Lung function trajectory in progressive fibrosing interstitial lung disease

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Shareable abstract (@ERSpublications)
Lung function trajectory varies considerably following ILD diagnosis and after satisfying proposed PF-ILD criteria according to ILD diagnosis. These findings suggest diagnosis should be taken into consideration when designing ILD clinical trials. https://bit.ly/2ZF8C7V

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Abstract

Background Proposed criteria for progressive fibrosing interstitial lung disease (PF-ILD) have been linked to increased mortality risk, but lung function trajectory after satisfying individual criteria remains unknown. Because survival is rarely employed as the primary end-point in therapeutic trials, identifying PF-ILD criteria that best predict subsequent change in forced vital capacity (FVC) could improve clinical trial design.

Methods A retrospective, multicentre longitudinal cohort analysis was performed in consecutive patients with fibrotic connective tissue disease-associated ILD (CTD-ILD), chronic hypersensitivity pneumonitis and idiopathic interstitial pneumonia at three US centres (test cohort) and one UK centre (validation cohort). 1-year change in FVC after satisfying proposed PF-ILD criteria was estimated using joint modelling. Subgroup analyses were performed to determine whether results varied across key subgroups.

Results 1227 patients were included, with CTD-ILD predominating. Six out of nine PF-ILD criteria were associated with differential 1-year change in FVC, with radiological progression of fibrosis, alone and in combination with other features, associated with the largest subsequent decline in FVC. Findings varied significantly by ILD subtype, with CTD-ILD demonstrating little change in FVC after satisfying most PF-ILD criteria, while other ILDs showed significantly larger changes. Findings did not vary after stratification by radiological pattern or exposure to immunosuppressant therapy. Near-term change in FVC after satisfying proposed PF-ILD criteria was heterogeneous depending on the criterion assessed and was strongly influenced by ILD subtype.

Conclusions These findings may inform future clinical trial design and suggest ILD subtype should be taken into consideration when applying PF-ILD criteria.

Introduction

Progressive fibrosing interstitial lung disease (PF-ILD) is a devastating clinical phenotype characterised by progressive lung function decline despite therapy and confers a high morbidity and mortality [1–4]. While nearly all patients with idiopathic pulmonary fibrosis (IPF) ultimately adopt this behaviour, variable proportions of other ILD subtypes develop a progressive phenotype. Among the most common ILDs to result in PF-ILD are connective tissue disease-associated ILD (CTD-ILD), chronic hypersensitivity pneumonitis (CHP) and non-IPF idiopathic interstitial pneumonia (IIP) [2, 5]. A number of criteria have

been proposed to identify a PF-ILD phenotype, including categorical decline in lung function, increasing fibrotic extent on chest imaging, symptomatic worsening and composite measures of these [5–7].

While most proposed PF-ILD criteria associated with increased mortality risk [8–13], survival is rarely employed as a primary end-point in therapeutic trials due to the follow-up time required. Instead, near-term disease progression, measured by change in forced vital capacity (FVC), is generally utilised as the primary end-point in ILD clinical trials [5, 14] given its association with survival [8, 10]. Whether proposed PF-ILD criteria identify those most likely to experience subsequent FVC decline remains unclear. A recent *post hoc* analysis of the INBUILD (Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing Interstitial Lung Disease) trial suggested that FVC decline was heterogeneous depending on the PF-ILD criterion satisfied [15]. Such heterogeneity may have implications for clinical trial design, as currently proposed PF-ILD criteria may differentially select patients most likely to experience near-term change in FVC.

In this investigation we conducted a multicentre, retrospective, longitudinal cohort analysis of patients with CTD-ILD, CHP and non-IPF IIP to estimate mean change in FVC following ILD diagnosis and after satisfying potential criteria for PF-ILD. We hypothesised that 1-year change in FVC after satisfying individual PF-ILD criteria would be heterogeneous. A test and validation approach was pursued, with three US centres comprising the test cohort and one UK centre the validation cohort. Heterogeneity analyses were performed to determine whether change in FVC after satisfying proposed PF-ILD criteria varied by key subgroups, including ILD subtype, CTD subtype, IIP subtype, radiological pattern, baseline FVC and treatment exposure.

Methods

Study cohorts

This study was performed at the University of California at Davis (UC-Davis; Sacramento, CA, USA), University of Chicago (UChicago; Chicago, IL, USA), University of Texas Southwestern (UTSW; Dallas, TX, USA) and Royal Brompton Hospital (RBH; London, UK), with US-based centres serving as the test cohort and RBH serving as the validation cohort. All US patients provided informed consent to participate in site-specific ILD registries (UC-Davis 928979, UChicago 13-1180, and UTSW 092017-007 and 082010-127) and UK approval for the study was obtained from the local Research Ethics Committee (19/LO/1879). Consecutive patients aged ⩾18 years with a multidisciplinary diagnosis of CTD-ILD, CHP and non-IPF IIP undergoing evaluation for ILD at UC-Davis (January 2014–June 2018), UChicago (January 2006–June 2018), UTSW (January 2006–June 2018) and RBH (January 2010–December 2014) were identified (supplementary figure E1). Patients with at least 6 months of follow-up and two pulmonary function tests (PFTs) performed following baseline PFT were eligible for inclusion. Patients were excluded when 1) fibrotic extent was determined to be <10% on high-resolution computed tomography (HRCT) performed at the time of presentation, as determined by site investigator, 2) baseline HRCT was unavailable, 3) baseline spirometry and gas transfer measures were unavailable or 4) first follow-up PFT was performed >24 months after baseline PFT.

The CTD-ILD cohort was comprised of patients with ILD due to systemic sclerosis (SSc), rheumatoid arthritis, idiopathic inflammatory myopathy (IIM), Sjögren's disease, systemic lupus erythematosus, mixed connective tissue disease and vasculitis. The IIP cohort was comprised of patients with idiopathic non-specific interstitial pneumonia, cryptogenic organising pneumonia and unclassifiable ILD. Treatment exposure was determined by review of the medical record with dates of antifibrotic (pirfenidone or nintedanib) and immunosuppressant (mycophenolate mofetil, azathioprine, rituximab or cyclophosphamide) therapy recorded for each patient. Treatment exposure was considered present when exposure time exceeded >50% of the follow-up period after satisfying each proposed PF-ILD criterion.

PF-ILD criteria

We assessed six previously proposed PF-ILD criteria and their constituent parts. Previously proposed PF-ILD criteria: ⩾5% absolute decline in FVC % pred [6, 7]; 5–9% relative decline in FVC % pred with worsening respiratory symptoms [5, 16]; 5–9% relative decline in FVC % pred with CT progression of fibrosis [5, 16]; 5–9% relative decline in FVC % pred with ⩾15% relative decline in diffusing capacity of the lung for carbon monoxide (D_{LCO}) % pred [16]; ⩾10% relative decline in FVC % pred [5, 16]; and CT progression of fibrosis with worsening respiratory symptoms [5, 16]. PF-ILD criteria constituent parts: ⩾5% relative decline in FVC % pred alone; CT progression of fibrosis alone; and ⩾15% relative decline in D_{LCO} % pred alone.

The PFT performed closest to the date of evaluation at each centre served as the entry date for time-to-event modelling and when determining annual change in FVC following ILD diagnosis. The date of increasing extent of fibrosis and first observed categorical decline in FVC and D_{LCO} was identified using the medical record and longitudinal PFT databases at each institution, respectively, and served as the entry date for estimating 1-year change in FVC after satisfying proposed PF-ILD criteria. The ⩾15% relative decline in D_{LCO} criterion was considered satisfied when unable to perform this manoeuvre. Date of worsening fibrosis extent on HRCT, defined qualitatively by any mention of fibrotic "worsening" or "progression", was ascertained by review of the radiology report. Worsening respiratory symptoms were considered present when documented within 180 days of the associated PF-ILD criterion of interest (CT progression or 5–9% relative FVC decline). PF-ILD criteria were applied until 1 July 2019 and follow-up PFTs evaluated through 30 June 2020.

Longitudinal FVC analysis

Mean annual change in FVC following ILD diagnosis and mean 1-year change in FVC after satisfying PF-ILD criteria were estimated using a joint model. Joint modelling includes a mixed effects submodel to account for repeated measures and a survival submodel to account for the effect of informative dropout (due to death or lung transplant) on the repeated measure of interest (FVC) [17, 18]. The longitudinal submodel employed included a random intercept term, a fixed slope term and an independent covariance structure. The survival submodel employed assumed a Weibull distribution. Each submodel was adjusted for cohort, ILD diagnosis, sex, race and HRCT pattern at baseline, age, FVC (% pred) and D_{LCO} (% pred) at the time a PF-ILD criterion was satisfied, and immunosuppressant exposure after satisfying a PF-ILD criterion. Missing D_{LCO} values at the time a PF-ILD criterion was satisfied were imputed to the lowest quartile mean (25%) when unable to be performed.

Cohorts were combined and heterogeneity testing performed using a subgroup-by-time interaction term to assess whether the association between PF-ILD criteria and subsequent FVC change varied between key subgroups, including cohorts, US centres, ILD subtype, CTD-ILD subtypes, IIP subtypes, radiological pattern subtypes, baseline FVC subgroups and treatment groups. All statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA). Statistical significance was set to $p<0.006$ to correct for multiple testing of nine PF-ILD criteria.

Results

Cohort characteristics

Of 1228 patients screened in the US cohort and 990 patients screened in the UK cohort, 754 and 473 met inclusion and exclusion criteria, respectively (figure 1). CTD-ILD was the most common ILD subtype, comprising ∼40% of each cohort, followed by non-IPF IIP and CHP (table 1). US cohort patients were older than UK cohort patients (61.7 *versus* 58.7 years), with slightly higher proportions of males and non-White race. Patients had moderate lung function impairment at the time of enrolment, with those in the US cohort having higher mean FVC and D_{LCO} % pred. A definite or probable usual interstitial pneumonia (UIP) pattern was observed in 26% of US patients and 11% of UK patients. Over half of patients in each cohort received immunosuppressant therapy during the follow-up period, with higher usage in the UK cohort (69% compared with 53% in the US cohort). A small percentage of each cohort received antifibrotic therapy during the follow-up period.

FVC trajectory after ILD diagnosis

Mean annual FVC change following ILD diagnosis was −69.9 mL (95% CI −75.5–−64.4 mL) in the US cohort and −50.0 mL (95% CI −55.6–−44.4 mL) in the UK cohort (figure 2a). After combining cohorts, mean annual FVC change was −37.2 mL (95% CI −42.9–−31.6 mL) in the CTD-ILD cohort (n=487), −92.0 mL (95% CI −99.6–−84.3 mL) in the CHP cohort (n=342) and −69.5 mL (95% CI −77.2–−61.8 mL) in the IIP cohort (n=398) (figure 2b). Among those with CTD-ILD, IIM-ILD patients demonstrated relatively little FVC change and more pronounced, yet similar, rates of FVC decline among other CTD-ILDs (figure 2c). Among those with IIP, unclassifiable ILD patients displayed significantly more annual FVC decline compared with those with idiopathic non-specific interstitial pneumonia (figure 2d). Among radiological subgroups, those with definite/probable UIP experienced more annual FVC decline compared with those with non-UIP patterns (figure 2e). After stratification by baseline FVC, little annual change in FVC was observed among patients with baseline FVC <45% predicted, while larger declines were observed in those with FVC 45–80% and >80% predicted (figure 2f).

PF-ILD natural history

The most common PF-ILD criteria satisfied was ⩾5% relative FVC decline, which was observed in 72.3% of patients in the US cohort and 65.8% of patients in the UK cohort (supplementary table E1). Among

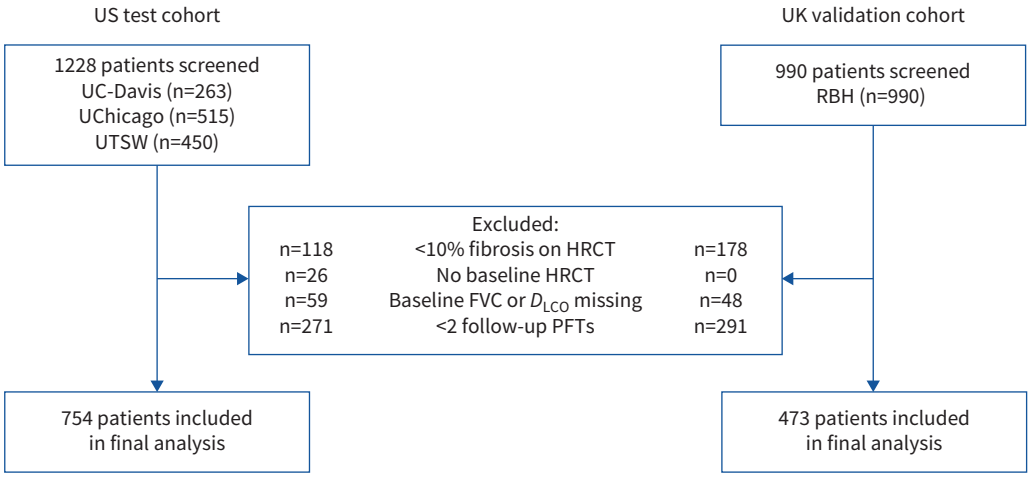


FIGURE 1 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram. UC-Davis: University of California at Davis; UChicago: University of Chicago; UTSW: University of Texas Southwestern; RBH: Royal Brompton Hospital; HRCT: high-resolution computed tomography; FVC: force vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; PFT: pulmonary function test.

those experiencing 5–9% relative decline in FVC, concurrent D_{LCO} decline of ⩾15% was more common than concurrent CT progression of fibrosis or worsening respiratory symptoms. When assessing the time to satisfy key features of the PF-ILD criteria (figure 3 and supplementary table E1), median time was shortest for ⩾5% relative FVC decline and longest for CT progression of fibrosis in each cohort. The median time to satisfy each feature was generally longer in the UK cohort compared with the US cohort. Similar PF-ILD natural history was observed when stratifying the combined cohort by ILD diagnosis (supplementary figure E2) and HRCT pattern (supplementary figure E3).

FVC trajectory after satisfying PF-ILD criteria

Differential 1-year change in FVC was observed after satisfying seven of nine proposed PF-ILD criteria in the US cohort, six of which replicated in the UK validation cohort (table 2). CT progression of fibrosis, alone and in combination with other measures, was associated with the largest subsequent FVC decline in both cohorts, followed by 5–9% FVC decline with worsening respiratory symptoms and 5–9% FVC decline with ⩾15% D_{LCO} decline. One-year change in FVC following categorical declines in FVC of ⩾5% and ⩾10% was roughly half that observed following ILD diagnosis alone. Interaction testing did not detect heterogeneity in FVC trajectory after satisfying individual PF-ILD criterion between US and UK cohorts (table 2) or between individual US centres (supplementary table E2).

Significant heterogeneity in FVC change after satisfying PF-ILD criteria was observed between ILD subgroups and was driven primarily by the CTD-ILD cohort, as no further heterogeneity was observed between the CHP and IIP cohorts (table 3). Stratified analysis showed that four PF-ILD criteria were associated with subsequent change in FVC for those with CTD-ILD (table 3), while all PF-ILD criteria were associated with significant subsequent decline in FVC in those with CHP and non-IPF IIP. CT progression of fibrosis, alone or in combination with other measures, was associated with the largest subsequent FVC decline in those with CHP and IIP (table 3), while 5–9% FVC decline with worsening respiratory symptoms was associated with the largest subsequent FVC decline in patients with CTD-ILD. Those with CTD-ILD had a significant subsequent increase in FVC after experiencing a categorical FVC decline of ⩾10%, while those with CHP experienced only modest subsequent FVC decline.

When assessing CTD-ILD subgroups, significant heterogeneity was observed between those with IIM-ILD and other CTD-ILDs for several PF-ILD criteria (supplementary table E3). No further heterogeneity was detected after excluding patients with IIM-ILD (supplementary table E3). No heterogeneity was detected between IIP subgroups (supplementary table E4). Heterogeneity in 1-year FVC change after satisfying several PF-ILD criteria was observed between radiological subgroups (supplementary table E5) and physiological subgroups stratified by baseline FVC (supplementary table E6). When assessing treatment subgroups, no heterogeneity was observed among patients with and without antifibrotic exposure, although antifibrotic-exposed subgroups were small (supplementary table E7). No significant heterogeneity was

TABLE 1 Baseline characteristics for the US test and UK validation cohorts

	US test cohort (n=754)	UK validation cohort (n=473)
Centre		
University of California at Davis	179 (23.7)	
University of Chicago	311 (41.3)	
University of Texas Southwestern	264 (35.0)	
Royal Brompton Hospital		473 (100)
Age (years)	61.7±12.3	58.7±12.7
Male	314 (41.6)	182 (38.5)
Race/ethnicity		
White	523 (69.4)	350 (74.0)
Black	141 (18.7)	18 (3.8)
Hispanic	60 (8.0)	0 (0)
Asian	25 (3.3)	105 (22.2)
Other/unknown	5 (0.7)	0 (0)
Ever-smoker	358 (47.5)	174 (36.8)
Body mass index (kg·m^{-2})	30.2±8.7	28.6±5.6
ILD classification		
CTD-ILD	303 (40.2)	184 (38.9)
RA-ILD	81 (10.7)	38 (8.0)
SSc-ILD	78 (10.3)	58 (12.3)
IIM-ILD	66 (8.8)	38 (8.0)
Other CTD-ILD	78 (14.7)	50 (14.8)
CHP	224 (29.7)	118 (25.0)
IIP (non-IPF)	227 (30.1)	171 (36.2)
iNSIP	90 (11.9)	78 (16.5)
uILD	136 (18.0)	72 (15.2)
COP	1 (0.2)	21 (6.5)
Pulmonary function		
FVC (% pred)	67.1±21.8	62.5±17.2
D_{LCO} (% pred)	42.6±19.1	37.5±12.4
HRCT pattern		
Definite/probable UIP	193 (25.6)	53 (11.2)
Indeterminate for UIP	96 (12.7)	95 (20.1)
Alternate diagnosis	465 (61.7)	325 (68.7)
Treatment		
Antifibrotic exposure	93 (12.4)	26 (5.5)
Immunosuppressant treatment	406 (53.9)	328 (69.3)

Data are presented as n (%) or mean±SD. ILD: interstitial lung disease; CTD-ILD: connective tissue disease-associated ILD; RA-ILD: rheumatoid arthritis-associated ILD; SSc-ILD: systemic sclerosis-associated ILD; IIM-ILD: idiopathic inflammatory myopathy-related ILD; CHP: chronic hypersensitivity pneumonitis; IIP: idiopathic interstitial pneumonia; iNSIP: idiopathic non-specific interstitial pneumonia; uILD: unclassifiable ILD; COP: cryptogenic organising pneumonia; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

observed among subgroups with and without immunosuppressant exposure, irrespective of ILD diagnosis (supplementary table E8).

Discussion

In this investigation we determined mean annual change in FVC following ILD diagnosis and 1-year change in FVC after satisfying previously proposed PF-ILD criteria in two geographically diverse non-IPF ILD cohorts. We demonstrated that mean annual change in FVC following ILD diagnosis was heterogeneous among key ILD strata and that mean 1-year change in FVC after satisfying proposed PF-ILD criteria was highly heterogeneous depending on the criterion satisfied. CT progression of fibrosis, alone and in combination with other features, better predicted subsequent FVC decline than categorical declines in FVC or D_{LCO}. We also showed that these associations were strongly influenced by ILD subtype, with CTD-ILD patients showing significantly less change in FVC when compared with those with CHP and IIP. To the best of our knowledge, this study is the first to assess proposed PF-ILD criteria as they relate to near-term change in FVC, and sheds important light on the concept of PF-ILD, proposed

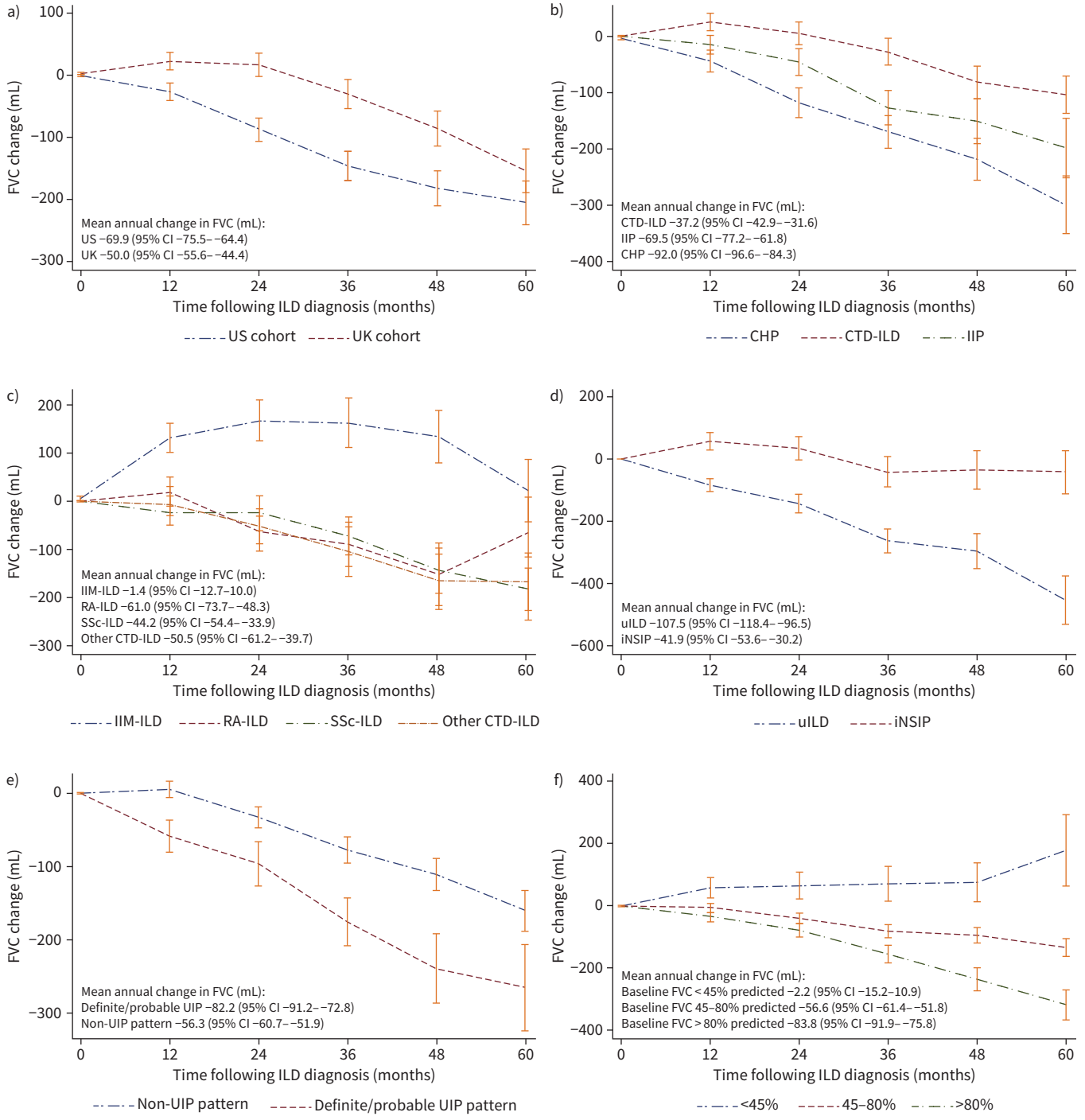
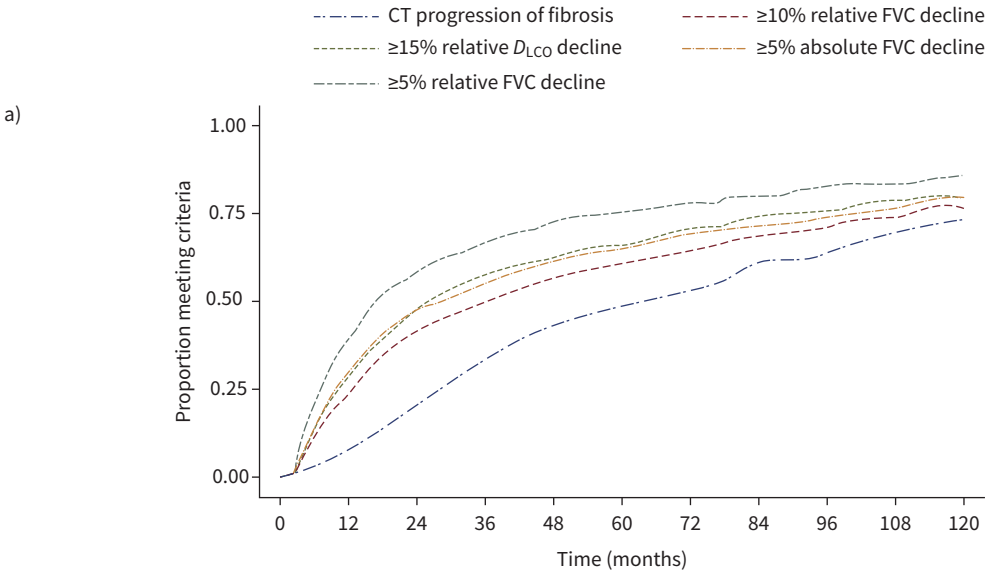


FIGURE 2 Mean annual change in force vital capacity (FVC) following interstitial lung disease (ILD) diagnosis for subgroups stratified by a) cohort, b) diagnosis, c) connective tissue disease-associated ILD (CTD-ILD) diagnosis, d) idiopathic interstitial pneumonia (IIP) diagnosis, e) baseline high-resolution computed tomography pattern and f) baseline FVC. CHP: chronic hypersensitivity pneumonitis; IIM-ILD: idiopathic inflammatory myopathy-related ILD; RA-ILD: rheumatoid arthritis-associated ILD; SSc-ILD: systemic sclerosis-associated ILD; uILD: unclassifiable ILD; iNSIP: idiopathic non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.

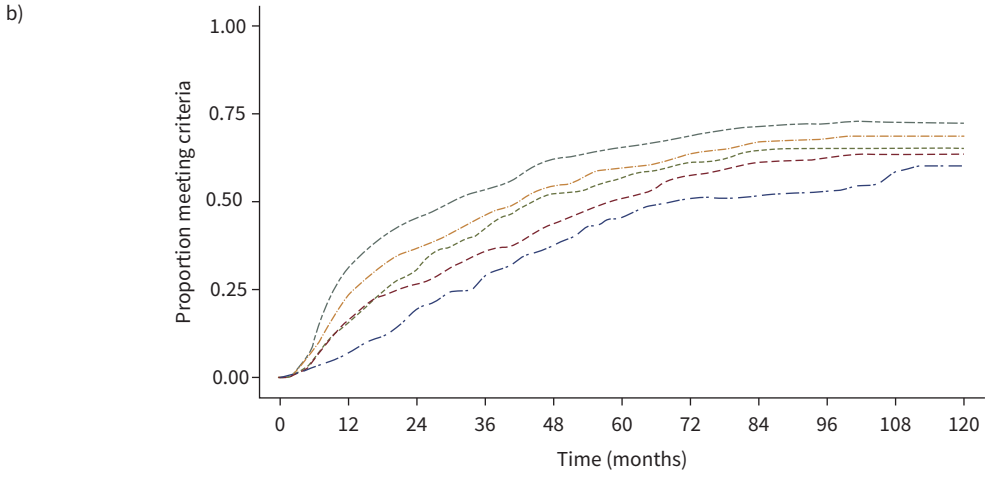
criteria underpinning this phenotype and the use of these criteria when designing future PF-ILD clinical trials.

The PF-ILD construct emerged from the observation that a proportion of patients with non-IPF ILD display an IPF-like natural history [1–3, 16]. This observation, and the shared pathobiology it implies,



At risk (n):

CT progression of fibrosis	634	568	453	300	200	145	100	64	45	32	27
≥10% relative FVC decline	754	567	396	276	177	119	85	58	42	32	26
≥15% relative D_{LCO} decline	754	531	353	232	160	116	78	55	38	28	22
≥5% absolute FVC decline	754	516	352	245	154	108	76	54	39	31	24
≥5% relative FVC decline	754	450	283	183	114	81	58	39	28	24	19



At risk (n):

CT progression of fibrosis	377	350	292	248	203	164	134	101	71	36	7
≥10% relative FVC decline	473	393	321	262	197	156	125	86	59	26	4
≥15% relative D_{LCO} decline	473	399	303	241	170	141	113	78	51	28	7
≥5% absolute FVC decline	473	364	276	222	160	128	107	75	51	24	4
≥5% relative FVC decline	473	329	240	192	136	111	92	66	43	22	4

FIGURE 3 Time to computed tomography (CT) progression of fibrosis and key measures of lung function decline in the a) US and b) UK cohorts. FVC: force vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

resulted in several clinical trials aimed at determining whether antifibrotic therapy approved for the treatment of IPF also slowed lung function decline in patients with a PF-ILD phenotype [5, 6, 19]. Two trials of pirfenidone suggested therapeutic efficacy but suffered from technical issues [6] and low enrolment [7]. The INBUILD trial demonstrated nintedanib to effectively slow FVC decline in this population [5], leading to its recent approval. While the pirfenidone trials relied largely on an absolute decline in FVC of ⩾5%, INBUILD inclusion criteria mandated that patients display ⩾10% relative decline

TABLE 2 One-year mean change in forced vital capacity (FVC) after satisfying proposed progressive fibrosing interstitial lung disease (PF-ILD) criteria

PF-ILD criterion	US test cohort			UK validation cohort			p-value US *versus* UK
	n	Change (mL (95% CI))	p-value	n	Change (mL (95% CI))	p-value	
⩾5% absolute FVC decline	467	−31.9 (−56.5–−7.2)	0.011	282	−37.7 (−63.6–−11.8)	0.004	0.578
⩾5% relative FVC decline	544	−32.0 (−53.9–−10.1)	0.004	310	−27.9 (−51.9–−51.9)	0.023	0.946
5–9% relative FVC decline with worsening respiratory symptoms[#]	124	−91.8 (−136.7–−46.9)	<0.001	81	−92.3 (−138.1–−46.6)	<0.001	0.956
5–9% relative FVC decline with CT progression of fibrosis[#]	86	−126.6 (−174.6–−78.6)	<0.001	63	−155.5 (−216.6–−94.4)	<0.001	0.483
5–9% relative FVC decline with ⩾15% relative decline in D_{LCO}[#]	179	−91.9 (−126.7–−57.1)	<0.001	102	−86.3 (−124.2–−48.4)	<0.001	0.920
⩾10% relative FVC decline	436	−7.8 (−33.6–18.0)	0.552	249	−42.3 (−71.7–−13.1)	0.005	0.066
⩾15% relative D_{LCO} decline	480	−64.0 (−87.6–−40.5)	<0.001	268	−69.0 (−96.4–−41.6)	<0.001	0.808
CT progression of fibrosis	291	−122.7 (−153.5–−91.8)	<0.001	186	−140.3 (−176.1–−104.5)	<0.001	0.491
CT progression of fibrosis with worsening respiratory symptoms	183	−144.1 (−185.1–−103.2)	<0.001	168	−152.7 (−191.2–−114.2)	<0.001	0.787

CT: computed tomography; D_{LCO}: diffusing capacity of the lung for carbon monoxide. Model adjusted for cohort, ILD diagnosis, sex, race and high-resolution CT pattern at baseline, age, FVC (% pred) and D_{LCO} (% pred) at the time a PF-ILD criterion was satisfied, and immunosuppressant exposure in the 12 months after a PF-ILD criterion was satisfied. [#]: excluded patients with ⩾10% relative FVC decline.

in FVC or a combination of 5–9% FVC decline, increasing extent of fibrosis on HRCT or worsening respiratory symptoms in the 2 years prior to trial enrolment.

While those with CHP and IIP experienced similar rates of FVC decline after satisfying proposed PF-ILD criteria when compared with placebo-treated patients in the INBUILD trial, the same was not true for patients with CTD-ILD. This group experienced relatively little FVC decline after satisfying proposed PF-ILD criteria in both US and UK cohorts. Some heterogeneity in FVC trajectories was also likely

TABLE 3 One-year mean change in forced vital capacity (FVC) after satisfying proposed progressive fibrosing interstitial lung disease (PF-ILD) criterion stratified by ILD subgroup

PF-ILD criterion	CTD cohort (n=487)		CHP cohort (n=342)		IIP cohort (n=398)		p-value CTD *versus* CHP/IIP	p-value CHP *versus* IIP
	n	Change (mL (95% CI))	n	Change (mL (95% CI))	n	Change (mL (95% CI))		
⩾5% absolute FVC decline	279	21.7 (−7.5–50.9)	236	−58.6 (−90.1–−27.1)	233	−79.1 (−112.8–−45.3)	<0.001	0.319
⩾5% relative FVC decline	321	18.8 (−6.7–44.2)	264	−60.9 (−90.3–−31.4)	269	−63.1 (−94.4–−31.9)	<0.001	0.770
5–9% relative FVC decline with worsening respiratory symptoms[#]	73	−84.5 (−142.0–−27.1)	59	−97.7 (−164.0–−31.4)	73	−95.8 (−143.7–−48.0)	0.684	0.851
5–9% relative FVC decline with CT progression of fibrosis[#]	55	−41.2 (−105.4–23.0)	46	−200.8 (−277.8–−123.8)	48	−188.6 (−238.4–−138.7)	<0.001	0.771
5–9% relative FVC decline with ⩾15% relative decline in D_{LCO}[#]	96	−49.7 (−94.7–−4.6)	78	−136.3 (−187.4–−85.1)	107	−87.8 (−128.7–−47.0)	0.028	0.108
⩾10% relative FVC decline	251	48.6 (18.3–78.8)	221	−55.3 (−88.9–−21.7)	213	−74.4 (−112.1–−36.6)	<0.001	0.400
⩾15% relative D_{LCO} decline	280	−25.3 (−52.3–1.7)	217	−103.6 (−135.5–−71.7)	251	−81.7 (−117.1–−46.3)	0.001	0.363
CT progression of fibrosis	191	−51.8 (−87.7–−16.0)	131	−187.2 (−237.2–−137.2)	155	−179.1 (−216.5–−141.7)	<0.001	0.929
CT progression of fibrosis with worsening respiratory symptoms	131	−65.8 (−113.4–−18.2)	101	−222.3 (−281.3–−163.4)	119	−180.8 (−223.1–−138.6)	<0.001	0.328

CT: computed tomography; D_{LCO}: diffusing capacity of the lung for carbon monoxide. Model adjusted for cohort, sex, race and high-resolution CT pattern at baseline, age, FVC (% pred) and D_{LCO} (% pred) at the time a PF-ILD criterion was satisfied, and immunosuppressant exposure in the 12 months after a PF-ILD criterion was satisfied. [#]: excluded patients with ⩾10% relative FVC decline

present in the INBUILD cohort, as a recent *post hoc* analysis by Wells *et al.* [20] showed variable nintedanib treatment effect across individual ILDs, although without reporting ILD-specific FVC trajectories. The reason for variable progression among those with CTD-ILD and other fibrosing ILDs remains unclear, but likely stems in part from extrapulmonary manifestations of CTD and widespread use of immunosuppression.

As opposed to most ILDs, which are lung predominant, CTD leads to a wide array of systemic manifestations. Several of these manifestations, including muscle weakness, sclerodactyly and pulmonary hypertension, may lead to declines in FVC or D_{LCO} [21–23]. Treatment also likely affects disease course, as this class of therapy is widely used to treat CTD-ILD [2, 24, 25]. Although clinical trials have only been performed in patients with SSc-ILD [26, 27], this approach is supported by retrospective studies suggesting that immunosuppressant therapy can stabilise or improve lung function [28, 29]. Large majorities of our CTD-ILD patients were treated with immunosuppressant therapy, which parallels the observations of Nasser *et al.* [12] when characterising outcomes in a French PF-ILD cohort. While we did not detect heterogeneity in FVC trajectory after satisfying PF-ILD criteria among those with and without exposure to immunosuppressant therapy, indication bias may have influenced these findings. Studies are needed to assess the effects of combined immunosuppressant and antifibrotic therapy.

While we found that CT progression of fibrosis was the strongest predictor of subsequent FVC decline, we also observed that FVC decline itself was a poor predictor of subsequent FVC decline. These findings parallel those reported in patients with IPF [30, 31] but stand in stark contrast to those reported in a recent *post hoc* analysis of the INBUILD trial, in which annual FVC decline was highest among patients who experienced an FVC decline of $\geqslant$10% as part of trial inclusion criteria [15]. The reason for this discordance may stem from the fact that background immunosuppression was not allowed among INBUILD participants. By requiring objective evidence of progression despite standard management, the INBUILD cohort was likely enriched with patients with immunosuppressant refractory PF-ILD. These findings, and ours, suggest that investigation aimed at determining the prevalence of PF-ILD among those with CTD-ILD, along with identifying reliable clinical and molecular biomarkers of progressive CTD-ILD, is warranted. These data also highlight the importance of ensuring optimal immunosuppression is achieved when indicated.

We also demonstrate that the time to satisfy key CT and PFT features of the PF-ILD criteria was highly variable. These findings are in line with those published by Nasser *et al.* [12] and mimic real-world experience, in which patients progress at variable intervals and by different measures. While roughly half of patients satisfied key PF-ILD features within 5 years of ILD centre evaluation, a substantial number progressed after 5 years. This suggests that vigilance is needed when choosing to observe patients for PF-ILD evolution, as this may manifest at any point during their care. The frequency at which PFTs and chest CT scans should be performed in patients with ILD remains unclear, but our data suggest that regular intervals should be considered for each.

This study had several limitations. There were several notable differences in baseline characteristics, and between the US and UK cohorts, and a modestly higher mean annual rate of FVC decline in the US cohort. This may reflect differences in referral patterns, PFT testing and management strategies between countries. Next, the retrospective approach resulted in variable follow-up time for each patient, which precluded assessing individual PF-ILD criterion over a standardised time frame. Prospective validation of these results using protocolised CT and PFT acquisition is needed. Another limitation stems from potential heterogeneity in ILD diagnosis and radiological interpretation across centres. While all four centres in this study are experienced ILD centres, diagnostic agreement for specific ILD subtypes is variable [32] and likely resulted in differential classification across centres. Except for CTD-ILD, the consistency of results across ILD subtypes suggests that ILD classification matters less than physiological measures when assessing PF-ILD. In accordance with INBUILD criteria [5], we excluded patients with <10% fibrosis on HRCT to ensure our study focused on fibrotic ILD. As such, it remains unclear how these findings apply to patients with more subtle fibrotic changes. We also excluded patients without follow-up PFTs, along with those who were unable to perform a D_{LCO} at baseline, which likely selected for patients with less severe disease. However, this approach is also in line with INBUILD inclusion criteria and ultimately necessary to identify patients with categorical FVC and D_{LCO} decline in this retrospective cohort. We also relied on the medical record to ascertain symptomatic worsening and increasing extent of fibrosis on HRCT. This is similar to INBUILD trial methodology but may have introduced ascertainment bias, especially with CT worsening defined qualitatively. With the emergence of quantitative CT analysis [33], efforts to establish quantitative thresholds for determining fibrotic progression are warranted. Finally, while our stratified analysis did not suggest heterogeneity in the rate of FVC change after satisfying PF-ILD

criteria between patients with and without immunosuppressant exposure, this analysis likely suffered from indication bias. These findings should be interpreted in this context and prospective testing of antifibrotic therapies in combination with immunosuppression is warranted. We focused our analysis of immunosuppressant drugs on steroid-sparing agents, ignoring prednisone use; however, prednisone monotherapy is rarely used at our institutions and is instead used in conjunction with steroid-sparing immunosuppressant agents.

Conclusions

Lung function trajectory varies considerably after ILD diagnosis and is influenced by several factors, including ILD diagnosis, HRCT pattern and baseline FVC. Near-term change in FVC after satisfying proposed PF-ILD criteria is also heterogeneous depending on the criterion of interest and is strongly influenced by ILD diagnosis. These findings may inform future clinical trial design and suggest ILD subtype should be taken into consideration when applying PF-ILD criteria.

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