Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease

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ABSTRACT

Objective. *Clinically meaningful change in systemic sclerosis (SSc) related interstitial lung (SSc-ILD) disease is unknown. The aim of this study was to quantify change in pulmonary function as a predictor of outcome in SSc-ILD.*

Methods. *All patients had SSc-ILD defined by HRCT chest. All PFTs during follow-up, including FVC (L), DLCO (ml/min/mmHg) and KCO (DLCO/alveolar volume ratio; DLCO/VA) (ml/min/mmHg/L) were retrieved. The rate of change over the first four years, and percentage change in the first year of follow-up were used in ROC curve analysis to determine the best cut-off points to predict adverse outcome (home oxygen, lung transplantation, or death).*

Results. *Among 264 patients, there were 49 events (38 deaths, 10 supplemental oxygen, one lung transplant) over a mean (±SD) follow-up of 3.0 (±1.7) years. The rates of decline over time and percentage change over one year in each of FVC, DLCO and KCO were predictive of adverse outcome. Stable PFTs over four years gave the optimal negative predictive values (NPVs) of 88–96%. The best sensitivity-specificity trade-off was a decline in FVC of 10% and in DLCO and KCO of 15% with NPVs of 92–93%.*

Conclusion. *The course that SSc-ILD takes is evident within the first 1–4 years of follow up. Patients who have no decline in PFTs over 4 years have better outcomes. A decline within one year in DLCO or KCO of 15% or more is a poor prognostic factor, and identifies patients who should be monitored more closely and considered for therapy.*

Introduction

Lung disease is one of the major causes of mortality in patients with systemic sclerosis (SSc) (1-4). While 65–91% of patients with SSc have changes of interstitial lung disease (SSc-ILD) on high resolution CT of the lung (HRCT) (5, 6), this is not severe or progressive in all patients. We and others (7, 8) have shown that more extensive lung disease on HRCT at baseline and on follow-up, predicts a worse outcome in SSc-ILD. Serial pulmonary function tests (PFTs) including forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) divided by alveolar volume ratio (DLCO/VA [KCO]) also predict outcome (2, 7), and have the potential to predict disease progression before it becomes extensive on HRCT, without repeated exposure to radiation. Expert guidelines recommend frequent monitoring of lung function in the early years of SSc- ILD (9, 10), although there are no established data on what is a clinically meaningful decline in these variables in SSc-ILD. Therefore, in this study, we sought to quantify change in pulmonary function as a predictor of disease outcome in SSc-ILD.

Methods

Patients

We included patients with SSc-ILD as defined by the presence of characteristic findings of fibrosis on HRCT, who were enrolled in the Australian Scleroderma Cohort Study (ASCS), a prospective multicentre study of risk and prognostic factors for cardiopulmonary outcomes in SSc. All patients fulfilled the ACR or Leroy/Medsger limited criteria for diagnosis of SSc (11, 12). Written informed consent was obtained. The ASCS has been approved by the human research ethics committee of each of the participating centre (Royal Perth Hospital Ethics Committee; Royal Adelaide Hospital Research Ethics Committee; St Vincent's Human

Table I. Patient characteristics.

Variable	n (%) or mean (±SD)
Total number of patients	262 (100.0%)
Sex: Female	220 (84.0%)
Male	42 (16.0%)
Disease subtype†:	
Limited	147 (56.1%)
Diffuse	100 (38.2%)
Overlap	15 (5.7%)
Smoker††	104 (39.7%)
Anti-Scl70 antibody positive	82/259 (31.7%)
Anti-centromere antibody positive	44/260 (16.9%)
Age at baseline PFT (years)	57.6 (±11.9)
Disease duration at baseline PFT (years)	12.2 (±10.8)
Mean follow-up††† (years)	3.0 (±1.7)
Time interval between PFTs (years)	1.6 (±0.8) (median 1.41)
Patients with matched HRCT to baseline PFT‡	60 (22.9%)
Baseline HRCT grade	
Limited	40 (33.3%)
Extensive	20 (66.7%)
Number of outcome events:	49 (18.7%)
Death	38
Home oxygen	10
Lung transplantation	1

ILD: interstitial lung disease; HRCT: high-resolution computed tomography; PFT: pulmonary function test; †Disease subtype defined according to extent and distribution of skin disease; ††Smoker ever (≥1 cigarette per day for ≥6 months); †††Time from baseline PFT to outcome event or most recent review; ‡Patients in whom baseline HRCT occurring ± 90 days of PFT could be retrieved for scoring.

Table II. Pulmonary function data.

Variable	Mean ± SD or n (%)
Lung function at baseline PFT	
FEV1 (% predicted)	80.9 (±19.0) (range 25.0-165.0)
FVC (% predicted)	82.9 (±20.8) (range 23.0-157.0)
FEV1/FVC (%)	80.4 (±8.2) (range 53.0-98.9)
DLCO (% predicted)	53.5 (±16.9) (range 13.0-120.0)
KCO (% predicted)	67.9 (±16.6) (range 33.0-120.0)
Over first year	
Percentage decline# in:	
FVC (n=125)*	2.66 (±11.18) (median=3.13, IQR=12.59)
DLCO (n=113)*	3.63 (±14.78) (median=3.62, IQR=14.60)
KCO (n=112)*	0.21 (±13.45) (median=2.33, IQR=13.69)
Stable PFTs**	
FVC (n=125)*	53 (42.4%)
DLCO (n=113)*	43 (38.1%)
KCO (n=112)*	42 (37.5%)
Over four years	
Number (%) of patients with decline in:	
FVC (>10%)	32 (25.6%)
DLCO (>15%)	18 (15.9%)
KCO (>15%)	10 (8.9%)
Mean (±SD) rate of decline in:	
FVC (L/year)	0.08 (±3.00) (median=0.05, IQR=0.48)
DLCO (ml/min/mmHg/year)	0.27 (±2.85) (median=0.34, IQR=1.34)
KCO (ml/min/mmHg/L/year)	0.02 (±0.70) (median=-0.01, IQR=0.30)

DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; IQR: interquartile range; KCO: DLCO by alveolar volume ratio (DLCO/VA); PFT: pulmonary function test.
*analysis limited to patients in whom there were 2 or more measurements of PFT variables in the first year; #relative to baseline; **less than 5% decline relative to baseline.

Research Ethics Committee A; Southern Health Human Research Ethics Committee; Tasmanian Health and Medical Human Research Ethics Committee; and University of Wollongong Human Research Ethics Committee).

Clinical and laboratory variables

All available serial PFTs were retrieved for each patient through detailed review of all medical records, including those from prior to enrolment in the ASCS. 'Baseline' PFT was the first retrievable PFT. PFT parameters including FVC (L), DLCO (ml/min/mmHg) and KCO, defined as DLCO by alveolar volume ratio (DLCO/VA) (ml/min/mmHg/L) were recorded. Demographic data included sex, age and smoking history. Disease related variables included duration of disease from the first non-Raynaud's phenomenon symptom, disease subtype (13), overlap with other connective tissue diseases based on clinical features and where relevant, autoantibodies, and SSc-related and antibody profile. In addition, all serial lung HRCTs were obtained.

Evaluation of PFT parameters

Change in PFT values was assessed in several ways. Firstly, the rate of change over four years in the absolute value for each variable was calculated using a regression line of best fit for the variable plotted against time. The coefficient of regression was the slope of the line and represented the rate of decline. Secondly, percentage change in values relative to baseline over the first year of follow-up (±90 days) was determined.

Evaluation of HRCT scans

Where available, baseline lung HRCTs were scored using a staging system we have previously validated (7). Specifically, each HRCT was graded based on the total extent of lung disease: <20% was scored as 'limited', >20% was scored as 'extensive' (8).

Outcome variable

The primary outcome variable was a composite of death (all-cause), need for supplemental oxygen (ambulatory and/or continuous) or lung transplantation. In the ASCS, ambulatory oxygen

Table III. Univariate comparison of demographic and disease-related variables in patients with and without event.

Variable		n (%) or mean (±SD) with event	n (%) or mean (±SD) without event	*p*-value
Gender	Male	1 (22.4%)	31 (14.6%)	0.17
	Female	38 (77.6%)	182 (85.4%)	
Smoker	Yes	24 (49.0%)	80 (39.0%)	0.16
	No	25 (49.0%)	125 (61.0%)	
Anti-Scl70 positive	Yes	10 (20.8%)	72 (34.1%)	0.07
	No	38 (79.2%)	139 (65.9%)	
Anti-centromere positive	Yes	7 (14.6%)	37 (17.5%)	0.63
	No	41 (85.4%)	175 (82.5%)	
Age at baseline PFT		61.78 (±10.92)	56.59 (±11.95)	0.99
Disease duration at baseline PFT		14.23 (±12.59)	11.66 (±10.22)	0.95
Base HRCT grade	Limited	5 (41.7%)	59 (77.6%)	0.009
	Extensive	7 (58.3%)	17 (22.4%)	

Table IV. Univariate comparison of PFT variables in patients with and without event.

Variable	Mean (±SD) in those with event n=49	Mean (±SD) in those without event n=213	*p*-value
FEV1 value at baseline (L/sec)	1.75 (0.62)	2.09 (0.55)	0.0001
FEV1 percentage predicted at baseline	70.72 (17.07)	83.13 (18.65)	<0.0001
FVC value at baseline (L)	2.23 (0.88)	2.61 (0.69)	0.0007
FVC percentage predicted at baseline	71.94 (19.13)	85.33 (20.39)	<0.0001
FEV1/FVC percentage predicted at baseline	80.42 (10.57)	80.27 (7.48)	0.54
DLCO value at baseline (ml/min/mmHg)	9.72 (3.99)	13.55 (4.69)	<0.0001
DLCO percentage at baseline	41.11 (14.12)	97.20 (3.99)	<0.0001
KCO value at baseline (ml/min/mmHg/L)	2.98 (0.74)	3.56 (0.83)	<0.0001
One year % decline in FVC	8.02 (10.44)	1.93 (11.13)	0.0006
One year % decline in DLCO	15.85 (19.74)	2.04 (13.33)	<0.0001
One year % decline in KCO	8.31 (13.19)	-0.86 (13.18)	<0.0001
Rate of decline in FVC over four years (L/year)	-0.20 (0.33)	-0.05 (0.29)	0.004
Rate of decline in DLCO over four years (ml/min/mmHg/year)	-1.51 (1.66)	-0.07 (2.96)	0.006
Rate of decline in KCO over four years (ml/min/mmHg/L/year)	-0.27 (0.36)	0.06 (0.73)	0.009

DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; KCO: DLCO by alveolar volume ratio (DLCO/VA); PFT: pulmonary function test.

Table V. Univariable association of change in pulmonary function variables and outcome determined using Cox regression.

Variable	n. patients*	n. events§	HR$	*p*-value$
FVC4-year#	211	34	1.94	<0.0001
DLCO4-year#	200	28	1.37	<0.0001
KCO4-year#	197	28	1.94	<0.0001
FVC1-year^	124	15	1.06	0.04
DLCO1-year^	109	13	1.07	<0.0001
KCO1-year^	106	13	1.05	0.04

DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; KCO: DLCO by alveolar volume ratio (DLCO/VA); HR: Hazards ratio.
#Rate of decline in first 4 years of follow-up; FVC4-year measured in L/year; DLCO4-year measured in ml/min/mmHg/year; KCO4-year measured in ml/min/mmHg/L/year; ^Percentage decline over 1yr (±90 days); *Number of patients in whom a regression coefficient is calculable. These are patients who have 3 or more PFT measurements over 4 years, with the first set at diagnosis and the last set at 4 years (±90 days); §Remaining number of events in these patients; $Cox univariable model.

is prescribed to patients with desaturation on exercise, measured by pulse oximeter, to an oxygen saturation (SpO2) ≤88%. Other indications are having an arterial partial pressure of oxygen ≤55 mmHg at rest or <60 mmHg at rest, with evidence of pulmonary hypertension or cor pulmonale (14).

To enable time-to-event analysis, the date of 'first' occurrence of each outcome was recorded as either the date of death or lung transplantation, or the clinic date at which oxygen therapy was first prescribed in those who were alive and had not undergone lung transplantation at the time of the last clinic visit. For patients who remained outcome-free, data were censored at the last clinic visit.

Statistical analyses

Univariable Cox regression models were used to determine the relationship between each of rate of decline and percentage decline in each PFT variable, and event-free survival. Receiver operating characteristics (ROC) curves and diagnostic testing procedures were used to determine the best cut-off points to predict adverse outcomes.

In subgroup analysis of patients in whom the HRCT score was available at baseline, Kaplan-Meier (K-M) survival curves were used to determine the relationship between percentage decline in PFT and outcome, after adjustment for HRCT score (*i.e.* limited *vs.* extensive).

Results

Patient characteristics

Patient characteristics are presented in Table I. Among 1170 patients in the ASCS, 311 (26.6%) were recorded as ever having ILD; PFT data were retrievable in 262 of these patients. Mean (±SD) age and disease duration at baseline PFT were 57.6 (±11.9) and 12.2 (±10.8) years, respectively. In total, there were 49 events (38 deaths, 10 supplemental oxygen, one lung transplant) in these 262 patients over a mean (±SD) follow-up of 3.0 (±1.7) years.

Pulmonary function data are presented in Table II. Overall, our analyses were based on 958 PFTs in 262 patients, with a median of 3.66 PFTs per patient, and mean (±SD) time interval between

Table VI. ROC curve analysis to determine optimal cut-points for PFT variables in predicting outcome.

Variable	ROC AUC	Sensitivity % (CI)	Specificity % (CI)	Correctly classified (%)	LR+	LR-	PPV % (CI)	NPV % (CI)
FVC#	0.33	26.50 (20.55-32.46)	62.20 (55.66-68.74)	56.40	0.70	1.18	18.52 (12.56-26.32)	88.16 (78.22-94.11)
DLCO#	0.26	10.70 (6.42-14.98)	59.30 (52.49-66.11)	52.50	0.26	1.51	19.69 (13.37-27.88)	95.89 (87.66-98.93)
KCO#	0.26	14.30 (9.41-19.19)	48.00 (41.02-54.98)	43.20	0.27	1.79	22.64 (15.31-31.99)	95.70 (88.74-98.61)
FVC^	0.67	53.33 (44.55-62.11)	78.18 (70.91-84.45)	75.20	2.44	0.60	25 (12.13-43.75)	92.47 (8.46-96.66)
DLCO$^{\Delta}$	0.69	46.15 (36.79-55.51)	88.00 (81.90-91.10)	83.19	3.85	0.61	33.33 (14.36-58.95)	92.63 (84.91-96.73)
KCO$^{\Delta}$	0.66	38.46 (29.20-47.72)	94.95 (90.78-99.12)	88.39	7.62	0.65	50 (20.14-79.86)	92.16 (84.68-96.30)

DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; KCO: DLCO by alveolar volume ratio (DLCO/VA); LR: likelihood ratio; NPV: negative predictive value; PFT: pulmonary function test; PPV: positive predictive value.
#Rate of decline in first 4 years of follow-up <5%; ^Percentage decline over 1yr (±90 days) = 10%; $^{\Delta}$Percentage decline over 1yr (±90 days) = 15%; FVC# measured in L/year; DLCO# measured in ml/min/mmHg/year; KCO# measured in ml/min/mmHg/L/year.

PFTs of 1.6 (±0.8) years. Fifty-one of the 311 (16%) patients with ILD in this study had pulmonary arterial hypertension (PAH) diagnosed on right heart catheterisation (mean pulmonary artery pressure ≥25mmHg at rest and pulmonary capillary wedge pressure ≤ 15mmHg).

Univariate comparison of characteristics of patients with and without events

Univariate comparison of the disease-related characteristics of patients with and without an event is presented in Table III. There were no significant differences in sex, autoantibody profile, age or disease duration at baseline PFT in those with, compared to those without an event during follow-up. Patients with events during follow-up were more likely to have extensive changes on baseline HRCT.

Univariate comparison of PFT variables in patients with and without an event is presented in Table IV. Patients who had events over follow-up had lower FVC, DLCO and KCO at baseline, and a higher rate of decline in each of these PFT variables over 4 years.

Rate of change in PFTs over the first four years of follow-up

The rate of decline in PFT variables was approximately linear in all patients. Lines of best fit for each of the PFT variables (FVC, DLCO and KCO) were plotted against time over the four years from baseline PFT. We limited our analyses to the first four years following baseline PFT because in our data set, few patients had follow-up beyond four years. The coefficients of regression equated to the rates of decline over time and, were significantly related to deterioration or death in a univariable Cox proportional hazards model for each of FVC, DLCO and KCO (hazard ratios [HR] of 1.94, 1.37 and 1.94 respectively, *p*-values all <0.0001) (Table V).

The rate of decline in each variable was analysed using ROC curves and a cut-off value that gave the best sensitivity-specificity trade-off was selected. Stable PFT parameters (*i.e.* less than 5% change in PFT parameter over four years) gave the optimal trade-off, with negative predictive values (NPV) ranging from 88.2% (95% confidence intervals [CIs] 78.2–94.1) for FVC, to 95.7% (95% CIs 88.7–98.6) for KCO. Positive predictive values (PPVs) were less than 25% (Table VI).

Percentage decline in variables over one year

The percentage changes over one year from baseline (±90 days) in FVC, DLCO and KCO were also significantly associated with deterioration or death in univariable modeling (HRs 1.06 [*p*<0.04], 1.07 [*p*<0.0001] and 1.05 [*p*<0.04] respectively) (Table V). In an ROC curve analysis, the best sensitivity-specificity trade-off was a decline in FVC of 10% and in DLCO or KCO of 15% with NPVs ranging from 92.2% (95% CIs 84.7–96.3) for a 15% decline in KCO to 92.6% (CIs 84.9–96.7) for a 15% decline in DLCO (Table VI). PPVs ranged from 25.0% (95% CIs 12.1–43.8) for a 10% decline in FVC to 50.0% (95% CIs 20.1–79.9) for a 15% decline in KCO. A 15% decline in KCO also predicted a poor outcome with the highest likelihood ratio (LR) of 7.62.

Independent predictors of outcome

As presented in Tables VII and VIII, in Cox regression models in which FVC, DLCO and KCO were defined based on the cut-points determined in earlier ROC curve analysis, after adjustment for age and disease duration at baseline PFT, disease subtype and anti-Scl70 antibodies, only a 15% one-year decline in either DLCO (HR=1.71, 95% CI: 1.51, 1.91, *p*=0.01) or KCO (HR=1.38, 95% CI: 1.15, 1.60, *p*<0.0001) were predictive of outcome. As DLCO and KCO were highly collinear, we placed these variables into separate models. In these analyses, a 10% one-year decline in FVC was not significantly predictive of outcome. Analysis of the subgroup of patients in whom there was no documented PAH yielded similar results.

Stratifying by extent of disease on baseline HRCT lung

The extent of disease on HRCT scan of the lung at baseline enabled further stratification of patients' risk of adverse outcome beyond change in FVC over 1 year (Fig. 1), though our analyses in this section were limited to only 60 patients who had HRCT chest at the time (±90 days) of baseline PFT. Those with limited disease on HRCT and less than 10% decline in FVC over one year had the best event-free survival and those with extensive disease on HRCT and greater than 10% decline in FVC had the worst outcome.

Discussion

We have previously shown that age, the extent of disease on HRCT chest, FVC and KCO on serial PFTs are significantly associated with outcome (a compos-

Table VII. Multivariable regression analysis of variables correlated with event (DLCO included in model).

Variable	HR (95% CI)	*p*-value
Age at baseline PFT	2.00 (1.99, 2.004)	0.48
Disease duration at baseline PFT	2.00 (1.99, 2.01)	0.80
Diffuse disease subtype	1.93 (1.79, 2.07)	0.30
Anti-Scl70 antibody	1.91 (1.77, 2.06)	0.23
10% one-year FVC decline	1.94 (1.79, 2.09)	0.43
15% one-year DLCO decline	1.71 (1.51, 1.91)	0.01

DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; PFT: pulmonary function test.

Table VIII. Multivariable regression analysis of variables correlated with event (KCO included in model).

Variable	HR (95% CI)	*p*-value
Age at baseline PFT	2.00 (1.99, 2.004)	0.66
Disease duration at baseline PFT	2.00 (1.99, 2.006)	0.97
Diffuse disease subtype	1.96 (1.83, 2.08)	0.50
Anti-Scl70 antibody	1.92 (1.79, 2.05)	0.23
10% one-year FVC decline	1.92 (1.79, 2.05)	0.22
15% one-year KCO decline	1.38 (1.15, 1.60)	<0.0001

FVC: forced vital capacity; ILD: interstitial lung disease; KCO: DLCO by alveolar volume ratio (DLCO/VA); PFT: pulmonary function test.

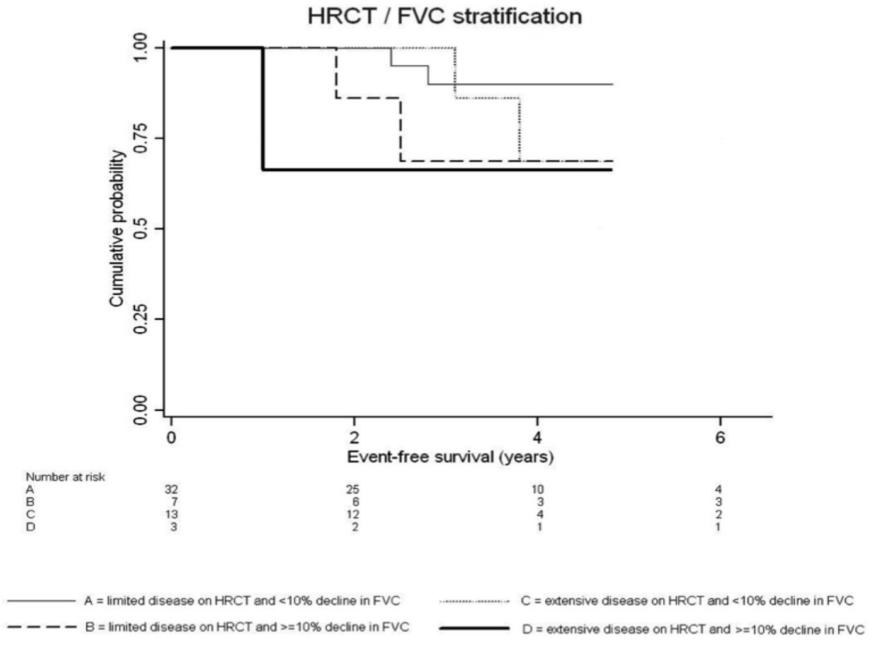

Fig. 1. Time to first event stratified by extent of disease on chest HRCT scan and percentage decline in FVC in one year.

ite of decline and death) in our Australian cohort (7). In this report, we evaluated the relationship between change in PFT variables in the first 1 to 4 years following baseline PFT, and outcome. We found that the rate of change over the first four years of follow-up, and the percentage change over one year in FVC, DLCO and KCO relative to baseline, predicted mortality and clinical deterioration. Optimal sensitivity-specificity trade-offs and NPVs of 88-96% were seen when these variables were stable over four years, implying that if PFT variables do not change more than the expected 5% test-retest variability in the first four years of follow-up, the outcome is likely to be good. On the other hand, those with a decline in FVC over four years and extensive disease on baseline HRCT chest, had the worst outcomes. Declines in FVC of 10% and in DLCO and KCO of 15% over one year had the strongest PPVs and NPVs. A decline in KCO of 15% had the highest PPV, NPV and LRs for a poor outcome. These associations were also borne out in multivariable regression analysis for each of one-year decline in KCO of 15% and one-year decline in DLCO of 15%.

It is generally accepted that in patients with severe SSc-ILD, the decline in FVC is greatest early in the disease and tends to plateau after 4-6 years (3, 15). In the Scleroderma Lung Study (SLS), which included patients with SSc-ILD of up to four years' duration, the rate of decline was greatest in patients with more extensive disease on HRCT, especially in patients with duration of ILD less than 2 years, although the mean annual decline in FVC % predicted in the placebo group was less than 10%, irrespective of disease duration (16). One possible explanation for DLCO and KCO decline being more strongly and robustly associated with outcome in our study than FVC decline may be the 'prevalent' nature of the cohort, where mean disease duration at baseline PFT was 12.2 years.

Another likely explanation is that DLCO and especially KCO, which represents diffusing capacity corrected for alveolar volume, reflect the development of pulmonary vascular disease, an important contributor to poor outcome for patients with ILD, either in addition or secondary to the ILD.

In IPF, change in FVC has been associated with mortality in many cohorts (17-19) although it is variously analysed as a continuous variable or according to a certain threshold. A decline in the percentage predicted value from baseline for FVC of 10% or more over six or 12 months is an independent predictor of mortality (20) but changes of this magnitude may be insensitive for real disease progression as smaller decreases in FVC of 5–10% predict survival and have been statistically significant primary endpoints in clinical trials (17, 21). Indeed, the estimated minimum

clinically important difference for percentage predicted FVC is only 2–6%. Furthermore, a relative decline in the absolute percentage predicted value may be more sensitive for detecting a decline in FVC, for example by 10% or more, than an absolute decline and with a similar predictive accuracy for outcome (22). The threshold values for decline in FVC (10%), DLCO and KCO (both 15%) found in our study are the same as those validated in IPF (20). Although smaller declines in FVC and KCO are also predictive of outcome in ILD, this has not been replicated in SSc-ILD, perhaps due to the slower rate of progression in the latter (21). However, the NPV of stable PFTs indicates that even a smaller decline in PFT variables may be significant in SSc-ILD.

In our study, the relatively long duration of disease at baseline PFT contrasts the report by Steen *et al*., where those with decline in lung function in the first 4 years following SSc diagnosis had the worst outcomes (3). We envisage three possible explanations for this observation. The first is that our cohort comprised a relatively larger number of patients with limited disease, in whom ILD may be diagnosed later in the disease course. Secondly, there may be an element of survivor bias in our 'prevalent' cohort, wherein no limitations were placed on disease duration at recruitment. As such, patients with severe diffuse disease and ILD may have died before being recruited. Finally, 'baseline' PFTs in this study were the first available set that could be retrieved for analysis, and may have been some time after the true onset or diagnosis of ILD.

In this observational study, we are unable to evaluate the effect of therapy on ILD outcomes as treatment assignment was not random and subject to confounding by indication. The effect of therapy on SSc-ILD is the subject of current and future clinical trials.

In conclusion, the course that SSc-ILD takes is evident within the first 1-4 years of follow-up. Patients who have no decline in PFTs over 4 years follow-up have better outcomes. As in IPF, a one-year decline in DLCO or KCO of 15% or more, or in FVC of 10% or more is a poor prognostic marker and identifies patients who should be monitored more closely and considered for therapy. This provides a simple "rule of thumb" assessment of SSc-ILD that could complement the HRCT grading system for determining prognosis in SSc-ILD.

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