0.58 (-1.49 to 0.37)	-	-0.56 (-1.44 to 0.30)	-
Vulnerable	-2.66 (-5.67 to 0.01)	<0.001	-2.65 (-5.34 to -0.20)	0.02
Frail	-2.40 (-5.32 to 0.21)	0.07	-2.28 (-5.73 to 0.08)	0.09

Mean annual changes are significantly different from zero, if 95% confidence intervals (CI) do not cross zero. Negative estimates signify a decline. P-values for interaction refer to differences in slopes between vulnerable or frail and fit (reference) patients.
†accounting for informal drop out due to death or lung transplantation
¥adjusted for age, sex, body mass index, ever smoking, and ILD drug treatment (fixed effects).

Abbreviations: CFS, clinical frailty scale; Fit, CFS ≤3; Vulnerable, CFS 4; Frail, CFS ≥5
CTD-ILD, connective tissue disease associated interstitial lung disease; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; 6MWD, 6-minute walk distance

e-Figure 1. Survival by frailty in the derivation (A) and validation (B) cohort.





Number at risk												
Fit	570	537	438	346	252	191	288	275	261	212	177	141
Vulnerable	257	215	172	123	88	62	143	124	101	78	53	41
Frail	257	189	128	83	59	30	72	63	50	35	29	24

Abbreviations: CFS, clinical frailty scale

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